NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Bosutinib for previously treated chronic myeloid leukaemia [ID495]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Bosutinib for previously treated chronic myeloid leukaemia [ID495]

Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Bosutinib for previously treated chronic myeloid leukaemia

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- Bosutinib is licensed for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options
- Current NICE guidance is that nilotinib and imatinib may both be used either 1st or 2nd line.
  - What is current clinical practice?
  - Where should bosutinib be considered in the treatment pathway: 2nd line after either imatinib or nilotinib, 3rd line after imatinib and nilotinib, and/or later?
- What treatment(s) would people be expected to receive following bosutinib in clinical practice? How might post-bosutinib treatments impact on overall survival?
- When would stem cell transplant (SCT) be considered in the treatment pathway?

Clinical effectiveness

- The clinical evidence for bosutinib is from Study 200. This was a single arm study in which 52 out of 570 people were defined as having 'unmet medical need'. The population included in the trial received imatinib first line (the average duration of treatment with first line imatinib was 1.5 to 2.7 years) and approximately 40% of patients had previously taken interferon.
  - Does Study 200 demonstrate improvements in clinical outcomes for the unmet medical need subgroup?
  - Is the clinical effectiveness evidence from Study 200 generalisable to people who would be considered for treatment with bosutinib in UK clinical practice?

- The evidence for the comparator treatments is from small, non-randomised studies in which participants were younger than might be expected in UK clinical practice. Overall survival for hydroxycarbamide was based on data from a group of 61 patients in the Kantarjian (2007) trial who had received a range of treatments (12 received hydroxycarbamide). Overall survival after SCT was based on 16 chronic phase patients from the Jabbour (2011) study. Are the data for comparator treatments sufficiently reliable for the purposes of informing a comparison of clinical effectiveness with bosutinib?
- The manufacturer suggested that the adverse event profile of bosutinib is different to that of the other tyrosine kinase inhibitors as it has a different mechanism of action. Additionally bosutinib does not require fasting when it is taken. Would bosutinib be an alternative treatment option for people who are intolerant of imatinib, dasatinib or nilotinib?

Cost effectiveness

- In the absence of mature overall survival estimates from Study 200 (median OS not reached except for blast phase) for the chronic phase population the manufacturer used major cytogenetic response as a surrogate for overall survival using data from a study (Jabbour 2009) in which a population received standard dose imatinib followed by high dose imatinib

  - Is the relationship between major cytogenetic response and overall survival independent of treatment?

- The survival estimates from the manufacturer's modelled base case were:
  - For the 3rd line chronic phase population:10.3 life years with bosutinib, 3.52 life years with hydroxycarbamide, 3.62 life years with interferon and 6.60 life years with stem cell transplant.
  - For the accelerated phase population: 4.48 life years with bosutinib, 1.37 years with hydroxycarbamide and 3.02 years with stem cell transplant.
  - For the blast phase population: 1.77 life years with bosutinib, 0.54 life years with hydroxycarbamide and 2.64 with stem cell treatment.

  Are these estimates plausible on the basis of the evidence?
- In the manufacturer's model, time on treatment after bosutinib was calculated as overall survival minus time spent on bosutinib treatment. In the bosutinib arm this resulted in a longer survival time on hydroxycarbamide after treatment with bosutinib than the survival on hydroxycarbamide when taken in the equivalent point in the treatment pathway to bosutinib. Is this clinically plausible?
- In its base case the manufacturer did not use utility values derived from Study 200 and assumed the same utility value for bosutinib as hydroxycarbamide.
  - Is health related quality of life independent of the treatment received for people with CML?
- The manufacturer asserted that bosutinib met end of life criteria for the advanced phase CML populations as i) patients have a short life expectancy (around 16 months - 10 months accelerated phase, 6 months blast phase) ii) bosutinib extends life by approximately 1.7 years in the accelerated phase and 1.2 years in blast phase and iii) the anticipated population is expected to be small (around 80 people). Does bosutinib meet end of life criteria for people with accelerated or blast phase CML?

1 Background: clinical need and practice

1.1 Chronic myeloid leukaemia (CML) is characterised by the production of an excessive number of white blood cell precursors (stem cells) by the bone marrow. Ninety-five percent of people with CML have a specific chromosomal abnormality commonly known as the 'Philadelphia chromosome'. This is caused by an exchange of genetic material between parts of chromosome 22 and chromosome 9 that contain the break point cluster region (BCR) and the Abelson kinase (c-abl) genes respectively. This gene fusion leads to the production of an abnormal tyrosine kinase oncoprotein (bcr-abl) that is constitutively (continually) active. This disrupts cell signalling pathways involved in the control of cell proliferation. This BCL ABL fusion gene and associated abnormal tyrosine kinase is the only known cause of CML.

1.2 CML is a rare disease with an incidence of approximately 1 per 100,000 people every year. It accounts for about one in six diagnoses of leukaemia in adults. Approximately 600 to 800 people are diagnosed with CML in England and Wales each year. The median age at diagnosis is between 50 and 60 years. The manufacturer estimated that the current prevalence of CML in England and Wales is around 5,922 and that of the incident population there would be around 80 people per year for whom treatment with bosutinib may be considered.

1.3 CML progresses slowly through 3 phases. The initial chronic phase lasts for several years. In this phase the symptoms are usually mild and non-specific and can include fatigue, weight loss, night sweats, anaemia, a feeling of 'fullness' and a tender lump on the left side of the abdomen caused by enlargement of the spleen. The majority of people with CML (90%) are diagnosed in the chronic phase. In approximately 40% of chronic phase diagnoses the patients are asymptomatic and are diagnosed as a result of a routine blood test. The disease may then

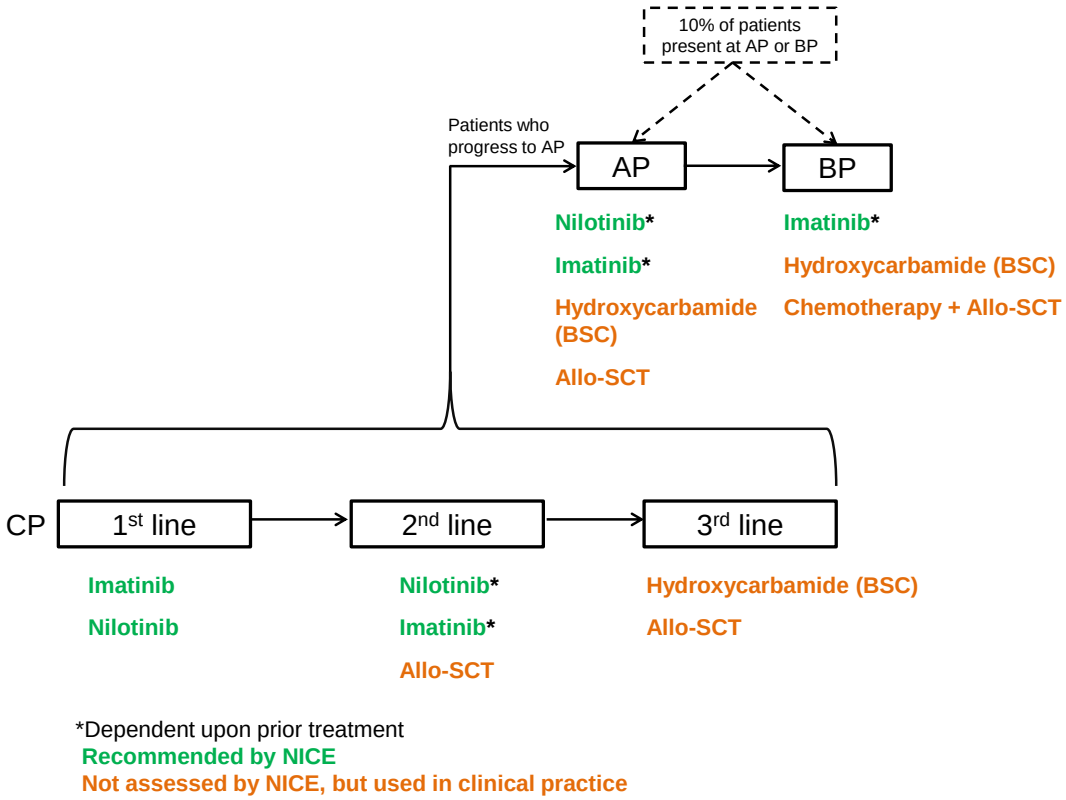
progress to an accelerated phase. During this phase, disease progression is more rapid, and immature blast cells in blood and bone marrow proliferate. Symptoms include bruising, bleeding and infections. The final phase is called the blast phase because a blast cell crisis occurs. This is a rapid increase in immature forms of cells (blasts), which replace normal cells in bone marrow and affect other organs. Symptoms include fever, sweating pain and enlargement of organs. When this phase is reached CML is often fatal within 3-6 months.

1.4 The progression of chronic myeloid leukaemia can be slowed by tyrosine kinase inhibitors which inhibit the activity of the Bcr-Abl protein. NICE has produced guidance for the use of 1st and 2nd line tyrosine kinase inhibitors for CML. NICE technology appraisal guidance 251 ('Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia [part review of technology appraisal guidance 70]') issued in April 2012, recommends the tyrosine kinase inhibitors imatinib (standard dose) or nilotinib (with a patient access scheme) as first line treatment options for adults with chronic phase Philadelphia-chromosome positive CML, but does not recommend dasatinib. NICE technology appraisal guidance 241 ('Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance'), issued in January 2012, recommends nilotinib (with a patient access scheme) as a second line treatment for people with chronic or accelerated phase Philadelphia- chromosome-positive CML whose CML is resistant to treatment with standard dose imatinib or are intolerant to imatinib. Dasatinib and high-dose imatinib are not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib. NICE technology appraisal guidance 70

recommendations allow for the use of standard dose imatinib following prior treatment.

1.5 Allogeneic stem cell transplantation (bone marrow transplantation) is the only curative strategy for CML. However, there is a limited population who receive a transplant and it is associated with a substantial rate of morbidity and mortality. Following failure of tyrosine kinase inhibitors interferon alpha, hydroxycarbamide or best supportive care may be used (See figure 1).

Figure 1: NICE recommended clinical pathway of care (from manufacturer's submission page 29



2 The technology

2.1 Bosutinib (Bosulif, Pfizer) is a second generation tyrosine kinase inhibitor, which inhibits Abl-kinases including Bcr-Abl kinase. It additionally inhibits another group of kinases called Src family kinases which have been implicated in driving the progression of CML. Bosutinib is administered orally. In April 2013 it received a conditional marketing authorisation for 'the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options'. The recommended dose is 500 mg once daily. A dose escalation of up to 600 mg is permitted if a complete haematologic response has not occurred by week 8 or a complete cytogenetic response by week 12. The Summary of Product Characteristics (SPC) states that 'In clinical trials treatment with bosutinib continued until disease progression or until it was no longer tolerated by the patient'.

2.2 The summary of product characteristics lists the following adverse reactions for bosutinib: diarrhoea, nausea, thrombocytopenia (low platelet counts), vomiting, abdominal pain, rash, anaemia (low red blood cell counts), pyrexia (fever) and increased levels of liver enzymes. The most serious adverse effects (which may affect more than 1 in 20 people) are thrombocytopenia, anaemia, diarrhoea and rash as well as neutropenia (low levels of neutrophils, a type of white blood cell) and increased levels of liver and digestive enzymes. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Bosutinib is not yet listed on the British National Formulary. The manufacturer has stated that bosutinib is available in two pack sizes: 500 mg x 28 tablets (£3,436.67) and 100 mg x 28 tablets (£859.17), with an

average cost of £122.74 for 500mg/day (all costs exclude VAT). The annual cost of bosutinib at this dose is £44,799. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of bosutinib within its licensed indication for the treatment of chronic myeloid leukaemia.

Population	Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia	In line with the marketing authorisation, the submission is based on a subset of this population. Those previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options
Intervention	Bosutinib	As per scope
Comparators	– Allogeneic stem cell transplantation (with or without leukaemia- style chemotherapy depending on phase of CML) – Hydroxycarbamide – Interferon alfa – Best supportive care	– Allogeneic stem cell transplantation (with or without leukaemia- style chemotherapy depending on phase of CML) – Hydroxycarbamide (best supportive care) – Interferon alpha
Outcomes	– Overall survival – Event-free survival – Progression-free survival – Time to progression – Response rates: cytogenetic, haematological and molecular, including time to response and duration of response – Time to treatment failure – Adverse effects of treatment – Health-related quality of	As per scope. In addition, transformation rates from CP to AP/BP and then to BP will be considered.

	life	
Economic evaluation	Cost–utility analysis from an NHS and PSS (personal social services) perspective with a time horizon sufficiently long to reflect any differences in costs or outcomes	As per scope

Population

3.2 The manufacturer's marketing authorisation application was initially for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase (CP). During the marketing authorisation process, the proposed indication was narrowed to a subset of people with high unmet need (patients who are resistant or intolerant to all TKIs currently available [imatinib, dasatinib and nilotinib]). This submission therefore reflects the revised indication from the European Medicines Agency for bosutinib. The ERG noted that only a small proportion of the trial population from which the clinical efficacy estimates of bosutinib were derived (52 out of a total of 546 patients with CML) were not suited to all three tyrosine kinase inhibitors.

Comparators

3.3 The manufacturer stated that hydroxycarbamide is accepted as the best supportive care for adult patients with Philadelphia chromosome positive CML in clinical practice and the ERG agreed with this. The ERG noted that the manufacturer presented no evidence for the clinical effectiveness of interferon and that this was not assessed as a comparator for the people with accelerated phase or blast phase CML.

Outcomes

3.4 The ERG noted that the manufacturer used cytogenetic response as a surrogate for overall survival in the bosutinib arm of the 3rd line chronic phase CML population.

4 Clinical-effectiveness evidence

4.1 The manufacturer's application for marketing authorisation was initially based on data from a pivotal phase III study (3160A4-3000-WW), a randomised, open-label study to assess whether 1st line bosutinib was superior to 1st line imatinib for treating chronic phase CML. Superiority of bosutinib for the primary outcome of complete cytogenetic response rate at 1 year was not established therefore bosutinib could not be considered for the 1st line indication in CML. However as data from this trial had demonstrated bosutinib to be an active drug in CML a revision to the marketing authorisation application was made to assess bosutinib for people with unmet medical need (people previously treated with one or more tyrosine inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment option). Following this change to the marketing authorisation application a phase I/II study (Study 200) became the pivotal study. Study 200 was an open-label, multicentre, 2-part, safety and efficacy study of 500 mg once daily bosutinib in participants with Philadelphia chromosome positive (Ph+) leukaemia after resistance or intolerance to imatinib. For this appraisal, the key evidence for the clinical effectiveness of bosutinib comes from Study 200.

Study 200 population and follow up

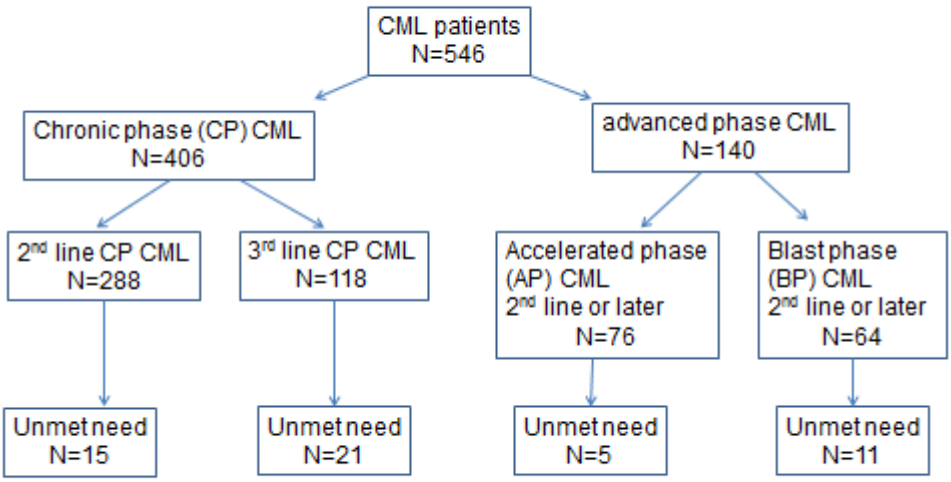
4.2 Part 1 of Study 200 was a dose-escalation study in 18 patients to determine a dose for part 2 and was not considered further within the Manufacturer's submission. Part 2 of Study 200 studied the efficacy and safety of 500mg once daily bosutinib in 570 Ph+ patients with resistance

to or intolerance of prior therapy. Within this population were 24 Ph+ acute lymphoblastic leukaemia patients; data for these patients were not relevant to the submission and not considered further. The remaining 546 participants with CML in the trial were considered within the following populations:

- **Second line CP CML population**: 288 people with chronic phase CML who received bosutinib second line following imatinib.
- **Third line CP CML population**: 118 people with chronic phase who received bosutinib second line following imatinib and nilotinib or dasatinib (3 people in this group received bosutinib 4th line)
- **Advanced phase CML (second line or later):**140 people who had advanced phase CML .Of these, 76 people had accelerated phase CML and 64 people had blast phase; 45 people with accelerated phase and 35 people with blast phase CML received bosutinib second line; 31 people with accelerated phase CML received bosutinib following multiple tyrosine kinase treatment ('multi-TKI'- imatinib followed by nilotinib and/or dasatinib) and 29 people with blast phase CML received bosutinib following multi-TKI (See figure 2).

4.3 Study 200 was not designed to assess bosutinib for an unmet medical need population. In order to demonstrate efficacy and safety in this setting a post-hoc defined subpopulation of Study 200 was requested by the European Medicines Agency. This included 52 people who had the presence of a mutation that would be reasonably expected to confer resistance to dasatinib or nilotinib and people who had medical conditions or prior toxicities that may predispose them to unacceptable risk with nilotinib or dasatinib therapy (see figure 2).

Figure 2: unmet medical need population in Study 200



4.4 Patients in Study 200 were treated until disease progression, unacceptable toxicity or withdrawal of consent. Dose escalations to 600 mg/day and reductions to 300 mg/day were permitted; 85 patients (15.2%) received a dose escalation to 600mg. Patients who discontinued treatment with bosutinib were followed up for survival for 2 years, people who remained on treatment continued to be followed. The manufacturer presented data from two data snapshots for the chronic phase population. On 28 March 2011 the median duration of follow up was 28.5 months (range 0.29 to 56.21 months), the minimum follow up was approximately 12 months, the median duration of treatment was 8.3 months (range, 0.2 to 51.8) and 29% of people were still on treatment at this time. On15 February 2012 the median duration of follow-up was 31.4 months (range 0.29 to 66.04) and the minimum follow up was approximately 24 months. The median duration of treatment was 8.6 months (range, 0.2 to 60.8) and 24% of people were still on treatment. For the advanced phase populations only the 28 March 2011 data was presented. At this time for

the accelerated phase population the median duration of follow up of was 26.45 months (0.32 to 56.07), the minimum follow-up was12 months, the median duration of treatment was 10.1 months (0.10 to 51.64) and 20% of people were still on treatment. For the blast phase population the median duration of follow up was 11.64 months (0.39 to 48.04), the minimum duration of follow up was 18 months, the median treatment duration was 2.8 months (0.03 to 44.24) and 5% of people were still on treatment at this time point.

4.5 All people in Study 200 had prior treatment with imatinib. The **second line chronic phase population** had a median age of 53 years (range 18 to 91), 47% were female, 33% had received treatment with interferon and 8 people (3%) had received a prior SCT. The median duration of CML was 3.6 years. The median time duration of treatment of previous imatinib was 2.2 years. The **third line chronic phase population** had a median age of 56 years (range 20 to 79) and 55% were female. The median duration of CML was 6.7 years (range 0.6-18.3) and the average treatment duration with prior imatinib was 2.7 years. In the chronic phase 3rd line population 37 were resistant to both imatinib and dasatinib, 50 were intolerant to imatinib and dasatinib, and 27 were resistant to imatinib and nilotinib. Three people had received imatinib, nilotinib and dasatinib prior to bosutinib. In this population 52% of people had received interferon and 9 people (8%) had received a SCT. In the **advanced phase population** the median age was 48.5 years (range 19 to 82), 64% were male. The majority of people had an ECOG performance status of 0 or 1 (78%); the remaining people had a performance status of 2. The majority of people (70%) had received prior interferon and 4 people (6%) had received a prior stem cell transplant. Patients were allowed to receive hydroxycarbamide and anagrelide while taking part in the study. The manufacturer reported in their response to clarification questions that the percentages of patients who had a drug interruption was

[redacted] for the second line chronic phase CML, third line chronic phase CML, accelerated phase and blast phase CML populations respectively. The mean number of days for which drug treatment was interrupted was [redacted] for each population respectively. See table 1.

Table 1 Study 200 baseline characteristic (Table 20 ERG report page 69)

Population		**Age (years) [Median (range)]**	**Male [N (%)]**	**CML duration (years) [Median (range)]**	**IM duration (years) [Median (range)]**	**ECOG Performance Status [N (%)]**		
						0	*1*	*2*
CP2L (N=288)	IM-R CP2L (N=200)	51.0 (18–86)	116 (58%)	4.0 (0.1–15.1)	2.6 (0.4–8.8)	151[a] (77%)	44[a] (23%)	0[a] (0%)
	IM-I CP2L (N=88)	54.5 (23–91)	38 (43%)	2.8 (0.1–13.6)	1.5 (<0.1–8.3)	68[a] (76%)	21[a] (23%)	1[a] (1%)
	Total CP2L (N=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	IM + DAS resistant CP3L (N=37)	54.0 (23–69)	14 (38%)	7.5 (1.2–17.6)	2.6 (0.02–6.4)	28 (76%)	9 (24%)	NA
	IM + DAS intolerant CP3L (N=50)	58.0 (25–79)	23 (46%)	5.6 (0.6–18.3)	3.3 (0.1–6.6)	31 (62%)	18 (36%)	NA
	IM + NI resistant CP3L (N=27)	52.0 (20–79)	14 (52%)	5.9 (1.2–16.3)	2.5 (0.7–5.9)	25 (93%)	2 (7%)	NA
	IM + DAS ± NI CP3L (N=4)	54.5 (31–62)	2 (50%)	11.7 (2.2–11.9)	3.0 (1.4–6.4)	2 (50%)	2 (50%)	NA
	Total CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	AP IM only (N=45)	47.0 (18–73)	24 (53%)	3.85 (1.1–22.1)	NR	26 (58%)	18 (40%)	1 (3%)
	AP Multi TKI (N=31)	56.0 (21–83)	18 (58%)	8.25 (1.5–19.2)	NR	15 (48%)	15 (48%)	1 (3%)
	AP Total (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.1–22.1)	NR	16 (46%)	10 (29%)	9 (26%)
BP (N=64)	BP IM only (N=35)	37.0 (19–75)	24 (69%)	1.75 (0.4–5.6)	NR	16 (46%)	10 (29%)	9 (26%)
	BP Multi TKI (N=29)	53.0 (22–82)	17 (59%)	5.75 (1.1–14.6)	NR	6 (21%)	18 (62%)	5 (17%)
	BP Total (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.4–14.5)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need[b](N=52)	CP2L (N=15)	65 (24-81)	10 (67%)	NR	NR	6 (40%)	9 (60%)	0
	CP3L (N=21)	58 (30-79)	11 (52%)	NR	NR	13 (62%)	8 (38%)	0
	AP (N=5)	66 (48-73)	6 (60%)	NR	NR	1 (20%)	4 (80%)	0
	BP (N=11)	51 (19-80)	7 (64%)	NR	NR	2 (18%)	6 (55%)	3 (27%)
	Total (N=52)	58	31	NR	NR	22	27	3

		(19-81)	(60%)			(42%)	(52%)	(6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor, a Information taken from Cortes (2012)[1] b Information taken from EPAR

Efficacy of bosutinib from Study 200

4.6 The primary efficacy outcome for the chronic phase population was rate of major cytogenetic response (MCyR) by 24 weeks. A MCyR means that less than 35% of bone marrow cells test positive for the Philadelphia chromosome. The primary outcome for patients with advanced phase CML was rate of attainment or maintenance of overall haematological response (OHR) by week 48. Overall haematological response was defined in the manufacturer's submission as any one of: complete haematological response, no evidence of leukaemia or a return to chronic phase. For all cohorts, analyses of the primary and key secondary endpoints except for progression free survival and overall survival were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline efficacy assessment.

4.7 In the third-line CP CML evaluable population, 27% (29 patients, 95% confidence interval [CI] 19 to 36) achieved major cytogenetic response (MCyR) by week 24, with [redacted] attaining complete cytogenetic response (CCyR). By the March 2011 snapshot (12 months follow up) 32% (32 patients 95% CI, 23.7 to 42.1) had achieved MCyR and 24% (26 patients 95% CI 16.4 to 33.3) had achieved CCyR. The median time to MCyR among responders in this analysis was 12.4 weeks. Data from the February 2012 snapshot (24 months follow up) for these outcomes were not available. The protocol specified that people who had MCyR or CCyR at baseline should be considered non-responders (meaning that they would not show a new response from baseline with treatment) and should not be included in the analysis, however the manufacturer presented a post hoc analysis that included

these patients. At the March 2011 snapshot MCyR and CCyR were attained or maintained by 39% and 31% respectively. The manufacturers used Kaplan Meier curves to estimate a probability of maintaining MCyR at 1 and 2 years of 74.0% and 70.9% respectively using the February 2012 snapshot data. Analysis of complete haematological response included patients who had complete haematological response at baseline. Seventy three percent of patients maintained or attained a CHR at both snapshots. Using Kaplan Meier curves and the February 2012 snapshot the estimates of maintaining CHR at 1 and 2 years were 72.6% and 67.4% respectively. Using the February 2012 data the 1-year and 2-year Kaplan Meier estimates of progression free survival were 78.3% and 75.1% respectively, estimates of overall survival were 91.4% and 84.0% (see table 3). Five patients had confirmed on-treatment transformation to accelerated phase CML. A summary of key results for the 2nd line chronic phase population are given in tables 2 and 3.

4.8 In the advanced phase patient population haematological response was assessed in 69 of the 76 people with advanced phase CML and 60 of the 64 people with blast phase CML. At the March 2011 data snapshot (1 year follow up) 38 (55.1%) people with accelerated phase had overall haematological response (OHR); 25 (64.1%) of accelerated phase patients receiving bosutinib second line and 13(43.3%) of patients receiving bosutinib following multiple tyrosine kinase inhibitors met this primary outcome. For people with blast phase CML 17 (28.3%) people had overall haematological response; 12 (55.1%) people receiving bosutinib second line and 5 (18.5%) people receiving bosutinib following multiple tyrosine kinase inhibitors met this outcome. The Kaplan Meier estimates of maintaining OHR at 1 and 2 years was 80% and 67% respectively for the accelerated phase patients and 25% and 18.8% respectively for the blast phase patients. The rate of MCyR was 34.8% in people with accelerated phase CML and 29.6% in people with blast phase

CML. The Kaplan Meier estimates of maintaining a MCyR at 2 years were 48.0% in the AP population and 7.9% in the BP population. The Kaplan Meier estimates of progression free survival and overall survival at 2 years were 47.7% and 65.6% respectively for the accelerated phase population and 11.5% and 35.4% for the blast phase population (see table 3). There were 4 (6.4%) patients with accelerated phase CML who transformed to blast phase while undergoing treatment with bosutinib.

Table 2 Major cytogenetic response in the second line chronic phase population and unmet need populations (from tables 21 page 72 ERG report)

Major cytogenetic response		
	Responding/N	MCyR% (95% CI)
CP 2nd line (March 2011)	142/266	53.4% (47.2, 59.5)
CP 3rd line (March 2011)	42/108	38.9%[c] (29.7, 48.7)
CP 2nd line unmet need	9/15	60% (32.3, 83.7)
CP 3rd line unmet need	9/21	42.9%[g] (21.8, 66.0)
AP unmet need	3/5	60.0% (14.7, 94.7)
BP unmet need	2/11	18.2%[h] (2.3, 51.8)

Abbreviations, CP chronic phase, AP accelerated phase, BP blast phase. [c] this is the probability of attaining or maintaining MCyR, [g] different results in manufacturer's economic model: 47.6% (25.7, 70.2). [h] different results in manufacturer's economic model 36.4% (10.9, 69.2).

Efficacy estimates for comparator treatments from systematic review

4.9 The manufacturer performed a systematic review to identify relevant published literature on the efficacy and safety of hydroxycarbamide,

allogeneic stem cell transplant (hereafter referred to as SCT) and interferon alpha for adult patients with CML who had previously received at least one tyrosine kinase inhibitor (imatinib). No randomised controlled trials were identified. Of the 13 studies identified, 5 were excluded as they reported data for a mixed phase CML population only. Eight studies reported outcomes for people who received SCT and 2 for people who had received hydroxycarbamide. For a summary of characteristics of studies of comparator therapies please see table 4). The manufacturer noted that the 2 hydroxycarbamide studies did not meet their eligibility criteria (one study the population received hydroxycarbamide 2nd line following imatinib, one study second line following interferon alpha) but were included as they were the sole source of evidence for hydroxycarbamide in a population with some comparability to the licensed population for bosutinib. No studies reporting efficacy or safety for interferon alpha were identified. The manufacturer presented a naïve comparison which was a qualitative description predominantly of survival and progression results from the comparator studies and Study 200. The studies from which the manufacturer and ERG subsequently based their overall survival estimates in their base case and sensitivity analyses were:

- Kantarjian (2007) included a population of 61 people who had received 2nd line hydroxycarbamide following imatinib. People in this group had received a range of different treatments; only 12 out of the 61 received hydroxycarbamide. The 2 year overall survival for people with CP CML in the 'other treatment' arm was 77%, the 3 year overall survival was 70%.
- Jabbour (2011) included 47 people with CML (Chronic phase n=16, accelerated phase n=12, blast phase n=9) who received 2nd, 3rd or 4th line stem cell transplant. The 2 year overall survival for people with chronic phase CML who received SCT was 72% and was 59% for people with advanced phase CML.

- Oehler (2007) included 145 people receiving stem cell treatment second line. The overall survival at 3 years for people with accelerated phase CML was 55%. The manufacturer did not report the overall survival estimates for the chronic phase population.

Table 3 summary of the overall survival estimates for bosutinib and comparator treatments in the manufacturer's submission (Oehler (2007) data reported in ERG report)

Treatment	Line	Overall survival at 1 year (95% CI)	Overall survival at 2 years (95% CI)	Source
Chronic phase CML				
Bosutinib	2nd	96.8% (94.0, 98.3)	90.6% (86.5, 93.5)	Study 200 (March 2011)
Bosutinib	3rd	91.2% (84.3, 95.2)	82.9% (74.1, 88.9)	Study 200 (March 2011)
Bosutinib	3rd	91.4% (84.6, 95.3)	84.0% (75.8, 89.6)	Study 200 (February 2012)
Hydroxycarbamide	2nd	-	77%	Kantarjian (2007)
SCT	2nd or later	-	72% (49, 96)	Jabbour (2011)
SCT	2nd line	-	3 year overall survival 78%	Oehler (2007)
Interferon	No data presented			
Accelerated phase				
Bosutinib	2nd or later	76.0% (64.7, 84.2)	65.6% (53.4 to 75.4)	Study 200 (March 2011)
Blast phase				

Bosutinib	2nd or later	43.8% (95.	35.4% (23.8 to 47.3)	Study 200 (March 2011)
Overall survival was not reported for the unmet need population				

Safety of bosutinib and comparator treatments

4.10 In Study 200 all patients who received at least 1 dose of bosutinib were included in the safety analyses. The adverse event profile with bosutinib was similar for patients with chronic or advanced phase CML. In both populations the most common treatment related adverse events were predominantly gastrointestinal. Diarrhoea was reported by 83.1%, 85.5% and 65.6% of people with chronic, accelerated and blast phase CML respectively. Of the 98 people with chronic phase CML who had diarrhoea in 10 this was of grade 3 or 4 severity. Sixty five percent of people with CP CML and 68% of people with advanced phase CML took concomitant diarrhoea medication. Nausea and vomiting was reported by 47.5% and 39.0% of people with CP CML, 44.7 and 44.7 of people with accelerated phase CML, and 50.0% and 39.1% of people with blast phase. The most commonly observed haematological treatment emergent adverse events in the third line chronic phase population were thrombocytopaenia (34.7%) neutropaenia (17.8%) and anaemia (15.3%). Although grade 3 or 4 treatment emergent adverse events were reported in 62.7% of people with chronic phase CML receiving bosutinib 3rd line thrombocytopaenia and neutropenia were the only grade 3 or 4 treatment emergent adverse events reported by at least 10% of patients. Grade 3 or 4 treatment emergent adverse events were reported in 86.8% of accelerated phase patients and 76.7% of blast phase patients; the most common grade 3 and 4 treatment emergent adverse events were thrombocytopaenia (32.9%), anaemia (30.3%) and neutropaenia (14.5%) in the accelerated phase group cohort; thrombocytopaenia (26.6%) neutropaenia (20.3%), anaemia (18.8%) and leukopaenia (10.9%) in the blast phase cohort. As

of the 15 February 2012 shapshot 23 (19%) patients from the 3rd line chronic phase population died during the study. Ten of these deaths were due to disease progression, 9 deaths were determined to be because of an adverse event considered unrelated to treatment and 1 death was deemed to be treatment related as a result of lower gastrointestinal bleeding alongside grade 4 thrombocytopaenia (page 71 of the manufacturer's submission). Of the 90 people who discontinued treatment 26 did so because of an adverse event and 45 did so because of lack of efficacy or disease progression. The manufacturer stated that owing to the lack of data on adverse events for hydroxycarbamide and the nature of the data for stem cell transplant from the comparator studies that it was not possible to conduct a qualitative comparison of the safety profile of bosutinib and comparator treatments.

Quality of life with bosutinib from Study 200

4.11 [redacted]. The manufacturer said that people who were nilotinib intolerant or those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (n=4). Utility values for the health related quality of life for the comparator technologies were derived through systematic review of economic studies (see section 6.7).

Evidence Review Group comments

4.12 The ERG's main concern with the submitted clinical effectiveness evidence was that the data for bosutinib and the comparator treatments were from non-randomised studies. In addition, the evidence for bosutinib was from a non-comparative study in which only 52 participants met the definition of the population in the licensed indication. The ERG highlighted that although some effectiveness results are presented for the unmet need group of patients; other key effectiveness results such as time on bosutinib treatment are not.

4.13 The ERG noted that the manufacturer had assumed that in clinical practice bosutinib may be used mostly 4th line after 3 previous lines of TKIs, but as they did not have 4th line data they have focussed on their third line chronic phase data and thought that 2nd line use would be rare. The ERG disagreed and suggested that if recommended by NICE bosutinib may be used most often either as a 2nd or 3rd line treatment, but rarely 4th line. It suggested that nilotinib, being a more potent inhibitor, has replaced imatinib as a first line TKI inhibitor of choice. The ERG noted that in Study 200 all patients had received 1st line imatinib. Furthermore, it suggested clinicians may be unlikely to prescribe imatinib following nilotinib. The ERG was of the opinion that dasatinib will be rarely used. The ERG therefore suggested that bosutinib may be used most often as a 2nd line treatment following nilotinib. Additionally the ERG commented that the treatments that people received following discontinuation of bosutinib in Study 200 were not described.

4.14 The ERG discussed the generalisability of study 200. The ERG commented that the performance status characteristics of the participants in Study 200 were similar to what would be observed in clinical practice. The ERG was concerned that the median treatment durations of prior imatinib in chronic phase patients in Study 200 (1.5 years - 2.7 years

across the 2nd and 3rd line populations), was much lower than the 8 year median duration of imatinib in a trial of imatinib for 1st line treatment for chronic phase CML. The ERG suggested that if patients in study 200 were truly representative of people who fail on imatinib that it would be expected that median duration of imatinib treatment should be approximately 8 years. The ERG noted that approximately 40% of patients had previously taken interferon while interferon is a very rare CML treatment in England and Wales. The ERG noted that there was only 1 third line patient in Study 200 who was intolerant to nilotinib but noted that the lack of participants in the nilotinib resistant subgroup may have been due to a small sample size.

4.15 The ERG commented on the overall survival estimates for bosutinib. It said that the overall survival data for patients with chronic phase CML who received bosutinib from Study 200 is very immature. The ERG said that additionally no data are available on patients' treatment after bosutinib failure which adds to the uncertainty of the relevance of the overall survival data from Study 200.

4.16 The ERG commented on the quality of the clinical evidence submitted for the comparator treatments. The ERG said that the clinical effectiveness evidence for the comparator treatments was very poor. It noted that most of the studies were small and the outcomes that were reported across the studies were inconsistent. It also noted that the participants in the comparator studies appear to be younger and the manufacturer had not presented any evidence for interferon, accepting that it is hardly used in England and Wales. Regarding the manufacturer's naïve comparison of the single arm Study 200 with non-randomised comparator studies, the ERG highlighted that this comparison was strongly susceptible to bias.

Table 4 characteristics of studies of comparator therapies (abridged from table 31 in the manufacturer's submission, pages 91-93)

Study	Intervention and population	Number enrolled	Phase of CML	Duration of follow-up
Kantarjian 2007[36]	**Second-line hydroxycarbamide:** Post imatinib • SCT (n=8) • Other, n=61 *[12/61 received hydroxycarbamide]*	420¶	CP, n=277 AP, n=112 BP, n=73	3 years
Ibrahim 2011[37]	**Second-line hydroxycarbamide:** Following IFN in the IFN arm patients were treated with: • Hydroxycarbamide, n=117/246 (48%)	Imatinib, n=283 IFN, n=246	All patients were in CP	IFN cohort: Median 50.4 months
Bornhäuser 2006[72]	**Second-line SCT**: SCT after imatinib	61	CP, n=19 AP, n=17 BP, n=24	Median 18 months
Oehler 2007[74]	**Second-line SCT:** SCT after imatinib	145	CP, n=117† AP, n=22† BP, n=6†	3 years
Saussele 2010[60]	**Second-, third- and fourth-line SCT:** SCT after imatinib; of these 5 patients received a second or third TKI prior to SCT. The proportion of patients receiving SCT at third or fourth line is not known.	65	CP, n=37 AP, n=3 BP, n=25	Median, 26 months
Schleuning 2010[57]	**Second- and third- line SCT:** SCT after nilotinib and/or dasatinib (had not received first-line imatinib) .The proportion of patients receiving one versus both of the above TKIs is not known.	56	NR	19 months
Jabbour 2011[58]	**Second-, third- and fourth-line SCT after imatinib** • Second-line: 18 (38%) • Third-line: 29 (62%) • Fourth-line: 5 (11%)	47	CP, n=16 AP, n=12 BP, n=9 Second CP, n=10‡	Median 22 months (range 5–53 months)
Holroyd 2010[62]	**Second-, third- and fourth-line SCT:** • Second line: 33 patients received only 1 TKI (imatinib or dasatinib) • Third-line: 8 patients received a second TKI (dasatinib) • Fourth-line: 2 patients received a third TKI (nilotinib)	43	NR	3 years

5 Comments from other consultees

5.1 The professional groups stated that chronic myeloid leukaemia is treated with tyrosine kinase inhibitors. The first line tyrosine kinase inhibitors are imatinib or nilotinib (although dasatinib is available through the Cancer Drugs Fund or a separate application to the PCT for a limited number of patients). Approximately 75-80% of patients respond to imatinib/nilotinib and achieve complete cytogenic responses, but the remaining 25% of patients either cannot tolerate the drugs due to side effects and toxicity or are refractory to these drugs and fail to achieve adequate responses. The

professional groups stated that one cause of failure to respond is the acquisition of bcr mutations which prevent the binding of, or block the action of the tyrosine kinase inhibitor. There are over 40 known bcr-abl mutations and response to a particular TKI is mutation specific. Patients who are refractory or intolerant of their first line treatment are eligible to receive nilotinib; dasatinib is not recommended by NICE for first or second line use. There is a difference in opinion as to whether imatinib or nilotinib should be the first treatment a patient receives, but there is increasing use of nilotinib as a first line treatment. As nilotinib is generally accepted as a more potent bcr-abl inhibitor than imatinib, with activity in many of the known mutations, patients who have failed nilotinib first line may not be switched to imatinib unless they experienced toxicity on nilotinib. Patients who respond to tyrosine kinase inhibitors currently continue the tyrosine kinase inhibitors indefinitely.

5.2 The professional groups said that the only other treatment options are interferon or allogeneic haemopoietic stem cell transplantation. Interferon has a low response rate of 10-15% and a significant side effect profile, limiting its usefulness as a treatment for CML. Allogeneic bone marrow transplantation depends on a suitable fully matched donor and on the performance status of the patient, limiting the number of people who can receive a transplant. It is additionally associated with a 10-15% transplant-related mortality and a significant number of patients develop graft versus host disease resulting in significant co-morbidities and the need for ongoing immunosuppressive treatments. The professional group said bosutinib would offer an alternative drug treatment in particular for patients at higher risk of being refractory to imatinib, and people who are over 70 years or from ethnic minority backgrounds who may be less likely to receive an allogeneic bone marrow transplant. The professional groups also highlighted that a greater selectivity of bosutinib for the bcr-abl protein may result in a differing side effect profile for bosutinib compared

to imatinib/nilotinib meaning that it may be beneficial for people at risk of significant side effects while taking the other tyrosine kinase inhibitors. Bosutinib, a once daily tablet taken as an outpatient, requires the same monitoring that is already used for imatinib and nilotinib, and is more straightforward treatment option than interferon or bone marrow transplant. The professional groups anticipated no significant issues in terms of delivery of care for these patients if bosutinib was approved.

5.3 The patient group stated that patients have concerns with the management of distinct side effects associated with each tyrosine kinase inhibitor and in clinical trials the treatment side effects of bosutinib appeared manageable for the majority of patients. It said that the total number of patients currently being treated with bosutinib in the UK is between 30 and 50 patients and that they had not received any reports from this group of patients that their experiences are worse than reported in clinical trials. The patient group noted considerable differences between the trial population and the population likely to be treated with bosutinib. In particular a greater number of patients received interferon than would be expected in UK clinical practice. It commented that allogeneic stem cell transplant is only available to a small minority of patients and that this is a high risk intervention. The patient group commented that interferon alpha and allogeneic stem cell transplant would qualify as 4th line treatment options and hydroxycarbamide and best supportive care would only be used when all other treatment options capable of affecting a cytogenetic response have been tried.

5.4 The patient group said that for patients with narrowing therapeutic options following more than one TKI failure, bosutinib may be a possible solution to their unmet need. The usefulness of bosutinib lies in the extension of choice it grants to patients given the distinct difference in the type and severity of side effects between bosutinib and other TKIs. They additionally noted that bosutinib does not have the strict fasting regime

that is necessary for the twice daily dose of nilotinib which may be difficult for some patient groups to adhere to such as people with diabetes. The patient group expected a quality of life benefit gained by use of a home based, oral, once a day therapy with routine outpatient visits to a local clinic or specialist centre; the availability of a treatment would benefit mood. They also suggested bosutinib treatment may result in patients who stopped work being able to return and patients being able to return to enjoying family and social life.

6 Cost-effectiveness evidence

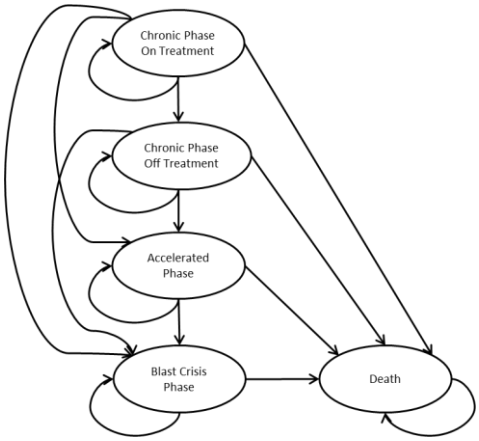
6.1 The manufacturer performed a systematic review to identify cost effectiveness studies in CML patients previously treated with one or more tyrosine kinase inhibitor but did not identify any economic evaluations of bosutinib in refractory CML. The search identified three publications relating to the health technology assessment of NICE Technology Appraisal Guidance 241 (hereafter referred to as TA 241). Subsequently the HTA report for NICE technology Appraisal Guidance 251 (hereafter referred to as TA 251) was identified for health related quality of life and resource use data.

6.2 The manufacturer presented 3 semi Markov models for the chronic phase, accelerated phase and blast phase populations. The chronic phase model comprised 4 health states; the accelerated phase model had 3 health states and the blast phase model had 2 health states. In addition, all three models included a state for death. The model cohorts were the Study 200 populations for each CML phase (using the 3rd line chronic phase CML population as the base case population in the chronic phase CML model). The models had a lifetime time horizon (50 years), a cycle length of one month with no half cycle correction. During the clarification

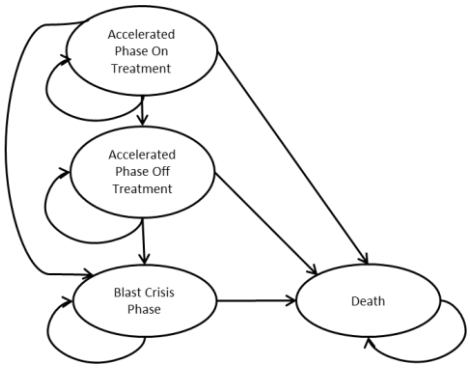
stage, the ERG identified an error in the model relating to the overall survival estimate for bosutinib in the chronic phase model. The manufacturer submitted an updated model with this error corrected and presented their amended base case and sensitivity analyses. All results for the chronic phase model presented in subsequent sections of this briefing paper are from the manufacturer's response to clarification incorporating this correction.

Figure 3 Schematic of the manufacturer's chronic phase, accelerated phase and blast phase models (Pages 109-110 Manufacturer's submission)

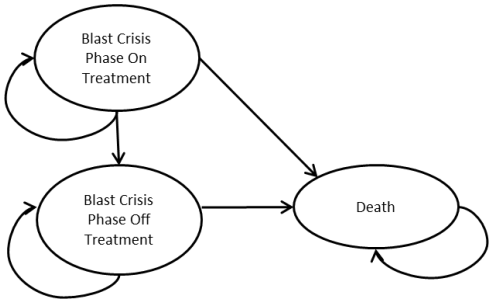
Chronic phase



Accelerated phase model



Blast crisis phase model



6.3 Each model included an on and off treatment state for the CML stage the patient enters each model in. People who receive initial treatment with bosutinib or continue to receive that treatment until they discontinue due to intolerance or resistance, progress to a later disease stage (AP or BP for those in CP, BP for those in AP), or die. Time on bosutinib is

incorporated into the model by fitting a lognormal distribution to the individual patient data for discontinuation in Study 200 for the relevant cohort. Following discontinuation of bosutinib all people switch to hydroxycarbamide (and remain on hydroxycarbamide even if they then progress further). Interferon alpha was only considered a comparator in the chronic phase model because effectiveness estimates were not available for this treatment in the advanced and blast phases. In the chronic phase model people receive hydroxycarbamide following discontinuation from interferon. People who received initial treatment with hydroxycarbamide remain on this treatment until they die regardless of disease progression. People who receive a stem cell transplant are regarded as cured in the base case and are assumed to not progress to later disease stages and do not receive any drug treatment after their SCT. In all models overall survival curves are used to estimate the total proportion of people alive and background mortality. The time spent in blast phase is fixed as 6 months prior to death in the chronic phase and accelerated phase models and the time spent in accelerated phase is fixed as 10 months prior to blast phase in the chronic phase model.. In all three models the manufacturer assumed equal proportions of males and females in the patient population and no assumptions were made about prior treatments. The mean age of the chronic phase, accelerated phase and blast phase model cohorts are 54, 50 and 47 years respectively. See table 5 for a summary of the assumptions used in the model.

6.4 To model overall survival the manufacturer fitted parametric curves to empirical overall survival data for bosutinib from Study 200 and overall survival estimates for hydroxycarbamide, interferon and SCT from the published literature (see table 5). The only exception was for overall survival for bosutinib in the chronic phase model. The manufacturer said that appropriate overall survival data was only available for 2 years in Study 200 as after 2 years only people who remained on treatment were

followed up which would bias the estimate. The manufacturer said that 2 year data was premature to assess overall survival in a chronic phase population as over 90% of patients survived at this point. The overall survival for bosutinib patients in the chronic phase model was therefore calculated by extrapolating from the surrogate outcome of major cytogenetic response (MCyR). The manufacturer assumed a hazard ratio for overall mortality of 0.370 for patients achieving a MCyR versus those not achieving a MCyR. This was based on a study that investigated high dose imatinib following standard dose imatinib (Jabbour (2009). The manufacturer assumed a MCyR rate of 38.9% for bosutinib which corresponds to the best cumulative response at a minimum follow up of 12 months for the entire 3rd-line population (the proportion of patients achieving a MCyR at any time or maintaining a MCyR present at baseline- see section 4.7). In the absence of any clinical effectiveness evidence for interferon the manufacturer assumed that interferon would have a similar efficacy to hydroxycarbamide.

Table 5 Methods used to calculate overall survival (OS) in the manufacturers base case (Table 41 ERG report, page 118) and other assumptions in model

Model	Treatment	Base case OS	Scenario analysis OS
CP	Bosutinib	MCyR surrogate relationship based on Jabbour and colleagues (2009)[44]	MCyR surrogate with different hazard ratio for OS Exponential distribution fitted to third line CP cohort from Study 200 "Cumulative survival approach"
	Hydroxycarbamide	Exponential distribution with mean OS = 3.5 years following Kantarjian (2007)[3]	Exponential distribution with different mean OS
	Interferon	Exponential distribution with mean OS = 3.6 years following Loveman (2012)[40]	*None*
	SCT	Exponential distribution fitted to Jabbour (2011)[10]	Weibull distribution fitted to Jabbour (2011)[10] Exponential distribution fitted to Oehler (2007)[12]
AP	Bosutinib	Exponential distribution fitted to AP cohort OS in Study 200	Extreme value distribution fitted to AP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 16 months to match length of time spent in AP and BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Jabbour (2011)[10]
BP	Bosutinib	Exponential distribution fitted to OS in Study 200	Weibull distribution fitted to BP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 6 months to match length of time spent in BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Saussele (2010)[13]

Additional assumptions made in the manufacturer's model (summarised from table 38, manufacturer's submission page 128 -130)

• Patients treated with bosutinib in clinical practice will be treated in clinical practice for the same period of time as in Study 200 (manufacturers have 5 years of patient level discontinuation data from study 200)
• Following bosutinib treatment all patients receive hydroxycarbamide and receive it until death. Manufacturers noted that there is no consensus on what patients receive following bosutinib. Additionally assumed that
• The single arm studies used (for efficacy estimates of bosutinib and comparator treatments) have patients with similar baseline demographics and risk factors and are thus comparable
• Overall survival can be predicted as a function of MCyR rate and this independent of line of treatment
• In the chronic phase model, following chronic phase all patients (irrespective of previous treatment) spend 10 months in accelerated phase before progressing to blast phase. In the chronic phase and accelerated phase models, following chronic phase and accelerated

phase, all patients spend the final 6 months in blast crisis.
• In blast phase patients who are to receive a stem cell transplant are first treated with chemotherapy (the FLAG-IDA regimen) for 2 cycles prior to receiving stem cell transplant

6.5 In the models, the dose of bosutinib was 1 x 500 mg per day, with a unit cost of £122.74 and a monthly cost of £3,735.84, the dose of hydroxycarbamide was 4 x 500 mg per day, the unit cost was £0.10 (BNF 63) and the monthly cost was £12.75, the dose of IFN in the model was 2 x 0.5mL 9 million units/ mL per day pre-filled syringes, with a unit cost of £21.29 (BNF 63) and a monthly cost of £1,296.03. The model also included a cost of a district nurse visit of £39, for 25% of patients who required assistance with injections which meant that the total monthly cost for IFN was £1,305.78. Stem cell transplant was associated with a one-off cost of £76,560 (NHS Blood and Transplant 2010 incorporating inflation). The monthly costs for months 1-6 (£5,299), months 7-12 (£3,299)and months13-24 (£1,166) post transplantation were based on NHS Blood and Transplant 2010. Post 25 months the monthly costs of immunosuppressives (cyclosporine 100mg/day) and a quarterly haematologist visit was based on expert opinion and was £140. In the blast phase model the cost of the acute leukaemia style chemotherapy consisting of fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) was included (£29,212).

6.6 Resource use data were largely drawn from a survey by Oxford Outcomes on behalf of Bristol Myers Squibb for its submission for TA251. Cost data were derived from the Department of Health National Schedule of Reference costs 2011-12 for NHS trusts and foundation trusts. The manufacturer said that the first line resource costs from TA251 were appropriate as resource use is expected to be driven primarily by phase of disease rather than line of treatment. Resource costs included the costs of inpatient and outpatient appointments CML testing (£231 per month CP,

£377per month for AP and BP, inflated from Hoyle et al (2011 a) using HCHS Pay and Price index). A cost of £6,004 was associated with death. A per-patient adverse event cost of £506.25 was applied in the first cycle only for bosutinib based on the costs of managing treatment- emergent adverse events of grade 3 or 4. For patients in blast phase costs of palliative care, inpatient stays and home visits were included.

6.7 Patients in the 'on treatment' and 'off treatment' initial phases in each model were assumed to have the same quality of life. The utility values presented for each model were for a person aged 54 and these were assumed to decline with age. The utility values derived from Study 200 for bosutinib were not used in the base cases. In the chronic phase model people receiving initial treatment with bosutinib or hydroxycarbamide were assumed to have a utility value of 0.85 based on the values used in TA251. People receiving SCT in the CP model were assigned a utility value of 0.71 (the mid-way value between the values proposed by BMS and Novartis in TA241), a utility value of 0.71 was assigned for people receiving interferon (from the ERG's estimate from TA241). In the AP model the utility value for bosutinib and hydroxycarbamide was 0.73 (based on the ERG estimates for hydroxycarbamide in TA 251). The utility value for stem cell transplant was 0.71. The blast phase model assumed a utility value of 0.52 for treatment with bosutinib, hydroxycarbamide and stem cell transplant. Adverse events that were incorporated in the model for resource uses were assumed to not affect quality of life (see table 6).

Table 6 Summary of utility values (manufacturer's submission page 137)

State	Utility value	Confidence interval	Reference in submission	Justification
CP on treatment - bosutinib	0.85	(0.77 – 0.91)	Section 7.4.6	Assumed to be same as for other TKIs
CP off treatment - bosutinib	0.85	(0.77 – 0.91)		
AP - bosutinib	0.73	(0.64 – 0.81)		
CP - hydroxycarbamide	0.85	(0.77 – 0.91)		Used in previous economic evaluations [Hoyle
AP - hydroxycarbamide	0.73	(0.64 – 0.81)		
CP - SCT	0.71	(0.62 - 0.79)		

AP - SCT	0.71	(0.62 - 0.79)		et al, 2011a][80], [Loveman et al, 2012][85], [Rogers et al, 2012][84]
CP on treatment - interferon	0.71	(0.62 - 0.79)		
CP off treatment - interferon	0.85	(0.62 - 0.79)		
AP - interferon	0.73	(0.64 – 0.81)		
BP – all treatments	0.52	(0.42 – 0.62)		

Utility values presented are for a 56 year old patient.

6.8 The deterministic ICERS from the manufacturer's base case analysis were presented separately for the chronic phase, accelerated phase and blast phase populations. In the chronic phase, interferon was dominated by (was more costly and less effective than) hydroxycarbamide and stem cell transplant was dominated by bosutinib. Bosutinib was associated with an additional cost of [redacted] compared to hydroxycarbamide with 4.83 additional QALYs (incremental cost effectiveness ratio [ICER[redacted] per QALY gained). In the accelerated phase, bosutinib was associated with an additional cost of [redacted] compared to hydroxcarbamide with 1.86 additional QALYs (ICER [redacted] per QALY gained). Stem cell transplant was dominated by bosutinib. In the blast phase, bosutinib was associated with an additional cost of [redacted] compared with hydroxycarbamide with an additional 0.60 QALY (ICER [redacted] per QALY gained). Stem cell transplant was associated with an additional cost of [redacted] compared to bosutinib with an additional 0.40 QALY (ICER [redacted] per QALY gained. The probabilistic ICERs for bosutinib compared with hyrdroxcarbamide were [redacted] for the chronic phase, accelerated phase and blast phase cohorts respectively (see table 7).

Table 7: Manufacturer's base case (deterministic and probabilistic) for CP, AP and BP populations (response to clarification letter page 29; manufacturer's submission pages 170 [table B71] and 181 [table B79])

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		
Chronic phase Deterministic results						
Hydroxycarbamide	£29,473	2.43				
Interferon	£38,268	2.42	£8,795	-0.01	Dominated	Dominated
Bosutinib	[redacted]	7.26	[redacted]	4.83	[redacted]	[redacted]
SCT	£171,539	3.70	[redacted]	-3.56	Dominated	£111,511
Chronic phase Probabilistic results						
Hydroxycarbamide	£29,389	2.43				
Interferon	£36,091	2.39	£6,702	-0.04	Dominated	Dominated
Bosutinib	[redacted]	7.15	[redacted]	4.72	[redacted]	[redacted]
SCT	£173,948	3.84	[redacted]	-3.31	Dominated	£102,873
Accelerated phase Deterministic results						
Hydroxycarbamide	£26,078	0.90				
Bosutinib	[redacted]	2.76	[redacted]	1.86	[redacted]	[redacted]
SCT	£178,093	1.96	[redacted]	-0.80	Dominated	£142,982
Accelerated phase Probabilistic results						
Hydroxycarbamide	£26,095	0.91				
Bosutinib	[redacted]	2.75	[redacted]	1.84	[redacted]	[redacted]
SCT	£175,420	1.95	[redacted]	-0.80	Dominated	£143,454
Blast phase Deterministic results						
Hydroxycarbamide	£14,170	0.28				
Bosutinib	[redacted]	0.88	[redacted]	0.60	[redacted]	[redacted]
SCT	£200,526	1.28	[redacted]	0.40	[redacted]	£186,265
Blast phase Probabilistic results						
Hydroxycarbamide	£15,262	0.32				
Bosutinib	[redacted]	0.89	[redacted]	0.57	[redacted]	[redacted]
SCT	£201,228	1.29	[redacted]	0.40	[redacted]	£192,016

***** This was reported as [redacted] by the manufacturer, this was presumed to be a typographical error, therefore has been corrected using the incremental cost and QALYs in this table.

Manufacturer's scenario analyses

6.9 The Manufacturer conducted a large number of scenario analyses for the chronic, accelerated and blast phase models. In the chronic phase analyses interferon remained dominated by hydroxycarbamide and stem cell transplant remained dominated by bosutinib in most scenarios, in the accelerated phase bosutinib remains dominant to SCT in most scenarios, in the blast phase analyses SCT remains more costly and more effective than bosutinib. The following results are for bosutinib compared with hydroxycarbamide for the scenarios with the greatest impact on the ICER in the chronic phase, accelerated phase and blast phase models. In the chronic phase model 3 scenarios in which assumptions surrounding overall survival in the bosutinib arm were changed resulted in in the base case ICER increasing to over £30,000 per QALY gained. These scenarios were: MCyR hazard assumed to be 0.156 (which was the lower bound of 95% confidence interval) rather than 0.37 in the base case, resultant ICER [redacted] per QALY gained; exponential curve fitted to overall survival in third line CP CML population from Study 200, resultant ICER [redacted] per QALY gained; a "Cumulative survival approach" used (where overall survival = progression free survival +10 months in accelerated phase + 6 months in blast phase), resultant ICER [redacted] per QALY gained. One scenario in which the mean overall survival for hydroxycarbamide was increased to 78 months from 42 months in the base case increased the ICER to [redacted] per QALY gained. One scenario in which the bosutinib time on treatment was assumed to be equal to progression free survival minus discontinuation due to adverse events increased the ICER to [redacted] per QALY gained. There were 4 scenarios where the ICER of bosutinib versus hydroxycarbamide was substantially reduced. These were: patient

population set to second line rather than 3rd line for bosutinib (resultant ICER [redacted] per QALY gained); hydroxycarbamide overall survival set to 2 years (resultant ICER [redacted] per QALY gained); resource use from TA 241 rather than TA 251 is assumed (resultant ICER [redacted] per QALY gained); Hazard ratio for survival in MCyR surrogate method of 0.876 (the upper bound of the 95% confidence interval) rather than 0.37 [resultant ICER [redacted]]). The full results of the manufacturer's scenario analyses for the chronic phase population are presented on pages 31 to 34 of the manufacturer's response to clarification questions.

6.10 In the accelerated phase model, with the exception of the scenarios in which the time horizon was shortened, the ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] per QALY gained. Assuming medical management costs in TA 241 rather than TA 251 resulted in the greatest decrease in the ICER for bosutinib versus hydroxycarbamide from the base case (resultant ICER [redacted] per QALY gained). Assuming that the bosutinib time on treatment was equal to progression free survival from Study 200 (AP to BP) rather than using a lognormal curve fitted to discontinuation data from study 200 resulted in the greatest increase of the ICER of bosutinib compared to hydroxycarbamide [redacted] per QALY gained). The full results of the manufacturer's scenario analyses for the accelerated phase population are presented on pages 172 to 174 of the manufacturer's submission.

6.11 In the blast phase model, the scenarios in which the ICER was lowest for bosutinib compared with hydroxycarbamide were: a scenario in which utility values from Study 200 were used for patients receiving bosutinib and hydroxycarbamide patients (instead of IRIS trial utilities used in TA 241 and TA 251), resultant ICER [redacted]; overall survival for bosutinib was estimated using the second best fitting curve (Weibull) instead of exponential distribution, [redacted] per QALY gained. The scenarios in which the ICER for bosutinib versus hydroxycarbamide was highest was: time

spent in blast phase set to 13 months rather than 6 months in the base case, [redacted]; time on treatment equal to PFS from study 200, [redacted], cost of BP health state doubled, [redacted] per QALY gained. The full results of the manufacturer's scenario analyses for the blast phase population are presented on pages 183- 184 of the manufacturer's submission.

Evidence review group comments on the cost effectiveness estimates

6.12 The ERG said that the manufacturer's analyses were clearly described in their report. The ERG said that the structure of the manufacturer's model was mostly consistent with the natural history of CML and was consistent with the models used in TA 241 and TA251 (with the exception of a cumulative survival approach used in one scenario analysis). The ERG said that the time on treatment analysis from study 200 is mature and that extrapolations from this data seem reasonable. The ERG said that the modelled unit costs were appropriate, utility values were plausible and the 50 year time horizon was sufficient to account for all costs and benefits relevant to the decision problem.

6.13 The ERG believed there to be serious problems with the manufacturer's methods for estimating overall survival for bosutinib, hydroxycarbamide, interferon and SCT. Firstly, the methods of estimating overall survival were not consistent across the four comparator treatments. The overall survival estimate for bosutinib in the chronic phase model was estimated using a surrogate relationship using MCyR measured at minimum follow up of 12 months in Study 200, whereas OS for the comparators in all models and bosutinib in the advanced phase model was estimated by extrapolation directly from single arm trials or expert opinion. Secondly the evidence base for the overall survival estimates was limited to small non-randomised trials (meaning that patient baseline characteristics and medical management may differ between the trials which informed the estimates) and from studies in which the population does not match the

population for whom bosutinib is indicated (i.e. the unmet need population). Thirdly, the ERG said that there was limited evidence available to support the validity of the MCyR surrogate relationship. The overall survival estimates for the surrogate relationship come from Jabbour et al (2009) which had a 2nd line rather than a 3rd line population and included a mixture of people who were suitable and unsuitable for treatment with a tyrosine kinase inhibitor. In Jabbour (2009) the surrogate relationship is based on patients taking high dose imatinib following standard dose imatinib, but the manufacturer assumed that the relationship was independent of treatment and depth of response. The manufacturer further assumed that all patients in Jabbour (2009) received only hydroxycarbamide after high dose imatinib – which the ERG considers to be inappropriate. The ERG stated that the manufacturer's methods for estimating overall survival result in the highly implausible result that the mean time on 4th line hydroxycarbamide following bosutinib is greater than the mean time on 3rd line hydroxycarbamide in the hydroxycarbamide arm in each model (See table 8). They said that their clinical expert said that this is unreasonable and that this assumption acts dramatically in favour of the cost-effectiveness of bosutinib verses each comparator as the price of hydroxycarbamide is very low.

Table 8 Summary of overall survival while taking hydroxycarbamide in the manufacturer's base case. All values are in years.

Model	hydroxycarbamide arm	Duration of hydroxycarbamide following bosutinib	Duration of hydroxycarbamide following IFN
Chronic phase	2.6	[redacted]	2.1
Accelerated phase	1.0	[redacted]	na

Blast phase	0.5	[redacted]	na

6.14 The ERG presented a cumulative survival method which was the same as that used in TA251 by the ERG and one manufacturer; this had been accepted by the Committee as an appropriate base case model structure. The cumulative survival method assumes that patients who survive to start treatment with hydroxycarbamide or with SCT following treatment with bosutinib should have a similar life expectancy on these treatments as people starting treatment in the hydroxycarbamide and SCT arms in each model respectively. This means that for the 3rd line bosutinib population in the chronic phase model the mean time on 4th line treatments is almost the same as the mean time on treatment when hydroxycarbamide or SCT is taken 3rd line (the mean time taking either hydroxycarbamide or SCT following bosutinib is slightly lower as not all people initially taking bosutinib will survive to move onto 4th line treatments). This is illustrated in figure 4 and is described on pages 189 to 203 of the ERG report. The ERG stated that its cumulative survival method was different to the 'cumulative survival approach' that the manufacturer used in its scenario analysis of the chronic phase model (section 6.9 and table 7). The manufacturer's cumulative survival approach assumed overall survival to be progression free survival plus 10 months (fixed time in accelerated phase) in the chronic phase model plus 6 months (fixed time in blast phase) in the chronic phase and accelerated phase models.

Figure 4. Bar charts showing the time on treatment and estimated survival in each arm using manufacturers estimate (top panel) and ERG's cumulative survival method (bottom panel). See pages 31 and 192 of ERG report. These are commercial in confidence (CiC) as the time on bosutinib treatment is CiC.

6.15 The ERG additionally did not agree with the manufacturer's overall survival estimates for hydroxycarbamide or stem cell treatment in the chronic phase model. The ERG noted that the estimates for hydroxycarbamide were based on Kantarjian (2007) and this study had had been used to estimate overall survival on hydroxycarbamide in TA 251. However the ERG said that their analysis fitting an exponential fit to the empirical data resulted in a mean overall survival of 7 years rather than the 3.5 estimated by the manufacturer. They therefore made an adjustment to the manufacturer's model to allow for a mean OS in the hydroxycarbamide arm in CP of 7years. The ERG noted that the manufacturer had based its OS estimates for people receiving SCT in the chronic phase on Jabbour (2011) as the majority of people in this trial received SCT third-line. However the ERG felt that it was more appropriate to use the data from Oehler (2007) in which SCT had been a 2nd line option as the sample size of 72 patients that informs the estimate of OS is larger than the 16 patients from Jabbour (2011). Additionally the ERG said that the data was more consistent with two other studies that had been identified by the manufacturer's systematic review (Schleuning (2010), Saussele (2010)). The manufacturer said that as there is debate about which line of treatment best represents the population who would be eligible for bosutinib that it was appropriate to use the mostly second

line data from Oehler (2011). The 2 year overall survival in Jabbour 2011 was 72%; the estimated overall survival at 3 years was 78% in Oehler (2007).

6.16 The ERG noted that the manufacturer's assumptions for medical management, monitoring and testing were based on those that were used originally in TA 251. However during TA251 one manufacturer had said that the frequencies of some resource items were over-estimated by the assessment group, and these were subsequently amended during the appraisal. For the current appraisal the ERG used the updated assumptions from TA251, which assumed no nurse visits or bone marrow aspirations per month and a reduced frequency of haematologist visits per month from the manufacturer's base case. Following advice from their clinical specialist the ERG further updated the assumptions surrounding haematologist visits for people receiving bosutinib (compared to people receiving imatinib, dasatinib or nilotinib first line in TA 251) and people who had a stem cell transplant. (See table 9 for a summary of these assumptions) When the ERG altered the manufacturer's model to reflect their preferred resource assumptions the manufacturer's ICER decreased from [redacted] per QALY gained.

Table 9 ERG's selected resource assumptions for CP CML (table 70, page 183)

	Treatment	Nurse visits / month	Haematologist visits / month	Bone marrow aspirations / month
Pfizer current HTA	Bosutinib	0.4	0.9	0.3
	HU, IFN	0.4	0.9	0.3
	SCT	0.4	0.9	0.3
PenTAG TA251	Imatinib, dasatinib, nilotinib	0	0.33	0
	HU	0	0.72	0
	SCT	0	0	0

PenTAG current HTA	Bosutinib	0	0.33 per month, plus 2 at t = 0	0
	HU, IFN	0	0.72	0
	SCT	0	Many visits in months 0–24 included in ongoing costs from van Agthoven (2002)[57] 0.31 visits per month for month 24 onwards	0

6.17 The ERG believed that the most important comparator for bosutinib was hydroxycarbamide rather than SCT as fewer than 30% of people may have a SCT and the remaining population would receive hydroxycarbamide. The ERG said bosutinib followed by hydroxycarbamide was an appropriate treatment sequence for patients who are unsuitable for a stem cell transplant and the relevant comparators for this population are bosutinib followed by hydroxycarbamide (bosutinib, hydroxcarbamide), hydroxycarbamide and interferon followed by hydroxycarbamide (chronic phase population only). However, the ERG said that for people for whom a stem cell transplant is suitable the main comparators are Bosutinib followed by SCT and SCT.

6.18 The ERG's exploratory base case analysis for the chronic phase population derived survival using the cumulative survival method and incorporated the ERG's preferred estimates of mean overall survival for hydroxycarbamide and stem cell transplant and revised medical management costs. For the advanced phase populations, the exploratory analyses incorporated the cumulative survival method assumption only. The ERG presented deterministic ICERS for a treatment sequence of bosutinib followed by hydroxycarbamide and a treatment sequence of bosutinib followed by stem cell transplant for the chronic phase, accelerated phase and blast phase populations. For the treatment sequence of bosutinib followed by hydroxycarbamide the ICER compared with hydroxycarbamide was [redacted] per QALY gained in the chronic phase, accelerated phase and blast phases respectively. For

the bosutinib followed by stem cell transplant sequence the ICERs compared with hydroxycarbamide were [redacted] respectively. The ICERs compared with stem cell transplant for this treatment sequence were [redacted] for the chronic phase, accelerated phase and blast phase populations respectively. See table 10.

Table 10 derivation of ERG base case ICERS (£ per QALY) – summary of tables 80, 82 and 84 ERG report page 204, 207 and 210

Chronic phase CML

Intervention	(Bosutinib, HU) vs.	(Bosutinib, SCT) vs.

	Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	Dominant	[redacted]	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

Accelerated phase CML

	Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

Blast phase CML

	Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

b- interferon is more costly and more effective than hydroxycarbamide, c- interferon is less costly and less effective than hydroxycarbamide.

6.19 The ERG conducted an additional 8 exploratory scenario analyses for the chronic phase population. As the manufacturer only considered a sequence of bosutinib followed by hydroxycarbamide, only the results relating to this sequence are presented in this briefing document (results for impact of these scenarios on the bosutinib followed by stem cell transplant sequence are presented on page 214 of the ERG report). One

of the scenarios assumed the 2nd line cohort from Study 200 as the model population. This differed from the 2nd line scenario the manufacturer had assessed in its scenario analysis as it took into account length of time on treatment and MCyR rates for second line treatment (the manufacturer's scenario only took into account 2nd line MCyR rates). When applied to the manufacturer's base case this scenario raised the ICER of bosutinib vs. hydroxycarbamide from [redacted] per QALY gained in the manufacturer's base case to [redacted] per QALY gained. Applying this scenario to the ERG base case had a more minimal effect on the ICER from the ERG base case for bosutinib compared with hydroxycarbamide which rose from [redacted] per QALY gained. The ERG assessed 4 scenarios in which the overall survival for hydroxycarbamide and SCT was increased or decreased by 50% from the values used in the manufacturer's and ERG's base case (the ERG base case had revised estimates of the OS of these two treatments [see section 6.15]). These scenarios had a minimal impact on the ICER for bosutinib compared with hydroxycarbamide. Using the utility values from Study 200 for bosutinib and hydrocarbamide or using the utility value for SCT from TA 251 had a minimal effect on either base case. Assuming that all people would stay on bosutinib treatment until they transformed from chronic phase to accelerated phase had a major impact on the ICERS in each base case compared to all comparator treatments (ICER bosutinib vs. hydroxycarbamide increased to [redacted] per QALY gained in the ERG base case and to [redacted] per QALY gained in manufacturer's base case.

6.20 The ERG conducted 2 exploratory scenario analyses for the accelerated phase population and the blast phase population. Using Study 200 utility values decreased the ICERs of bosutinib vs. hydroxycarbamide in all of the base cases. Applying this scenario to the manufacturer's base case for the blast phase population reduced the ICER from [redacted] per QALY gained to [redacted] per QALY gained. In the second scenario the

hydroxycarbamide overall survival in the hydroxycarbamide arm was assumed to equal the time off treatment (from bosutinib) in the bosutinib arm (page 215 ERG report). The ERG, in response to the manufacturer's fact check, made a modification to how they modelled this assumption (page 6 Erata to ERG report). Both before and after this amendment this scenario marginally increased the ICER of bosutinib vs. hydroxycarbamide in both the manufacturer's and ERGs base case for the accelerated phase population. The impact of this scenario was greater when this scenario was applied to the manufacturer's base case for the blast phase population in which the ICER increased from [redacted] to [redacted] per QALY gained (page 8 Erata to ERG report).

7 End-of-life considerations

The manufacturer considered that bosutinib for the treatment of accelerated or blast phase CML met end of life criteria as follows:

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Expected survival for advanced phase patients for whom imatinib, dasatinib and nilotinib are all unsuitable is around 16 months (10 months in accelerated phase and 6 months in blast phase). (Manufacturer's submission page 103).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Depending on the survival assumed for hydroxycarbamide the incremental life year gain of bosutinb over hydroxycarbamide is approximately 1.7 years in accelerated phase and 1.2 years in blast phase (manufacturer's submission page 103).
The treatment is licensed or otherwise indicated for small patient populations	The patient population eligible for bosutinib is expected to be around 80 patients per year of which 10% (8) might be in accelerate or blast phase (manufacturer's submission page 103)

The ERG agreed with the manufacturer's estimates that a small number of people with advanced phase CML would be eligible for bosutinib each year (less than 8). The ERG noted that in addition to the three criteria outlined above a requirement for a technology meeting end of life criteria is that estimates of the extension to life and the assumptions used in the reference case economic modelling are plausible, objective and robust. The ERG said that while it was possible that people with accelerated phase and blast phase CML have a short life expectancy and that bosutinib may extend life however both the assumptions used in the economic modelling and the estimates of extension to life were not robust. This was because the clinical effectiveness data came from non-randomised single arm trials meaning that the patient characteristics and medical management may have varied between the studies on which the estimates were made. Additionally the ERG questioned the validity of the assumptions that the manufacturer had used to model overall survival.

8 Equalities issues

8.1 Comments received during consultation on the scope, from the professional and patient groups and from the manufacturer's submission did not identify equality issues relating to bosutinib itself but did highlight the equality issues relating to stem cell transplant, one of the comparators outlined in the scope issued by NICE for this appraisal. They said that stem cell transplant is available only to people who meet eligibility criteria and who for whom there is a matched donor. They said that eligibility is determined by performance status which means that some people may not receive treatment on the basis of their age. One professional group said that this 'effectively rules out people over 70 years of age'. There are a limited number of available matched donors for people with CML who are black, from an ethnic majority or are mixed race. The patient group quoted a study that said that around 90% of North European Caucasian patients might typically find a match, the matching rates for black or

minority ethnic group donors may be 40% or lower, especially for patients of mixed ethnic heritage. One consultee commented that any drug therapy that reduces the need for stem cell transplantation therefore increases the availability of successful teratment for these minority patients. It was determined during scoping that the Committee must give full consideration to alternative treatment options other than stem cell transplantation to take into consideration groups of people who cannot undergo stem cell transplantation due to lack of suitable donors. Furthermore, as only a small number of people would be eligible for stem cell transplantation this could raise equity issues in relation to race, age (older people), and people with comorbidities, the Committee must ensure that the recommendatons do not differentiate between any groups of people, and that they do not limit access to the technology for any specific group compared with other groups. The manufacturer also highlighted that there is unequal access to dasatinib through the Cancer Drugs Fund and applications to commissioning bodies, however as dasatinib is not a listed comparator for this appraisal; this is not considered to be an equalities issue.

9 Innovation

9.1 The manufacturer said that bosutinib is innovative as it is effective across a broad range of Bcr- Abl mutations including those conferring clinical resistance to nilotinib and dasatinib. Additionally it has a different adverse event profile to the currently available tyrosine kinase inhibitors which means that it may be a treatment option for people who cannot take imatinib or nilotinib owing to their toxicities. The manufacturer said that currently the main treatment option for people for whom imatinib, nilotinib and dasatinib are not considered appropriate is hydroxycarbamide, and bosutinib is a step-change in the management of CML for specific cohorts of patients whose only current treatment option is hydroxycarbamide. The manufacturer further asserted that bosutinib shows efficacy and

improvements in health related efficacy and advanced phase CML who have failed on previous TKI treatment.

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Appendix A: Supporting evidence

Related NICE guidance

Published

Related Technology Appraisals:

Technology Appraisal No.251, April 2012. 'Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)'. Review date May 2014

Technology Appraisal No. 241, January 2012. 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review TA70) and dasatinib and nilotinib for people with chronic myeloid leukaemia for whom treatment with imatinib has failed because of intolerance. Review date September 2014.

Technology Appraisal No.70, October 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia'.

Related Guidelines:

Cancer Service Guidance, October 2003, Improving outcomes in haematological cancers.

The European Public Assessment report is available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002373/human_med_001613.jsp&mid=WC0b01ac058001d124

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Bosutinib for previously treated chronic myeloid leukaemia

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

March 2013

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Abbreviations

AE/SAE/TEAE	Adverse event/ Serious adverse event/ Treatment-emergent adverse event
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance (statistical technique)
ANR	Accelerated phase, non-responder
AP	Accelerated phase
AR	Accelerated phase, responder
Ara-C	Arabinofuranosyl Cytidine (Cytarabine)
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BC	Blast crisis
Bcr-Abl	Breakpoint cluster region-Abelson (an oncogene fusion protein consisting of BCR and ABL)
BCSH	British Committee for Standards in Haematology
BL	Baseline
BM	Bone marrow
BMJ	British Medical Journal
BMS	Bristol-Myers Squibb
BMSCT	Blood and marrow stem cell transplantation
BNF	British National Formulary
BNHI	Bureau of National Health Insurance (Taiwan)
BNR	Blast phase, non-responder
BP	Blast phase
BR	Blast phase, responder
BSC	Best supportive care
C(A)T	Computerised (axial) tomography
CBC	Complete blood count
CC	Complication/comorbidity (HRG code)

CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CENTRAL	The Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMR	Complete molecular response
CNR	Chronic phase, non-responder
CNS	Central nervous system
CP	Chronic phase
CR	Chronic phase, responder
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CSR	Clinical Study Report
CU	Compassionate use
DARE	The Database of Abstracts of Reviews of Effects
DET	Data extraction table
DFS	Disease-free survival
DFWB	Daily functioning and well-being
DLI	Donor lymphocyte infusion
ECF	Emotional and cognitive function
ECOG	Eastern Cooperative Oncology Group
EGD	Upper endoscopy
EHA	European Haematology Association
EKG	Electrocardiogram
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life- 5 Dimensions questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EURD	European Union reference dates
EWB	Emotional well-being
FACT-BRM	Functional Assessment of Cancer Therapy- Biologic Response Modifier
FACT-G	Functional Assessment of Cancer Therapy- Generic
FACT-Leu	Functional Assessment of Cancer Therapy- Leukemia
FDA	US Food and Drug Administration
FISH	Fluorescence *in situ* hybridisation
FLAG-IDA	Fludarabine, cytarabine, idarubicin and G-CSF chemotherapy

	regimen
FWB	Functional well-being
GBP	Great British Pounds (currency)
G-CSF	Granulocyte-colony stimulating factor
GP	General Practitioner
GRC	Global Rating of Change
GVHD	Graft versus host disease
HCHS	Hospital and community health services
HCRU	Health care resource utilisation
HDI	High-dose imatinib
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HTA	Health Technology Assessment
HTN	Hypertension
HU	Hydroxyurea/hydroxycarbamide
IBS	Integrated Brier Score
ICER	Incremental cost-effectiveness ratio
ICLLM	International Congress on Leukemia Lymphoma Myeloma
ICU	Intensive-care unit
IFN	Interferon alpha
IFR	Individual funding requests
IM-I	Imatinib-intolerant
IM-R	Imatinib-resistant
INR	International Normalised Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LDAC	Low-dose cytarabine
LEUS	Leukaemia subscale
LSCG	London Specialised commissioning group
LY	Life years
MAH	Market authorisation holder
MCS	Mental component summary
MCyR	Major cytogenetic response
mg	milligrams
MHR	Major haematological response
MiCyR	Minor cytogenetic response
MID	Minimally important difference
MMR	Major molecular response
MRC	Medical Research Council (UK)
NA	Not applicable

NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	No evidence of leukaemia
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation Database
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
NR	Not reported
NSRC	National Schedule of Reference Costs
NTD	New Tawain Dollars (currency)
OHR	Overall haematological response
ONS	Office for National Statistics
OS	Overall survival
PAOD	Peripheral arterial occlusive disease
PAS	Patient Access Scheme
PB	Peripheral Blood
PCR	Polymerase chain reaction
PCS	Physical component summary
PCT	Primary Care Trust
PCyR	Partial cytogenetic response
PDGF	Platelet-derived growth factor
PenTAG	Peninsula Technology Assessment Group
PFLY	Progression-free life-years
PFS	Progression-free survival
PFT	Post-failure treatment
Ph^+	Philadelphia chromosome-positive
PP	Per-protocol
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PSUR	Periodic Safety Update Report
PTL	(EMA) Product Team Leader
PWB	Physical well-being
QALY	Quality-adjusted life years
QoL	Quality of life
QTc	Corrected QT interval
RCP	Return to chronic phase
RCT	Randomised controlled trial
RMP	Risk Management Plan
RUB	Russian ruble (currency)

SD	Standard deviation
SE	Standard error
SF-36	Short Form (36) Health Survey
SG	Standard gamble
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
SmPC/SPC	Summary of Product Characteristics
STC	Stem cell transplant
SUS	Unified Health System (Brazil)
SWB	Social well-being
TA[number]	Technology appraisal [number]
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
TOI	Trial Outcome Index
TOT	Time on treatment
TTD	Time to treatment discontinuation
TTO	Time trade-off
UHB	University Hospital Bristol
UK	United Kingdom
ULN	Upper limit of normal
USA/US	United States of America
VAT	Value added tax
WBC	White blood cell
WHO	World Health Organisation
WTP	Willingness to pay

Executive summary

Chronic myeloid leukaemia (CML) affects a small number of patients but poses a significant and progressive health related quality of life (HRQL) and economic burden.

CML is a cancer of myeloid blood cells characterised by a proliferation of granulocytes in blood and bone marrow. Philadelphia chromosome positive (Ph^+) CML is associated with an increasing symptomatic and HRQL burden as the disease progresses from chronic phase (CP) to accelerated phase (AP) and finally blast phase (BP).[1, 2] The prevalent population with CML is estimated to be around 5000, with approximately 500-600 patients newly diagnosed in England and Wales each year. Of these 90% are in CP, so only 50 CML patients are diagnosed in the advanced phases of CML each year in England and Wales.

If left untreated CML will typically progress from the CP to AP in 3-5 years, and then to BP within 6-24 months.[3, 4] Median survival in the BP, without treatment, is around 6 months.[4] As such, typical life expectancy for a CML patient diagnosed in CP is around 4-7 years without treatment.

The advent of TKIs, notably imatinib, has improved the survival of patients with CML. Most patients on currently available TKIs (imatinib, dasatinib and nilotinib) have survival outcomes similar to those of the general population with minimal impact on HRQL, as noted in previous CML NICE appraisals, TA241 and TA251. As CML is a chronic disease, long-term treatment and monitoring can have a significant impact on healthcare budgets.

A high unmet medical need exists for those patients who are unsuitable for treatment with the current TKIs (imatinib, dasatinib and nilotinib).

Despite the introduction of TKIs, a high medical need for additional treatment options exists. There remain a number of CML patients who are unsuitable for treatment with the current TKIs as a result of previous intolerance or lack of efficacy, the presence of a mutation that confers resistance to these agents, or of pre-existing co-morbidities that would preclude treatment with current TKIs.

Stem cell-transplantation (SCT) is an option for patients who have failed on previous TKI treatment, but is restricted by the number of matched donors available and is associated with high levels of morbidity and mortality. For most patients, cytotoxic agents in use before the introduction of TKIs, such as interferon or hydroxycarbamide, are the only options. These drugs are associated with poor survival and in the case of interferon, poor quality of life.

Bosutinib is an innovative and effective therapy targeted towards those CML patients with the greatest unmet need, since they are unsuitable for all currently available TKIs.

Bosutinib (Bosulif®) has received positive CHMP recommendation for a conditional marketing authorisation for: *The treatment of adult patients with CP, AP and BP Ph^+ CML previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.* In addition, the COMP adopted a positive opinion on the maintenance of orphan designation for bosutinib in EU in this indication on February 13th 2013.

According to this indication, bosutinib may be used in second, third or fourth line patients where current TKIs have been unsuccessful or are inappropriate due to mutations or co-morbidities. Bosutinib therefore offers an innovative step-change in the management of CML across all phases, where treatment is based on unmet need rather than line of therapy in patients whose current options are limited to hydroxycarbamide, SCT and interferon.

Bosutinib is a second-generation TKI therapy that inhibits the abnormal Bcr-Abl fusion protein; a constitutively active tyrosine kinase that results in enhanced cell proliferation and promotes CML. By binding and blocking the ATP binding site of this kinase, bosutinib inhibits downstream signalling and prevents uncontrolled cell differentiation. Bosutinib is additionally an inhibitor of Src family kinases, which have also been implicated in driving the progression of CML. Bosutinib, however, minimally inhibits the PDGF-R or c-KIT, unlike other licensed TKIs.

Bosutinib is an oral treatment and the recommended dose is 500mg once daily. Bosutinib is available in two pack sizes: 500mg x 28 tablets (£3,436.67) and 100mg x 28 tablets (£859.17), with an average cost of £122.74 for 500mg/day. Treatment should continue until disease progression or until bosutinib is no longer tolerated.

Bosutinib provides clinical benefit and a tolerable safety profile across CP, AP and BP in patients for whom the other TKIs have failed or are inappropriate, providing an important treatment option for patients, fulfilling a critical unmet need.

The data for the proposed indication is derived from Study 200, an open-label, phase I/II single-arm study of 546 Ph^+ CML patients. Study 200 had multiple cohorts including 288 patients with CP CML in second line, 118 patients with CP CML in third line and 76 and 64 patients in second line or later AP and BP CML respectively.

Study 200-WW comprises the pivotal data set upon which the EMA reviewed the revised proposed indication for bosutinib, and upon which positive CHMP opinion was granted. Although Study 200 was not specifically designed to evaluate the unmet need population described by the license, the EMA accepted that Study 200 includes patients from the licensed population and is representative of this population. This submission therefore focuses on the full Study 200 populations, in particular the third-line CP cohort, as this is likely to include a larger proportion of appropriate patients than the second-line cohort.

Bosutinib is associated with durable responses and good survival across all phases of CML in patients previously treated with TKIs, with a broad range of Bcr-Abl mutations.

In the third-line CP evaluable population, major cytogenetic response (MCyR) was attained by 32% of patients (primary outcome). If those patients who also maintained MCyR from baseline are included, the MCyR rate increases to 39% (28 Mar 2011 snapshot, minimum follow up 12 months, median treatment duration 8.3 months) and a similar rate of 41% is seen with longer follow up (15 Feb 2012 snapshot, minimum follow up 24 months, median treatment duration 8.6 months). Durable responses (MCyR) were observed in patients; amongst responders the Kaplan-Meier (K-M) estimate of maintaining MCyR was 71% at year 2 (15 Feb 2012 snapshot).

In advanced phase patients, as of data cutoff 28 Mar 2011, the cumulative overall haematological response (OHR) (primary outcome) while on bosutinib was 55.1% for AP patients (median treatment duration 10.1 months, minimum follow up 12 months) and 28.3% for BP patients (median treatment duration 2.8 months, minimum follow up 18 months).

Furthermore, mutation analysis demonstrated that these clinical responses were observed across a broad range of Bcr-Abl mutations, including those that confer clinical resistance to dasatinib and nilotinib (with the exception of the T315I and V299L mutation).

There is also evidence that bosutinib is associated with progression-free survival (PFS) and overall survival (OS) benefits. For third line CP CML patients, as of 15 Feb 2012, the 2 year K-M estimate in the all-treated population was 75.1% for PFS and 84.0% for OS respectively. The cumulative incidence of on-treatment transformation from CP to AP at 2 years was only

4%, while 71% of patients discontinued treatment without transformation and no patients transformed to BP.

For the advanced phase patients, as of 28 Mar 2011, the median PFS was 22.1 months for the AP CML and 5.5 months for the BP CML all-treated populations. In the AP all-treated cohort, the 2-year K-M estimate of OS was 65.6%, and the median OS was not reached. In the BP all-treated cohort, the 2-year K-M estimate of OS was 35.4% and the median OS was 11.1 months.

Bosutinib is generally well tolerated, with a manageable and differentiated safety profile, making it a valuable alternative for patients who are unable to tolerate existing TKIs.

In both the third-line CP CML and advanced phase CML populations of Study 200, the most commonly observed treatment-emergent adverse events were gastrointestinal in nature (diarrhoea, nausea, vomiting), mostly grade 1/2 in severity, and transient. The most common haematological adverse events were thrombocytopaenia, neutropaenia and anaemia. Clinicians have confirmed that most gastrointestinal and haematological side-effects are manageable with minimal additional costs.

Additionally, cross-intolerance with dasatinib was low in the third-line CP cohort, with only 22% of patients with prior dasatinib intolerance experiencing the same adverse event on bosutinib as a grade 3/4 event, thus showing the value of bosutinib in patients unable to tolerate existing TKIs. This favourable profile of limited cross-intolerance to dasatinib is in addition to an observed limited cross-intolerance of bosutinib to prior imatinib.[5]

As well as exhibiting a tolerable adverse event profile, data on patient-reported outcomes, including EQ-5D, from Study 200 shows that bosutinib leads to maintenance or improvement of quality of life in both third-line CP CML patients and advanced phase patients.

Bosutinib provides clinical benefit compared with the limited alternative treatments available for this population of unmet need.

A broad systematic review found only observational studies for bosutinib and its relevant comparators SCT, interferon and hydroxycarbamide. One hydroxycarbamide study, no interferon studies and 6 SCT studies reported relevant outcomes in patients previously treated with TKIs.

Only a naïve indirect comparison was possible owing to the observational nature of studies and the differences in populations included and outcomes presented. However, this was a pragmatic approach and consistent with that in a previous technology appraisal (TA241).

Nonetheless, the comparison indicates that bosutinib provides survival benefits over treatment alternatives for patients unsuitable for current TKIs. The OS estimate at 2 years for hydroxycarbamide in CP second line patients was 77%. For SCT in CP patients, OS at 2 years ranged from 72% (mainly third-line patients, Jabbour 2011) to 85% (mainly second-line patients, Schleuning 2010). This compares to an OS of 84% at 2 years for third line CP bosutinib patients (Khoury 2012). It should be noted that the prognosis for patients at second line is expected to be more favourable than third line.

Bosutinib represents a cost-effective use of NHS resources in the subpopulation of CML patients for whom all current TKIs are inappropriate. Bosutinib appears to be more cost-effective in CP, however it is proposed that advanced phase patients meet end of life criteria. This population of high unmet need is small and therefore expected to have minimal budget impact on the NHS.

Model Approach

Three semi-Markov models were developed to evaluate the use of bosutinib in the three different phases of CML (CP, AP and BP). The cost-effectiveness of bosutinib was compared to hydroxycarbamide, SCT and interferon. Data for the efficacy of bosutinib were taken from Study 200 (third-line CP CML population and advanced CML population), while comparator data was taken from a range of published sources for SCT, hydroxycarbamide and interferon. The model approaches taken are similar to those in previous CML appraisals (TA241 and TA251).

Base Case Results

In the chronic phase, the total costs and QALYs associated with bosutinib and hydroxycarbamide are [redacted] and £29,473 and 6.25 QALYs and 2.43 QALYs respectively. The base-case ICER for bosutinib over hydroxycarbamide was [redacted]. In the incremental analysis, interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib.

In the advanced phases, the ICERs for bosutinib versus hydroxycarbamide are greater than £30,000 per QALY, however it is proposed that bosutinib meets the end-of-life criteria in these subpopulations of CML that represent fewer than 10% of all CML patients and will be associated with a small budget impact. In the accelerated phase model, SCT is dominated by bosutinib and in the blast phase model, SCT is more expensive and more effective (ICER for SCT versus bosutinib is [redacted]).

As identified in previous CML appraisals, there are two major sources of structural uncertainty, time on treatment and overall survival. These, as well as assumptions relating to population, efficacy, HRQL and resource use are explored extensively in sensitivity analyses. In the chronic phase, bosutinib is always more expensive and more effective than hydroxycarbamide, with ICERs ranging from [redacted] per QALY. For the advanced phase CML models, in general, the ICER for bosutinib remains [redacted] per QALY compared to hydroxycarbamide.

A pragmatic approach to estimating the cost-effectiveness of bosutinib was required due to the available evidence. Nonetheless most of the assumptions in this model have been previously used and validated in prior CML appraisals (TA241 and TA251) and there is precedence in interpreting the cost-effectiveness of TKIs based on naive comparisons of single-arm studies (TA241).

Estimated Budget Impact

Based on the proportion of patients who discontinue treatment with current TKIs and the proportion of patients for whom these TKIs are also inappropriate due to mutations or co-morbidities, the eligible population for bosutinib is expected to be around 80 new patients per year. Given the step-change in survival associated with bosutinib over hydroxycarbamide for this CML population with high unmet need, it is assumed that bosutinib will largely replace treatment with hydroxycarbamide, which is used in the majority of patients. The introduction of bosutinib is therefore expected to be associated with an incremental budget impact of [redacted] in year 1, increasing to [redacted] in year 5.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Bosulif®

Approved name: bosutinib

Therapeutic class: bosutinib is a second-generation protein kinase inhibitor. The Anatomical Therapeutic Chemical Classification System code is L01XE06.

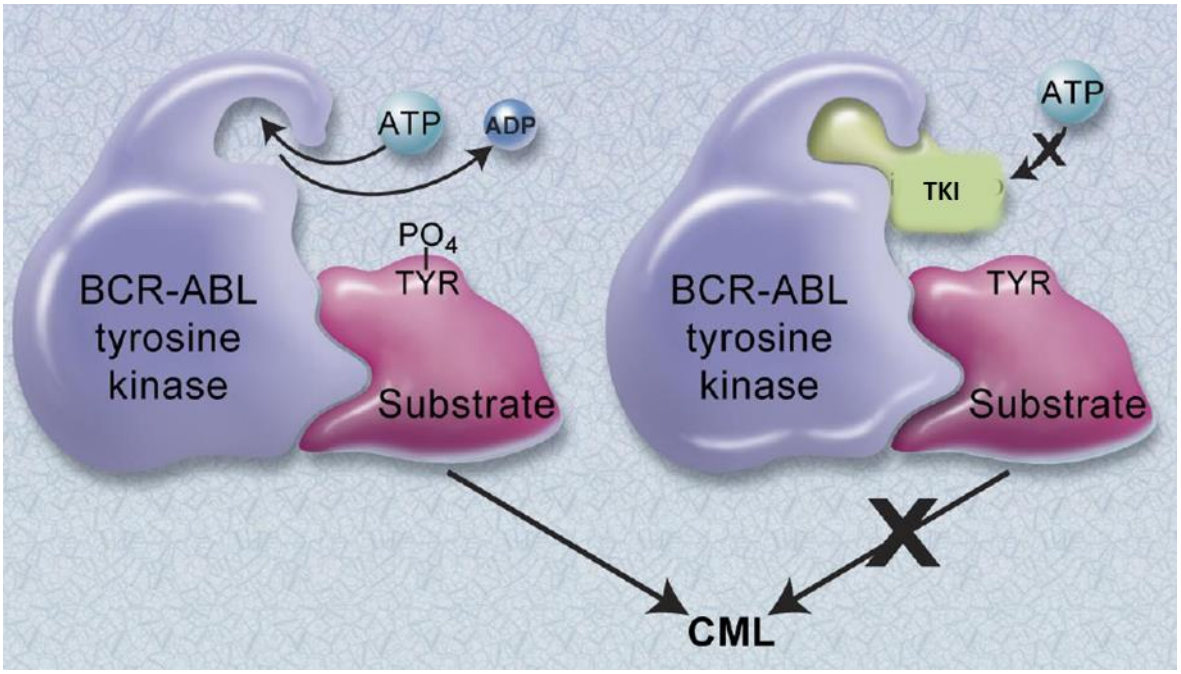
1.2 What is the principal mechanism of action of the technology?

In chronic myeloid leukaemia (CML), the breakpoint cluster region-Abelson kinase (Bcr-Abl) fusion protein is a constitutively active tyrosine kinase which is resistant to the usual cellular mechanism of apoptosis (programmed cell death), resulting in enhanced cell proliferation and genomic instability.

Bosutinib is a second-generation tyrosine kinase inhibitor (TKI) and inhibits the abnormal Bcr-Abl kinase that promotes CML. Bosutinib binds to the ATP binding site of the Bcr-Abl protein, blocking the ability of the tyrosine kinase (TK) to phosphorylate substrates, therefore preventing downstream signalling and thus inhibiting uncontrolled cell division.

Bosutinib is also an inhibitor of Src family kinases including Src, Lyn and Hck. Src kinases have been implicated in driving the progression of CML and dual inhibition may provide a more effective treatment strategy in CML. Bosutinib minimally inhibits PDGF receptor and c-Kit.

Figure A1: TKI effect on the Bcr-Abl protein



Adapted from Druker *et al*, 2008 [6]
Abbreviations: ADP, adenosine di-phosphate; ATP, adenosine tri-phosphate; Bcr-Abl, breakpoint cluster region-Abelson kinase fusion protein; CML, chronic myeloid leukaemia; PO_4, phosphate; TYR, tyrosine.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

European Medicines Agency (EMA) filing originally occurred on 29th July 2011 for the indication stated below. This application was initially based on data from a pivotal phase III study, 3160A4-3000-WW (Study 3000). This was a randomised, open-label study comparison with imatinib. At this time the proposed indication applied for was:

Bosutinib is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph^+ CML) in chronic phase (CP).

Following ongoing discussions with the EMA, Pfizer agreed to revise the indication for bosutinib to:

Bosutinib is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

With this revision in indication Study 200, a phase I/II trial of bosutinib in imatinib-refractory patients, became the pivotal study, while Study 3000 remained as a supportive trial. The Rapporteurs and EMA Product Team Leader (PTL) accepted to assess the Addendum to the Clinical Overview and corresponding revised SmPC and Risk Management Plan (RMP), which accompanied the Day 180 responses submitted on the 15th October 2012.

On the 17th January 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for bosutinib in this indication. Full EMA marketing authorisation is anticipated in mid-April 2013.

In addition, the COMP adopted a positive opinion on the maintenance of orphan designation for bosutinib in EU in this indication on February 13th 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

A draft EPAR is available for bosutinib and details the recommendations of the CHMP, as described below.

The CHMP have recommended the granting of a conditional marketing authorisation for bosutinib. The CHMP noted that the subpopulations of patients meeting the proposed indication of bosutinib were small, but that the efficacy of bosutinib in these patients was further supported by the results from the larger reference populations of Study 200. Therefore, the CHMP deemed bosutinib to possess a favourable benefit/risk profile sufficient to grant a conditional marketing authorisation. The specific conditions of this conditional marketing authorisation are outlined below.

Periodic safety update reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder (MAH) shall submitperiodic safety update reports for this product in

accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal. When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time. In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/ risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Post-Authorisation Measures

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

- To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
- Final Clinical Study Report: 30 September 2018

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Bosutinib has received positive CHMP recommendation for a conditional marketing authorisation for the *treatment of adult patients with chronic phase (CP), accelerated phase (AP) and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph$^+$ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.*

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Study 200, a phase I/II, multi-centre study, is an ongoing study of the efficacy and safety of bosutinib in imatinib-resistant or imatinib-intolerant leukaemia patients. Data from the 28 March 2011 data cutoff, which represents, 12 month follow-up data for the third-line CP population and 12 month and 18 month follow-up for the AP and BP populations, respectively, will be considered in this submission.

Additionally, results for the third-line CP CML population as of the data cutoff on 15 February 2012 were presented as a poster at the 54th American Society of Hematology (ASH) Annual Meeting and Exposition, 8-11th December 2012. This cutoff represents a minimum follow-up of 24 months for this third-line CP CML patient population and efficacy data from this updated data cut-off will be presented in this submission. No further follow-up data is currently available; it is anticipated that more recent follow-up data from the second-line CP CML and third-line CP CML populations of Study 200 will be presented at ASH in December 2013.

A phase I/II study (NCT00811070) on the safety and efficacy of bosutinib in Japanese subjects has an estimated completion date of September 2014. This dose-escalation study includes patients with imatinib resistant/refractory or imatinib-intolerant CP CML.

[redacted]

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

[redacted]

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Bosutinib is approved by the Food and Drug Administration (FDA) in the United States for the treatment of adult patients with chronic, accelerated or blast phase Ph^+ CML with resistance or intolerance to prior therapy.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

It is anticipated that a submission to the Scottish Medicines Consortium (SMC) will occur in Q2 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1: Unit costs of technology being appraised

<table>
<tr><td>Pharmaceutical formulation</td><td>Bosutinib is supplied as 100 mg and 500 mg film-coated tablets.

Each film-coated tablet contains bosutinib monohydrate equivalent to 100 mg or 500 mg of bosutinib.</td></tr>
<tr><td>Acquisition cost (excluding VAT)</td><td>The list price for bosutinib is as follows:
<table>
<tr><th></th><th>£/tablet</th><th>£/pack (28-pack)</th><th>£/year</th><th>Dose assumption</th></tr>
<tr><td>500 mg</td><td>£122.74</td><td>£3,436.67</td><td>£44,799</td><td>Assumes 500 mg/day for 1 year</td></tr>
<tr><td>100 mg</td><td>£30.68</td><td>£859.17</td><td>£44,799</td><td>Assumes 400 mg/day for 1 year</td></tr>
</table></td></tr>
<tr><td>Method of administration</td><td>Oral</td></tr>
<tr><td>Doses</td><td>The recommended dose of bosutinib is 500 mg per day.</td></tr>
<tr><td>Dosing frequency</td><td>Once daily with food</td></tr>
<tr><td>Average length of a course of treatment</td><td>Treatment is not curative and therefore patients should continue bosutinib long-term, until disease progression or until bosutinib is no longer tolerated

In the study demonstrating efficacy of bosutinib in third-line use, patients received bosutinib for median duration of 8.3 months.</td></tr>
</table>

Average cost of a course of treatment	Assuming an average length of a course of treatment of 8.3 months, as observed in Study 200, and assuming 1 month to have 28 days, the average cost of a course of treatment based on the list price is as follows: £28,524.36 This cost is the same for a dose regimen of 500 mg/day or 400 mg/day.
Anticipated average interval between courses of treatments	None - bosutinib should be taken daily without interruption
Anticipated number of repeat courses of treatments	Treatment is taken continuously until disease progression or intolerance
Dose adjustments	<u>Dose Escalation</u> In the Phase II part of the Study 200 clinical trial of adult patients with previously treated Ph^+ leukaemia, dose escalation to 600 mg once daily with food was allowed in patients who did not experience severe or persistent-moderate adverse reactions, under any of the following circumstances. A total of 85 subjects (15.2 %) who started treatment at ≤ 500 mg (n=558) received dose escalations to 600 mg of bosutinib. Doses greater than 600 mg/day have not been studied and therefore should not be given. Circumstances for dose escalation: • Failure to achieve complete haematological response (CHR) by week 8 • Failure to achieve complete cytogenetic response (CCyR) by week 12 <u>Dose reduction</u> Recommended dose adjustments differ depending on the nature of the toxicity: haematological or non-haematological. For non-haematological adverse reactions: • If clinically significant moderate or severe non-haematological toxicity develops, bosutinib should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 500 mg once daily should be considered. • If elevations in liver transaminases > 5 x institutional upper limit of normal (ULN) occur, bosutinib should be interrupted until recovery to ≤ 2.5 x ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered. If transaminase elevations ≥ 3 x ULN occur concurrently with bilirubin elevations >2 x ULN and alkaline phosphatase <2 x ULN, bosutinib should be discontinued. • For NCI CTCAE Grade 3-4 diarrhoea, bosutinib should be interrupted and may be resumed at 400 mg once daily upon recovery to grade ≤1.

	For haematological adverse reactions: • Dose reductions are recommended for severe or persistent neutropaenia and thrombocytopenia. If absolute neutrophil count (ANC) <1.0 x 10^9/L and/or platelets <50 x 10^9/L, then recommendations are to: ○ Hold bosutinib until ANC ≥ 1.0x 10^9/L and platelets ≥ 50 x 10^9/L. ○ Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for > 2 weeks, reduce dose by 100 mg and resume treatment. ○ If cytopoenia recurs, reduce dose by 100 mg upon recovery and resume treatment. ○ Doses < 300 mg/day have not been evaluated.

Abbreviations: ANC, absolute neutrophil count; CCyR, complete cytogenetic response; CHR, complete haematological response; L, litre; mg, milligram; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ULN, upper limit of normal

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests are required for selection of patients for this orally administered treatment, bosutinib.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Additional monitoring over and above usual clinical practice for TKIs in CML is not expected. Patients receiving bosutinib should have monthly liver function tests and complete blood counts taken for the first three months of treatment, or as clinically indicated. The required monitoring across all TKIs is outlined in Table A2.

Table A2: Required monitoring detailed in TKI SPCs

Test	Bosutinib	Imatinib[7]	Nilotinib[8]	Dasatinib[9]
Liver function tests	Monthly for first 3 months, or as clinically indicated	Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly	Bilirubin or hepatic transaminases should be performed monthly or as clinically indicated	-
CBCs	Monthly for first 3 months, or as clinically indicated	Regularly	Every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated	Weekly for the first 2 months, and then monthly thereafter, or as clinically indicated
Serum lipase levels	-	-	Monthly or as clinically indicated	-

Abbreviations: CBC, complete blood count.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other therapies are likely to be administered at the same time as the intervention as part of a course of treatment.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

CML is a form of cancer of the blood typified by overproduction of granulocytes by the bone marrow. It accounts for approximately 15% of all adult leukaemias.[10]

CML is characterised by the presence of the *BCR-ABL* fusion gene as the result of a reciprocal chromosome translocation between chromosomes 9 and 22; t(9q34;22q11). This acquired (non-inherited) translocation results in a truncated derivative chromosome 22 known as the Philadelphia chromosome. Approximately 90–95% of the CML population are Philadelphia chromosome positive (Ph^+).[4] A further 5% do not exhibit the characteristic Philadelphia chromosome, but have cryptic chromosomal rearrangements resulting in the *BCR-ABL* fusion gene.[4] The resulting Bcr-Abl fusion protein is a constitutively active tyrosine kinase, resistant to apoptosis (programmed cell death). It phosphorylates numerous substrates, disrupting the regulation of intracellular signal transduction pathways, promoting proliferation and genetic instability.[11-13]

CML has three phases: chronic (CP), accelerated (AP) and blast (BP), each corresponding to increasing leukaemic blast counts in the blood and bone marrow and clinical severity (Table A3).[14, 15] Blast is a term which describes an immature blood cell of any type. Normally, a blast will develop into a mature blood cell, but in CML these cells are abnormal and do not fully develop, becoming known as leukaemic blasts.[16] Approximately 90% of patients are diagnosed while in CP, 9% in AP and 1% in the BP. If left untreated, the average time a patient would remain in CP, AP and BP is 3–5 years,[1, 2] 6–24 months[3, 4] and 6 months[4], respectively.

Table A3: WHO criteria for CML phases

Phase	Criteria
Chronic	Definition of CP implies that conditions for AP or BP are not met
Accelerated	Diagnose if one or more of the following is present: • Blasts 10% to 19% of PB white cells or BM cells • PB basophils at least 20% • Persistent thrombocytopenia (<100 x 10^9/L) unrelated to therapy, or persistent thrombocytosis (>1000 x 10^9/L) unresponsive to therapy • Increasing spleen size and increasing WBC count unresponsive to therapy • Cytogenetic evidence of clonal evolution (ie, the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML) • Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia, should be considered as suggestive of AP CML. These findings have not yet been analysed in large clinical studies, however, so it is not clear if they are independent criteria for accelerated phase. They often occur simultaneously with one or more of the other features listed.
Blast	Diagnose if one or more of following is present: • Blasts 20% or more of peripheral blood white cells or bone marrow cells • Extramedullary blast proliferation • Large foci or clusters of blasts in bone marrow biopsy

Source: Vardiman 2002, Baccarani 2006. Abbreviations: BM, bone marrow; PB, peripheral blood; WBC, white blood cell

Patients in the CP may experience mild and non-specific symptoms such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss.[17] Approximately 40% of CP patients are asymptomatic and diagnosed as a result of a routine blood test.[18] Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising, bleeding and infections.[18] In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.[18, 19]

Health-Related Quality of Life (HRQL) for CML patients can vary greatly, depending on the treatment regime used. The introduction of effective therapies such as those of the TKI class has led to improvements in the HRQL of CML patients.[20] In contrast, there is some evidence that CML patients treated long-term with interferon alpha may experience reduced HRQL.[21]

At diagnosis, an evaluation is performed to categorise a CML patient into low-, intermediate- or high-risk groups corresponding with the relative risk of progression and death. Two evaluations have been developed; the Sokal score and the Hasford score. The Sokal score is based on the diagnostic markers of spleen size, platelet count, age and blast count.[22] The Hasford score is based on the diagnostic markers of spleen size, platelet count, age, blast count, eosinophil count and basophil count.[23] Thresholds for categorisation of patients by these two different scoring methods are displayed in Table A4.

Table A4: Thresholds for Sokal score and Hasford score

Risk Category	Sokal score	Hasford Score
Low	<0.8	≤780
Intermediate	0.8—1.2	>780 and ≤1480
High	>1.2	>1480

CML occurs in all age groups, but is most common in older adults [24, 25] and the median age at diagnosis is 59.1 years.[26] A French study has shown that the prevalence of CML is increasing.[27] In the pre-imatinib era, prevalence increased 4.1% annually (from 1998 to 2002), however, since the introduction of imatinib a mean annual increase of 9.3% has been observed (from 2003 to 2007).[27] Apart from the impact of imatinib, better diagnosis and an aging population may play a part in increasing prevalence.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

In 2003, the prevalence of CML in England and Wales was estimated at 2,660[28]. Therefore, assuming a mean annual increase in cases of 9.3% since then,[27, 28] current prevalence of CML in England and Wales is estimated at 5,922. However, the estimate of patients potentially eligible for bosutinib annually has been calculated using the incident population of patients diagnosed with CML in England and Wales. This gives rise to an estimated 80 patients per year becoming newly eligible for treatment with bosutinib in England and Wales. The assumptions and data sources used to determine this estimated population size are presented in Section 8.1, Table C1.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

If left untreated CML will typically progress from the CP to the AP in 3-5 years,[12, 13] and then to BP within 6-24 months.[3, 4] Median survival in the BP, without treatment, is around 6 months.[4] As such, the typical life expectancy for a CML patient diagnosed in CP is around 4-7 years without treatment.

The majority (>90%) of patients are diagnosed with CML in CP.[29] Imatinib currently represents the established first-line treatment for these CP CML patients in clinical practice, having replaced interferon alpha upon its introduction.[30] This new treatment paradigm has led to a dramatic improvement in the prognosis for patients diagnosed with CP CML. The estimated median survival with imatinib exceeds 25 years with median age of diagnosis of almost 60 years.[26, 31]

Patients who respond well to standard-dose imatinib treatment (approximately 55% of patients[32]) will often continue to receive this treatment for life and have a normal life expectancy. Nilotinib, the other NICE-recommended TKI for first-line treatment of CP Ph^+ CML, has demonstrated a similar influence on life expectancy when administered as a first-line treatment.[33] Dasatinib is also licensed for first-line use, but is not NICE recommended in this setting and therefore rarely used at first-line.

Approximately 45% of CP patients develop intolerance or resistance to first-line imatinib and may then be treated with a second-generation TKI, nilotinib or dasatinib. Dasatinib is not recommended by NICE as a second-line treatment and therefore most patients receive nilotinib at second-line. The 40-50% of patients who exhibit a good response to treatment with a second-generation TKIs can expect to receive this treatment for the rest of their lives and have a nearly normal life expectancy (at least 10 more years).[18,34]

However, for 50-60% of second-line patients treatment is unsuccessful, due to resistance, intolerance or progression. At third-line there are no NICE recommended options available, however clinicians may try a third TKI, usually dasatinib, if appropriate and accessible (for example, through the cancer drugs fund).

Treatment options are limited for patients who have previously tried all three currently available TKIs (i.e. fourth-line patients) or second- and third-line patients for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. There is a clear unmet need for an effective treatment for these patients, the majority of who will currently be managed with hydroxycarbamide, which represents best supportive care (BSC). There is a paucity of data describing the life expectancy associated with hydroxycarbamide in this population, but it is expected to be similar to or worse than that associated with its use in earlier lines of treatment. Previous NICE technology appraisals (TA241[18] and TA251[35]) considered efficacy data for hydroxycarbamide from a single study[36] of non-TKI treatments (including hydroxycarbamide) in imatinib-failure patients. Based on this study, the mean survival time used in the model in TA241 (CML in imatinib-resistant patients) for hydroxycarbamide used at second line was estimated at 3.5 years for CP patients, at a mean age of 65 at diagnosis.

Although rarely used since the introduction of TKIs, interferon alpha may also be used in patients who experienced disease progression on or intolerance to TKIs, or who are unsuitable for currently available TKIs. Median life expectancy with interferon alpha treatment has been reported as 5-7 years in CP patients: substantially lower than the life expectancies achieved by most patients who can be treated with the currently licensed TKIs.[31] In TA241, NICE, in consultation with clinicians, agreed that the appropriate estimate for overall survival on interferon alpha in imatinib-failure CP patients was 3.6 years. Ibrahim 2011 reported that for patients for whom interferon treatment was unsuccessful, and who were then treated with interferon, hydroxycarbamide or busulfan, adjusted probability of overall survival at 5 years was approximately 60%.[37] A similar

overall survival was reported for those patients who did not have a response on second- and third-line second-generation TKIs.

The use of TKIs in clinical practice has also been effective in extending the life expectancy of BP CML patients. Median survival in BP ranges from 7-11 months with imatinib treatment, compared to 6 months with no treatment.[4, 38] However, as in CP, advanced phase patients for whom treatment with the currently recommended TKIs has been unsuccessful or is considered inappropriate will mostly be treated with hydroxycarbamide (BSC). In the NICE first-line appraisal (TA251), time spent in the advanced phases of CML was fixed for patients treated unsuccessfully with imatinib and receiving hydroxycarbamide, at approximately 9 months for AP and 6 months for BP.[35]

One final option, for patients in CP, AP or BP is allogeneic stem cell transplant (SCT). There is considerable mortality and morbidity associated with SCT; in the first-line CML NICE appraisal[35], 25% of patients ('high-risk' patients) receiving SCT are assumed to have a constant probability of death of 0.55. However, the overall life-expectancy is expected to be similar to the TKI overall survival at the corresponding line of treatment (i.e. 17 years at first line and 13 years at second line). Nonetheless, SCT does not represent a viable treatment option for many patients, due to poor availability of matched donors and strict eligibility criteria, for example SCT is not recommend in patients over 65.

As such, for the majority of CP and advanced phase patients in whom the current recommended TKIs have been unsuccessful or are inappropriate due to resistance, intolerance or co-morbidities, the only option is best-supportive care with hydroxycarbamide. Bosutinib represents an effective and active alternative to hydroxycarbamide and addresses a clear unmet need for patients.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Relevant NICE technology appraisals are:

- Technology Appraisal No. 251, April 2012, 'Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)'.[35]
- Technology Appraisal No. 241, January 2012, 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review TA70) and dasatinib and nilotinib for people with chronic myeloid leukaemia for whom treatment with imatinib has failed because of intolerance'.[18]
- Technology Appraisal No. 70, October 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia.[28] This guidance has now been partially updated by TA241 and TA251 (above).

Relevant NICE guidelines are:

- Cancer Service Guidance, October 2003, 'Improving outcomes in haematological cancers'[39]

NICE recommendations for first-line treatment of adult patients with Ph^+ CML are as follows, and are additionally represented in Figure A2. Figure A2.

Figure A2

- NICE recommends standard-dose (400 mg once daily) imatinib as an option for the first-line treatment of Ph^+ CML in the chronic phase.
- NICE also recommends imatinib for the treatment of CML that initially presents in the accelerated or blast-crisis phase, and for CML that presents in the chronic

phase and then progresses to the accelerated or blast-crisis phase, if imatinib has not been used previously.

- Nilotinib is recommended as an option for the first-line treatment of chronic phase Ph^+ CML if the manufacturer makes nilotinib available with the discount agreed as part of the Patient Access Scheme (PAS).
- Dasatinib has a marketing authorisation from the EMA for the treatment of adult patients with newly diagnosed Ph^+ CP CML. However, NICE does not recommend dasatinib for the first-line treatment of chronic phase Ph^+ CML.

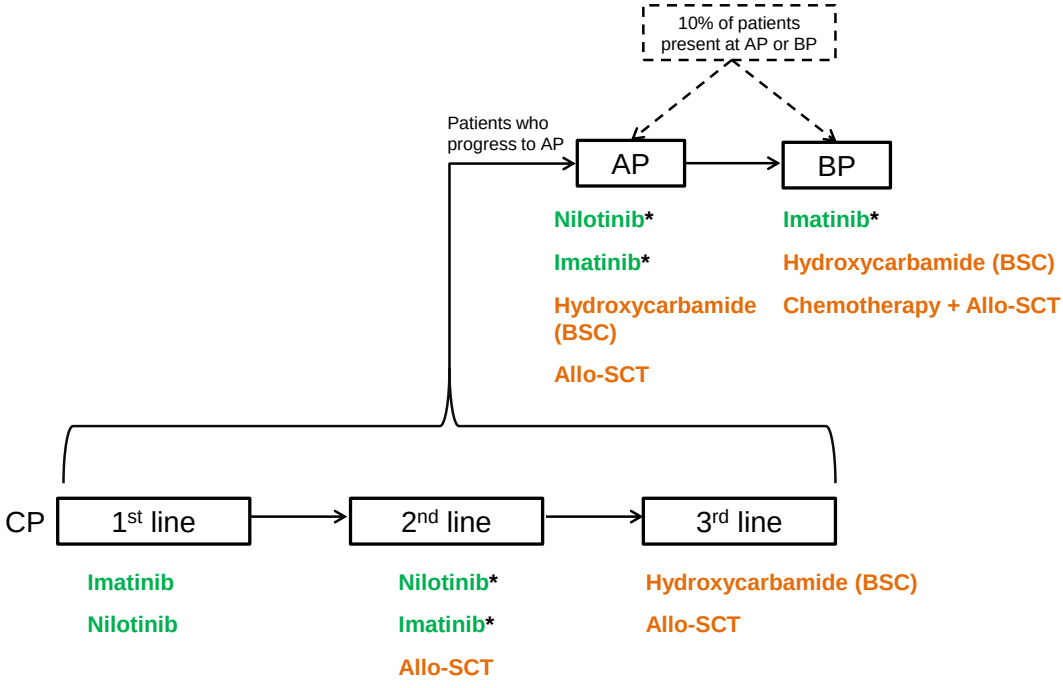
NICE recommendations for the second-line treatment of adult patients with Ph^+ CML are as follows, and are additionally represented in:

- NICE recommends nilotinib for the treatment of chronic or accelerated phase Ph^+ CML that is resistant or intolerant to standard dose imatinib, if the manufacturer makes nilotinib available with the discount agreed as part of the PAS.
- Dasatinib also holds an EMA marketing authorisation for second-line use, being indicated for the treatment of adult patients with CP, AP or BP Ph^+ CML with resistance or intolerance to prior therapy including imatinib. Similar to first-line use, NICE does not recommend dasatinib for the treatment of chronic, accelerated or blast-crisis phase Ph^+ CML that is resistant or intolerant to standard-dose imatinib. NICE concluded that dasatinib could not be recommended as a cost-effective use of NHS resources because, given the PAS for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is considerably more expensive but no more effective than nilotinib.
- NICE recommendations allow for the use of standard-dose imatinib in the second line after unsuccessful treatment with first-line nilotinib.
- NICE does not recommend high-dose imatinib for the treatment of chronic, accelerated or blast-crisis phase Ph^+ CML that is resistant to standard-dose imatinib.

NICE does not make any recommendations for treatment of patients with BP Ph^+ CML that is resistant or intolerant to standard-dose imatinib. Furthermore, NICE has not issued any recommendations for the treatment of adult patients whose disease progresses whilst on nilotinib, or who have experienced intolerance to nilotinib.

The treatment options and recommendations for this multi-phase disease in line with NICE recommendations are presented in Figure A2.

Figure A2: NICE-recommended clinical pathway of care



*Dependent upon prior treatment
Recommended by NICE
Not assessed by NICE, but used in clinical practice

Note: Dasatinib possesses a UK marketing authorisation for first- and second- line treatment of CML in CP, AP and BP. However, appraisals by NICE for the use of dasatinib in first-line treatment of CML (TA251[35]) and in second-line treatment of imatinib-intolerant CML (TA241[18]), concluded that NICE does not recommend dasatinib for the treatment of CML at either line of treatment. Dasatinib is therefore not included in Figure A2 of the NICE-recommended clinical pathway of care, but dasatinib may be accessed in practice, for example via the cancer drugs fund or individual funding requests.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There remains significant unmet need in the treatment of CP, AP and BP CML. Development of resistance, progression of disease despite treatment and intolerance to the currently recommended TKIs (imatinib, nilotinib and dasatinib) pose a significant challenge in the treatment of these patients and may cause withdrawal of therapy and can adversely affect compliance and outcomes. Furthermore, the presence of specific mutations or co-morbidities may render current therapies inappropriate. Hydroxycarbamide represents the main option in this patient population and therefore equates to best supportive care (BSC) for these patients. Given the limited efficacy of hydroxycarbamide (BSC), these patients represent a population of significant unmet need, for whom bosutinib offers an effective alternative.

First-line treatment of CML

The current standard-of-care first-line treatment for adult CP CML patients is imatinib,[40] which has been recommended by NICE since September 2002 (TA50, TA70[28]). Nilotinib is also licensed and recommended as a first-line option for adult CP CML patients (TA251).[35] Dasatinib is also licensed for first-line use, but is not recommended by NICE

in this setting and therefore rarely used at first-line. Bosutinib is not indicated for the first-line treatment of newly-diagnosed patients with CP CML.

Second-line use of bosutinib

Approximately 40% of patients cannot remain on first-line imatinib long-term and require an effective second-line treatment option.[32] For most patients, the second-line treatment offered will be nilotinib, which is recommended by NICE in this position on the clinical pathway of care (TA241).[18] Dasatinib is also licensed for use in second-line patients, but is not recommended by NICE in this setting and therefore rarely used as a second-line option.

For a small minority of imatinib-resistant or intolerant patients (i.e. second-line patients), treatment with nilotinib or dasatinib may not be appropriate due to a pre-existing medical condition, TKI intolerance or a mutation that would be expected to confer resistance to the TKI. For these patients, bosutinib represents an alternative to hydroxycarbamide (BSC) in a second-line setting.

Third-line use of bosutinib

In approximately 50-60% of patients treated with a second-line TKI, treatment fails to induce a response, response is lost or the patient may discontinue treatment due to toxicity or co-morbidity.[34] For these patients there is no treatment specifically recommended by NICE, however in practice clinicians may try a third TKI, usually dasatinib, if appropriate and accessible (for example, through the cancer drugs fund).

For a small minority of third-line patients, treatment with a third-line TKI may not be not be appropriate due to a pre-existing medical condition, TKI intolerance or a mutation that would be expected to confer resistance to the TKI. For these patients, bosutinib represents an alternative to hydroxycarbamide (BSC) in a third-line setting.

Fourth-line use of bosutinib

Third-line treatment will be unsuccessful in around 50% of patients and for these patients, bosutinib represents an alternative to hydroxycarbamide (BSC) at fourth line.

Use of bosutinib in advanced-phases (AP and BP)

AP patients may currently be treated with imatinib or nilotinib according to NICE recommendations. Dasatinib is licensed for use in AP, but is not recommended by NICE in this population and is therefore rarely used. For AP patients who have previously tried one or more TKI and for whom imatinib, nilotinib and dasatinib are inappropriate options, bosutinib would represent an alternative option to hydroxycarbamide (BSC).

The primary goal of treatment of BP CML patients is to establish haematological control (and possibly a return to a second CP).[38] Imatinib is licensed for use in BP, although there are no specific NICE guidelines for this. Nilotinib is not licensed for use in BP patients and whilst dasatinib does possess a license for treatment of BP patients, it is not currently recommended by NICE and is therefore rarely used. As such, for patients in BP who have previously tried one or more TKI and for whom imatinib and dasatinib are considered inappropriate options, bosutinib represents an alternative to hydroxycarbamide (BSC) in BP patients.

Allogeneic stem cell transplantation (SCT)

SCT is a treatment option for patients in CP, AP and BP and may be used in patients who have failed (due to lack of efficacy or tolerability) on currently available TKIs or for whom TKIs are inappropriate. In BP, SCT is typically preceded by treatment with acute leukaemia-style chemotherapy to try and establish haematological control.[38] Bosutinib may therefore be considered as an alternative to SCT in CP, AP and BP patients, however as noted in Section 2.3, SCT is restricted by the number of matched donors available and is associated with high levels of morbidity and mortality.[41]

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The use of dasatinib in the treatment of patients with CP, AP or BP CML at the first- or second-line of the therapy is not recommended by NICE due to the unfavourable cost-effectiveness profile demonstrated.[18, 35] Dasatinib is, however, accessible through the Cancer Drugs Fund in England and so its use in the treatment of patients with CML in England cannot be excluded.[42] The extent to which dasatinib is used in clinical practice through this alternative mode of funding is currently unclear.

A second issue concerns the decision to carry out SCT in the treatment of patients with CML. The probability of success of this procedure is influenced by many factors, including (but not limited to): patient age, timing of the transplant, availability of a matched donor and level of progression of the disease.[43-45] Therefore, SCT does not occupy a single, well-defined space in the CML pathway of care and could be applied at various stages of this pathway depending upon a complement of patient-related factors and the preference of the responsible physicians. This tends to be reflected in the evidence base for SCT, whereby the population is frequently heterogeneous including patients at different lines of treatment and even phases of CML. Additionally, its use in patients who are not suitable for or who have failed on all currently available TKIs is not known.

A third issue concerns the management of BP patients. It is known that acute leukaemia-style chemotherapy regimens, such as FLAG-IDA (combinatorial chemotherapy consisting of fludarabine, cytarabine, G-CSF and idarubicin), are used in BP patients.[46] However, no evidence has been found on the use of chemotherapy in the management of BP CML and the option of chemotherapy in BP was not specifically considered in previous NICE appraisals.[18] Given this lack of evidence, it will be assumed in this submission that chemotherapy is only used in combination with SCT in BP patients and not as a comparator in isolation; however there is some uncertainty in how this assumption reflects clinical practice.

2.7 Please identify the main comparator(s) and justify their selection.

The relevant comparators identified for bosutinib in the treatment of adult patients with CP, AP and BP Ph^+ CML, previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options are as follows:

- Hydroxycarbamide (BSC)- in this submission, the manufacturer considers hydroxycarbamide to be best supportive care (BSC) for the CML patient population with an unmet clinical need - a view supported by clinical experts from the Royal College of Pathologists and British Society of Haematology.[47] As the only therapeutic option for the majority of these patients, hydroxycarbamide (BSC) will represent the base-case comparator for this submission.
- Allogeneic SCT (with or without leukaemia-style chemotherapy depending on phase of CML)
- Interferon alpha

Justification

- In line with the marketing authorisation, bosutinib can only be used in adult patients with CP, AP, and BP Ph^+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

- Given the current treatment pathway and the anticipated indication (above), comparison with other currently available TKIs is not appropriate for this submission.
- For CP or AP Ph^+ CML patients who have previously tried one or more TKI and for whom the other TKIs are inappropriate, hydroxycarbamide (BSC), SCT and interferon alpha represent the only remaining treatment options and hence are relevant comparators to bosutinib in this submission.
- For BP Ph^+ CML patients who have previously tried one or more TKI and for whom the other TKIs are inappropriate, the only remaining treatment options are hydroxycarbamide (BSC), SCT with leukaemia-style chemotherapy and interferon alpha.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

As with other TKI therapies for CML, bosutinib can be associated with toxicity, particularly in the early stages following treatment initiation. In the phase I/II trial in third-line use, the most frequent non-haematological adverse events were gastrointestinal toxicities (diarrhoea, nausea, vomiting). These adverse gastrointestinal events frequently resolved spontaneously or with supportive care and/or dose adjustments of bosutinib. Concomitant medication for management of diarrhoea was received by 65% of patients, with loperamide being the primary medication used (59% of patients).[48]

In the evaluation of second-line patients in this phase I/II study, the most frequent non-haematological adverse events were also observed to be gastrointestinal toxicities (diarrhoea, nausea, vomiting). Rash was also observed as one of the more frequent non-haematological adverse events. As was the case for third-line patients, these adverse gastrointestinal events frequently resolved spontaneously or with supportive care and/or dose adjustments of bosutinib. Concomitant medication for management of diarrhoea was received by 68% of patients, with loperamide being the primary medication used (58%).[5]

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Table A5: Resource use associated with bosutinib

Location of care	Patients will receive bosutinib as outpatients.
Staff usage	Bosutinib will be prescribed by a haematologist. No additional staff will be required beyond those currently required for the management of CML patients treated with TKIs.
Administration costs	No administration costs are expected to be associated with bosutinib.
Monitoring and testing	Guidelines for monitoring and testing of response to treatment have been published by European Leukemia Net (ELN)[49] and dictate the following resource use, depending on the type of response monitored: • *Haematological response:* Check at diagnosis, then every 15 days until CHR has been achieved and confirmed, then at least every 3 months or as required • *Cytogenetic response:* Check at diagnosis, 3 months, 6 months and every 6 months thereafter until CCyR has been achieved and confirmed. Following this a check should be

	performed every 12 months if regular molecular monitoring cannot be assured • *Molecular response*: By RT-Q-PCR every 3 months, until MMR has been achieved and confirmed then at least every 6 months. A mutational analysis should be performed in occurrences of suboptimal response or failure and is always required before changing to other TKIs or other therapies

2.10 Does the technology require additional infrastructure to be put in place?

No.

3 Equality

3.1 Identification of equality issues

There are no specific equality issues relating to bosutinib itself, however, the inclusion of bosutinib as an additional treatment option in the clinical pathway of care may help to address some of the equality issues associated with SCT, which is the only proven cure for CML. Patients from ethnic minorities are less likely to find a matched donor[a, 50, 51] due to the lower numbers of donors available and therefore experience a higher mortality rate from CML than more prevalent ethnic groups. SCT is also not generally performed in older patients due to the high morbidity and mortality rates associated with the procedure.[41, 52] Increasing the number of alternative therapies available provides additional options for those for whom SCT is not a viable treatment option.

It has been reported that there are regional variations across England in terms of the drugs made available through the CDF and the rate of approval of requests for a given drug, such as dasatinib.[53, 54] Furthermore, the CDF operates in England only and so patients in Wales do not have access to many cancer drugs through this route. Therefore, the location in which a patient lives can therefore influence the number of treatment options available to them across England and Wales. NICE approval of bosutinib would ensure a more equitable access to a new drug for patients who currently have a clear unmet need.

3.2 How has the analysis addressed these issues?

None of the above issues relate to the data or evidence presented in the analysis and so the analysis will not specifically address these issues.

[a] Due to a lack of ethnic minority donors, the chances of finding a match for a patient from an ethnic minority background can be as low as 30–40%, compared with 90% for a white Northern European patient.

4 Innovation

4.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Efficacy across TKI resistance mutations

The proposed indication for bosutinib is as a treatment for patients who have been previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are inappropriate. In some cases, a patient may be inappropriate for one of these TKIs as a result of the presence of Bcr-Abl mutations that confer resistance to currently available TKIs. Bosutinib has demonstrated clinical activity in CML patients with mutations that confer resistance to currently available TKIs. In a study of CP CML patients, treatment with bosutinib in the third-line setting resulted in complete haematological responses and major cytogenetic responses across a broad range of Bcr-Abl mutants, including those conferring clinical resistance to nilotinib (Y253H, E255K/V, F359C/I/V) and dasatinib (F317L).[48] Efficacy of bosutinib in CML patients with a broad range of Bcr-Abl mutations have also been demonstrated for bosutinib in a second-line setting.[5] Bosutinib is therefore innovative in its potential to treat a patient group, with unmet needs, which is identifiable by its genetic characteristics: Bcr-Abl kinase mutations conferring resistance to current TKIs.

Differential side-effect profile of bosutinib

Clinical studies of bosutinib in patients with CML have revealed that this agent is typically associated with a different adverse event profile to the currently available TKIs. Given the differential adverse event profile, bosutinib provides an efficacious TKI treatment option for patients who are unable to take current TKIs due to specific co-morbidities or who have failed on previous TKIs due to intolerance.

Position of bosutinib in clinical pathway of care

The use of bosutinib according to the proposed indication represents an innovative application of technology as its use would be determined upon the clinical need of the patient and not the line of therapy. Although Study 200 was not designed specifically to evaluate this population, the CHMP has recognised the importance of this unmet need sub-population, and the potential role of bosutinib in this population, based on this trial. Currently, the main treatment option for patients previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate is hydroxycarbamide (BSC); a therapy that has limited impact on the course of the disease and overall survival.[4] Bosutinib therefore represents a step-change in the management of CML for specific cohorts of CP, AP and BP patients whose only current treatment option is hydroxycarbamide.

Bosutinib is associated with significant health-related benefits in those patients for whom current TKI therapies are not appropriate or have not been successful and this benefit is demonstrated at all lines of therapy and across all phases of CML where bosutinib could be used.

High rates of clinical response

Bosutinib is associated with high rates of clinical response across CP CML and advanced phase CML patients who have failed on previous TKI treatment. In third- line CP CML patients, a high proportion of patients demonstrated a clinical response to bosutinib, with 38.9% experiencing a cumulative MCyR and 30.6% experiencing a cumulative CCyR.[48]

Bosutinib has also been observed to produce a substantial response in advanced phase CML patients whose disease has progressed on, or who have experienced intolerance to at least one prior TKI. Rate of Overall Haematological Response (OHR) by week 48 in an

AP CML cohort was 55.1%. Among AP CML patients who received bosutinib in the second line, rate of OHR by week 48 was 64.1% and for AP CML patients who received bosutinib after prior exposure to multiple TKIs, the OHR rate by week 48 was 43.3%. For BP CML patients, OHR rate by week 48 was 28.3%, with an OHR rate by week 48 of 36.4% for BP CML patients receiving bosutinib in the second line, judged to be clinically meaningful.

Durable response

Bosutinib is associated with durable responses in those who have been previously treated with one or more TKI therapies. Treatment of CP CML patients with bosutinib in the third-line setting resulted in a Kaplan-Meier (K-M) estimate of maintaining MCyR amongst responders of 71% at 2 years.[55]

Responses in the AP and BP populations were also seen to be durable, with K-M estimates of maintaining OHR of 80% (year 1) and 67% (year 2) for AP CML patients and 25.0% (year 1) and 18.8% (year 2) for BP CML patients.[56]

Low rate of transformation to AP/BP

Treatment of CP CML patients with bosutinib is associated with low rates of transformation to AP/CP CML in both the second-line and third-line setting.

Among CP CML patients for whom previous treatment with two prior TKIs had been unsuccessful, 4% experienced transformation to advanced phase CML while on bosutinib treatment (median follow-up of 28.5 months).[48]

Progression-free survival (PFS) and overall survival (OS)

The value of bosutinib in extending life expectancy has also been demonstrated, across CP and advanced phase CML patients.

At a median follow-up of 31.4 months (15 Feb 2012), for CP CML patients treated with bosutinib in the third-line setting, the Kaplan-Meier estimates for PFS and OS at 2 years were 75.1% and 84% respectively.

Amongst advanced phase CML patients whose disease had progressed on treatment with at least one prior TKI, the estimated PFS at 2 years for AP and BP patients was 47.7% (95% CI, 33.2% to 60.8%) and 11.5% (95% CI, 4.1% to 23.2%), respectively. Overall survival at 2 years for this patient group was estimated at 65.6% (95% CI, 53.4% to 75.4%) and 35.4% (95% CI, 23.8% to 47.3%) for the AP and BP patients, respectively.[56]

Health-related quality of life

Statistically significant improvements from baseline in HRQL were seen in third-line CP CML patients receiving bosutinib, as measured by the Functional Assessment of Cancer Therapy- Leukaemia (FACT-Leu) and EQ-5D.

In advanced phase CML patients with prior treatment, clinically meaningful improvements in HRQL were observed at weeks 24 and 48 in AP patients and at week 24 in BP patients, as measured by FACT-Leu.

4.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

No additional health-related benefits additional to those accounted for in the QALY calculation are expected.

4.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Study 200 was an open-label, 2-part study of the efficacy and safety of bosutinib once daily orally in subjects with Ph^+ leukaemia and provides the data used in this submission. The submission considers only those patients in the study who possessed CML (n=546) and not those who possessed acute lymphoblastic leukaemia (n=24). The 546 Ph^+ CML patients included CP, AP and BP patients treated with bosutinib at the second line and third line of treatment. All patients had been treated previously with imatinib, to which they were intolerant or resistant. These patient groups are considered as separate populations, as follows:

- **Second-line CP CML population: n=288**
- **Third-line CP CML population: n=118**

The base-case patient population for in the chronic phase economic model is the third-line cohort from Study 200. In the absence of fourth-line data, this cohort is expected to be the most representative of patients who would be unsuitable for nilotinib, dasatinib and imatinib and therefore receive bosutinib in practice. Given that there may be a small number of second-line bosutinib patients in practice for whom imatinib, dasatinib and nilotinib are inappropriate, the second-line CP population from Study 200 will be considered in a sensitivity analysis.

- **Advanced phase CML population (n=140), including AP CML patients (n=76) and BP CML patients (n=64)**.

This population was composed of a group of patients previously treated either with imatinib only (receiving bosutinib as a second-line therapy) and of a group of patients with prior exposure to multiple TKIs (imatinib, dasatinib and/or nilotinib, hence receiving bosutinib at the third- or fourth line of therapy):

  - Imatinib only: AP = 45; BP = 35
  - Multi-TKI: AP = 31; BP = 29

In addition, a post hoc analysis, requested by the EMA, of data from Study 200 identified 52 patients who met criteria for being unsuitable for nilotinib or dasatinib. Unsuitability was determined based on Bcr-Abl kinase domain mutation(s) that would be reasonably expected to confer resistance to dasatinib (F317, E255) or nilotinib (E255, Y253, F359) and expected to have sensitivity to bosutinib, or the presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatinib therapy.

This post-hoc subpopulation reflects a mix of patients with an unmet clinical need, who could be eligible for bosutinib in clinical practice. However, because the post-hoc analysis serves only as an illustration of the clinical benefit of bosutinib in patients meeting the licensed indication, drawn from populations not pre-selected for this evaluation (the Study 200 populations), the patient numbers in this post-hoc analysis are small. Therefore, it is more appropriate to use the full Study 200 third-line CP CML and advanced phase populations as the focus of clinical evidence and as the basis of the cost-effectiveness model. Limited data for the post-hoc 'unmet clinical need' subpopulation will be presented in an appendix to demonstrate that the efficacy and safety of bosutinib demonstrated in this 'unmet clinical need' subpopulation reflects the results observed in the larger populations of Study 200.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia	Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options	This reflects the revised indication from the EMA for bosutinib.
Intervention	Bosutinib	Bosutinib	N/A
Comparator(s)	• Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML) • Hydroxycarbamide • Interferon alpha • Best supportive care	• Hydroxycarbamide (BSC) • Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML) • Interferon alpha	Hydroxycarbamide (hydroxycarbamide) is accepted as the best supportive care for adult Ph^+ CML patients in clinical practice.
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • progression-free survival • time to progression • response rates: cytogenetic, haematological and molecular, including time to response and duration of response • time to treatment failure • adverse effects of treatment • health-related quality of life	Transformation rates from CP to AP/BP and then to BP will be considered in addition to those outcomes listed in the NICE scope.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	Cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year. Costs will be considered from an NHS and Personal Social Services perspective. The time horizon will be life-time.	N/A

	technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.	The proposed indication would include patients from second-line or later at all phases of disease (CP, AP and BP). Study 200 consists of populations for all of the above subgroups (second-line CP CML; third-line CP CML; AP CML and BP CML) and it is expected, as agreed by the CHMP, that these populations will include patients that match our indication.	
Special considerations, including issues related to equity or equality	N/A	N/A	N/A

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Summary of clinical evidence

- The pivotal study from which the licence for bosutinib is derived is a single arm phase I/II trial (Study 200, n=570). This study evaluated the efficacy and safety of once-daily bosutinib 500 mg in leukaemia patients after resistance/intolerance to imatinib. The systematic review identified no further studies evaluating the use of bosutinib in patients who were representative of its licence indication.
- Although not specifically designed to evaluate patients with the unmet clinical need described in the licence indication for bosutinib, the CHMP have accepted results from Study 200 as being representative of this population. This study demonstrated the efficacy and safety of bosutinib in patients in the following clinical scenarios:
    - Second-line CP CML (n=288)
    - Third-line CP CML (n=118)
    - Advanced phase CML (AP and BP) (n=140: AP=76; BP=64)
    - *The remaining 24 patients enrolled in this study were Ph^+ acute lymphoblastic leukaemia (ALL) patients and are not relevant to this submission*
- It is expected that in chronic phase, the third-line and advanced phase populations from Study 200 will be most representative of the likely bosutinib patients in practice for whom imatinib, dasatinib and nilotinib are unsuitable options.
    - The submission therefore focuses on the evidence from the third-line CP CML and advanced phase populations of Study 200, whilst the evidence of efficacy and safety of bosutinib in the second-line CP CML population is reported in Appendix 10.15.
- Where possible, the data presented is taken from the most recent data snapshots available for a given outcome for each population.

Evidence for efficacy and safety of bosutinib

Clinical responses

- Bosutinib was associated with good cytogenetic and haematological response rates
    - In CP, cumulative MCyR was 41% for third-line patients (15 Feb 2012 snapshot, minimum follow-up duration of 24 months).
    - In advanced phases, cumulative OHR was 55.1% for the AP population and 28.3% for the BP population (28 Mar 2011 snapshot, minimum follow-up durations of 12 months and 18 months, respectively).
- The cytogenetic responses achieved with bosutinib are durable and observed across a broad range of Bcr-Abl mutations, including those that confer clinical resistance to nilotinib and dasatinib (with the exception of the T315I mutation)

Survival

- Bosutinib is associated with clinical benefit in terms of PFS and OS
    - CP: The K-M estimates of PFS and OS at 2 years were 75% and 84%, respectively, for the third-line CP CML population (24 month minimum follow-up). Median OS had not yet been reached**.**
    - AP: The K-M estimates of PFS and OS at 2 years were 47.7% and 65.6%, respectively (12 month minimum follow-up). Median OS had not yet been reached.
    - BP: The K-M estimates of PFS and OS at 2 years were 11.5% and 35.4%, respectively (18 month minimum follow-up). Median OS for BP patients was 11.1 months.

- Low rates of transformation were observed on bosutinib treatment for both the CP and advanced phase populations. The transformation rate for third line patients from CP to AP was 4% (24 month minimum follow-up) and for AP patients transforming to BP was 6.4% (12 month minimum follow-up).
- As of the 28 March 2011 snapshot, 71% of patients in the third-line CP CML population were observed to have discontinued treatment. Median time on treatment at this snapshot was 8.3 months and was 8.6 months at the more recent follow up (15 Feb 2012).

Safety

- Bosutinib has an acceptable safety profile across all phases of the disease and lines of treatment. Adverse events are restricted primarily to gastrointestinal toxicities (diarrhoea, nausea and vomiting) in both the chronic and advanced phases of the disease and in the majority of cases these toxicities are mild in severity.
- The most common haematological events in CP patients are thrombocytopaenia, neutropaenia and anaemia, which occurred with grade 3/4 severity in 25.4%, 14.4% and 5.1% of patients, respectively. These adverse events are also amongst the most common in the advanced phase population, with anaemia additionally observed as a more common haematological adverse event.

Evidence for efficacy and safety of comparators

- No indirect or mixed-treatment comparison is possible given the lack of controlled studies of bosutinib and its comparators (hydroxycarbamide, interferon and SCT); therefore only a naïve indirect comparison can be performed. Few studies present evidence on response rate or adverse event data; but estimates of OS or mortality are more frequently presented.
- Estimates of OS observed with hydroxycarbamide and SCT were generally observed to be lower than the survival results achieved with bosutinib in Study 200 in comparable populations.
    - In the chronic phase, the OS at 2 years for second-line hydroxycarbamide patients was reported as 77% (Kantarjian, 2007)[36]. For SCT, OS at 2 years was reported as 85% by Schleuning 2010[57] (majority second-line) and 72% by Jabbour 2011[58] (majority third-line). In comparison, the 2-year K-M estimate for OS in patients treated with bosutinib at third-line was 84% as of the most recent data snapshot (15 Feb 2012, minimum follow-up duration 24 months).
    - In advanced phases, no hydroxycarbamide studies were found, but Jabbour 2011 reports 2-year OS in advanced phase SCT patients as 59%. In comparison, patients treated with bosutinib had K-M estimates of OS at 2 years of 65.6% for AP and 35.4% for BP in Study 200 (data snapshot 28 Mar 2011).
- The evidence base indicates that bosutinib may offer a more efficacious alternative to hydroxycarbamide and SCT in terms of improving survival rates across all phases of the disease and multiple lines of treatment.

6.1 Identification of studies

6.1.1 Search strategies

A broad systematic review was performed to identify relevant published literature on the efficacy and safety of selected treatments for adult patients with CML (CP, AP or BP)

who had previously tried at least one TKI (imatinib), as per the bosutinib license. Identified studies were then reviewed to determine whether they included patients who may be unsuitable for treatment with dasatinib and nilotinib, either due to previous intolerance or lack of efficacy with these agents or due to existing mutations or co-morbidities that would make the use of these agents inappropriate.

The selected treatments included in the systematic review consisted of bosutinib and its relevant comparators, as identified by the NICE scope:

- Hydroxycarbamide (assumed to be a proxy for best supportive care)
- Allogeneic stem cell transplantation (SCT)
- Interferon alpha (IFN)

Searching of the below electronic databases was carried out on 21st January 2013, using database search strings to identify all clinical studies:

- MEDLINE (R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE (R) 1946 to present (via OVID)
- EMBASE, 1980 to present (via OVID)
- The Cochrane Library (via OVID), searching the following databases:
    - The Cochrane Central Register of Controlled Trials (CENTRAL)
    - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - The Database of Abstracts of Reviews of Effects (DARE)
    - The Health Technology Assessment Database (HTA)

In addition, the following conference proceedings were searched (2010-2012):

- American Society of Haematology (ASH)
- American Society of Clinical Oncology (ASCO)
- European Haematology Association (EHA).

Full details of search strategies employed are presented in Appendix 10.2

Overall, 16 published papers were identified by the systematic review: 12 full-text studies from searches of the electronic databases and 4 abstracts from conference proceedings. Of these 16 studies, 13 reported on comparator treatments (11 on SCT, 1 on hydroxycarbamide, 1 on SCT and hydroxycarbamide) and 3 reported on bosutinib (all related to Study 200). Additional information on Study 200 was extracted from the clinical study report (CSR)[56] and also two conference posters presented at the American Society of Hematology (ASH) Annual Meeting and Exposition, 2012.[55, 59] A flow-diagram of the relevant evidence included in the systematic review is presented in Figure B1.

6.2 Study selection

6.2.1 Selection criteria

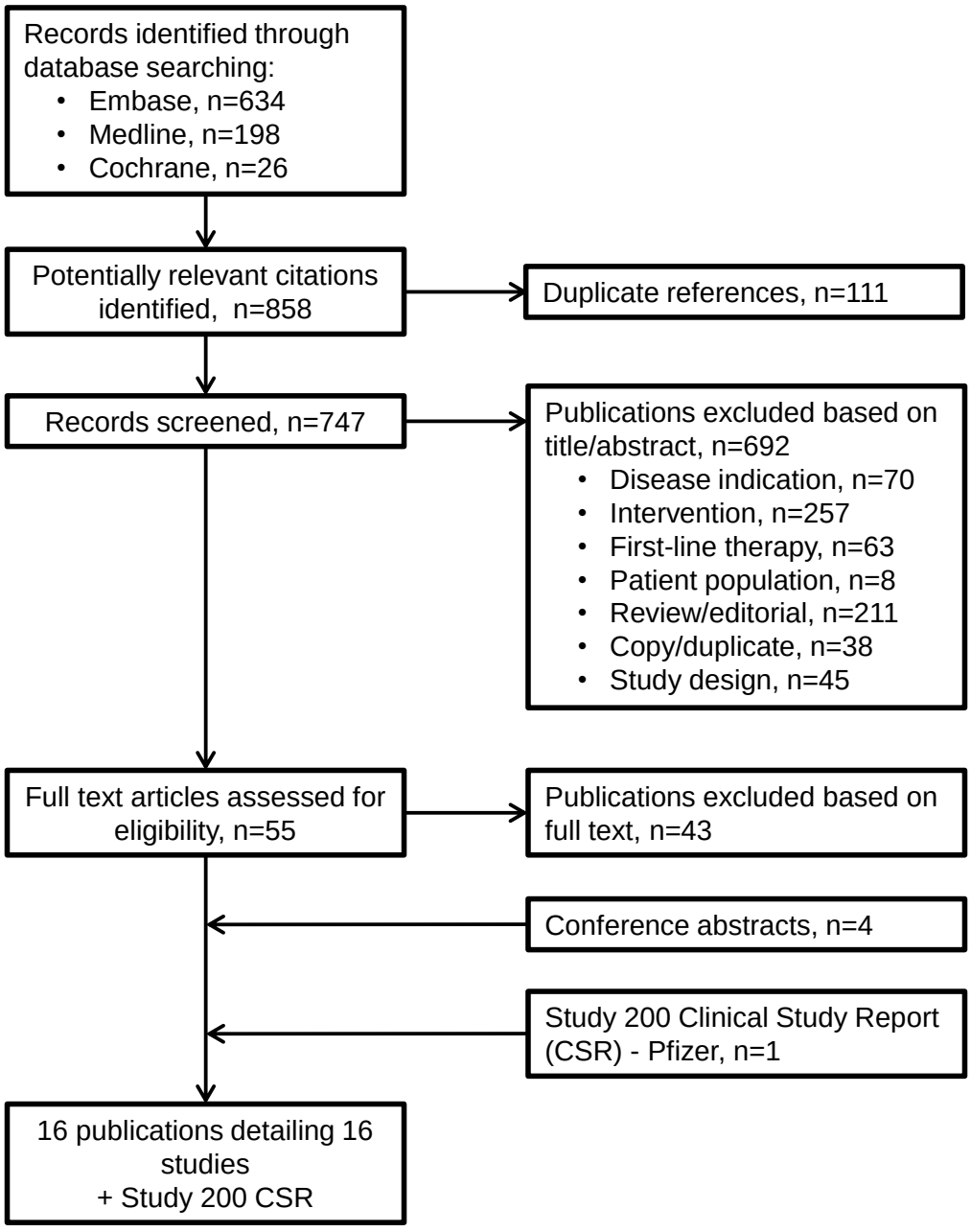
Following the database search, duplicate results were excluded. The identified papers were assessed against the eligibility criteria presented in Table B1, based on the paper title/abstract. For those papers that were considered potentially relevant, or for which the relevance was unclear from the title/abstract, full texts were obtained and screened for relevance to the submission. This screening was performed by one reviewer, with inclusion or exclusion decisions verified by a second party. Any disputes as to eligibility were referred to a third party.

Table B1: Eligibility criteria used in search strategy

Inclusion criteria	Population • Adult patients (≥18 years) with CP, AP and/or BP CML who have failed imatinib treatment Interventions • Bosutinib • Interferon alpha • Hydroxycarbamide (hydroxyurea) • SCT Outcomes Efficacy: • Treatment response rates (including molecular, cytogenetic and haematological responses) • Time to and duration of response • Overall survival • Event-free survival • Progression-free survival • Time to treatment failure • Health-related quality of life Safety/Tolerability: • Adverse events (all grades) • Incidence of serious adverse events Study Design • Prospective randomised controlled trials (RCTs) • Observational studies
Exclusion criteria	Study design Single case studies Language restrictions Non-English publications were excluded. However, English abstracts of foreign language publications were included

6.2.2 Flow diagram of included studies

Figure B1: Flow diagram of included studies



6.2.3 When data from a single RCT have been drawn from more than one source this should be made clear.

No RCTs were identified in the systematic review that specifically matched the licensed population for bosutinib. The data on which the license has been derived comes from a single-arm study, Study 200. The Study 200 Clinical Study Report (CSR),[56] provides data across four cohorts of patients recruited separately into the study. In addition, a number of publications and conference abstracts/posters based on Study 200 are also available and are presented in this submission. The data sources used as the evidence base for the third-line CP CML population and advanced phase CML population of Study 200 are

detailed in Table B2, organised by the data snapshot and follow-up period that they present.

Table B2: Data sources for Study 200 populations relevant to this submission

Third-line CP CML population	Advanced phase population (AP and BP)
Data snapshot 28 Mar 2011 (minimum/median follow-up: 12/28.5 months): • Khoury et al, 2012 publication[48] *(This publication presented results for the primary efficacy analysis for this patient population)* • CSR[56] **Data snapshot 15 Feb 2012 (minimum/median follow-up: 24/31.4 months):** • Khoury et al, ASH 2012 poster.[55] This source is in the form of a poster presented at the 54th ASH Annual Meeting and Exposition, December 8-11, 2012	**Data snapshot 28 Mar 2011 (minimum follow-up: 12 months for AP; 18 months for BP):** • CSR[56]

Note: Data from the data snapshots detailed in Table B2 is also available as part of an addendum submitted to the EMA. This EMA addendum represents an additional data source for this population, to support the data from the above-named sources

In the economic model, patient level data from the most recent snapshot available, which is February 2012, is used. However, it should be noted that this data has not been statistically analysed for the advanced phase population in either a publication, CSR or poster/abstract format.

Complete list of relevant RCTs

6.2.4 Details of relevant RCTs

As detailed above, there are no RCTs comparing bosutinib with other relevant therapies (active or placebo) in patients with CML previously treated with one or more TKI(s).

List of relevant non-RCTs

6.2.5 Details of relevant non-RCTs

Bosutinib

The license for bosutinib is based on Study 200, which is an open-label, 2-part, efficacy and safety study of bosutinib once daily in patients with Ph^+ CML. Although not specifically designed to evaluate the licensed population, Study 200 includes patients that meet the licensed indication of bosutinib and has been accepted by the CHMP as representative of the population of unmet clinical need stipulated by the indication.

Part 1 of this study was a dose escalation study in 18 patients with CP Ph^+ CML refractory to imatinib. This part of Study 200 is not relevant to the decision problem of this submission as it represented a dose-finding study designed to define the maximum tolerated dose of bosutinib and hence determine the starting dose for Part 2 of the trial. Part 1 will therefore not be considered further in this submission.

Part 2 was a study of the efficacy and safety of bosutinib 500 mg daily in 546 Ph^+ CML patients with resistance/intolerance to prior therapy (including the 18 patients enrolled in

Part 1 of the study) and 24 Ph^+ acute lymphoblastic leukaemia (ALL) patients (total study enrolment of 570). The latter patients are not relevant to this submission and will not be considered further.

Study 200 evaluated the efficacy and safety of bosutinib in the following CML patient populations:

- Second-line CP CML
- Third-line CP CML (includes 3 fourth line patients)
- Advanced phase CML (second-line or later)

With regards to the use of bosutinib in CP in practice, very few second-line patients are likely to be unsuitable for imatinib, nilotinib and dasatinib. As such, the third-line cohort from Study 200 is the focus for this submission as this is more likely to be representative of the patients expected in clinical practice, the majority of whom will likely be at least third-line. Data from the second-line CP CML patient population are only presented in Appendix 10.15 for completeness.

Further details of Study 200 are supplied in Table B3. The systematic review did not identify any additional studies of bosutinib in patient populations relevant to this submission, other than Study 200.

Post-hoc subpopulation analyses

In addition to the pre-specified populations of Study 200 noted above, a post-hoc analysis was performed on the data from Study 200, as requested during consultation with the EMA. The purpose of this post-hoc analysis was to provide evidence on those patients that may have an unmet clinical need according to the proposed indication and would therefore be eligible to receive bosutinib in practice: *Adult Ph^+ CML patients previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are deemed to be inappropriate.*

The post-hoc selection algorithm was developed based on advice from the Rapporteurs and considered the following criteria:

- The presence of a mutation that would be reasonably expected to confer resistance to dasatinib or nilotinib
- The presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatinib therapy. These prior toxicities were selected based on adverse drug reactions associated with treatment with other TKIs.

A total of 52 patients were identified for inclusion in this post-hoc analysis, drawn from the second-line CP CML population, third-line CP CML population and advanced phase CML population of Study 200.

The results from the post-hoc analysis, although based on a small sample size, demonstrated that bosutinib has an efficacy and safety profile in this subpopulation consistent with that observed in the larger populations of Study 200 as a whole. Since the safety and efficacy profiles are similar, and Study 200 as a whole was pre-specified, contains more subjects and has more statistical power than the post-hoc analysis, the main Study 200 results are used in the base case economic model in this submission.

The post-hoc analysis is included as a sensitivity analysis for completeness. Full details of eligibility criteria and results for this post-hoc subpopulation are provided in the Appendix 10.16).

Table B3: Details of the identified relevant non-RCT (Study 200)

Intervention	Population	Objectives	Study reference	Justification for inclusion
Bosutinib	The overall Study 200 population comprised 570 patients with Ph^+ leukaemia. These 570 patients were present in the trial as part of the following populations: • CP CML patients with imatinib resistance/intolerance (second-line population[1]); n=288 • CP CML patients with imatinib resistance/intolerance followed by dasatinib resistance/intolerance or nilotinib resistance/intolerance or both dasatinib and nilotinib resistance/intolerance (third-line population[2]); n=118 • Advanced phase leukaemia patients with imatinib resistance/intolerance or resistance/intolerance to imatinib, dasatinib and/or nilotinib: ○ AP CML; n=76 ○ BP CML; n=64 ○ Ph^+ ALL; n=24[3] • Acute lymphoblastic leukaemia	Study 200 is a 2-part study with the following objectives: • Part 1: ○ To define the maximum tolerated dose of bosutinib in patients with CP CML resistant or refractory to imatinib ○ Evaluate the overall pharmacokinetic parameters in this population • Part 2: ○ Determine the efficacy and safety of bosutinib 500 mg once daily in patients of the described populations	The data sources for the different populations within Study 200 have been described previously in Section 6.2.3 (Table B2)	According to the license for bosutinib, patients must have been *previously treated with one or more TKIs* and will therefore receive bosutinib at the second-line of therapy or later. Study 200 is the only study that evaluates bosutinib in patients who have tried one or more prior TKI therapy (i.e. received bosutinib at the second-line or later). Study 200 provides evidence of the clinical efficacy and safety of bosutinib in patients from all disease phases (CP, AP and BP) and at multiple lines of therapy. As previously noted, although not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate, some patients enrolled in Study 200 met these criteria and the CHMP has accepted that the Study 200 population is likely to be representative of the population of unmet clinical need stipulated by the indication.

[1]As discussed, this patient population does not represent the focus of this submission and as such is presented as part of Appendix 10.15
[2]Although described as a third-line population in the CSR, this population includes 3 patients who had prior exposure to imatinib, dasatinib and nilotinib and so received bosutinib in the fourth-line setting
[3] Although the overall Study 200 design included a population of patients with Ph^+ ALL, these patients are not relevant to the scope of this submission and will therefore not be considered in detail. A description of this sub-population is included in Table B3 purely for completeness.

Comparators

No studies specifically evaluating comparator treatments in patients for whom imatinib, nilotinib and dasatinib are unsuitable were found. However, the systematic review identified 13 comparator studies that, like bosutinib, considered the use of the comparators in the broad second-line or later populations, in CP, AP and BP.

A summary of all identified studies included in the systematic review, including those that report on bosutinib and those that report on comparators (16 in total), is provided in Table B30 in the comparator data section.

The clinical evidence provided by these studies is considered in Section 6.8.5 (for bosutinib studies) and Section 6.9 (for comparator studies).

6.3 Summary of methodology of relevant RCTs

As detailed above, no relevant RCTs were identified in the systematic review.

Given this, the remainder of Section 6.3 is not applicable in this submission. Please refer to Section 6.8 for the presentation of non-RCT data which constitutes the evidence base for this submission.

6.4 Critical appraisal of relevant RCTs

Since no relevant RCTs were identified in the systematic review, Section 6.4 is not relevant to this submission. Please refer to Section 6.8.5 for the presentation of non-RCT data which constitutes the evidence base for this submission.

6.5 Results of the relevant RCTs

Since no relevant RCTs were identified in the systematic review, Section 6.5 is not relevant to this submission. Please refer to Section 6.8 for the presentation of non-RCT data which constitutes the evidence base for this submission.

6.6 Meta-analysis

It is not possible to undertake a meta-analysis of the RCTs relevant to this intervention, as no RCTs evaluating the efficacy and safety of bosutinib within the licence indication for CML patients were identified in the systematic review described in Section 6.1 and Section 6.2. Furthermore, for the bosutinib and comparator treatment observational studies identified by the systematic review, no pooling of results was possible, since all studies had a single-arm design and there were numerous differences between studies in terms of design and patient characteristics.

6.7 Indirect and mixed treatment comparisons

All studies identified in the systematic review were of an uncontrolled, single-arm design, therefore no indirect comparison or network meta-analysis was possible since there is no connected network with one or more common comparator(s). The clinical data from the respective bosutinib and comparator studies are presented in Section 6.8 and Section 6.9 and only a naïve indirect comparison of bosutinib and its comparators is possible following the consideration of these results.

With regard to adverse events (AEs), although comprehensive AE data are available for Study 200[5, 48, 56], no AE data were reported in the two studies containing hydroxycarbamide patients [36, 37] and AE data reported in four SCT studies were restricted to the incidence of acute/chronic graft-versus-host-disease (GVHD)[58, 60-62].Therefore, it is not possible to conduct a robust qualitative comparison of the safety profile of bosutinib and comparator treatments.

Given that the nature of the studies identified by the systematic review renders an indirect comparison or network meta-analysis inappropriate, the remainder of Section 6.7 is not relevant to this submission.

6.8 Non-RCT evidence

6.8.1 Quality assessment of relevant non-RCTs

The systematic review eligibility criteria were inclusive of both RCT and non-RCT study designs; the only excluded study design being that of single case studies. The details of the systematic review search strategy, search results screening and study selection criteria relevant to the identification of bosutinib and comparator non-RCT evidence are described below (and in Appendix 10.2).

A quality assessment was performed on relevant non-RCTs identified from the systematic review, using the Chambers et al, 2009, checklist.[63] The Study 200 CSR was also subject to the same quality assessment. The likelihood of bias of non-RCTs was assessed according to the reporting of patient eligibility criteria and method of recruitment, representative patient population, outcome measurement, follow-up and prognostic factors, resulting in a score of 'good', 'satisfactory' or 'poor'. Please see Appendix 10.7 for further details of the Chambers criteria for quality assessment of non-RCTs and completed quality assessments for the bosutinib and comparator non-RCT evidence.

6.8.2 Summary of methodology of relevant non-RCTs

6.8.3 Study 200 design

Study 200, a phase I/II 2-part single-arm clinical trial (NCT00261846) was identified as relevant to this submission. The main populations included in the study are presented in Table B4. This study consisted of:

- **Part 1:** a dose-escalation study with the primary objective of defining the maximum tolerated dose of bosutinib in patients with CP Ph^+ CML which was refractory to imatinib, and thus determining a starting dose for part 2 of the study.
- **Part 2:** an evaluation of the efficacy and safety of bosutinib 500 mg daily in Ph^+ leukaemia patients with resistance/intolerance to prior TKI therapy.

The sample size and characteristics of the Study 200 patient populations that represent the focus of this submission are presented in Table B4.

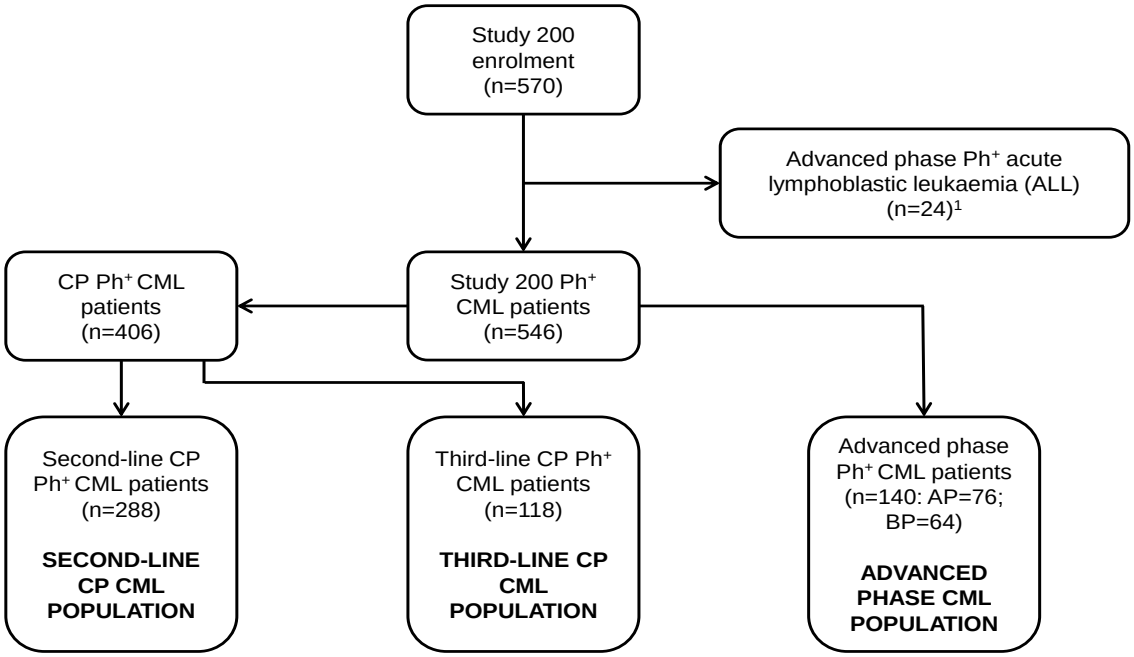
Table B4: Patient populations of Study 200

Patient population	N	Patient characteristics
Third-line CP CML population	118	Adult patients with Ph^+ CP CML previously treated with imatinib followed by dasatinib and/or nilotinib and to all of which their CML was resistant or intolerant
Advanced phase CML population	140 (76 AP patients; 64 BP patients)	Adult patients with advanced phase Ph^+ CML with resistance or intolerance to imatinib (treated second-line) or to imatinib, dasatinib and/or nilotinib (treated third-line or fourth-line)

The populations within Study 200 reflect the different phases of the disease and stages of treatment for CML. Patients were recruited into these distinct cohorts and each cohort was analysed separately and results are presented separately below.

Figure B2 describes the patient flow through Study 200 and into the distinct populations into which the patients were recruited.

Figure B2: Patient flow in Study 200



[1]These patients had Ph+ ALL, not Ph+ CML and are therefore excluded from this submission

Resistance and intolerance

Study 200 evaluated patients with resistance or intolerance to imatinib, dasatinib and/or nilotinib. Primary resistance is broadly defined as failure to achieve or maintain a response by certain time points and acquired resistance is loss of response. The exact definitions of resistance and intolerance used in Study 200 were consistent across all populations and are defined in Appendix 10.14, Table B97.

Outcomes

The outcomes used in Study 200 are listed in Table B5 below. The justification and definitions for the outcomes can found in Table B9 and Appendix 10.14, Table B98.

Study design

Table B5 summarises the details of the design of Study 200. Some aspects of the study design are variable between these different populations (for example, since cohorts were recruited separately, differing data snapshots correspond to different minimum follow-up durations across the populations). Table B5 highlights where such variation exists.

Table B5: Comparative summary of the methodology applied to Study 200 populations

Parameter	Third-line CP CML population (n=118)	Advanced phase CML population (n=140; AP=76, BP=64)
Location	Multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. The 5 countries enrolling the most patients were the United States (147), Russia (66), Italy (53), China (43) and Germany (39)	
Design	Patients were treated with bosutinib 500mg once-daily until disease progression, unacceptable toxicity or withdrawal of consent. Dose escalation to bosutinib 600 mg once daily was permitted in cases of lack of efficacy (CHR not reached by week 8 or CCyR not reached by week 12) and dosage could be reduced in increments of 100 mg, as necessary in accordance with observed toxicities, down to a minimum of 300 mg/day. The dosing regimen used in Study 200 is reflective of the SPC recommendations, discussed in Table A1.	
Method of randomisation, blinding and interventions	Study 200 was a single-arm trial with no randomisation or blinding procedures. The only intervention was bosutinib 500mg once daily. There were no comparators.	
Duration of study	Study 200 began in January 2006 and is currently still ongoing. Patients remain in the trial until death or lost to follow-up.	
	Third-line CP CML population (n=118)	**Advanced phase CML population (n=140; AP=76, BP=64)**
Duration of follow-up	As of 28 March 2011, median duration of follow-up was 28.5 months (range 0.29 to 56.21 months), minimum follow-up was approximately 12 months (CSR, EMA addendum and Khoury et al, 2012 publication). As of 15 February 2012 the median duration of follow-up was 31.4 months (range 0.29 to 66.04) and the minimum follow up was approximately 24 months (EMA addendum, Khoury et al, ASH 2012 poster).	The CSR and EMA addendum present data from a 28th March 2011 data snapshot, which corresponds to a minimum follow-up of 12 months for the AP population and 18 months for the BP population.
Primary outcomes	The primary analysis was rate of MCyR by 24 weeks	Patients of the advanced phase CML population were evaluated for rate of attainment or maintenance of OHR by Week 48
Secondary outcomes (including scoring methods and timings of assessments)	Other outcomes reported for this population were: • Further response rates for efficacy endpoints: CCyR, MiCyR, CHR, CMR and MMR • Median time to MCyR • Median duration of MCyR, CCyR and CHR • Probability of retaining MCyR and probability of retaining CHR	Other outcomes reported for this population were: • Duration of OHR, CHR and MCyR • Median time to confirmed (attained or maintained) OHR and CHR • Cumulative haematological response (for OHR, MHR and CHR) • Cumulative MCyR

Parameter	Third-line CP CML population (n=118)	Advanced phase CML population (n=140; AP=76, BP=64)
	• PFS at 1 year and 2 years • OS at 1 year and 2 years • HRQL: FACT-Leu & EQ-5D The analysis also considered the following safety outcomes: • Incidence rate of any AEs • Incidence rate of Grade 3/4 AEs • Rate of patient deaths	• BP transformation rate • PFS at 1 year and 2 years • OS at 1 year and 2 years • Time to treatment failure • HRQL: FACT-Leu & EQ-5D

Participants

6.8.3.1 Study 200 eligibility criteria

The third-line CP CML and advanced phase populations from Study 200 considered in this submission were enrolled in Part 2 of this study, and so the eligibility criteria from this part of the study are applicable to both these populations. Table B6 details these overall Study 200 eligibility criteria and also further eligibility criteria specific to the third-line CP CML population and advanced phase CML population for which clinical evidence is presented in Section 6.8.5.

Table B6: Eligibility criteria for Study 200

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Signed and dated informed consent prior to any protocol-specific screening procedures • Cytogenetic- or PCR- based diagnosis of any phase of Ph^+ CML or Ph^+ ALL whose disease was resistant to full-dose imatinib (≥600 mg) or was intolerant of any dose of imatinib (please see Appendix 10.14 for definitions of resistance/intolerance) • Adequate duration of prior imatinib therapy • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for CP patients and 0, 1 or 2 for advanced phase leukaemia patients • No antiproliferative or antileukaemia treatment within 7 days of the first dose of bosutinib (except hydroxycarbamide and anagrelide) • At least three months post allogeneic stem cell transplantation • Recovery to grade 0/1, or to baseline, from any toxicities of prior anticancer treatment (excluding alopecia) • Able to take daily oral capsules or tablets reliably • Adequate bone marrow function (for imatinib-resistant patients in chronic phase only) ○ Absolute neutrophil count (ANC) >1000/mm3 (>1 x109/L) ○ Platelets ≥100,000/mm3 (≥100 x 109/L) and absence of any platelet transfusions during the preceding 14 days • Adequate hepatic function ○ AST/ALT ≤2.5 x ULN or ≤5 x ULN if attributable to liver involvement of leukaemia ○ Total bilirubin ≤1.5 x ULN • Adequate renal function	• Ph negative leukaemia or Bcr-Abl negative leukaemia • Overt leptomeningeal leukaemia (free of CNS involvement for <2 months) • Extramedullary disease only • GVHD (treated or untreated) within 60 days of study start • Documented history of the T315I Bcr-Abl mutation (this criterion added as of 10th June 2008 based on lack of efficacy in this group) • Pregnant or breastfeeding • Major surgery within 14 days or radiotherapy within 7 days before the first dose of bosutinib (recovery from any previous surgery should have been completed before day 1) • History of clinically significant or uncontrolled cardiac disease including: ○ history of or active congestive heart failure ○ uncontrolled angina or hypertension within 3 months ○ myocardial infarction within 12 months ○ clinically significant ventricular arrhythmia ○ diagnosed or suspected congenital or acquired prolonged QT syndrome ○ unexplained syncope ○ history of prolonged corrected QT interval (QTc) • Prolonged QTc (>0.45 seconds, average of triplicate readings at screening) • Concomitant use of or need for medications known to prolong the QT interval • Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval

○ Creatine ≤1.5 x ULN • Willingness to use reliable birth control (if applicable) throughout the study and 30 days after the last dose • Documented normal INR if not on oral anticoagulant therapy, or if on oral anticoagulant therapy, consistent target INR ≤3 **Additional inclusion criteria specific to Study 200 populations** Third-line CP CML population • Imatinib-resistant or imatinib-intolerant CP Ph+ CML also previously treated with dasatinib and/or nilotinib, to which the patient developed resistance or intolerance Advanced phase CML population • Advanced phase Ph+ CML previously treated with 1 or more TKIs (imatinib only or imatinib and dasatinib and/or nilotinib)	• Recent (within 30 days of study entry) or ongoing clinically significant gastrointestinal disorder • Evidence of serious active infection, or significant medical or psychiatric illness • Known seropositivity to human immunodeficiency virus or current acute or chronic hepatitis B or hepatitis C (antigen positive), cirrhosis or clinically significant abnormal laboratory findings that would, in the investigator's judgement, make the patient inappropriate for this study

6.8.3.2 Patient characteristics at baseline.

Third-line CP CML population

Patient characteristics at baseline for the third-line CP CML population (n=118) are presented in Table B7.

Table B7: Baseline characteristics for the third-line CP CML population

Characteristic	IM + DAS resistant (n=37)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NI (n=4)*	Total (n=118)
Median age, y (range)	54.0 (23-69)	58.0 (25-79)	52.0 (20-73)	54.5 (31-62)	56.0 (20-79)
Sex, n (%)					
Female	23 (62)	27 (54)	13 (48)	2 (50)	65 (55)
Male	14 (38)	23 (46)	14 (52)	2 (50)	53 (45)
Race, n (%)					
White	27 (73)	38 (76)	17 (63)	3 (75)	85 (72)
Asian	4 (11)	9 (18)	3 (11)	0	16 (14)
Other	6 (16)	3 (6)	7 (26)	1 (25)	17 (14)
Median duration of CML disease, y (range)	7.5 (1.2-17.6)	5.6 (0.6-18.3)	5.9 (1.2-16.3)	11.7 (2.2-11.9)	6.7 (0.6-18.3)
ECOG Performance Status, n (%)†					
0	28 (76)	31 (62)	25 (93)	2 (50)	86 (74)
1	9 (24)	18 (36)	2 (7)	2 (50)	31 (26)
Median duration of prior therapy, (range)					
Imatinib,	2.6	3.3	2.5	3.0	2.7

Characteristic	IM + DAS resistant (n=37)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NI (n=4)*	Total (n=118)
years	(0.02-6.4)	(0.1-6.6)	(0.7-5.9)	(1.4-6.4)	(0.02-6.6)
Dasatinib, months	18.3 (1.7-47.9)	17.3 (1.1-35.7)	0	4.1 (1.3-6.9)	17.7 (1.1-47.9)
Nilotinib, months	0	0	12.7 (1.7-38.9)	5.4 (0.8-6.1)	9.2 (0.8-38.9)
Additional prior therapies, n (%)					
Interferon	25 (68)	24 (48)	10 (37)	2 (50)	61 (52)
SCT	2 (5)	5 (10)	0	2 (50)	9 (8)

IM = Imatinib; DAS = Dasatinib; NI = Nilotinib; ECOG = Eastern Cooperative Oncology Group
*Includes 3 patients who previously received all 3 inhibitors (2 DAS + NI resistant; 1 DAS + NI intolerant) and 1 patient with NI intolerance
†ECOG Performance Status at baseline was missing for 1 patient with DAS intolerance

Advanced phase CML population

Patient characteristics at baseline for the advanced phase CML population (n=140) are presented in Table B8.

Table B8: Baseline characteristics for the advanced phase CML population

Characteristic	AP IM only (n=45)	AP Multi TKI (n=31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Age, y						
Median	47.00	56.00	50. 50	37.00	53.00	48.50
Range	18.00-73.00	21.00-83.00	18.00-83.00	19.00-75.00	22.00-82.00	19.00-82.00
Sex, n (%)						
Female	21 (47)	13 (42)	34 (45)	11 (31)	12 (41)	23 (36)
Male	24 (53)	18 (58)	42 (55)	24 (69)	17 (59)	41 (64)
Race, n (%)						
Asian	15 (33)	5 (16)	20 (26)	12 (34)	2 (7)	14 (22)
Black	3 (7)	2 (6)	5 (7)	5 (14)	6 (21)	11 (17)
Other*	3 (7)	2 (6)	5 (7)	0	1 (3)	1 (2)
White	24 (53)	22 (71)	46 (61)	18 (51)	20 (69)	38 (59)
ECOG Performance Status, n (%)						
0	26 (58)	15 (48)	41 (54)	16 (46)	6 (21)	22 (34)
1	18 (40)	15 (48)	33 (43)	10 (29)	18 (62)	28 (44)
2	1 (2)	1 (3)	2 (3)	9 (26)	5 (17)	14 (22)
Number of prior therapies						
1	29 (64)	0	29 (38)	30 (86)	0	30 (47)
2	16 (36)	6 (19)	22 (29)	5 (14)	11 (38)	16 (25)
3	0	19 (61)	19 (25)	0	16 (55)	16 (25)
4	0	6 (19)	6 (8)	0	2 (7)	2 (3)
Prior interferon therapy						
No	29 (64)	9 (29)	38 (50)	30 (86)	15 (52)	45 (70)
Yes	16 (36)	22 (71)	38 (50)	5 (14)	14 (48)	19 (30)
Prior imatinib†						
Yes	45 (100)	31 (100)	76 (100)	35 (100)	29 (100)	64 (100)

Characteristic	AP IM only (n=45)	AP Multi TKI (n=31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Prior dasatinib†						
No	45 (100)	6 (19)	51 (67)	35 (100)	6 (21)	41 (64)
Yes	0	25 (81)	25 (33)	0	23 (79)	23 (36)
Prior nilotinib†						
No	45 (100)	16 (52)	61 (80)	35 (100)	17 (59)	52 (81)
Yes	0	15 (48)	15 (20)	0	12 (41)	12 (19)
Prior stem cell transplant						
No	41 (91)	28 (90)	69 (91)	34 (97)	26 (90)	60 (94)
Yes	4 (9)	3 (10)	7 (9)	1 (3)	3 (10)	4 (6)
Reasons for stopping imatinib						
Adverse event (intolerance)	3 (7)	6 (19)	9 (12)	5 (14)	7 (24)	12 (19)
Disease progression/ Inadequate response	41 (91)	24 (77)	65 (86)	30 (86)	22 (76)	52 (81)
Other‡	0	1 (3)	1 (1)	0	0	0
Regimen completed	1 (2)	0	1 (1)	0	0	0

IM only= only prior TKI exposure is to imatinib; Multi TKI = Multiple TKI exposure
*Race Other: Afghan (1), Hispanic (7), Turkish (1)
†If a patient received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the patient is only counted once for the respective treatment
‡Other reason for discontinuing imatinib: Unknown

Outcomes

6.8.3.3 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem.

Table B9: Evaluation of outcomes of the Study 200 non-RCT

Outcome measure	Relevance to the decision problem	Reliability/validity/ current use in clinical practice
Rate of Major Cytogenetic Response (MCyR) by 24 weeks	Key measure to evaluate the clinical effectiveness of bosutinib	Rate of MCyR is a highly important outcome in clinical practice, as shown by its inclusion in European Leukaemia Net[49], the NCCN[1] and BCSH[64] published guidelines. Furthermore, rate of MCyR has been used as the primary endpoint by other TKIs.[7-9] A MCyR means that less than 35% of bone marrow cells test positive for the Philadelphia chromosome, indicating successful treatment of the disease at the source of the abnormal cells- the bone marrow. A MCyR is strongly associated with prolonged patient survival[65] This outcome was used as the primary analysis in the Khoury publication for the third-line CP CML population
Duration of MCyR	Key measure to evaluate the clinical	Durable responses are associated with reduced probability of progression to advanced stage disease for other TKIs in CML. For imatinib at 8 years follow-up,

	effectiveness of bosutinib	CP CML patients responding to imatinib had a low overall risk of progression to AP/BP. Most AP/BP events occurred early, with minimal risk after year 3 and no evidence for an increase over time[32]
Rate of Cytogenetic Response (CCyR), Partial cytogenetic response (PCyR) and Minor cytogenetic response (MiCyR)	Key measure to evaluate the clinical effectiveness of bosutinib	Cytogenetic response remains the desired standard for the monitoring of response to treatment in CML. The association between cytogenetic response and positive outcomes has been well established and so it is an important and useful measure in clinical practice.[66] In a study by Milojkovic et al, 2010, patients who had less than 95% Ph^+ metaphases at 3 months, those with 35% or less Ph^+ metaphases at 6 months (MCyR) and patients in CCyR at 12 months all had significantly better outcomes than patients with lesser degrees of cytogenetic response[67]
Rate of Major molecular response (MMR) and Complete molecular response (CMR)	Key measure to evaluate the clinical effectiveness of bosutinib	A molecular response is defined by the level of BCR-ABL transcript that is detectable in the bone marrow, usually using PCR as the detection technique. With the advent of TKIs that are able to induce a CCyR in the majority of patients, it has become increasingly important to use the more sensitive measure of molecular response in order to detect minimal residual disease. The degree of molecular response has been associated with reduced risk of cytogenetic relapse, improved duration of CCyR, progression-free survival and event-free survival and so it is an important measure in clinical practice.[49, 66] There is evidence that imatinib treatment can be safely discontinued if a CMR of 2 years duration is obtained, which highlights the value of a molecular response[68]
Progression-free survival (PFS) at 1 year and 2 years (K-M estimate)	Key measure to evaluate the clinical effectiveness of bosutinib	PFS is a highly important outcome for patients in clinical practice. Disease progression has quality of life implications and is related to overall survival
Overall survival (OS) at 1 year and 2 years (K-M estimate)	Key measure to evaluate the clinical effectiveness of bosutinib	Extension of life is arguably the most important outcome for a patient in clinical practice
Functional Assessment of Cancer Therapy-leukaemia (FACT-Leu)	Key measure of HRQL for bosutinib	The FACT-Leu is regarded as a valid, reliable and efficient measure of leukaemia-specific HRQL for CML[69]
European Quality-of-life Health Utilities Index – 5 dimensions (EQ-5D)	Key measure of HRQL for bosutinib	EQ-5D is a standardised instrument for measuring health outcomes, which is increasingly being used as a stand-alone measurement (as opposed to being used as a complement to other measures). EQ-5D is in widespread use in the healthcare industry and is recommended for use in cost-effectiveness analyses as part of a number of guidelines[70]
Incidence rate of any adverse events (and grade 3/4 adverse events)	Key measure for evaluating safety of bosutinib	Adverse events are a standard measure for reporting safety results from clinical trials and in clinical practice

Rate of patient death	Key measure for evaluating the safety of bosutinib	Death of a patient is the final outcome, which arguably all therapies for life-threatening conditions are trying to prevent

6.8.3.4 Statistical analysis and definition of study groups

The primary hypotheses, statistical analyses and power calculations for Study 200 were determined separately for different patient populations, dependent upon their experience with prior TKI therapy. The details relevant to the third-line CP CML and advanced phase CML Study 200 populations previously described are considered in turn, below.

The third-line CP CML population was comprised of patients with varying prior TKI exposure: previously treated with imatinib and resistant to dasatinib; previously treated with imatinib and intolerant to dasatinib; previously treated with imatinib and resistant to nilotinib. The details of the statistical analyses of these patient groups are presented in Table B10.

Table B10: Statistical analysis details for the third-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients previously treated with imatinib and who were resistant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.30 and p0=0.10 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=29 patients with 10 in the first stage. If the response rate was no greater than 1/10 at stage 1, consideration was given to early termination. The expected sample size under the null was 15.0 and probability of early termination under the null was 0.74.
CP CML patients previously treated with imatinib and who were intolerant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.37 and p0=0.17 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=35 patients with 12 in the first stage. If the response rate was no greater than 2/12=0.17 at stage 1, consideration was given to early termination. The expected sample size under the null was 19.7 and probability of early termination under the null was 0.67.
CP CML patients previously treated with imatinib who were resistant to nilotinib	Sample size calculation This cohort was sized using the same statistical considerations as in the dasatinib-resistant cohort, yielding a sample size of n=29 and an identical Simon 2-stage design. . Patients previously treated with imatinib who were either nilotinib intolerant or treated with both nilotinib and dasatinib were described. No testing was planned for this group.

The initial statistical analysis plan investigated bosutinib in AP, BP and Ph^+ ALL cohorts combined. However, based on futility testing of 24 week results of two initial hypotheses, investigations of bosutinib in Ph^+ ALL were discontinued. New hypotheses were generated for patients in AP and BP CML, based on evolving scientific information and

differed for those treated exclusively with imatinib and those treated with more than one TKI, as described in Table B11.

Table B11: Statistical analysis details for the advanced phase CML population

TKI exposure history	Statistical analysis details
Imatinib-resistant/intolerant CML patients in AP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.61 and p0=0.43 based on published nilotinib and dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=49 patients with 42 in the first stage. If the response rate was no greater than 22/42 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 42.6 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant patients in BP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.48 and p0=0.30 based on published dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=45 patients with 41 in the first stage. If the response rate was no greater than 16/41 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 41.3 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant CML patients, exposed to other TKIs	Both AP and BP patient populations fitting this description were analysed descriptively.

Statistical analysis populations

For all cohorts, analyses of the primary and key secondary efficacy endpoints, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline efficacy assessment. PFS and OS were calculated based on the all-treated population, which was defined as all enrolled patients who received at least one dose of bosutinib.

All patients who received at least 1 dose of bosutinib (the all-treated population) were included in the analysis of safety.

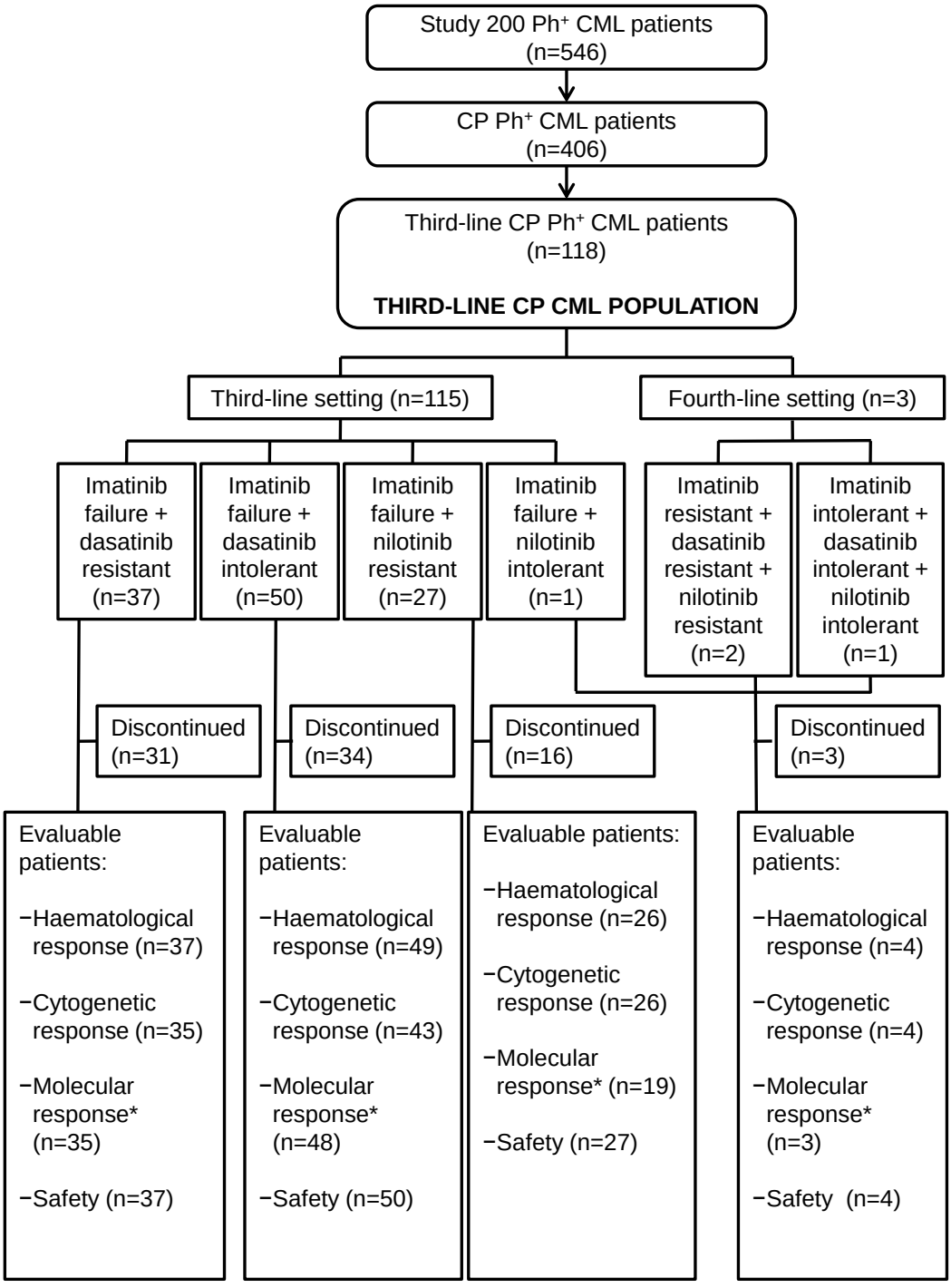
6.8.3.5 Details of subgroup analyses (and whether they are pre-specified or post-hoc)

A post-hoc analysis was performed on Study 200, as requested during consultation with the EMA, to provide evidence on those patients within Study 200 for whom imatinib, nilotinib and dasatinib could have been inappropriate. This subgroup analysis is described in more detail in Section 6.2.5.

6.8.3.6 Participant flow

The flow of participants for the third-line CP CML population is shown in Figure B3.

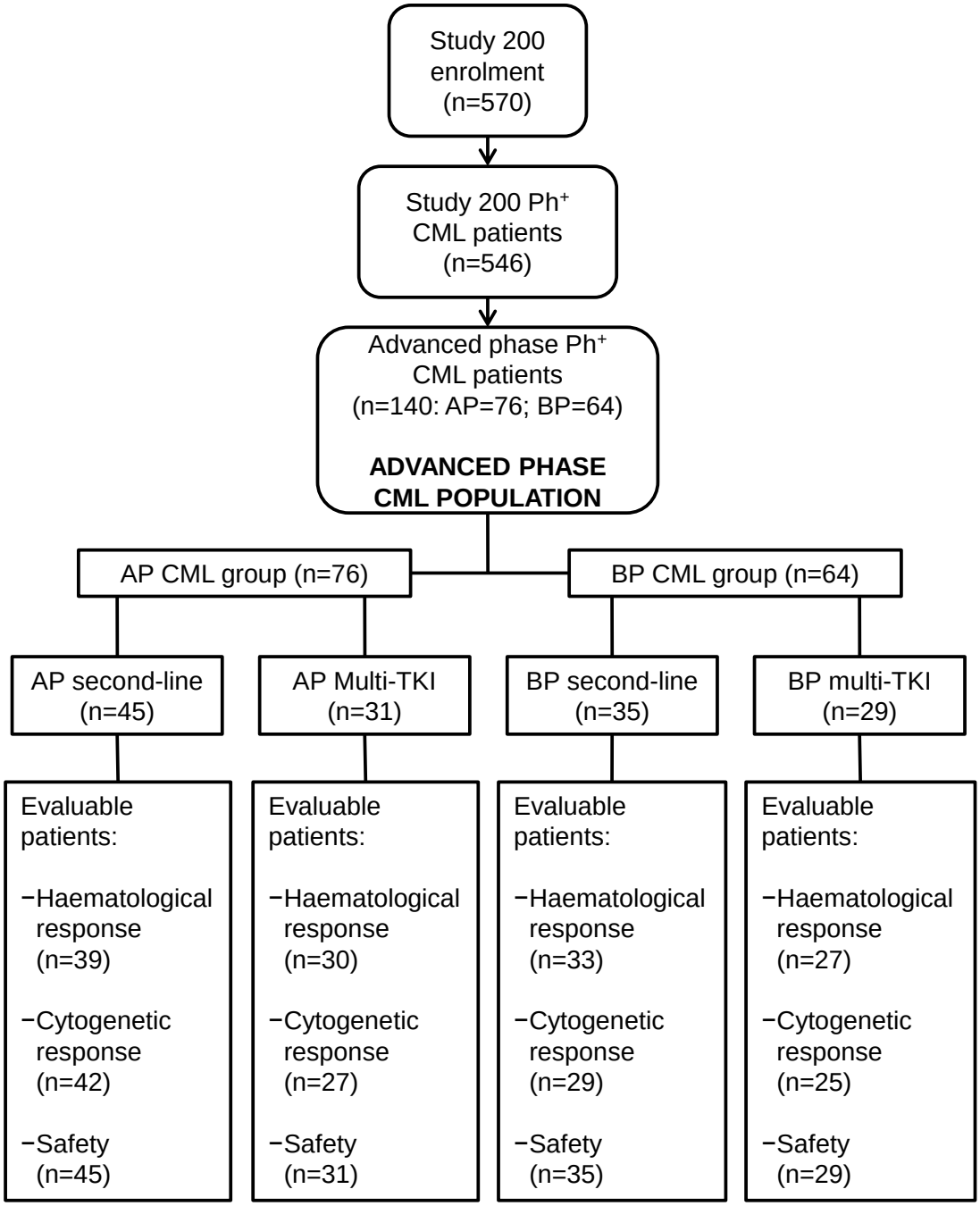
Figure B3: Patient flow for the third-line CP CML population



*Due to logistical constraints, patients from sites in China, India, Russia and South Africa were not assessed for Molecular Response

The flow of participants for the advanced phase CML population is shown in Figure B4.

Figure B4: Patient flow for the advanced phase CML population



6.8.4 Critical appraisal of relevant non-RCTs

The quality assessment of non-RCTs was performed according to the Chambers et al, 2009 criteria.[63] Full details of the Chambers criteria for quality assessment and the results of the quality assessment are summarised in Appendix 10.7.

6.8.5 Results of the relevant non-RCTs

Study 200: A phase 1/2 study of bosutinib in Philadelphia chromosome positive leukaemias

Clinical evidence from Study 200 will be presented for the third-line CP CML population, followed by the advanced phase (AP and BP) CML population.

THIRD-LINE CP CML POPULATION

Summary of efficacy: third-line CP CML population

- Bosutinib was associated with high rates of cytogenetic and molecular response, long duration of responses and high rates of PFS and OS. This efficacy was observed in all treatment groups and across all Bcr-Abl mutations, including those that confer resistance to nilotinib and dasatinib, except for T315I.
- **High rates of cytogenetic response**
  - The primary endpoint of MCyR at 24 weeks was met by 27% of evaluable third-line CP CML patients with a minimum follow-up of 12 months.
  - As of 28 Mar 2011 snapshot, MCyR was attained by 32% of third-line CP CML patients (minimum follow-up of 12 months) and if those who also maintained MCyR (from baseline) were included, MCyR increased to 39%. At the more recent data snapshot of 15 Feb 2012 this rate had increased to 41% (minimum follow-up of 24 months).
- **Durable clinical response**
  - As of 15 Feb 2012, the K-M estimated probability of maintaining a MCyR at 2 years was 71% (minimum follow-up 24 months).
  - As of the 28 March 2011 snapshot, the treatment discontinuation rate was 71% and median time on treatment was 8.3 months. By the 15 February 2012 snapshot, treatment discontinuation rate was 76%, with a median time on treatment of 8.6 months.
- **High levels of PFS and OS and low rates of transformation**
  - Durable responses were seen to translate into high rates of PFS and OS; as of 15 Feb 2012, the 2-year K-M estimate of PFS was 75% and of OS was 84%
  - The cumulative incidence of on-treatment transformation from CP to AP CML was 4% at a minimum follow-up of 24 months. No patient transformed to BP CML.

Data Sources

The details of the data sources for this third-line CP CML patient population can be found in Table B2.

The primary population for efficacy was the evaluable population, which included all subjects with an adequate baseline assessment. For the analysis of MCyR by week 24, analyses were also performed for the all-treated and per-protocol (PP) populations. The PP population included subjects in the all-treated population with no major protocol violations who had adequate baseline and post-baseline assessments.

Baseline characteristics for the third-line CP CML population are presented in Table B7. Safety outcomes are based on the 12 month minimum follow-up data (28 Mar 2011 snapshot) as the main safety results are only available in the CSR. These safety results are presented in Section 6.9.

Treatment characteristics

Table B12 provides details of treatment duration, follow-up and discontinuation for the third-line CP CML population at both the 28 March 2011 and 15 Feb 2012 snapshot.

Table B12: Treatment characteristics in the third-line CP CML population

Parameter	28 March 2011 snapshot	15 February 2012 snapshot
Median duration of follow-up	28.48 months (range, 0.29-56.21)	31.4 months (range, 0.3-66.0 months)
Minimum duration of follow-up	13.4 months	24 months
Median duration of treatment	8.3 months (range, 0.2-51.8)	8.6 months (range, 0.2-60.8)
% of patients still on treatment as of data snapshot	29%	24%

Response Rates by Week 24

In the third-line CP CML evaluable population, 27% (29 subjects, 95% CI: [19, 36]) achieved MCyR by Week 24, with [redacted] attaining CCyR.

Cumulative Response Rates

Cytogenetic Response

As noted in the Khoury et al, 2012 publication, MCyR was attained by 32% (n=35) of patients in the all-treated third-line CP CML population, with CCyR in 24% (n=26) of patients, including one of the 3 patients who was previously treated with all 3 TKIs (28 Mar 2011 snapshot).

It is worth noting that for this pre-specified (protocol-defined) analysis, patients with MCyR or CCyR at baseline were considered non-responders and hence not included, despite the fact that they may potentially have maintained the response on treatment with bosutinib. The median time to MCyR among responders in this analysis was 12.4 weeks (28 Mar 2011 snapshot). Results for the analysis of response rates according to this pre-specified definition of responders are not available at the later 15 February 2012 snapshot, with a minimum follow-up of 24 months.

A post-hoc analysis was additionally performed in order to evaluate cytogenetic response rates when patients who maintained a cytogenetic response present at baseline were included as responders (see Table B2). As of the 15 February 2012 snapshot, with a minimum of 24 months follow-up, MCyR and CCyR were attained or maintained by 41% and 32% of patients with a valid baseline cytogenetic measurement, respectively, in the

evaluable population, which are similar to the 39% and 31% for MCyR and CCyR, respectively, from 28 March 2011 database snapshot.

In this analysis, the median time to attaining or maintaining MCyR for responders only was 12.3 weeks (95% CI: [12.0, 22.3]) for the 15 February 2012 data snapshot. Responders were required to have an on-treatment assessment of MCyR at least 4 weeks after first dose.

Table B13 presents rates of MCyR and CCyR, under both the pre-specified and post-hoc definitions of responder. These data are presented for both the earlier 28 March 2011 snapshot and the later 15 February 2012 snapshot where available. As discussed, response rates for the pre-specified analysis are not available for the later snapshot.

Table B13: Cytogenetic response rates for the third-line CP CML population

	28 Mar 2011 Snapshot			15 February 2012 Snapshot		
Cohort	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**
Pre-specified analysis: patients who attained a response not present at BL[b]						
IM + D resistant	35	11 (31) (16.9, 49.3)	5 (14) (4.8, 30.3)	**Data not available for pre-specified analysis at later snapshot**		
IM + D intolerant	43	13 (30) (17.2, 46.1)	12 (28) (15.3, 43.7)			
IM + NI resistant	26	9 (35) (17.2, 55.7)	7 (27) (11.6, 47.8)			
IM + (NI + D) or IM + NI intolerant*	4	2 (50) (6.8, 93.2)	2 (50) (6.8, 93.2)			
Total	**108**	**35 (32) (23.7, 42.1)**	**26 (24) (16.4, 33.3)**			
Post-hoc analysis: patients who attained a response or maintained a response present at BL[c]						
IM + D resistant	35	12 (34.3) (19.1, 52.2)	6 (17.1) (6.6, 33.7)	36	12 (33.3) (18.6, 51.0)	7 (19.4) (8.2, 36.0)
IM + D intolerant	43	19 (44.2) (29.1, 60.1)	18 (41.9) (27.0, 57.9)	44	21 (47.7) (32.5, 63.3)	19 (43.2) (28.4, 59.0)
IM + NI resistant	26	9 (34.6) (17.2, 55.7)	7 (26.9) (11.6, 47.8)	26	10 (38.5) (20.2, 59.4)	7 (26.9) (11.6, 47.8)
IM + (NI + D) or IM + NI intolerant*	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)
Total	**108**	**42 (38.9) (29.7, 48.8)**	**33 (30.6) (22.1, 40.2)**	**110[d]**	**45 (40.9) (31.6, 50.7)**	**35 (31.8) (23.3, 41.4)**

	28 Mar 2011 Snapshot			15 February 2012 Snapshot		
Cohort	n[a]	MCyR N (%) (95% CI)	CCyR N (%) (95% CI)	n[a]	MCyR N (%) (95% CI)	CCyR N (%) (95% CI)

Abbreviations: CI=confidence interval; CCyR= complete cytogenetic response; D=dasatinib; IM=imatinib; MCyR=major cytogenetic response; n=number of patients; NI=nilotinib; BL = baseline
*Includes 3 patients who previously received all 3 inhibitors and 1 patient with NI intolerance
[a]Evaluable patients had a baseline disease assessment
[b]Patients with CCyR or PCyR at baseline were considered non-responders for assessment of cytogenetic response
[c]Note: Percentages are based on number of patients in each analysis. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with MCYR at baseline who were allowed to maintain best response post-baseline.
[d]Includes Patients 200-060-001446 and 200-075-001612. Patient 200-075-001612 had a valid baseline cytogenetic assessment in 15FEB2012 but not 28MAR2011

Haematological response

In the evaluable population, 73% of CP CML patients who had received imatinib and also dasatinib and/or nilotinib attained a confirmed CHR or maintained a baseline CHR during treatment with bosutinib, as of both database snapshots (28 March 2011 and 15 February 2012; Table B14). Attainment of confirmed CHR or maintenance of a baseline CHR represented the pre-specified (protocol-defined) definition of a responder for CHR.

The median time to attaining or maintaining CHR for responders only was 1.6 weeks (95% CI: [1.1, 2.3]) for the 28 March 2011 data snapshot and 1.8 weeks (95% CI: [1.1, 2.3]) for the 15 February 2012 data snapshot. Responders were required to have an on-treatment assessment of CHR at least 1 week after first dose with confirmation at least 4 weeks after initial response.

In addition, rates of CHR were evaluated when only patients who had no baseline CHR and attained a CHR on treatment were considered. Of these 68 patients without a baseline CHR, 44 (64.7%) achieved a confirmed CHR. This analysis is only available at the earlier 28 Mar 2011 snapshot.

Table B14 presents rates of CHR from the pre-specified analysis of responders, including patients who attained or maintained a confirmed CHR

Table B14: CHR rates for the third-line CP CML population

	28 Mar 2011 Snapshot		15 February 2012 Snapshot	
Cohort	n	CHR N (%) (95% CI)	n	CHR N (%) (95% CI)
CHR including subjects with CHR at baseline[a,b]				
IM + (NI + D) or IM + NI Intolerant	4	3 (75.0) (19.4, 99.4)	4	3 (75.0) (19.4, 99.4)
IM + D Resistant	37	23 (62.2) (44.8, 77.5)	37	23 (62.2) (44.8, 77.5)
IM + D Intolerant	49	39 (79.6) (65.7, 89.8)	49	39 (79.6) (65.7, 89.8)
IM + NI Resistant	26	20 (76.9) (56.4, 91.0)	25	19 (76.0) (54.9, 90.6)

Total	**116**	**85 (73.3) (64.3, 81.1)**	**115[c]**	**84 (73.0) (64.0, 80.9)**

Abbreviations: CHR=major hematologic response; CI=confidence interval; D=dasatinib; IM=imatinib; n=number of patients; NI=nilotinib.
[a]Analysis includes patients who have a valid baseline hematologic measurement.
[b]Subjects with CHR at baseline are eligible for response post-baseline. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with CHR at baseline who were allowed to maintain best response post-baseline.
[c]Analysis includes Patient 200-060-001446 but excludes Patients 200-093-002244 and 200-093-002246 due to missing baseline hematologic assessment in 15 February 2012

Molecular response

MMR has not been evaluated at the more recent snapshot (15 Feb 2012) and so only the results for the 28 Mar 2011 are summarised. MMR was evaluated for 105 subjects in the all-treated population. This analysis excluded 13 subjects from China, India, Russia and South Africa, where molecular assessment was not performed due to logistical constraints.

Sixteen (15.2%; 95% CI:[9.0, 23.6]) subjects achieved a MMR, with 11.4% (12 subjects, 95% CI: [6.1, 19.1]) achieving CMR. In the dasatinib-resistant cohort, 1 subject (2.9%, 95% CI: [0.1, 14.9]) had MMR, but not CMR; in the dasatinib-intolerant cohort, the incidence of MMR was 25.0% (12 subjects; 95% CI: [13.6, 39.6]), with 9 subjects (18.8%, 95% CI [9.0, 32.6]) achieving CMR; and in the nilotinib-resistant cohort, the incidence of MMR was 10.5% (2 subjects;95% CI: [1.3, 33.1]), with both subjects achieving CMR.

Duration of response

MCyR

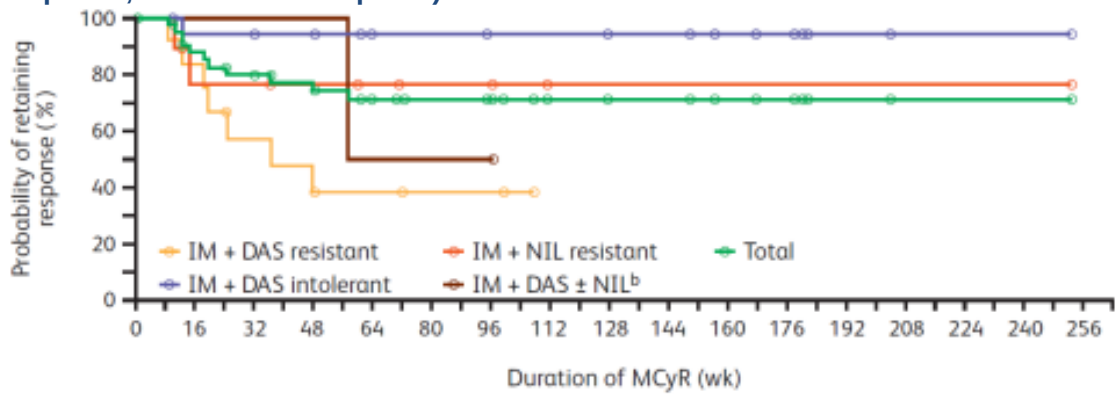
As of the 28 Mar 1011 snapshot, the K-M estimates of attaining or maintaining MCyR at 1 year and 2 years were 72.2% and 68.6%, respectively, and the median duration had not been reached. With continued follow-up (15 February 2012), the estimates of MCyR durability were consistent: the 1-year and 2-year K-M estimate of maintaining MCyR were 74.0% and 70.9%, respectively; the median duration has still not been reached (Table B15 and Figure B5).

Table B15: Kaplan-Meier estimates of duration of MCyR in third-line evaluable patients who attained or maintained a response

	28 Mar 2011 Snapshot			15 Feb 2012 Snapshot		
Cohort	**n**	**K-M Estimate at Year 1 (95% CI)**	**K-M Estimate at Year 2 (95% CI)**	**n**	**K-M Estimate at Year 1 (95% CI)**	**K-M Estimate at Year 2 (95% CI)**
IM + (NI + D) or IM + NI intolerant	2	N/A*	N/A*	2	N/A	N/A
IM + D resistant	12	30.0 (7.7, 56.9)	30.0 (7.7, 56.9)	12	38.1 (12.1, 64.3)	38.1 (12.1, 64.3)
IM + D intolerant	19	94.1 (65.0, 99.1)	94.1 (65.0, 99.1)	21	94.1 (65.0, 99.1)	94.1 (65.0, 99.1)
IM + NI resistant	9	85.7 (33.4, 97.9)	85.7 (33.4, 97.9)	10	76.2 (33.2, 93.5)	76.2 (33.2, 93.5)
Total	**42**	**72.2 (54.3, 84.0)**	**68.6 (50.2, 81.4)**	**45**	**74.0 (56.9, 85.1)**	**70.9 (53.5, 82.8)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; n=number of patients; N/A=not applicable; NI=nilotinib.
*This sample size is too small to suggest accurate estimates
One month is assumed to have 28 days. One year is assumed to have 48 weeks

Figure B5: Kaplan-Meier estimate of duration of MCyR (attained or maintained response, 15 Feb 2012 snapshot)



CHR

The 1-year and 2-year K-M estimates of maintaining CHR response were 71.9% and 66.5%, respectively, for the evaluable population, and the median duration had not been reached as of 28 March 2011. With longer follow-up (15 February 2012 data snapshot), the 1-year and 2-year K-M estimates of maintaining CHR were 72.6% and 67.4%, respectively, and the median duration has still not been reached. These K-M estimates were produced based on CHR response rates which included those patients who maintained a baseline CHR. The K-M estimates of duration of response are displayed in Table B16.

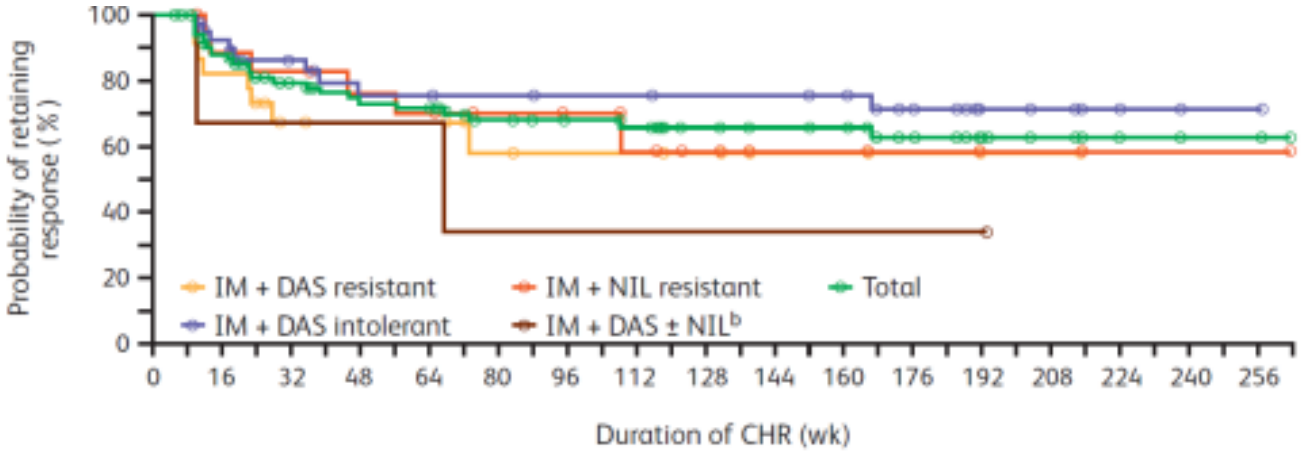
Table B16: K-M Estimate of Maintaining CHR in third-line CP evaluable population

	28 Mar 2011 Snapshot			15 Feb 2012 Snapshot		
Cohort	**n[a]**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**	**n[a]**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**
IM + (NI + D) or IM + NI Intolerant	3	N/A[b]	N/A[b]	3	N/A[b]	N/A[b]
IM + D Resistant	23	[redacted]	[redacted]	23	67.1 (42.9, 82.9)	57.5 (30.3, 77.4)
IM + D Intolerant	39	[redacted]	[redacted]	39	75.3 (56.3, 87.0)	75.3 (56.3, 87.0)
IM + NI Resistant	20	[redacted]	[redacted]	19	76.0 (48.0, 90.3)	69.7 (41.7, 86.1)
Total	**85**	[redacted]	[redacted]	**84**	**72.6 (60.7, 81.5)**	**67.4 (54.9, 77.2)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; n=number of patients; N/A=not applicable; NI=nilotinib.
a. No. of patients attaining complete hematologic response.
b. The sample size is too small to suggest accurate estimates.
Note: One year is assumed to have 48 weeks. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with CHR at baseline who were allowed to maintain best response post-baseline.

The K-M estimates of duration of CHR are further summarised in Figure B6, which presents the K-M estimates at the latest 15 Feb 2012 snapshot.

Figure B6: Kaplan-Meier estimate of duration of CHR (15 Feb 2012 snapshot)



Progression-free survival (PFS)

At the time of the 28 March 2011 database snapshot, the 1-year and 2-year K-M estimates of PFS in the all-treated population were 76.6% and 73.2%, respectively (Table B17), and the median PFS had not been reached. With continued follow-up (15 February 2012), the 1-year and 2-year K-M estimates of PFS were consistent: 78.3% and 75.1%, respectively. The median PFS has still not been reached.

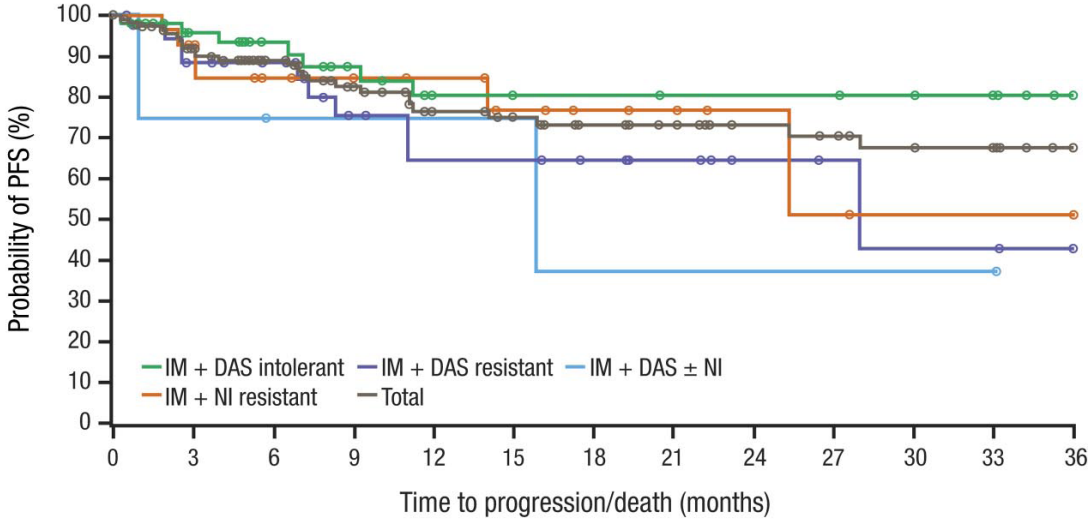
Table B17: K-M estimate of PFS in third-line CP all-treated population

	28 March 2011 Snapshot			15 February 2012 Snapshot		
Cohort	n	K-M Estimate At Year 1 (95% CI)	K-M Estimate At Year 2 (95% CI)	n	K-M Estimate At Year 1 (95% CI)	K-M Estimate At Year 2 (95% CI)
IM + (NI + D) or IM + NI Intolerant	4	N/A[a]	N/A[a]	4	N/A[a]	N/A[a]
IM + D Resistant	37	64.7 (41.7, 80.5)	64.7 (41.7, 80.5)	[redacted]	[redacted]	[redacted]
IM + D Intolerant	50	80.5 (62.8, 90.4)	80.5 (62.8, 90.4)	[redacted]	[redacted]	[redacted]
IM + NI Resistant	27	84.5 (63.8, 93.9)	76.9 (50.7, 90.3)	[redacted]	[redacted]	[redacted]
Total	**118**	**76.6 (66.0, 84.3)**	**73.2 (61.9, 81.7)**	**119**	**78.3 (67.9, 85.6)**	**75.1 (64.2, 83.1)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; N/A=not applicable; n=number of patients; NI=nilotinib.
a. The sample size is too small to suggest accurate estimates.
Note: One year is assumed to have 12 months.

The K-M plot of PFS is shown in Figure B7; this is only available based on the 28 March 2011 snapshot (i.e. 12 month minimum follow-up duration).

Figure B7: K-M estimates of PFS for the third-line CP all-treated population (28 Mar 2011 snapshot)



Transformation

Of the 117 CP CML patients in the third-line CP CML population who had received imatinib and either dasatinib and/or nilotinib with a valid post-baseline hematologic assessment, 5 patients (4%, 95% CI, 2-10) had confirmed on-treatment disease transformation to AP, while 71% of patients discontinued treatment without transformation. No patient transformed to BP CML, as of the 28 March 2011 database snapshot. No patients had disease transformation to BP while on treatment.

With continued follow-up (15 February 2012 database snapshot), no additional patients had confirmed disease transformation to AP or BP.

Overall survival

As of 28 March 2011, the 1-year and 2-year K-M estimates of OS in the all-treated population were 91.2% and 82.9% and the median OS had not been reached. With continued follow-up (15 February 2012), the 1-year and 2-year K-M estimates of OS in the all-treated population were 91.4% and 84.0%, respectively. The median OS has still not been reached. The K-M estimates of overall survival are presented in Table B18.

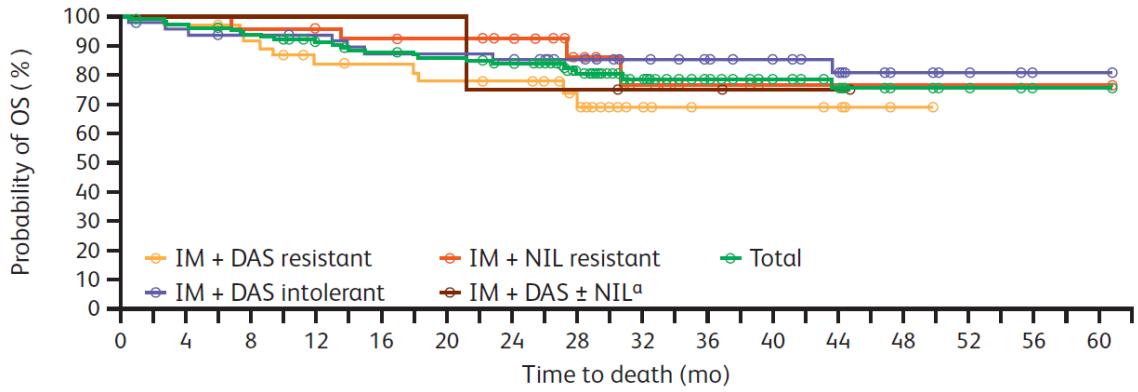
Table B18: K-M estimate of OS in third-line CP all-treated population

	28 March 2011 Snapshot			15 February 2012 Snapshot		
Cohort	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**
IM + (NI + D) or IM + NI Intolerant	4	N/A	N/A	4	N/A	N/A
IM + D Resistant	37	82.8 (65.6, 91.9)	75.2 (56.1, 86.9)	38	83.6 (67.0, 92.3)	77.4 (59.7, 88.0)
IM + D Intolerant	50	93.9 (82.3, 98.0)	85.4 (71,7, 92.8)	50	93.9 (82.3, 98.0)	85.4 (71.7, 92.8)
IM + NI Resistant	27	96.3 (76.5, 99.5)	91.7 (70.5, 97.9)	27	96.3 (76.5, 99.5)	92.4 (73.0, 98.1)
Total	**118**	**91.2 (84.3, 95.2)**	**82.9 (74.1, 88.9)**	**119**	**91.4 (84.6, 95.3)**	**84.0 (75.8, 89.6)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; N/A=not applicable; n=number of patients; NI=nilotinib.
a. The sample size is too small to suggest accurate estimates.
Note: One year is assumed to have 12 months.

The K-M plot of OS is shown in Figure B8; the plot shown is for the latest available timepoint: the 15 Feb 2012 snapshot.

Figure B8: K-M estimates of OS for the third-line CP all-treated population (15 Feb 2012 snapshot)



Deaths

As of the 15 Feb 2012 snapshot, a total of 23 (19%) patients from the third-line CP CML population died during the study, including 6 deaths that occurred within 30 days of the

last dose of bosutinib. Most deaths were due to disease progression (10 deaths, 8%) or an AE considered unrelated to treatment (9 deaths, 8%).

One death in the third-line CP CML population that occurred during the study was deemed to be treatment-related. This death occurred in the group of patients previously treated with imatinib, followed by dasatinib to which they were intolerant (IM + DAS intolerant) and was a result of lower gastrointestinal bleeding occurring after a therapy duration of 78 days in the setting of grade 4 thrombocytopaenia

Response by baseline mutation status

The third-line CP CML population was assessed for MCyR and CHR, stratified by baseline mutation status. Of 86 patients assessed for baseline mutation status, 40 (47%) had ≥1 of 19 unique Bcr-Abl kinase domain mutations, including 7 (8%) with the T315I mutation.

For the analysis of response by baseline mutation status, the Khoury 2012 publication do not present data from the 28 March 2011 snapshot, as for other outcomes, but from a snapshot on 17 May 2011. Response rates by baseline mutation status for the 17 May 2011 and 15 February 2012 snapshots are presented in Table B19.

Table B19: Response by baseline mutation status in the third-line CP CML population

	17 May 2011 snapshot			15 February 2012 snapshot		
Bcr-Abl mutation status	**n**	**Cumulative response, n/n evaluable[a] (%)**		**n**	**Cumulative response, n/n evaluable[a] (%)**	
		CHR	**MCyR**		**CHR**	**MCyR**
No mutation	44	34/44 (77)	15/43 (35)	46	35/45 (78)	18/45 (40)
≥1 mutation	39	26/39 (67)	11/35 (31)	40	26/39 (67)	14/37 (38)
≥2 mutations	9	3/9 (33)	2/9 (22)	9	3/9 (33)	2/9 (22)
Most common individual mutations[b]						
F317L[c]	8	4/8 (50)	1/7 (14)	8	4/8 (50)	1/7 (14)
T315I[c,d]	7	2/7 (29)	0/6	7	2/7 (29)	1/7 (14)[e]
G250E	6	3/6 (50)	0/5	6	3/6 (50)	0/5
Y253H[d]	6	5/6 (83)	4/6 (67)	6	5/6 (83)	5/6 (83)
M244V	3	3/3 (100)	2/3 (67)	3	3/3 (100)	2/3 (67)
F359V[d]	2	0/2	1/2 (50)	3	1/3 (33)	2/3 (67)
V299L[c]	2	1/2 (50)	0/2	2	1/2 (50)	0/2
F359C[d]	2	2/2 (100)	1/2 (50)	2	1/1 (100)	1/2 (50)
F359I	2	2/2 (100)	2/2 (100)	2	2/2 (100)	2/2 (100)

[a]Evaluable patient had received ≥1 bosutinib dose and had a valid baseline disease assessment for the corresponding endpoint
[b]Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
[e]The patient with the T315I mutation at baseline who responded with a MCyR had a PCyR at baseline that was maintained at Week 12 allowing the patient to be counted as a responder. The patient discontinued treatment due to an AE around Week 24 and did not have any further cytogenetic assessments

Responses to bosutinib were observed across baseline mutations, including several that confer resistance to other TKIs. However, responses in patients with the T315I mutation were low with rate of MCyR and CHR of 14% and 29%, respectively.

When patients with the T315I mutation (n=7) are excluded from the analysis, response rates were 43% for MCyR and 75% for CHR among the remaining patients with ≥1 baseline mutation.

Treatment discontinuation

As of the most recent data snapshot (15 February 2012), a total of 90 patients (76%) discontinued treatment with bosutinib during the study. Median duration of bosutinib treatment was 8.3 months at the 28 March 2011 snapshot and 8.6 months by the 15 February 2012 snapshot. The reasons for discontinuation are summarised in Table B20.

Patient-reported Outcomes

FACT-Leu

HRQL was assessed through the FACT-Leu scale. Improvement in LEUS was statistically significant in dasatinib-intolerant subjects at weeks 12 and 24 (1-sided $p<0.01$) and in nilotinib-resistant subjects at weeks 4 and 8 (1-sided $p<0.05$).

Since EQ-5D was also captured in Study 200 and this represents the preferred utility measure for the NICE reference case, the full FACT-Leu results are not reported here.

EQ-5D

Improvements or maintenance of baseline levels of overall health status as assessed by the EQ-5D was observed for dasatinib-intolerant, dasatinib-resistant and nilotinib-resistant patients over the course of treatment, as of the 28 March 2011 snapshot. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (n=4).

The mean and median EQ-5D scores, and the number of patients with an EQ-5D score at each observation are presented in Section 7.4.3 as part of the cost-effectiveness analysis, as these data are considered to be more relevant to this section.

Table B20: Treatment discontinuation in the third-line CP CML population

Reason for discontinued treatment	28 March 2011 Snapshot					15 February 2012 Snapshot				
	IM + DAS resistant (n=37)	IM + DAS intolerant (n=50)	IM + NIL resistant (n=27)	IM + DAS ± NIL[a] (n=4)	Total (n=118)	IM + DAS resistant (n=38)	IM + DAS intolerant (n=50)	IM + NIL resistant (n=27)	IM + DAS ± NIL[a] (n=4)	Total (n=119)
Discontinued treatment, n (%)	31 (84)	34 (68)	16 (59)	3 (75)	84 (71)	32 (84)	37 (74)	18 (67)	3 (75)	90 (76)
AE	6 (16)	15 (30)	3 (11)	0	24 (20)	6 (16)	17 (34)	3 (11)	0	26 (22)
Lack of efficacy	12 (32)	7 (14)	5 (19)	1 (25)	25 (21)	12 (32)	7 (14)	5 (19)	1 (25)	25 (21)
Disease progression	8 (22)	4 (8)	6 (22)	2 (50)	20 (17)	7 (18)	4 (8)	7 (26)	2 (50)	20 (17)
Patient request	0	2 (4)	1 (4)	0	3 (3)	2 (5)	3 (6)	1 (4)	0	6 (5)
Death	2 (5)	2 (4)	0	0	4 (3)	2 (5)	2 (4)	0	0	4 (3)
Investigator Request	0	0	1 (4)	0	1 (1)	0	0	2 (7)	0	2 (2)
Lost to follow-up	2 (5)	0	0	0	2 (2)	2 (5)	0	0	0	2 (2)
Protocol violation	0	1 (2)	0	0	1 (1)	0	1 (2)	0	0	1 (1)
Other	1 (3)	3 (6)	0	0	4 (3)	1 (3)	3 (6)	0	0	4 (3)

ADVANCED PHASE CML POPULATION

Summary of efficacy: advanced phase CML population

- Bosutinib was associated with clinically important rates of haematological and cytogenetic response and of PFS and OS. Response durations were also observed to be good. This efficacy was observed in both AP and BP patient groups and across all Bcr-Abl mutations, except for T315I.
- All data for the advanced phase patients is presented at the 28 Mar 2011 snapshot, which corresponds to a minimum follow-up of 12 months for AP and 18 months for BP patients
- **High rates of response**
  - Cumulative rate of OHR was 55.1% in AP and 28.3% in BP.
  - Rate of MCyR was 34.8% in AP and 29.6% in BP.
- **Durable clinical response**
  - The K-M estimates of maintaining OHR at 2 years were 67.0% in the AP population and 18.8% in the BP population.
  - The K-M estimates of maintaining a MCyR at 2 years were 48.0% in the AP population and 7.9% in the BP population.
- **Survival**
  - The K-M estimates of PFS at 2 years were 47.7% for the AP population and 11.5% for the BP population
  - The K-M estimates of OS at 2 years were 65.6% for the AP population and 35.4% for the BP population
  - 6.4% of AP patients experienced transformation to BP.

Data sources

The data sources for this advanced phase CML patient population are presented in Table B2.

Baseline characteristics for the advanced phase CML population are provided in Table B8. Safety outcomes are also based on the 28 Mar 2011 snapshot presented in the CSR as this represents the only data source for this patient population. These safety outcomes are presented in Section 6.9.

Treatment characteristics

Table B21 provides details of treatment duration, follow-up and discontinuation for the advanced phase CML populations at the 28 March 2011 snapshot.

Table B21: Treatment characteristics in the advanced phase CML population

Parameter	AP population (n=76)	BP population (n=64)
Median duration of follow-up	26.45 (range, 0.32-56.07)	11.64 (0.39-48.04)
Minimum duration of follow-up	12.3 months	18 months
Median treatment duration/median time on treatment	10.1 months (0.10-51.64)	2.8 months (0.03-44.24)
% of patients still on treatment as of data snapshot	20%	5%

Response rates

Haematological response

Patients in the advanced phase CML population were evaluated for rate of cumulative OHR and other haematological responses. Of the 76 AP patients in this population, 7 were not evaluable for haematological response due to inadequate baseline efficacy assessment. Of the 64 BP patients in this population, 4 were excluded from evaluation for the same reason. The results of this evaluation are displayed in Table B22.

Table B22: Cumulative haematological response rates for the advanced phase CML population (28 Mar 2011 snapshot)

Haematological response, n (%) [95% CI]	Accelerated phase			Blast phase		
	Second-line (n=39)	Multi-TKI (n=30)	Total (n=69)	Second-line (n=33)	Multi-TKI (n=27)	Total (n=60)
OHR	25 (64.1) [47.2-78.8]	13 (43.3) [25.5-62.6]	38 (55.1) [42.6-67.1]	12 (36.4) [20.4-54.9]	5 (18.5) [6.3-38.1]	17 (28.3) [17.5-41.4]
MHR	21 (53.9) [37.2-69.9]	11 (36.7) [19.9-56.1]	32 (46.4) [34.3-58.8]	8 (24.2) [11.1-42.3]	3 (11.1) [2.4-29.2]	11 (18.3) [9.5-30.4]
CHR	16 (41.0) [25.6-57.9]	8 (26.7) [12.3-45.9]	24 (34.8) [23.7-47.2]	8 (24.2) [11.1-42.3]	1 (3.7) [0.1-19.0]	9 (15.0) [7.1-26.6]

In patients with AP CML in the evaluable population, the K-M median time to confirmed (maintained or attained) OHR was 12.0 weeks (95% CI, 12.0—12.3). In patients with BP CML in the evaluable population, the K-M median time to confirmed (maintained or attained) OHR was not reached.

Cytogenetic response

Patients in the advanced phase CML population were also evaluated for rate of cytogenetic response. Patients were considered to be responders if they attained a MCyR not present at baseline. Cytogenetic response rates are presented in Table B23.

Table B23: Cytogenetic response rates for the advanced phase CML population (28 Mar 2011 snapshot)

Cytogenetic response, n (%)	Accelerated phase			Blast phase		
	Second-line (n=42)	Multi-TKI (n=27)	Total (n=69)	Second-line (n=29)	Multi-TKI (n=25)	Total (n=54)
MCyR	20 (47.6)	4 (14.8)	24 (34.8)	13 (44.8)	3 (12.0)	16 (29.6)
CCyR	14 (33.3)	3 (11.1)	17 (24.6)	9 (31.0)	2 (8.0)	11 (20.4)
PCyR	6 (14.3)	1 (3.7)	7 (10.1)	4 (13.8)	1 (4.0)	5 (9.3)

Duration of response

OHR

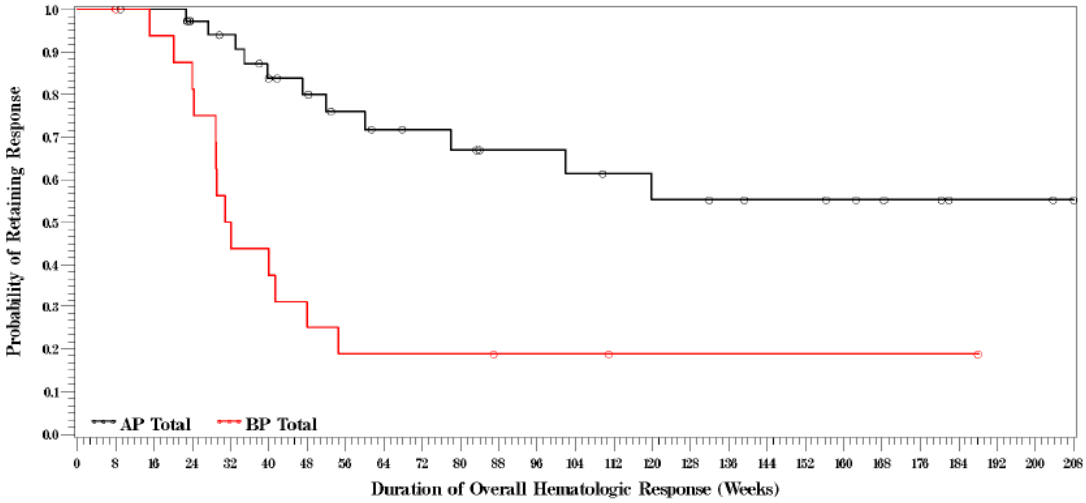
The K-M estimates of maintaining OHR at 1 year and 2 years are provided in Table B24. The median duration of OHR was not reached for AP patients and 31.5 weeks for BP patients.

Table B24: Kaplan-Meier estimates of maintaining OHR for the advanced phase CML population (28 Mar 2011 snapshot)

Kaplan-Meier estimate of maintaining OHR (%) [95% CI]	Accelerated phase			Blast phase		
	Second-line (n=39)	Multi-TKI (n=30)	Total (n=69)	Second-line (n=33)	Multi-TKI (n=27)	Total (n=60)
1 year	80.6 [56.0-92.3]	80.0 [40.9-94.6]	80.0 [60.5-90.5]	18.2 [2.9-44.2]	40.0 [5.2-75.3]	25.0 [7.8-47.2]
2 years	61.0 [34.0-79.7]	80.0 [40.9-94.6]	67.0 [45.4-81.6]	9.1 [0.5-33.3]	40.0 [5.2-75.3]	18.8 [4.6-40.2]

The Kaplan-Meier plot for duration of OHR in the advanced phase CML population is displayed in Figure B9.

Figure B9: Kaplan-Meier plot for duration of OHR in the advanced phase CML population (28 Mar 2011 snapshot)



MCyR

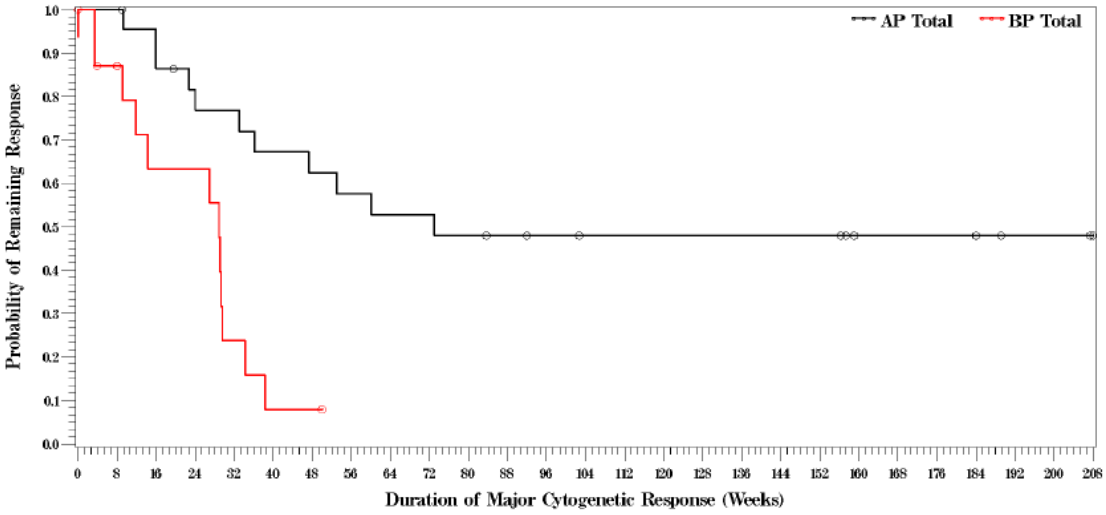
The K-M estimates of maintaining MCyR at 1 year and 2 years are given in Table B25. The median duration of MCyR was 73.0 weeks for AP patients and 28.9 weeks for BP patients.

Table B25: Kaplan-Meier estimates of maintaining MCyR for the advanced phase CML population (28 Mar 2011 snapshot)

Kaplan-Meier estimate of maintaining MCyR	Accelerated phase			Blast phase		
	Second-line (n=42)	Multi-TKI (n=27)	Total (n=69)	Second-line (n=29)	Multi-TKI (n=25)	Total (n=54)
1 year	70.8 [43.5-86.7]	25.0 [0.9-66.5]	62.4 [38.6-79.1]	10.5 [0.6-37.1]	0.0	7.9 [0.5-29.8]
2 years	53.1 [27.8-73.2]	25.0 [0.9-66.5]	48.0 [26.0-67.0]	10.5 [0.6-37.1]	0.0	7.9 [0.5-29.8]

The Kaplan-Meier plot for duration of MCyR in the advanced phase CML population is displayed in Figure B10.

Figure B10: Kaplan-Meier plot for duration of MCyR in the advanced phase CML population (28 Mar 2011 snapshot)



Response by baseline mutation status

The advanced phase CML population was assessed for MCyR, CHR and OHR, stratified by baseline mutation status. Of 117 patients assessed for baseline mutation status, 65 (55.6%) had Bcr-Abl kinase domain mutations, including 15 (12.8%) with the T315I mutation. Whereas all other data presented for the advanced phase CML population is taken from the 28 March 2011 snapshot, the analysis of response by baseline mutation status is based on a 17 May 2011 snapshot.

Response rates by baseline mutation status are presented in Table B26.

Table B26: Response by baseline mutation status in the advanced phase CML population (17 May 2011 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)		
		CHR	OHR	MCyR
No mutation	52	19/49 (38.8)	23/49 (46.9)	16/43 (37.2)
≥1 mutation	65	10/59 (16.9)	21/59 (35.6)	13/55 (23.6)
Most common individual mutations[b]				
T315I[c,d]	15	0/13	1/13 (7.69)	1/13 (7.69)
F317L[c]	9	0/9	2/9 (22.2)	0/6
G250E	7	4/6 (66.7)	4/6 (66.7)	2/7 (28.6)
Y253H[d]	7	1/7 (14.3)	2/7 (28.6)	2/7 (28.6)
E255V[d]	5	0/4	0/4	1/3 (33.3)
M351T	5	2/5 (40.0)	3/5 (60.0)	1/4 (25.0)
E255K[d]	4	0/4	1/4 (25.0)	1/3 (33.3)
M244V	3	1/2 (50.0)	2/2 (100)	1/2 (50.0)
F359I	2	0/2	1/2 (50.0)	1/2 (50.0)
F359V[d]	2	0/2	1/2 (50.0)	0/2
F486S	2	1/2 (50.0)	1/2 (50.0)	2/2 (100)

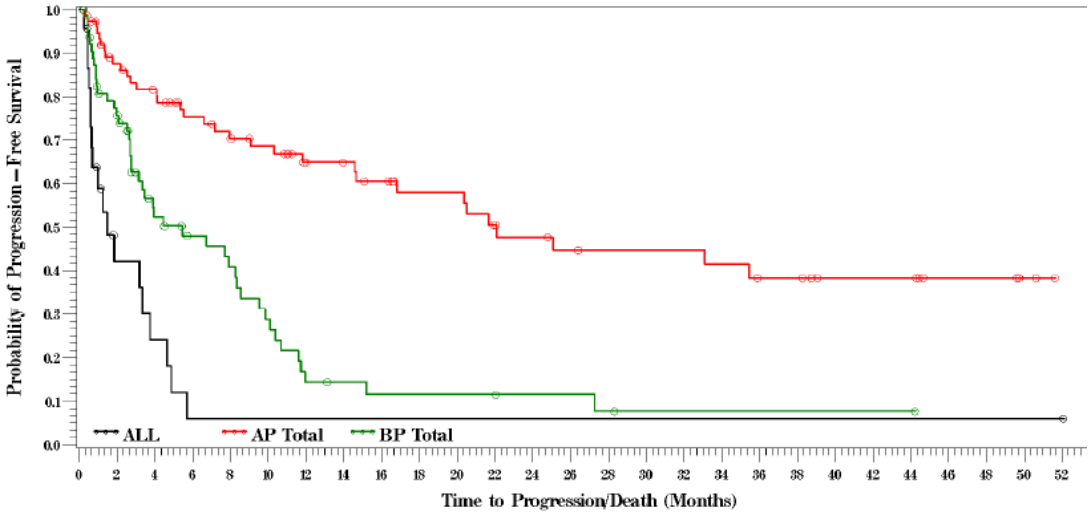
[a]The evaluable population includes patients who had a valid baseline disease assessment
[b]Includes all mutations reported for ≥2 patients assessed at baseline

[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
All haematological responses had to be confirmed

Progression-free survival (PFS)

Please see Table B98 for the definition of progression used in this study. PFS rate was calculated separately for the AP and BP groups of the advanced phase CML population, at 1 year and 2 years. The results for PFS are displayed graphically in Figure B11.

Figure B11: PFS for the advanced phase CML population (28 Mar 2011 snapshot)



NB: ALL: Acute Lymphocytic Leukaemia – not relevant to this submission

The K-M estimates of PFS for the AP group (n=76) of the advanced phase CML population were 64.9% (95% CI, 51.8-75.3) at 1 year and 47.7% (95% CI, 33.2-60.8) at 2 years. The K-M median PFS was estimated at 22.1 months for these AP patients.

For the BP group (n=64) of the advanced phase CML population, the K-M estimates of PFS were 14.4% (95% CI, 6.0-26.4) at 1 year and 11.5% (95% CI, 4.1-23.2) at 2 years. The K-M median PFS was estimated at 5.5 months for these BP patients.

Blast phase transformation

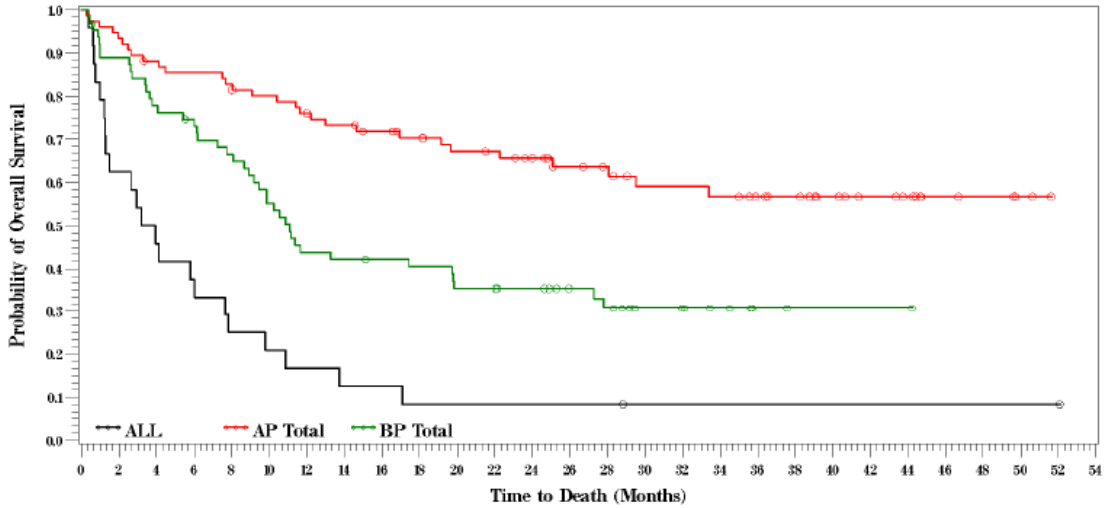
Of the 76 AP CML patients in the advanced phase CML population, 63 patients (39 in the second-line AP CML group and 24 in the multi-TKI group) had a valid post-baseline haematological assessment and were included in the analysis of BP transformation rate.

Overall, 4 (6.4%; 95% CI, 1.8-15.5) of these 63 patients had confirmed transformations to BP whilst undergoing treatment with bosutinib, 3 from the second-line group (3/39 = 7.7%; 95% CI, 1.6-20.9) and 1 from the multi-TKI group (1/24 = 4.2%; 95% CI 0.1-21.1).

Overall Survival

K-M estimates of OS at 1 year and 2 years were also generated for the advanced phase CML population. These are displayed graphically in Figure B12 .

Figure B12: Overall survival for the advanced phase CML population (28 Mar 2011 snapshot)



NB: ALL: Acute Lymphocytic Leukaemia – not relevant to this submission

The Kaplan-Meier estimates of OS for the AP group (n=76) of the advanced phase CML population were 76.0% (95% CI, 64.7—84.2) at 1 year and 65.6% (95% CI, 53.4—75.4) at 2 years. The Kaplan-Meier median OS was not reached for these AP patients.

For the BP group (n=64) of the advanced phase CML population, the Kaplan-Meier estimates of OS were 43.8% (95% CI, 31.3—55.6) at 1 year and 35.4% (95% CI, 23.8—47.3) at 2 years. The Kaplan-Meier median OS was estimated at 11.1 months for these BP patients.

Patient-reported outcomes

FACT-Leu

HRQL was assessed through the FACT-Leu scale. Clinically meaningful changes, in excess of the minimum important difference, in leukaemia symptoms were observed at weeks 12 and 24 in the AP CML group, and at weeks 4, 8, 12, 24 and 36 in the BP CML group. Since EQ-5D was also captured in Study 200 and this represents the preferred utility measure for the NICE reference case, the full FACT-Leu results are not reported here.

EQ-5D

Improvements in overall health status as assessed by the EQ-5D were observed for the AP CML and BP CML subjects over the course of treatment, as of the 28 Mar 2011 snapshot.

The mean and median EQ-5D scores, and the number of patients with an EQ-5D score at each observation, are presented along with cost-effectiveness data in Section 7.4.3, as these results are more relevant to this aspect of the submission.

6.9 Adverse events

Summary

- Adverse events in the Study 200 populations were generally transient and manageable with treatment modifications and/or concomitant medications.
- The most common non-haematological treatment-emergent adverse events (TEAEs) of any grade experienced by patients across the populations were gastrointestinal AEs including diarrhoea, nausea and vomiting.
- Notable haematological adverse events experienced by patients across the Study 200 populations included thrombocytopaenia, neutropaenia and anaemia.
- The safety profile of bosutinib was observed to be distinct from that of other TKIs, meaning that bosutinib represents a valid treatment option for patients who have experienced adverse events on other TKIs.

6.9.1 Details of any trials designed to assess safety outcomes

Study 200 was designed to primarily assess efficacy, and not safety, outcomes. Therefore the analysis of adverse events in each of the Study 200 populations is secondary to the analysis of efficacy.

6.9.2 Details of important adverse events

THIRD-LINE CP CML POPULATION

Summary of safety: Third-line CP CML population

- The most common TEAEs of any grade were predominately gastrointestinal in nature:
  - Diarrhoea: 83.1%
  - Nausea: 47.5%
  - Vomiting: 39.0%

  In the majority of cases, these events were mild in severity.
- Grade 3 or 4 TEAEs were reported in 62.7% of subjects; thrombocytopaenia and neutropaenia were the only grade 3 or 4 TEAEs reported by at least 10% of patients.
- The most commonly observed haematological TEAEs were thrombocytopaenia (34.7%), neutropaenia (17.8%) and anaemia (15.3%)
- The profile of drug-related TEAEs was similar to that of TEAEs, with diarrhoea, vomiting, thrombocytopaenia and rash representing the most common drug-related TEAEs.
- Cross-intolerance with dasatinib was low, with only 22% of patients with dasatinib intolerance experiencing the same adverse event on bosutinib as a grade 3/4 event.

All safety and tolerability data for the third line CP patient population is presented at the 28 Mar 2011 snapshot, as provided by the Khoury et al, 2012 publication[48] and the CSR[56] (minimum follow-up of 12 months).

Incidence rates of treatment-emergent adverse events (TEAEs):

Table B27 presents the incidence rates of the most common TEAEs of any grade and of grade 3/4 severity specifically.

Table B27: Rates of TEAEs (all grades) occurring in ≥10% and of TEAEs (grade 3/4) occurring in ≥5% of the third-line CP CML population

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
Any adverse event	118 (100)	74 (62.7)
Blood and lymphatic system disorders	58 (49.2)	35 (29.7)
Thrombocytopaenia	41 (34.7)	30 (25.4)
Neutropaenia	21 (17.8)	17 (14.4)
Anaemia	18 (15.3)	6 (5.1)
Cardiac disorders	13 (11.0)	5 (4.2)
Eye disorders	14 (11.9)	-
Gastrointestinal disorders	111 (94.1)	16 (13.6)
Diarrhoea	98 (83.1)	10 (8.5)
Nausea	56 (47.5)	-
Vomiting	46 (39.0)	-
Abdominal pain	23 (19.5)	-
Abdominal pain upper	20 (16.9)	-
Constipation	15 (12.7)	-
General disorders and administration site conditions	59 (50.0)	-
Fatigue	28 (23.7)	-
Pyrexia	18 (15.3)	-
Oedema peripheral	12 (10.2)	-
Hepatobiliary disorders	-	5 (4.2)
Infections and infestations	46 (39.0)	4 (3.4)
Injury, poisoning and procedural complications	15 (12.7)	-
Investigations	45 (38.1)	11 (9.3)
Alanine aminotransferase increased	18 (15.3)	8 (6.8)
Lipase increased	-	4 (3.4)
Aspartate aminotransferase increased	-	3 (2.5)
Metabolism and nutrition disorders	38 (32.2)	4 (3.4)
Decreased appetite	14 (11.9)	-
Musculoskeletal and connective tissue disorders	50 (42.4)	7 (5.9)

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
Arthralgia	17 (14.4)	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	-	4 (3.4)
Nervous system disorders	43 (36.4)	5 (4.2)
Headache	30 (25.4)	-
Dizziness	15 (12.7)	-
Psychiatric disorders	13 (11.0)	-
Respiratory, thoracic and mediastinal disorders	47 (39.8)	5 (4.2)
Cough	20 (16.9)	-
Pleural effusion	12 (10.2)	-
Skin and subcutaneous tissue disorders	59 (50.0)	8 (6.8)
Rash	34 (28.8)	5 (4.2)
Pruritus	17 (14.4)	-
Vascular disorders	12 (10.2)	-

[a]Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA)
[1]For 'All grades' adverse events, the incidence threshold of ≥10% was applied to the entire third-line CP CML population (n=118)
[1]For 'All grades' adverse events, only adverse events occurring in ≥10% of the entire third-line CP cohort (n=118)
[2] For grade 3/4 adverse events, adverse events occurring in ≥5% of any of the constituent subpopulations; see Figure B3 for details of these four subgroups (imatinib failure and dasatinib resistant, n=37; imatinib failure and dasatinib intolerant, n=50; imatinib failure and nilotinib resistant, n=27; imatinib failure and nilotinib intolerant or imatinib failure and dasatinib resistant/intolerant and nilotinib resistant/intolerant, n=4).

The most common TEAEs across all cohorts (≥ 20% incidence) were gastrointestinal toxicities (diarrhoea [83.1%], nausea [47.5%] and vomiting [39.0%]), thrombocytopaenia (34.7%), rash (28.8%), headache (25.4%) and fatigue (23.7%). The incidence of these AEs was observed to be generally similar across cohorts, with no clear pattern of differentiation based upon prior TKI exposure.

The profile of the most common drug-related TEAEs was similar to the most common TEAEs. The most common drug-related TEAEs (≥20.0% incidence) were diarrhoea (81.4%), nausea (43.2%), thrombocytopaenia (33.9%), vomiting (32.2%) and rash (22.0%). Although diarrhoea was a common drug-related TEAE, only 8% of patients experienced drug-related diarrhoea of grade 3 severity and no patients reported diarrhoea of grade 4 severity.

Diarrhoea was typically first experienced early during treatment, with a median time to onset of 1.5 days to the first diarrhoea AE event. Diarrhoeal events were also transient in nature, with median event duration of 2.0 days. In the majority of patients, diarrhoea was managed with concomitant antidiarrhoeal medication (65%). Only 3 (3%) of patients

discontinued treatment because of gastrointestinal AEs, with diarrhoea not considered the primary reason for treatment discontinuation in any patient.

Treatment-related pleural effusions were experienced by 9 (8%) patients; each of these patients had been previously exposed to dasatinib and 7 of the 9 patients had a history of pleural effusions on prior treatments. In one instance the pleural effusion was a grade 3 event; there were no cases of grade 4 severity.

Cross-intolerance of bosutinib and dasatinib

This study included a retrospective evaluation of cross-intolerance between dasatinib and bosutinib. This retrospective evaluation provides an indication of how likely it is that the reason(s) for inappropriateness of dasatinib may also render bosutinib inappropriate, where the reason(s) are based on intolerance due to adverse events. This is therefore highly relevant to the scope of this submission, since the indication for bosutinib includes patients for whom dasatinib is not appropriate.

Of 50 patients with dasatinib intolerance, 11 (22%) were found to experience the same adverse event as a grade 3/4 event when treated with bosutinib. Of 50 patients, 4 (8%) discontinued treatment with bosutinib as a result of the same AE.

The results of this retrospective evaluation by type of adverse event are presented in Table B28.

Table B28: Cross-intolerance between dasatinib and bosutinib for the third-line CP CML population

AE, n (%)*	Dasatinib intolerant	Grade 3/4 event	Discontinued bosutinib because of event
Any AE	50	11 (22)	4 (8)
Haematological events	20	8 (40)	2 (10)
Thrombocytopaenia	8	6 (75)	1 (13)
Pancytopenia	5	0	0
Neutropaenia	4	4 (100)	1 (25)
Haematoxicity	3	0	0
Cardiovascular events	3	0	1 (33)
Gastrointestinal events	6	0	0
Diarrhoea	3	0	0
Musculoskeletal events	4	0	0
Respiratory events	23	3 (13)	1 (4)
Pleural effusion	19	2 (11)	0
Dyspnoea	3	1 (33)	1 (33)
Skin disorders	5	0	0

*Includes all AEs with ≥3 patients categorized as intolerant on prior dasatinib

Death

As of the 15 February 2012 snapshot, 23 deaths were reported in the study overall. Of these, 6 occurred during treatment or within 30 days of receipt of the last dose of study medication, whilst the other 17 patients died at least more than 30 days after discontinuing bosutinib. Only one death was considered to be the result of a treatment-

related adverse event. This was a case of gastrointestinal bleeding which occurred 78 days after treatment initiation in the setting of grade 4 thrombocytopaenia.

ADVANCED PHASE CML POPULATION

Summary of safety: advanced phase CML population

- The most common TEAEs of any grade were predominately gastrointestinal in nature:
  - Diarrhoea (85.5% AP; 65.6% BP)
  - Nausea (44.7% AP; 50.0% BP)
  - Vomiting (44.7% AP; 39.1% BP)

  In the majority of cases, these events were mild in severity

- Grade 3 or 4 TEAEs were reported in 86.8% of AP patients and 76.7% of BP patients; the most common grade 3/4 TEAEs were
  - Thrombocytopaenia (32.9%), anaemia (30.3%) and neutropaenia (14.5%) in the AP cohort
  - Thrombocytopaenia (26.6%), neutropaenia (20.3%), anaemia (18.8%) and leukopaenia (10.9%) in the BP cohort

All safety and tolerability data for the advanced phase populations from Study 200 are from data snapshot 28 Mar 2011, and are taken from the Study 200 CSR as no publication is available of the advanced phase patients.[56]

Incidence rates of treatment-emergent adverse events (TEAEs)

Table B29 presents the incidence rates of the most common TEAEs of any grade and of grade 3/4 severity specifically.

Table B29: Rates of TEAEs (all grades) occurring in ≥10% and of TEAEs (grade 3/4) occurring in ≥5% of the AP or BP populations[2]

	All grades (≥10% incidence)[1]		Grade 3/4 (≥5% incidence)[2]	
AE[a], n (%)	**AP Total (n=76)**	**BP Total (n=64)**	**AP Total (n=76)**	**BP Total (n=64)**
Any adverse event	76 (100)	63 (98.4)	66 (86.8)	49 (76.7)
Blood and lymphatic system disorders	56 (73.7)	35 (54.7)	42 (55.3)	29 (45.3)
Anaemia	32 (42.1)	18 (28.1)	23 (30.3)	12 (18.8)
Thrombocytopaenia	32 (42.1)	18 (28.1)	25 (32.9)	17 (26.6)
Neutropaenia	12 (15.8)	13 (20.3)	11 (14.5)	13 (20.3)
Febrile neutropaenia	-	-	1 (1.3)	2 (3.1)
Leukopenia	6 (7.9)	7 (10.9)	3 (3.9)	7 (10.9)
Leukocytosis	-	-	3 (3.9)	2 (3.1)
Cardiac disorders	14 (18.4)	8 (12.5)	5 (6.6)	3 (4.7)
Eye disorders	15 (19.7)	8 (12.5)	0	3 (4.7)
Gastrointestinal disorders	72 (94.7)	53 (82.8)	14 (18.4)	14 (21.9)
Diarrhoea	65 (85.5)	42 (65.6)	3 (3.9)	4 (6.3)
Nausea	34 (44.7)	32 (50.0)	-	-
Vomiting	34 (44.7)	25 (39.1)	3 (3.9)	2 (3.1)

	All grades (≥10% incidence)[1]		Grade 3/4 (≥5% incidence)[2]	
AE[a], n (%)	**AP Total (n=76)**	**BP Total (n=64)**	**AP Total (n=76)**	**BP Total (n=64)**
Abdominal pain	20 (26.3)	11 (17.2)	1 (1.3)	2 (3.1)
Abdominal pain upper	10 (13.2)	5 (7.8)	-	-
Constipation	13 (17.1)	7 (10.9)	-	-
General disorders and administration site conditions	47 (61.8)	41 (64.1)	7 (9.2)	10 (15.6)
Pyrexia	28 (36.8)	22 (34.4)	1 (1.3)	2 (3.1)
Fatigue	15 (19.7)	12 (18.8)	3 (3.9)	2 (3.1)
Asthenia	10 (13.2)	4 (6.3)	-	-
General physical health deterioration	-	-	0	2 (3.1)
Hepatobiliary disorders	-	-	2 (2.6)	3 (4.7)
Hyperbilirubinaemia	-	-	0	3 (4.7)
Infections and infestations	42 (55.3)	34 (53.1)	12 (15.8)	14 (21.9)
Pneumonia	8 (10.5)	10 (15.6)	7 (9.2)	4 (6.3)
Sepsis	-	-	3 (3.9)	1 (1.6)
Upper respiratory tract infection	8 (10.5)	2 (3.1)	-	-
Investigations	38 (50.0)	31 (48.4)	14 (18.4)	11 (17.2)
Platelet count decreased	5 (6.6)	5 (7.8)	5 (6.6)	5 (7.8)
Alanine aminotransferase increased	10 (13.2)	4 (6.3)	6 (7.9)	1 (1.6)
Neutrophil count decreased	-	-	1 (1.3)	0
Aspartate aminotransferase increased	11 (14.5)	4 (6.3)	4 (5.3)	0
Lipase increased	-	-	1 (1.3)	2 (3.1)
Metabolism and nutrition disorders	27 (35.5)	22 (34.4)	9 (11.8)	7 (10.9)
Decreased appetite	6 (7.9)	12 (18.8)	-	-
Hypokalaemia	-	-	1 (1.3)	3 (4.7)
Hypophosphataemia	-	-	3 (3.9)	1 (1.6)
Musculoskeletal and connective tissue disorders	26 (34.2)	24 (37.5)	4 (5.3)	4 (6.3)
Arthralgia	10 (13.2)	7 (10.9)	-	-
Pain in extremity	10 (13.2)	6 (9.4)	-	-
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	11 (14.5)	7 (10.9)	7 (9.2)	4 (6.3)
Blast crisis in myelogenous leukaemia	-	-	2 (2.6)	1 (1.6)
Nervous system disorders	24 (31.6)	26 (40.6)	4 (5.3)	6 (9.4)
Headache	12 (15.8)	13 (20.3)	2 (2.6)	4 (6.3)

	All grades (≥10% incidence)[1]		Grade 3/4 (≥5% incidence)[2]	
AE[a], n (%)	**AP Total (n=76)**	**BP Total (n=64)**	**AP Total (n=76)**	**BP Total (n=64)**
Dizziness	8 (10.5)	9 (14.1)	-	-
Psychiatric disorders	16 (21.1)	11 (17.2)	1 (1.3)	2 (3.1)
Renal and urinary disorders	11 (14.5)	8 (12.5)	1 (1.3)	4 (6.3)
Renal failure acute	-	-	0	2 (3.1)
Respiratory, thoracic and mediastinal disorders	35 (46.1)	23 (35.9)	8 (10.5)	6 (9.4)
Dyspnoea	14 (18.4)	12 (18.8)	6 (7.9)	2 (3.1)
Oropharyngeal pain	8 (10.5)	2 (3.1)	-	-
Pleural effusion	9 (11.8)	4 (6.3)	4 (5.3)	2 (3.1)
Skin and subcutaneous tissue disorders	42 (55.3)	30 (46.9)	3 (3.9)	5 (7.8)
Rash	25 (32.9)	20 (31.3)	3 (3.9)	2 (3.1)
Vascular disorders	11 (14.5)	7 (10.9)	5 (6.6)	1 (1.6)
Hypertension	7 (9.2)	2 (3.1)	4 (5.3)	1 (1.6)

[a]Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA)
[1]For 'All grades' adverse events, only adverse events occurring in ≥10% of the entire AP (n=76) or BP cohorts are included (n=64)
[2] For grade 3/4 adverse events, adverse events occurring in ≥5% of any of the constituent subpopulations (AP second-line; AP multi-TKI; BP second-line; BP multi-TKI) are included (see Figure B4 for details of these 4 subgroups

The most common TEAEs were similar in both the AP and BP populations, with gastrointestinal toxicities, pyrexia, anaemia and thrombocytopaenia amongst the most common TEAEs in both populations.

The most common drug-related TEAEs were generally also the most common TEAEs, with diarrhoea (82.9% AP; 62.5% BP), vomiting (40.8% AP; 35.9% BP), nausea (39.5% AP; 43.8% BP) and rash (30.3% AP; 25.0% BP) amongst the most common drug-related TEAEs in both the AP and BP populations. The most common drug-related TEAEs of grade 3 or grade 4 severity were thrombocytopaenia (25.0%), neutropaenia (14.5%) and anaemia (10.5%) in the AP population and thrombocytopaenia (18.8%) and neutropaenia (18.8%) in the BP population.

6.9.3 Brief overview of the safety of the technology

Bosutinib demonstrates a manageable safety profile in CP patients and advanced phase patients previously exposed to one or more TKIs. Furthermore, the safety profile of bosutinib in these populations is seen to be differentiated from the safety profiles of the other currently available TKIs. This manageable and distinct safety profile of bosutinib means that bosutinib may offer a valuable alternative for those patients who are unsuitable for imatinib, dasatinib and nilotinib due to prior intolerance or the presence of specific co-morbidities. These patients represent a subgroup of CML patients with a high unmet medical need.

The following case report from Study 200 highlights the benefit provided by the distinct and manageable safety profile of bosutinib in enabling treatment to be provided to patients with intolerance to previous TKI therapy.[71]

[redacted]

A safety profile that is manageable (as observed with bosutinib treatment) is relevant to the decision problem because it means that treatment with bosutinib is not expected to have any impact on utility. This expectation is reinforced by the observed utility scores for bosutinib, as discussed in 6.8.5 and presented in Section 7.4.3.

It is noted that the safety profile of bosutinib, as observed in Study 200, will be associated with additional costs resulting from management of adverse events, for example, the management of diarrhoea AEs that occur. These additional costs will be fully incorporated into the evaluation of cost-effectiveness presented in Section 7.

COMPARATOR NON-RCT DATA

Summary of comparator non-RCT data

- The systematic review identified 13 publications that reported comparator data in a setting relevant to this submission. The majority of these studies presented data on SCT as a comparator.
- A naïve indirect comparison highlighted the potential benefits of bosutinib over SCT and hydroxycarbamide in terms of overall survival in both the chronic and advanced phases of the disease in patients previously treated with one or more TKIs.
- There was a notable lack of adverse event data in the comparator publications, making an indirect comparison with regards to safety unfeasible.

As described in Section 6.1, a systematic review was performed to identify all clinical evidence for bosutinib and the comparators to bosutinib relevant to this submission. The comparators considered were:

- Hydroxycarbamide (or hydroxyurea as a proxy for best supportive care)
- Allogeneic stem cell transplantation (SCT)
- Interferon alpha

In total, 13 publications were identified that reported comparator data in a setting relevant to this submission, as follows:

- Hydroxycarbamide/BSC: n=2[36, 37]
- SCT: n=12[36, 57, 58, 60-62, 72-77]
  (One study reported on both hydroxycarbamide/BSC and SCT)
- Interferon alpha: No studies were identified which reported on interferon alpha used in a refractory setting (post-TKI or post-other treatments)

Study design and data availability

All 13 studies were of a single-arm design. One study was a planned interim analysis of a cohort of 84 patients from a randomised controlled trial (RCT) of different imatinib regimens who underwent SCT (Saussele 2010)[60], while the remaining 12 comparator publications were retrospective reviews of medical records (n=7) or prospective single-arm cohort studies (n=5).

Studies were quality assessed and results of the quality assessment are reported in Appendix 10.7. Seven of the comparator studies were assessed to be of good quality (Saussele 2010[60], Jabbour 2011[58], Jabbour 2006[75], Markiewicz 2011[76], Jabbour 2007[73], Holroyd 2010[62], Weisser 2007[61]) with the remaining six (mainly retrospective) judged to be poor quality [36, 37, 57, 72, 74, 77]

Allogeneic stem cell transplant (SCT)

Allogeneic stem cell transplant is a procedure in which a person receives blood-forming stem cells (cells from which all blood cells develop) from a genetically similar, but not identical, donor. While this procedure is potentially curative in the context of CML, it is associated with considerable morbidity and mortality risks.[78]

Of the 12 SCT studies, sample sizes ranged from 8 to 145; four studies (Schleuning 2010[57], Holroyd 2010[62], Markiewicz 2011[76], Benedicte 2010[77]) were reported as conference abstracts only and therefore only limited results were available.

Five SCT studies (Jabbour 2006[75], Jabbour 2007[73], Markiewicz 2011[76], Benedicte 2010[77], Weisser 2007[61]) did not stratify results according to whether patients were in CP, AP or BP. These five studies are therefore of limited use for making comparisons with the bosutinib evidence due to observed differences in estimated survival times and treatment

responses previously observed in the CP, AP and BP phases of CML. [36, 56, 62] For this reason, the five studies reporting results for mixed phase populations only will not be considered further in this submission. However, studies that reported results for separate CP and advanced disease, but did not stratify by AP or BP were still included in the review (Bornhauser 2006[72], Jabbour 2011[58], Saussele 2010[60]).

Hydroxycarbamide (BSC)

Hydroxycarbamide (also known as hydroxyurea) is an oral medication (1–3 g per day as a single dose on an empty stomach) currently used in CML primarily to stabilise patients with hyperleukocytosis or as palliative therapy for patients who have not responded to other therapies.[79]

There was a paucity of data examining hydroxycarbamide following failure with a first-line treatment and only two studies were included in the systematic review.[36, 37] Neither of these studies were strictly eligible but were included because they were the sole source of evidence for hydroxycarbamide in a population with some comparability to the licensed population for bosutinib.

The first of the two studies (Kantarjian et al, 2007[36]), enrolled patients who had failed on prior imatinib, and had subsequently received treatment with SCT (n=8), dasatinib/nilotinib (n=35) or 'other' treatments (n=61). Although not recorded within the publication, Hoyle and colleagues[80] in TA251 (appraisal of the TKIs in newly diagnosed CML patients) report the details of the 'other' treatment arm.[35] Of the 'other' treatment group, only 12 of the 61 patients (20%) received hydroxycarbamide. The remaining patients received regimens including ionafarnib (n=9), decitabine (n=6), cytarabine (n=6), homoharringtonine (n=5), IFN-α (n=3) and other treatments (n=3). Survival data were reported for each of the three treatment groups but no separate survival data were reported for the subset of patients in the 'other' treatment group, including the hydroxycarbamide patients.

In the second included study (Ibrahim 2011[37]), 246 CP CML patients were enrolled on a clinical trial in which patients were randomised to receive either IFN-α or chemotherapy. In total, 122 patients failed to respond to IFN-α but then remained on IFN-α treatment, while 124 patients abandoned IFN-α (of these, 117 patients were then treated with hydroxycarbamide and 7 patients with busulfan, in a second-line setting). It should be noted that a second-line setting following IFN-α treatment in the first-line is not strictly comparable with the bosutinib licensed population or Study 200 population, since all patients in these populations must have failed one or more TKIs. Results were not reported separately for those patients who received hydroxycarbamide. This lack of data for hydroxycarbamide/BSC is unsurprising as current expert guidelines agree that in cases of suboptimal response or intolerance to imatinib, SCT or second-generation TKIs are the recommended treatment options.[81] Best-supportive care options such as hydroxycarbamide are rarely used, and only as a last resort, in clinical practice.

A summary of all studies identified by the systematic review as reporting on either bosutinib or its comparators (16 studies in total) is presented in Table B30. As described above, not all of these studies were considered for the presentation of results, and Table B30 notes those which were excluded. Those studies for which results are presented in this submission are highlighted in **bold** in Table B30. For these studies, the intervention under consideration and also the disease setting evaluated, in terms of the disease phase and line of therapy of the patient population, are noted.

Table B30: Summary of all non-RCT studies identified in the clinical systematic review

Publication	Intervention	Phase of disease	Included/excluded
Kantarjian 2007[36]	**Hydroxycarbamide SCT**	**All**	**Included: Second-line (post-imatinib failure)**
Ibrahim 2011[37]	**Hydroxycarbamide SCT**	**CP only**	**Included: Second-line (post IFN failure)**
Bornhäuser 2006[72]	**SCT**	**All**	**Included: Second-line (post-imatinib failure)**
Oehler 2007[74]	**SCT**	**All**	**Included: Second-line (post-imatinib failure)**
Saussele 2010[60]	**SCT**	**All**	**Included: Multiple lines**
Schleuning 2010[57] (Abstract only†)	**SCT**	**All**	**Included: Multiple lines**
Jabbour 2011[58]	**SCT**	**All**	**Included: Multiple lines**
Holroyd 2010[62] (Abstract only†)	**SCT**	**AP and BP only**	**Included: Multiple lines**
Jabbour 2006§ [75]	SCT	Mixed	Excluded: no stratification of results by disease phase
Markiewicz 2011‡ [76]	SCT	Mixed	Excluded: no stratification of results by disease phase
Benedicte 2010 [77]	SCT	Mixed	Excluded: no stratification of results by disease phase
Jabbour 2007§ [73]	SCT	Mixed	Excluded: no stratification of results by disease phase
Weisser 2007 [61]	SCT	Mixed	Excluded: no stratification of results by disease phase
Cortes 2011* [5]	**Bosutinib**	**CP**	**Included: Second-line (post-imatinib failure)**
Trask 2012* [82]	**Bosutinib**	**CP**	**Included: Second-line (post-imatinib failure)**
Khoury 2012* [48]	**Bosutinib**	**CP**	**Included: Third-line**

†These sources represent abstracts presented at the 52nd Annual Meeting of ASH; no full publication is available for these sources, hence the data presented is limited to that present in the abstract

*Please note that these three publications report on the same study (Study 200). The 'Cortes 2011' and 'Trask 2012' publications report on the same second-line CP CML population and results from these publications are not considered in the main submission. The results from the 'Khoury 2012' publication, which reports on the third-line CP CML population, are presented in Section 6.8.5, along with the other data demonstrating the efficacy and safety of bosutinib in this patient population

§Although results from this study were reported for individual patients, the number of patients in each disease phase at the time of transplantation is low and therefore this study has been considered as reporting a mixed disease status population

‡Note: 9 of these 48 patients underwent SCT at the third or later line of therapy. This study has been considered as reporting 'second-line therapy' because the majority (39/48=81%) underwent SCT in this setting

Outcome reporting

Comparator studies had relatively good survival outcome coverage with data reported in:

- Five studies of predominantly second line CP CML patients (Kantarjian 2007[36], Ibrahim 2011[37], Bornhauser 2006[72], Saussele 2010[60], Schleuning 2010[57])
- One study of predominantly third line CP CML patients (Jabbour 2011[58])
- One study of patients with stratified AP CML and BP CML results after multiple lines of treatment (Holroyd 2010[62]), and one study that included a sub-group of AP patients who had failed imatinib (Oehler 2007[74]).
- Three studies of patients with combined AP and BP advanced disease CML results (Bornhauser 2006[72], Jabbour 2011[58], Saussele 2010[60]) and one study (Oehler 2007[74]) reporting on a sub-group of advanced (AP and BP) CML patients

In contrast only two comparator SCT studies (Jabbour 2011[58]; Sauselle 2010[60]) reported response data for specific CML disease phases.

- One study reported complete molecular response (CMR) in CP patients in 1) the second-line setting and 2) patients with advanced (AP and BP) disease (Sauselle 2010).[60]
- A second study, (Jabbour 2011[58]) reported CCyR, CMR and major molecular response in patients with 1) CP in a third line setting, and 2) patients in advanced phase disease following multiple lines of prior therapy.
- Response data was reported in neither of the hydroxycarbamide studies (Kantarijan 2007[36], Ibrahim 2011[37]).

With regard to safety, no AE data were reported in the two hydroxycarbamide/BSC studies (Kantarjian 2007[36], Ibrahim 2011[37]) and otherwise AE data was restricted to the incidence of acute/chronic graft-versus-host-disease (GVHD), reported in three SCT studies (Saussele 2010[60], Jabbour 2011[58], Holroyd 2010[62]). Therefore, it was not possible to conduct a qualitative comparison of the safety profile of bosutinib and comparator treatments.

Study characteristics and results

Baseline characteristics of the eight comparator studies are presented inTable B31. Results from the eight comparator studies are stratified by response, survival/progression and safety results, presented in Table B32, Table B33 and Table B34, respectively.

Table B31: Characteristics of studies of comparator therapies in a second-line CP CML population

Study	Intervention and population	Number enrolled	Phase of CML	Duration of follow-up
Kantarjian 2007[36]	**Second-line hydroxycarbamide:** Post imatinib failure, patients received: •SCT (n=8) •TKI (n=35) •Other[§], n=61 *[12/61 received hydroxycarbamide]*	420[¶]	CP, n=277 AP, n=112 BP, n=73	3 years
Ibrahim 2011[37]	**Second-line hydroxycarbamide:** TKI cohort: following imatinib failure, patients treated with: *Second line* • Dasatinib (n=67) • Nilotinib (n=37)	Imatinib, n=283 IFN, n=246	All patients were in CP	TKI cohort: Median 67.9 months (range 14–122)

Study	Intervention and population	Number enrolled	Phase of CML	Duration of follow-up
	Third line • Alternative TKI (n=21) IFN cohort: following IFN failure (historical control) patients were treated with: • IFN-α containing regimen, n=122/246 (50%) • Hydroxycarbamide, n=117/246 (48%) • Busulfan, n=7/246 (3%)			IFN cohort: Median 50.4 months (range 2–202 months)
Bornhäuser 2006[72]	**Second-line SCT**: CML patients receiving SCT after imatinib failure (mean age 45 years; 57% male) receiving SCT in 10 centres.	61	CP, n=19 AP, n=17 BP, n=24	Median 18 months (range 2–62 months)
Oehler 2007[74]	**Second-line SCT:** CML patients (median age 40.1 years; 64% male†) receiving imatinib‡ (median duration 0.83 years) prior to SCT.	145	CP, n=117† AP, n=22† BP, n=6†	3 years
Saussele 2010[60]	**Second-, third- and fourth-line SCT:** CML patients (mean age 38 years; 57% male), all patients received imatinib; of these 5 patients received a second or third TKI prior to SCT. The proportion of patients receiving SCT at third or fourth line is not known.	65	CP, n=37 AP, n=3 BP, n=25	Median, 26 months (range 1–50)
Schleuning 2010[57]	**Second- and third- line SCT:** CML patients were treated with nilotinib and/or dasatinib (had not received first-line imatinib) prior to SCT. The proportion of patients receiving one versus both of the above TKIs is not known.	56	NR	19 months
Jabbour 2011[58]	**Second-, third- and fourth-line SCT:** CML patients (median age 44 years; 57% male) received SCT at: • Second-line: 18 (38%) patients received imatinib only • Third-line: 29 (62%) patients received imatinib and a second TKI • Fourth-line: 5 (11%) patients received imatinib and two more TKIs	47	CP, n=16 AP, n=12 BP, n=9 Second CP, n=10‡	Median 22 months (range 5–53 months)
Holroyd 2010[62]	**Second-, third- and fourth-line SCT:** CML patients (median age 40.8	43	NR	3 years

Study	Intervention and population	Number enrolled	Phase of CML	Duration of follow-up
	years) received SCT at: • Second line: 33 patients received only 1 TKI (imatinib or dasatinib) • Third-line: 8 patients received a second TKI (dasatinib) • Fourth-line: 2 patients received a third TKI (nilotinib)			

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia, CP, chronic phase; SCT, allogeneic stem cell transplantation; IFN, interferon; NR, not reported; TKI, tyrosine kinase inhibitor; NR: Not reported

[§]Other treatment in 61 patients included: tipifarnib ± other (n=17); hydroxycarbamide (n=12); lonafarnib ± other (n=9); decitabine (n=6); cytarabine ± other (n=6); homoharringtonine (n=5); interferon-a (n=3); and others (n=3).

[¶]Patients in whom imatinib therapy was discontinued for either clear-cut resistance or recurrence (n=374), or for imatinib toxicities (n=46)

[†]Data for whole population (n=145), not just the subset of patients who had suboptimal/loss of response to imatinib (n=31)

[‡]55 patients received therapies in addition to imatinib: IFN-α or IFN in combination with cytarabine (n=23), hydroxycarbamide (n=18), chemotherapy (n=13), vaccine (n=1)

[‡]AP, BP and second CP patients were grouped as 'advanced phase patients'

Table B32: Response results from studies of comparator therapies

Study	Response	
	Chronic phase	Advanced phase
Saussele 2010[60]	• CMR, 89%	• CMR, 93%
Jabbour 2011[58]	*Mutated BCR-ABL1(n=4)* • CMR, 100% *Non-mutated BCR-ABL1(n=12)* • CMR, 83% • CCyR, 8%	*Mutated BCR-ABL1 (n=15)* • CMR, 47% • CCyR, 33% *Non-mutated BCR-ABL1* (n=*16)* • CMR, 62% • MMR, 6% • CCyR, 31%
Holroyd 2010[62]	• *NR*	Post-transplant, 11 relapsed patients received TKIs: • Molecular relapse, n=5 • Cytogenetic relapse, n=1 • Haematological relapse, n=4 • GVHD, n=1

AP, accelerated phase; CMR, complete molecular response; CP, chronic phase; CCyR, complete cytogenetic response; MMR, major molecular response; NR: Not reported

Table B33: Survival/progression results from studies of comparator therapies

Study	Survival / Progression	
	Chronic phase	Advanced phase

Study	Survival / Progression	
	Chronic phase	**Advanced phase**
Kantarjian 2007[36]	**Mortality (5 years)** • 'Other treatment'¶ cohort: 24/68 (35%) • SCT cohort: 4/10 (40%) **Overall Survival** • 'Other treatment'¶ cohort (n=61) ○ 2 year OS: 77% ○ 3 year OS: 70% • SCT cohort: (n=8) ○ 2 year OS: 60% ○ 3 year OS: 45%	**Mortality (5 years)** • 'Other treatment'¶ cohort: ○ AP: 53/64 (83%) ○ BP: 85/95 (90%) • SCT cohort ○ AP: 1/5 (20%) ○ BP: 5/8 (63%)
Ibrahim 2011[37]	**Overall Survival (7 years)** • IFN failure cohort: 34.4%	**NR**
Bornhäuser 2006[72]	**Disease Free Survival** • 18 months, 34.6%	**Disease Free Survival** • 18 months, 29.4%
Oehler 2007[74]	**Mortality (3 years)** • Suboptimal/loss of response to prior imatinib: 26% (8/31) § • Good response to prior imatinib: 5% (2/38)	**Mortality (3 years)** • Patients whose disease progressed from CP whilst on imatinib: 45% (19/42) • Patients in advanced phases with no prior response to imatinib: 35% (6/17)
Saussele 2010[60]	**Overall Survival** *3 years,* 94.1 (95% CI 83.8–99.4%)	**Overall Survival** *3 years,* 59% (95% CI 38.6-77.5%)
	Mortality n=2 (transplant related)	**Mortality** n=10/28 (36%) Disease-related, n=4 Treatment-related, n=5 Unclassified, n=1
Schleuning 2010[57]	**Survival (transplanted in first CP)** *2 years*, 85%	**NR**
Jabbour 2011[58]	**OS** *2 years,* 72% (95% CI 49–96)	**OS** *2 years,* 59% (95% CI 41–77)
	Mortality (22 months) • Mutated *BCR-ABL1*: n=2 (50%) • Non-mutated *BCR-ABL1*: n=2 (17%)	**Mortality (22 months)** • Mutated BCR-ABL1: n=8 (53%) • Non-Mutated BCR-ABL1: n=4 (25%)
Holroyd 2010[62]	***NR***	**Mortality,** n=13/43
	NR	**Disease-free survival** • 1 year, 23% • 3 years, 16%

Study	Survival / Progression	
	Chronic phase	**Advanced phase**
	NR	**Overall survival** *AP* • 1 year, 54.2% • 3 years, 50% *CP>1* • 1 year, 49.4% • 3 years, 29.6% *BP* • 1 year, 0% • 3 years, 0%

NR: Not reported
[†]Evaluable population
[§]Active phase of the study defined as the period between the first dose of bosutinib until 30 days after the last dose of study drug.
[¶]Other treatment in 61 patients included: tipifarnib ± other (n=17); hydroxycarbamide (n=12); lonafarnib ± other (n=9); decitabine (n=6); cytarabine ± other (n=6); homoharringtonine (n=5); interferon-a (n=3); and others (n=3).

Table B34: Safety results from studies of comparator therapies

Study	Safety	
	Chronic phase	**Advanced phase**
Oehler 2007[74]	Results only reported for total population of imatinib-treated patients (n=145), not subset of patients who had suboptimal/loss of response to imatinib (n=31)	Results only reported for total population of imatinib-treated patients (n=145), not subset of patients who had suboptimal/loss of response to imatinib (n=31)
Saussele 2010[60]	**GVHD** All, 68% Grade 3–4, 19% Chronic, 36%	**GVHD** All, 71% Grade 3–4, 35% Chronic, 21%
Holroyd 2010[62]	NR	**GVHD** *Acute:* Grade 2–4, 24% *Chronic:* Extensive, 54%

Summary of results of comparators and naïve indirect comparison with bosutinib

CP patients in CML

Response

Two of the SCT studies reported response rates, while neither of the hydroxycarbamide studies reported these outcomes. However, the relevance of comparing response rates between SCT and a TKI is questionable, since SCT is essentially a cure and therefore the majority of patients would be expected to achieve complete remission.

One comparator study (Saussele 2010)[60] of SCT reported response data (CMR) following second-line treatment in CP CML patients and one study (Jabbour 2011[58]) of predominately third-line CP CML patients reported CCyR, MMR and CMR. The paucity of response data from the comparator studies limits the robustness of any conclusions drawn regarding the comparative efficacy of the comparators and bosutinib.

- In patients receiving SCT at second-line or later (majority third-line) CCyR occurred in 6% (1/16), at a median treatment duration of 22 months (Jabbour

2011[58]), **compared to 30.6% of third-line bosutinib patients (28 March 2011 snapshot)**

- Jabbour 2011 also reported a MMR of 0% in patients who received SCT at a median treatment duration of 22 months (Jabbour 2011[58]), **compared to 15% of third-line CP bosutinib patients (28 March 2011 snapshot).**
- Saussele 2010 reported that in patients receiving SCT at second-line, CMR was achieved by 89% (25/29) of patients (median follow-up of 26 months) (Saussele 2010).[60] Similarly Jabbour reported that CMR was 88% at a median treatment duration of 22 months [58], **compared to 11% for third-line bosutinib patients (28 Mar 2011 snapshot).**

Survival

Both studies that included patients treated with hydroxycarbamide at second-line reported survival estimates and three studies of SCT in patients previously treated with 1 or more TKI reported survival data:

- In Kantarjian (2007)[36], overall survival of 61 imatinib failure CP patients who received 'other therapy' (of which 12 received hydroxycarbamide) was estimated at 77% at 2 years and 70% at 3 years. Ibrahim (2011)[37] reported an unadjusted 7-year survival estimate of 34.4% for 246 patients who had failed interferon-alpha as first-line therapy and were receiving other second line treatments (of which 117 received hydroxycarbamide).
- Saussele 2010[60] reported OS at 3 years after SCT of 94.1% (95% CI 83.8–99.4%) in 37 CP patients who had failed imatinib. Schleuning 2010[57] reported a probability of OS at 2 years of 85% (for patients transplanted in first CP). Jabbour 2011[58] reported a 2-year OS of 72% (95% CI 49–96) in CP CML patients
- **In comparison, as of 28 March 2011, the 1-year and 2-year K-M estimates of OS in the all-treated population were 91% and 82% in the third-line CP patients. With continued follow up (15 February 2012), the 1-year and 2-year K-M estimates of OS in the all-treated population were 91.4% and 84.0%, respectively.**

Adverse events

AE data (incidence of GVHD) were provided for only one SCT study (Saussele 2010[60]). The remaining hydroxycarbamide/BSC and SCT studies either did not report AE data (Jabbour 2011[57, 58]; Schleuning 2010), or reported AE data for the total study population, but not the subset of patients with CP CML only (Kantarjian 2007[36], Ibrahim 2011[37], Bornhauser 2006[72], Oehler 2007[74]). This paucity of AE data from comparator studies in the second-line setting does not allow for a robust comparison of the safety profile of bosutinib and its comparators.

Advanced phase CML patients

Response

No comparator studies reported separate response data on patients with AP or BP CML. However, two SCT studies (Jabbour 2011[58], Saussele 2010[60]) reported response rate data for a combined group of CML patients with AP, BP, or in second CP.

Jabbour (2011)[58] reported on 31 patients in advanced phase (AP N=12, BP N=9, second CP N=10) at SCT, the majority of whom had received two prior TKI therapies, with response results stratified by BCR-ABL1 mutation. The only response outcome that was reported in both the bosutinib and comparator SCT studies was CCyR, and this was not reported in Saussele (2010).[60] As for the chronic phase studies, the paucity of response data from the advanced phase comparator studies limits the robustness of any conclusions drawn regarding the comparative efficacy of the comparators and bosutinib.

- For the mutated BCR-ABL1 population (N=15) and non-mutated BCR-ABL1 advanced disease population (N=16) the rates of CCyR were 33% and 31% respectively (Jabbour 2011).
- **In comparison rates of CCyR were 24.6% (17/69; 33% in 2nd line AP patients; 11.1% in multi-TKI AP patients) and 20.4% (11/54; 31% 2nd line BP patients; 8% in multi-TKI BP patients) in bosutinib patients at a minimum follow-up of 12 months in AP and 18 months in BP respectively.**

Survival

One comparator study reported stratified survival data on patients with AP or BP CML respectively. This study (Holroyd 2010[62]) focused exclusively on SCT in advanced disease patients who had received multiple TKIs. A second study (Oehler 2007[74]) reported survival for a subgroup of AP patients who had progressed from CP to AP on imatinib prior to SCT, and a second separate subgroup of advanced disease patients (AP+BP) who had no response to imatinib prior to SCT. Three additional SCT studies (Bornhauser 2006[72], Jabbour 2011[58], Saussele 2010[60]) reported survival data for a combined group of CML patients in AP, BP, or second CP.

- Holroyd 2010[62] reported OS estimates in CML patients in AP (N=24) and BP (N=2) post-SCT at 1 year (AP 54.2%; BP 0%) and 3 years (AP 50%; BP 0%)
- Oehler 2007[74] found that in a sub-group of 42 AP patients (progressed from CP to AP on imatinib prior to SCT) the OS rate at 3 years following transplantation was 55% (19/42 died), while in 17 patients with advanced disease (AP+BP) who had no response to imatinib the OS rate was 65% (6/17 died) at the same time-point.
- In a CML advanced disease group (AP+BP+2nd CP) of 31 patients, OS was 59% (95% CI 41-77%) at 2 years (Jabbour 2011[58]).
- A fourth study (Saussele 2010[60]) of 28 advanced disease (AP+BP) CML patients reported an OS of 58.8% (95% CI 38.6 – 77.5%) 3 years after SCT.
- **This compared with K-M OS estimates of 76% (95% CI 64.7- 84.2; AP N=76) and 43.8% (95% CI 31.3-55.6; BP N=64) at 1 year and 65.6% (95% CI 53.4 – 75.4; AP) and 35.4% (95% CI 23.8- 47.3; BP) at 2 years in advanced disease patients receiving bosutinib (AP minimum follow-up 12 months; BP minimum follow-up 18 months).**

Adverse events

The relevant comparator studies (Bornhauser 2006[72], Holroyd 2010[62],Jabbour 2011[58],Oehler 2007[74], Saussele 2010[60]) did not report AEs for advanced disease CML patients with the exception of the incidence of graft-versus-host disease (GVHD) reported in 3 studies (Bornhauser 2006[72], Holroyd 2010[62], Sauselle 2010[60]). Although some additional grade 3/4 AEs were reported in Bornhauser (2006)[72] this was only for the total cohort of patients and did not stratify results into CP and advanced disease CML sub-groups. Similarly Oehler (2007)[74] reported AEs for the total population of imatinib treated patients, but not for the sub-groups who could be defined as imatinib failures. Therefore it was not possible to conduct a naïve indirect comparison of the bosutinib AE data with the comparator studies.

6.10 *Interpretation of clinical evidence*

SUMMARY OF INTERPRETATION OF CLINICAL EVIDENCE

- The evidence for bosutinib (Study 200) in patients who have previously tried and failed on imatinib therapy and further treatment with dasatinib or nilotinib is robust and detailed for this population.
    - Study 200 represents a large study population for CML disease across all three phases of CML (third-line CP, n=118; AP, n=76; BP, n=64)
    - A variety of clinical endpoints have been considered, including response, OS, PFS and quality-of-life measures (EQ-5D)
- Bosutinib exhibited notable efficacy in terms of response, survival and quality of life across CP, AP and BP in Study 200 and a similar efficacy was seen in a post-hoc analysis of those patients expected to meet the unmet need population described by the license (see Appendix 10.16).
- Overall, the safety data indicate that bosutinib has a distinct yet manageable safety profile.
- The systematic review identified no RCTs evaluating the NICE-defined comparator treatments in the relevant population. Therefore, no meta-analyses of head-to-head studies or formal indirect comparisons using network meta-analysis (NMA) of bosutinib and its comparators were carried out.
- The clinical systematic review identified 2 comparator studies including patients treated with hydroxycarbamide and 12 studies investigating SCT. All studies had a non-randomised single arm-design. Therefore comparison of bosutinib and other treatments in the NICE scope conducted for purposes of economic modelling requires the use of a naïve, unadjusted indirect comparison.
- Survival rates from treatment with bosutinib observed in Study 200 appeared to be better than those achieved with hydroxycarbamide or SCT, from the perspective of a naïve indirect comparison of the relevant studies.

6.10.1 **A statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.**

Bosutinib is associated with clinical benefit in CP, AP and BP patients previously treated with one or more TKIs

Differences in response rates, PFS and OS are seen across the different Study 200 populations, but favourable rates are observed in all populations, demonstrating the clinical benefit provided by bosutinib across different phases of the disease.

In the third-line CP patients, the cumulative MCyR was 41% and cumulative CHR was 73% among evaluable patients (15 Feb 2012 snapshot, minimum follow-up of 24 months). Estimated survival rates were also high with K-M estimates of PFS at 1 year and 2 years of 77% and 73%, respectively, and estimates of OS of 91% and 83% at 1 year and 2 years, respectively (28 Mar 2011 snapshot).

In the advanced phase patients, survival rates were also good, with K-M estimates of 2 year PFS of 47.7% (AP) and 11.5% (BP) and an estimated 2 year OS of 65.6% (AP) and 35.4% (BP).

Bosutinib is associated with efficacy in patients with mutations that confer resistance to other TKIs

The analysis of clinical response according to baseline Bcr-Abl mutation status performed across all Study 200 populations demonstrated that the good clinical response rates observed in general for these populations (detailed above) were broadly observed across all Bcr-Abl mutations (except T315I). This analysis provides evidence of the clinical efficacy of bosutinib in patients for whom imatinib, nilotinib and/or dasatinib would be considered inappropriate due to the presence of Bcr-Abl mutations.

Bosutinib appears to be associated with survival benefit compared to the alternative treatments available for patients unsuitable for current TKIs

It is not possible to draw any robust conclusions regarding the efficacy of the comparators to bosutinib in terms of their clinical response rates. However, estimates of overall survival observed in patients receiving hydroxycarbamide or SCT in patients previously treated with one or more TKI appears to be lower than for bosutinib. For example, the estimate of OS at 2 years for second-line hydroxycarbamide patients is 77% (Kantarjian 2007), compared to 85% for SCT in second-line patients (Schleuning 2010) or 72% in mixed-line SCT patients (predominantly third-line, Jabbour 2011). Bosutinib estimates of OS at 2 years for third-line CP patients compare favourably to these, with K-M estimates of 84.0% as of the most recent data snapshot (15 Feb 2012).

Similar results are seen in the advanced phase populations compared to SCT (no data is available for OS in the hydroxycarbamide patients previously treated with one or more TKIs).

The evidence base therefore indicates that bosutinib offers a valuable alternative to both hydroxycarbamide and SCT in terms of improving survival rates across all phases of the disease and multiple lines of treatment.

Bosutinib appears to offer a manageable adverse event profile that is distinct from current TKIs

Bosutinib was observed to possess an acceptable safety profile in CP, AP and BP patients, with the safety profile observed being similar across all populations. The most prevalent TEAEs were mild diarrhoea and other gastrointestinal events, and the most common TEAEs of grade 3/4 severity were neutropaenia and thrombocytopaenia in all populations.

Bosutinib therefore offers patients with CP, AP or BP CML and for whom imatinib, nilotinib and dasatinib are not considered appropriate, a treatment option that is efficacious in terms of clinical response, progression-free and overall survival, with a tolerability and safety profile that is manageable and distinct from other TKIs, making it a valuable option for patients who are unable to tolerate current TKIs.

Safety data for comparators is limited

With regard to the evidence base for safety of the comparators, no adverse event (AE) data was reported in the two hydroxycarbamide studies and AE data reported in three SCT studies was restricted to the incidence of acute/chronic graft-versus-host-disease (GVHD).[58, 60-62,62] Given the paucity of safety data for the comparator treatments, it was not possible to conduct a robust qualitative comparison of the safety profile of bosutinib and comparator treatments in terms of AEs.

Mortality rates were reported for a considerable number of the comparator studies. Overall, mortality rates on hydroxycarbamide (35% in second-line CP CML, 90% in BP CML) were higher than those seen with bosutinib (e.g. 19% in third-line CP CML). Regarding SCT treatment, mortality rates were also higher than those achieved with bosutinib, particularly in the third-line CP CML population and the advanced phase CML populations.

Bosutinib therefore offers a treatment alternative to hydroxycarbamide and SCT that is associated with lower rates of mortality.

6.10.2 A summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths of the clinical evidence

The evidence base for bosutinib for the treatment of patients with CP, AP or BP Ph^+ CML previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options has the following key strengths:

Large study population: Study 200 has the largest third-line CP CML patient population (third-line CP CML population, n=118) of any trial investigating efficacy and safety of TKIs in the third-line population. Furthermore, Study 200 also considers a large study population in advanced phase disease patients.

Efficacy stratified by phase of treatment and mutational profile: The Study 200 populations demonstrate that bosutinib is efficacious in the treatment of CML at various disease stages, treatment phases and across a range of Bcr-Abl mutations.

Mature follow-up: The evidence presented represents data collected after relatively long durations of follow-up in Study 200, with a minimum duration of follow-up of 24 months for the third-line CP CML population and 12 and 18 months for the AP and BP populations, respectively.

Limitations of the evidence

The following limitations of the evidence base for bosutinib have been identified:

Uncontrolled evidence: There are no RCTs evaluating the clinical efficacy and safety of bosutinib in patients relevant to this submission, meaning that no comparative data (versus a placebo or other active comparator) for bosutinib in the proposed indication are available. This limits the strength of the conclusions that can be drawn on the relative efficacy of bosutinib vs. other treatment options in this patient population.

Paucity of comparator data: The systematic review identified a number of potential comparator studies of treatments for CML patients previously treated with one or more TKI. However, all studies were of a non-randomised single arm-design, allowing for only a naïve, unadjusted indirect comparison approach. Use of this approach means there is uncertainty around the comparative efficacy estimates and their generalisability to clinical practice.

Small unmet clinical need sample size: The patient population covered by the proposed indication for bosutinib is small, and this is reflected in the small size of the subpopulation of unmet clinical need identified within Study 200 (n=52), which formed the post-hoc analysis population described in Section 6.2.5. Of these 52 patients, 15 were second-line CP CML patients, 21 were third-line CP CML patients, 5 were AP CML patients and 11 were BP CML patients. Full details of this unmet clinical need subpopulation can be found in Appendix 10.16. Although the patient numbers for the unmet clinical need subpopulation were small, the results of this post-hoc analysis were consistent with the results in the larger Study 200 populations, suggesting that bosutinib is efficacious and has an acceptable safety profile in these specific patients with an unmet clinical need.

Lack of fourth line data: With the exception of 3 patients in the third-line CP CML population and 15 patients in the advanced phase CML population who were treated in the fourth line setting, Study 200 is unable to provide data supporting the use of bosutinib after failure or intolerance to three previous TKIs. It is therefore assumed that the evidence for the third-line CP and the AP/BP populations is representative of a fourth-line population. In practice, given that efficacy appears to worsen from first-line to third-line, it may be reasonable to assume that in practice fourth-line patients would be associated with worse efficacy than that of the third-line patients in Study 200.

6.10.3 **A brief statement of the relevance of the evidence base to the decision problem. Including a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.**

The analysis data from Study 200 has provided evidence that is highly relevant to the decision problem, for the following main reasons:

- The evidence presented in this submission from the Study 200 populations provides a broad evidence base for the efficacy and safety of bosutinib across CP, AP and BP in patients previously treated with one or more TKI, as per the licensed indication for bosutinib. The CP, AP and BP data presented in this submission is expected to include and be representative of patients who would have been unsuitable for imatinib, dasatinib and nilotinib.
- A post-hoc analysis of a subpopulation from Study 200 was undertaken to identify those patients with high unmet need specifically covered by the license. Although only a small subpopulation of Study 200, the efficacy and safety outcomes observed in these patients are broadly reflective of full Study 200 populations. Since this represents a post-hoc analysis, the results for this population are not presented in Section 6.8.5, but instead in Appendix 10.16.
- In addition to the results for the populations of chronic and advanced phase CML patients described above from Study 200, additional supportive information was provided to the EMA on 16 patients treated with bosutinib in the compassionate use setting, in which bosutinib was provided to patients with no alternative TKI treatment options, following unsolicited requests from clinicians. Bosutinib treatment led to clinical relevant benefit and appeared to be well tolerated in these patients with an “unmet medical need”. At least 10 of these 16 patients with no other TKI treatment option had a clinically relevant response to bosutinib. All patients had a diagnosis of Ph+ CML in CP, AP, or BP and patients were considered by their treating physicians to have no other available or suitable TKI option (see Appendix 10.17 for a summary of these patients).
- [redacted]The extent of compassionate use requests indicates that treating physicians recognise the therapeutic value of bosutinib and believe that bosutinib can meet the clear need for additional therapies in these patients.

6.10.4 **Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?**

Conduct of the trial as representative of clinical practice: As with any clinical trial, patient visits are mandated whilst on treatment. Weekly visits were required for the first

month on treatment, followed by further assessments at 2 and 3 months, and quarterly thereafter. According to the ELN guidelines, cytogenetic monitoring is required at 3, 6, 12, and 18 months, and molecular monitoring is required every 3 months, to monitor response to imatinib, reflecting current UK practice of quarterly follow-up as similarly provided in Study 200.[83] Most study procedures were as per standard of care, with additional requirements such as health outcomes assessment at baseline, 1,2 and 3 months, then quarterly.

Selection of eligible patients in clinical practice: The eligibility criteria for Study 200 as a whole (Table B6) may not be representative of the criteria used in clinical practice to identify patients who would qualify for treatment with bosutinib. However, the eligibility criteria for the post-hoc analysis of the unmet clinical need subpopulation (described in Appendix 10.16.1) may be more reflective of the types of criteria that clinicians may use in practice to identify patients who would be unsuitable for imatinib, dasatinib and nilotinib and therefore eligible for bosutinib.

When a clinician selects the most appropriate treatment, in consultation with the patient, standard practice would include consideration of mutational status (i.e. whether nilotinib or dasatinib resistant mutations are present), and the presence of concomitant medical conditions or prior toxicities. The post-hoc selection algorithm reflects this practice, and the data available for nilotinib and dasatinib, including that provided within their SPCs.

Dosing: The dosing schedule recommended in the SPC is 500 mg bosutinib once daily. Dose escalations of bosutinib to 600 mg once daily are recommended on condition of an inadequate response, with doses greater than 600 mg not recommended. The SPC also recommends dose reduction in the event of toxicity, noting that doses lower than 300 mg have not been evaluated (see Section 1.10 for full details on the recommended dose for bosutinib in CML).

All data presented in this submission corresponds to outcomes achieved under doses of bosutinib licensed in the SPC. As noted in the CSR,[56] any patients for whom it was required that the bosutinib dose was lowered to less than 300 mg were discontinued from the study, consistent with the dosing recommendations of the SPC. In Section 7.2.7, the expected proportions of patients who dose reduce and dose escalate in the trial is presented and the impact on the cost-effectiveness of bosutinib is considered as a sensitivity analysis. Similar proportions of dose reduction and dose escalations are expected in practice.

7 Cost effectiveness

Summary of Bosutinib Cost-Effectiveness

- No published economic evaluations of bosutinib were found in the literature
- Due to the three different phases in which bosutinib can be used (chronic phase, accelerated phase, and blast phase), three semi-Markov models were constructed, with three separate results sections presented
- We believe the base-case presented represents the most plausible scenario for the cost-effectiveness of bosutinib in CP CML. In this analysis we have used the most relevant sources of information where possible, and where data was not available, appropriate and conservative assumptions have been made:
    - OS on bosutinib is calculated using a published methodology, and validated by comparing to empiric OS data from Study 200.
    - Discontinuation is extrapolated directly from mature trial data (5 years, at which point 86% of patients had discontinued).
    - Interferon and hydroxycarbamide efficacy is taken from a recent NICE appraisal in CML, but for a second-line population that is likely to have a better prognosis compared with the third-line patients from Study 200.
    - SCT survival is taken from studies that were selected for having the most comparable patient population to Study 200 and the likely population in practice (Jabbour et al., 2011 in the chronic phase and Oehler et al, 2007 in the advanced phases)
    - Utilities and costs are also taken from previously validated economic evaluations (TA251), and the cost of SCT is taken from a recent NHS Blood and Transport report. Utilities were comparable to utilities measured by the EQ-5D administered to patients in Study 200
- In the deterministic base case, the ICER for bosutinib compared to hydroxycarbamide (standard of care) was [redacted] in chronic phase, [redacted] in accelerated phase, and [redacted] in blast phase
    - Throughout the results, interferon is dominated by hydroxycarbamide due to the low utility whilst on interferon treatment
    - Stem Cell Transplant in all phases, is either dominated by bosutinib, or provides similar efficacy, at much increased cost
    - The results are subject to a high degree of uncertainty, given the nature of the single arm trials in the disease area
- Extensive one way and scenario analyses are presented in the submission. The key sensitivities are:
    - The OS of patients on comparator treatments, the length of time patients remain on bosutinib, and the cost of the 'off-treatment' stage
- Patients in accelerated and blast crisis would meet the NICE 'End of Life' criteria:
    - First, the patient population eligible for bosutinib is only expected to be around 80 new patients per year, of which only 10% might be in accelerated or blast phase.
    - Second, the expected survival for advanced phase patients for whom imatinib, dasatinib and nilotinib are all unsuitable is around 16 months (10 months in AP and 6 months in BP), which is less than the 24 month criteria for end-of-life.
    - Finally, depending on the survival assumed for hydroxycarbamide, the incremental life year gain of bosutinib over hydroxycarbamide is approximately 1.7 years in AP, and 1.2 years in BP.

- It has been noted by clinicians that hydroxycarbamide is rarely, if ever used in CML patients and therefore SCT may be a more appropriate comparator. When compared to SCT, bosutinib is either dominant, or highly cost-effective in all scenarios and sensitivity analyses.

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of published cost-effectiveness evaluations

A broad systematic review was conducted in October 2012 to identify cost-effectiveness studies in CML patients previously treated with one or more TKI. It was assumed that these studies would include and be representative of patients inappropriate for imatinib, dasatinib and nilotinib as per the bosutinib license and as recognised by the CHMP.

A previous systematic review on the clinical and economic data associated with dasatinib, nilotinib and imatinib, and also on utility data in CML in general has been published by the Peninsula Technology Assessment Group (PenTAG), focussing on newly diagnosed CML. In this systematic review, exactly the same search terms as were employed by PenTAG were used; however search result eligibility criteria were adapted for refractory CML (Table B35), and searches were not limited by date or language (for full search strategies, please refer to Section 10.10.4).

Table B35: Eligibility Criteria and the Rationale for each Criterion

Inclusion Criteria		
Category	**Inclusion Criteria**	**Rationale**
Disease area	Studies that reported patients with chronic myeloid leukaemia, chronic granulocytic leukaemia, chronic myelogenous leukaemia or chronic myelomonocytic leukaemia	CML is also known under these terms, and therefore studies with these terms were included
Population	Studies that included adult patients with refractory chronic phase, accelerated phase or blast crisis phase, Philadelphia chromosome positive CML (treated with at least 1 prior TKI)	Patients being treated for CML after failing all prior TKI therapies are the population of interest. Any studies looking at 2nd line or later were included in line with the licensed population under consideration.
Study type	Full economic evaluation (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations) that compares two or more interventions	The aim of the review was to identify relevant economic evaluations
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which must report both costs and effects
Interventions	Interventions of interest include but are not limited to bosutinib, dasatinib, nilotinib or imatinib. (see Appendix 10.10.4 for the terms used to filter by these agents)	
Comparators	As identified by the scope, the key comparators are stem-cell therapy, hydroxycarbamide, interferon and best supportive care. In addition, any study that considered dasatinib, nilotinib, or imatinib as comparators were also included. Alternative names for these	Any of these agents could be used in a second or later line setting. The non-TKI agents are more relevant to the decision problem, but data was expected to be limited for

	comparators were also included (see Appendix 10.10.4 for a full list of terms)	these agents and therefore the TKIs were included as comparators in this review.
Other	Studies must provide sufficient detail regarding methods and results to enable the methodological quality of the study to be assessed, and the study's data and results must be extractable	Only studies which provided extractable data and results were usable

Exclusion criteria		
Category	**Exclusion Criteria**	**Rationale**
Publication Type	Letters; editorials; reviews of economic evaluations (although reference lists of these would be hand-searched)	Primary study articles were required.
Disease Area	Studies that did not report patients with CML	Articles that do not include patient data, or do not include data on CML are not of use to the decision problem
Population	Studies that did not report adult patients; studies that did not report patients with refractory CML; studies on patients that were not Philadelphia Chromosome Positive	The scope of this review is for adult patients being treated for refractory CML despite prior treatment with at least 1 tyrosine kinase inhibitor, who are Philadelphia Chromosome Positive

Comprehensive searches were run across EMBASE, MEDLINE, MEDLINE In-Process, Cochrane Library, EconLit, and NHS Economic Evaluations Database (via Cochrane Library and Centre for Reviews and Dissemination), from database inception to 2/10/2012. Additionally, horizon scanning through the Google search engine, and a search of the NICE website were performed. The following congresses were also searched for relevant articles that were not captured in the above searches: ISPOR, ASCO, ESMO, ASH and ICLLM.

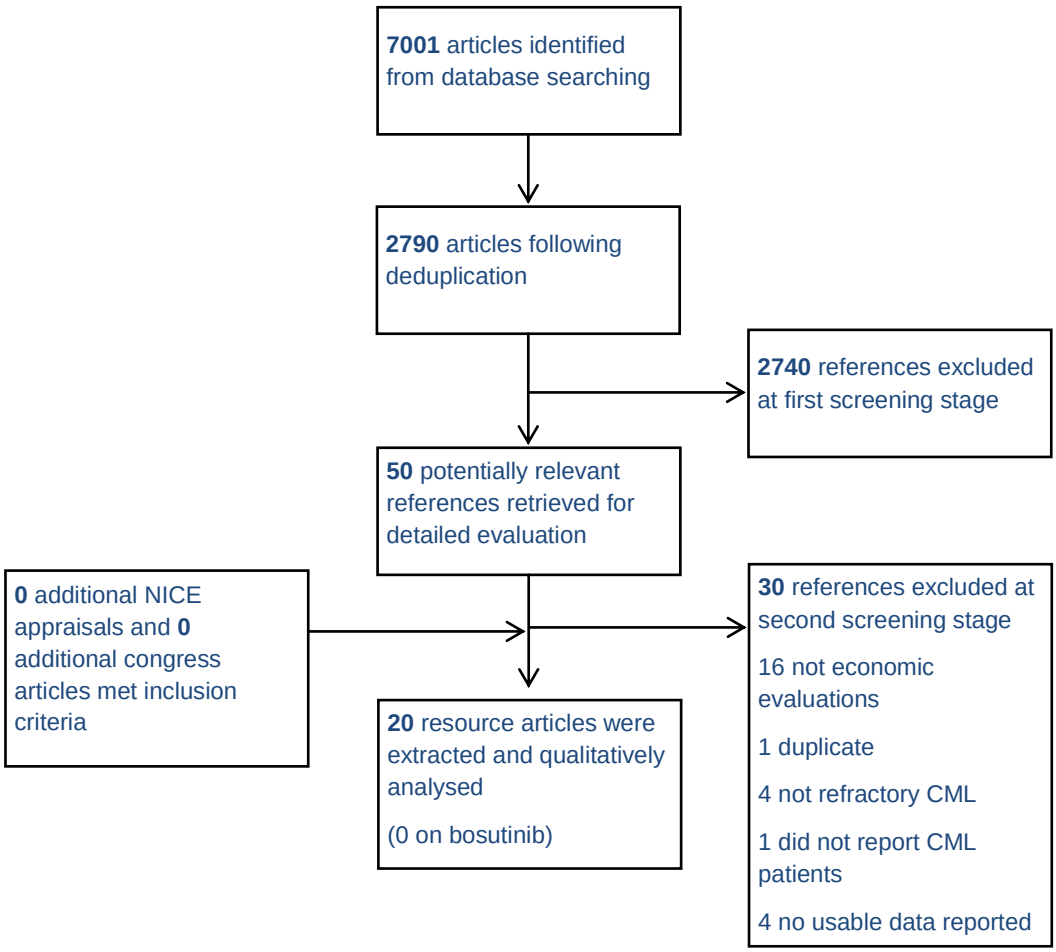
Citations found through the searches were assessed by two independent reviewers for inclusion based on abstract and title. Full-text copies of studies that potentially met the initial criteria were then obtained and reviewed against the inclusion criteria by two independent reviewers. Studies that met the eligibility criteria after the second screening stage were extracted by a reviewer and checked by a second party.

The flow diagram of the studies included in this systematic review is shown in Figure B13 and described below:

- A total of 6303 studies were identified from EMBASE, MEDLINE and MEDLINE In-Process, 651 from the Cochrane Library, 45 studies from NHS EED and 2 from EconLit.
- No additional articles to those captured through the database searching were identified from the horizon scanning or congress report searches.
- One technology appraisal was identified from the NICE website (TA241: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance); this model has been described in detail by Rogers (2012)[84] and Loveman (2012)[85]
- Following deduplication of the database results, 2790 abstracts remained for review.

- In the first screening stage, 50 articles were identified as potentially relevant by two independent reviewers, and full texts were obtained for these.
- Of the full texts, 20 articles met the inclusion criteria: 2 for 3rd line, and 18 for 2nd line CML treatment. 13 of these were congress abstracts.
- No cost-effectiveness studies that evaluated bosutinib in refractory CML were identified.

Figure B13: Study flow diagram for economic evaluations



7.1.2 Description of identified studies

No cost-effectiveness studies that evaluated bosutinib in refractory CML were identified.

Dasatinib, nilotinib and high-dose imatinib were appraised by NICE in imatinib-failure CML (i.e. second line) as part of TA241. The HTA reports for TA241 (Rogers 2012[84] and Loveman 2012[85]) were identified by the systematic review in refractory CML. In addition, Hoyle et al 2011b[86] have produced a publication based on the economic evaluation from TA241. These cost-effectiveness studies in refractory CML for other interventions are presented in Appendix 10.11.

More recently, imatinib, dasatinib and nilotinib were appraised in newly diagnosed CML (i.e. 1st line) as part of TA251. The HTA report (Hoyle 2011a[80]) for the technology appraisal in first-line use (TA251) was not captured as part of the systematic review described above, but was subsequently identified as an important source of HRQL and resource use data.

It should be noted that there is an inconsistency in the years that these reports have been published. The publications in 2012 (Rogers and Loveman) correspond to work performed earlier, in around 2010, and are the HTA reports (which have a publication lag), corresponding to the work for TA241. Whilst Hoyle et al (a)[80] was published in 2011, it represents the HTA report for the more recent TA251 appraisal and builds on the ERG reports from Rogers and Loveman.

These evaluations do not include bosutinib, nor do they specifically consider a population that match the license for bosutinib and as such the results are not reported here. However, where it is relevant and no other data is available, HRQL and resource use data is extracted and used in our economic evaluation. This is described in the sections below.

7.1.3 Quality assessment identified cost-effectiveness studies

A complete quality assessment of cost-effectiveness studies is provided in Appendix 10.11.

7.2 De novo analysis

7.2.1 Patient groups included in the analysis

The licensed indication for bosutinib is based on the data reported in Study 200 and as such the economic evaluation is based on this data. As noted in Section1.5, bosutinib is indicated for CML patients who have been previously treated with one or more TKI (i.e. second-line or later) across all three phases of CML patients (CP, AP, BP). In addition, the license states that patients must be unsuitable for treatment with imatinib, nilotinib and dasatinib.

Study 200 was not specifically designed to evaluate this population, however as recognised by the CHMP, Study 200 is expected to include patients who meet the license criteria and therefore likely to be representative of this population.

Owing to the considerable heterogeneity in terms of efficacy, quality of life and resource use between different phases of CML, three separate models evaluating the cost-effectiveness of bosutinib in CP, AP and BP are considered in this submission.

The base-case patient population for the CP model is the third-line cohort from Study 200, described in Section 6.8.3. In the absence of fourth-line data, this cohort is expected to be the most representative of patients who would be unsuitable for nilotinib, dasatinib and imatinib and therefore receive bosutinib in practice. Given that there may be a small number of second-line bosutinib patients in practice for whom imatinib, dasatinib and nilotinib are inappropriate, the second-line CP population from Study 200 will be considered in a sensitivity analysis. In addition, the post-hoc population of patients who would have been unsuitable for treatment with imatinib, nilotinib and dasatinib (n=52) considered by the EMA will be considered in sensitivity analysis (described in Section 6.2.5 and Appendix 10.16). The AP and BP cohorts from Study 200, which contained patients at second-line or later, described in Section 6.8.3, will be included in the AP and BP models respectively.

7.2.2 Diagram of Model Structure

As described above, in order to model the different stages of CML and the use of bosutinib at different points in this pathway, three models have been developed. The three models used are:

- Chronic Phase (CP)
- Accelerated Phase (AP)
- Blast Phase (BP)

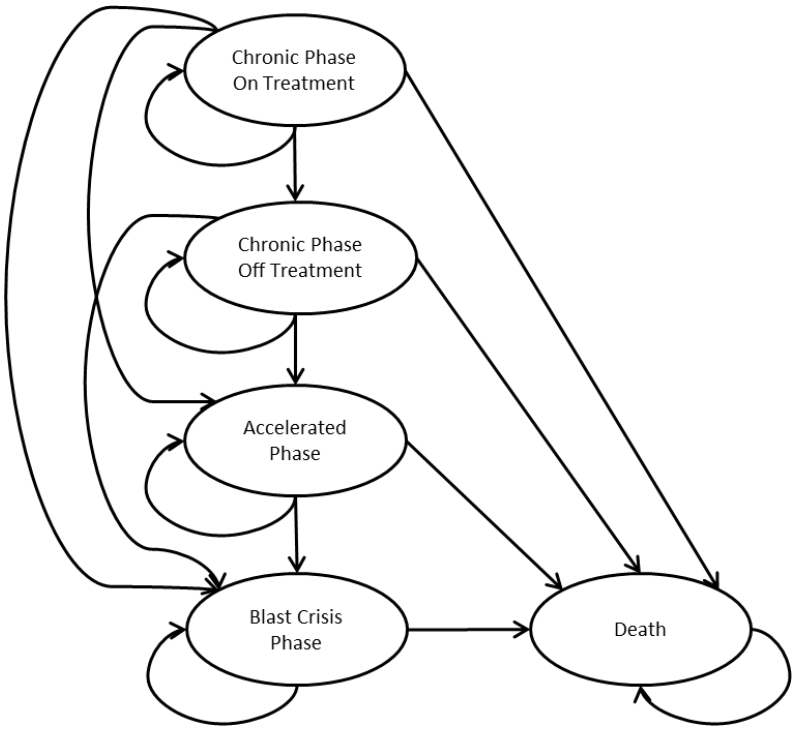
For the three models presented in this submission, comparators and assumptions are generally kept equal and similar comparators are considered for each phase of the disease, as specified by the scope. All three models are built in Microsoft Excel 2010 (Microsoft, Redmond, WA, USA).

Chronic Phase Model

The chronic phase model is a semi-Markov model using 5 health states (including death). All patients start in the 'Chronic Phase On Treatment' health state. For bosutinib patients, time spent in this initial 'On Treatment' phase is calculated by fitting parametric curves to discontinuation data from Study 200 before progressing to the 'Off-Treatment' state.

As in TA241 and TA251, it is assumed that all patients are managed with hydroxycarbamide after discontinuing active treatment and that hydroxycarbamide treatment is associated with a fixed duration of time spent in accelerated and blast phase (taken from TA251).

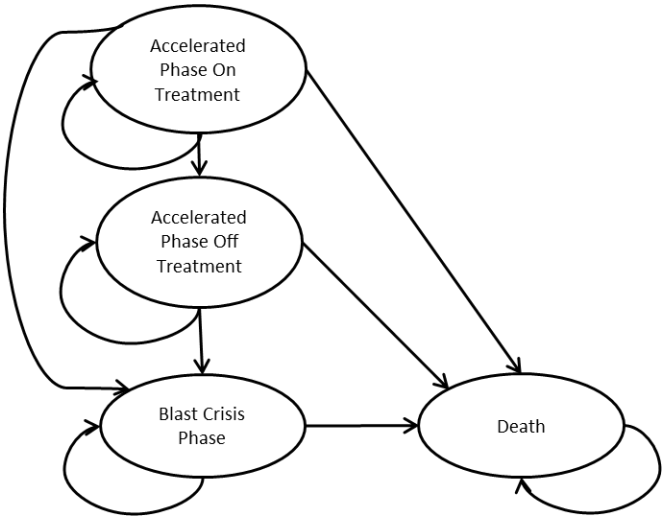
Time spent in the 'Chronic Phase Off Treatment' health state is calculated as a residual from OS (estimated from MCyR in Study 200) minus time spent in AP and BP. For hydroxycarbamide, interferon and SCT patients, time on treatment and OS is estimated using published literature (TA241, TA251 and Jabbour 2011). All assumptions are detailed in Section 7.3.



Accelerated Phase Model

The accelerated phase model is a semi-Markov model using 4 health states (including death). Patients start treatment (bosutinib, hydroxycarbamide or SCT) in the 'Accelerated Phase On Treatment' health state, after having developed accelerated phase disease.

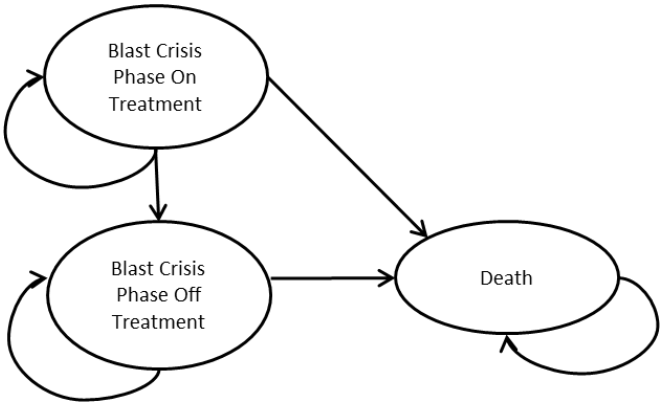
The approach is similar to that of the CP model, in that patients who discontinue active treatment (bosutinib) are subsequently managed with hydroxycarbamide and spend a fixed time in BP (same as in CP model). Time in the AP-off treatment is then calculated as the residual from overall survival less time in AP-on treatment and time in BP.



Blast Crisis Phase Model

The blast phase model is a semi-Markov model using 3 health states (including death). Patients start in the 'Blast Crisis Phase On Treatment' health state, after having experienced a blast crisis.

As in the CP and AP models, patients who discontinue active treatment (bosutinib) in the BP phase are assumed to be managed with hydroxycarbamide. The time spent in the BP-off treatment health state is calculated as the residual from overall survival less time in BP-on treatment. For patients who are initiated on hydroxycarbamide, the same fixed duration of time in BP prior to death is assumed as in the chronic and accelerated phase models.



Structural uncertainty

The model approaches described above are similar to those used in previous CML appraisals (TA241 and TA251) and, as noted in these appraisals, are subject to two key areas of structural uncertainty: Time on treatment and OS.

With regards to time on treatment, it was noted in TA241 and TA251 that PFS may not be an accurate reflection of time on treatment. Time on treatment was found to be a key driver of cost-effectiveness in TA241 and it is therefore important to ensure a robust approach to estimating time on treatment is used and the different approaches to discontinuation are discussed in more detail in Section 7.3.

With regards to OS, it is also a key driver of cost-effectiveness results and therefore equally important to ensure a robust method is used to estimate this parameter.

Given the short term nature of most trials in CML (~2 years) compared to a long extrapolation period of 50 years due to the chronic nature of the disease, there are considerable uncertainties associated with extrapolating OS based on empirical data. To overcome this challenge, in TA241, a surrogate approach is used which relies on the relationship between MCyR and OS (Rogers 2012)[84]. A similar approach is taken in TA251, which uses CCyR to predict OS (Hoyle 2011a)[80].

As this approach has been validated in these prior appraisals, a surrogate approach is used in the base-case, adopting a similar methodology as Rogers 2012[84]. PFS as a predictor of OS has not been used in previous appraisals and is therefore not considered in this submission. A sensitivity analysis is undertaken using parametric curves fitted to overall survival data taken from Study 200, and shows a high degree of consistency with the cytogenetic response predictions.

For the advanced phase models, it is more appropriate to use the OS data from Study 200, because the relationship between MCyR and OS is not validated in advanced populations. However, the uncertainties associated with short trial duration and long-term extrapolation should still be noted for this analysis.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model structure is aligned with two of the primary objectives of treatment CML, namely avoiding disease progression (from CP to AP or from AP to BP) and prolonging life. This model structure and the health states utilised are well established within CML and have been utilised in previous appraisals, including TA251, which considered the use of TKIs in newly diagnosed CML, and TA241 which considered the use of TKIs in refractory CML.

As noted in CML guidelines, it can be very difficult to categorise the phase of a patient's disease. Some clinicians would suggest that patients who have lost control but are still in chronic phase and accelerated phase patients are very similar, and others would suggest that accelerated and blast phase patients can be grouped together as 'advanced phase' patients. Nonetheless, CML guidelines do generally describe criteria for the three phases and these correspond to patient cohorts recruited into Study 200. As such, the 3 stages of CML have been maintained in our economic model.

In addition, as noted in TA241 and TA251, there are considerable changes in quality of life and resource use associated with chronic phase compared to accelerated phase compared to blast phase, further validating the 3 phase structure used.

As described in Section 2.7, for patients who have been previously treated with one or more TKI and who are unsuitable for imatinib, nilotinib and dasatinib, the only options are hydroxycarbamide (best-supportive care), SCT or interferon. The model structure captures patients at this stage of treatment pathway, separately for each of the three phases of CML.

7.2.4 Please define what the health states in the model are meant to capture.

The health states in the model are defined by disease stage; chronic phase, accelerated phase, and blast phase. These phases are considered clinically meaningful, and are associated with different levels of HRQL and resource use. The chronic phase health state is split into on and off treatment, as patients do not remain on treatment for the duration of chronic phase.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2?

The structure of the model has been chosen on the basis of a previously identified model of CML in both newly-diagnosed and refractory CML (TA241 and TA251) and was validated by a UK clinical expert. It contains the most relevant health states from a quality of life and cost perspective in CML: chronic phase, accelerated phase, blast crisis phase and death

In each model, the phase in which patients enter the model is split into on and off treatment because, as recognised in previous CML appraisals, patients do not necessarily continue treatment until progression. (All patients start in the 'on treatment' health state in each model).

As described in TA241 and TA251, HRQL and resource use assumptions vary according to phase of disease rather than by line of treatment of type of treatment

In the 'CP on treatment' phase, for patients receiving bosutinib or interferon, it is assumed that patients are in a responding state and incur drug costs, costs associated with the management of grade 3/4 adverse events (bosutinib only), and other healthcare resource use costs.

Although costs associated with the management of AEs are considered for bosutinib, this is not expected to translate into a worse utility compared to hydroxycarbamide. This approach is consistent with the HRQL assumptions for the other TKIs and hydroxycarbamide in TA241 and TA251, and is further supported by the quality of life seen in Study 200.

For interferon, as in TA241, a slight utility decrement is seen to account for its poor adverse event profile. However, owing to a lack of details about the types of adverse events, no costs have been attributed to the management of these adverse events.

In the 'CP off treatment' phase, patients are assumed to have the same quality of life and resource use profile as those in the 'CP on treatment' health state, as in TA241 and TA251. When patients discontinue bosutinib or interferon, they are assumed to incur the cost of hydroxycarbamide until death. Patients in the hydroxycarbamide arm continue to incur the cost of hydroxycarbamide until death.

In the advanced phases (AP & BP) of the chronic phase model, all patients are assumed to be on hydroxycarbamide. As previously noted, quality of life is impaired and healthcare resource use is increased in the advanced phases compared to chronic phase, and is the same for all patients, regardless of prior treatment. As noted in Section 7.2, the time spent in AP and BP, whilst on hydroxycarbamide, is fixed and independent of previous treatment.

Similar cost and HRQL assumptions are used in the AP and BP models.

The options for patients unsuitable for imatinib, dasatinib and nilotinib are limited and consist of SCT, hydroxycarbamide (BSC) or interferon-alpha (rarely used in the UK).

It is generally accepted that hydroxycarbamide is reflective of underlying disease progression as it only helps regain some level of haematological control, but does not alter the course of the disease. It may therefore be considered a proxy for best-supportive care. Hydroxycarbamide is a comparator in all three models.

Interferon, although rarely used in the UK, is thought to have some impact on the disease progression. As previously noted, no data was found for interferon in the systematic review. In TA241, the efficacy values for interferon were derived from clinician estimates of OS in the chronic phase[84]. It did not seem appropriate to extrapolate this data for use

in the advanced phases and therefore, interferon is not included as a comparator in the advanced phase models.

SCT is also a comparator in all three models. The same resource use assumptions are applied for the cost of the initial SCT procedure and ongoing treatment costs regardless of whether it occurs in CP, AP or BP. In addition, patients accrue the healthcare resource use costs (physician visits, for example) associated with the relevant phase they are in (CP, AP or BP), as described below. Patients who receive SCT do not receive any other CML treatments post-transplant, although there are ongoing management costs related to SCT. SCT is associated with a slight utility decrement, in order to reflect the morbidity associated with SCT, as described in more detail in Section 7.4.6.

As SCT is a curative treatment, it is assumed that patients do not progress post-SCT, but stay in their initial health state. However, this is a conservative assumption because, in practice, SCT patients are likely to experience a period of time prior to death associated with higher resource use and worse HRQL. As such, a sensitivity analysis is considered in which SCT patients spend the same fixed periods in AP and BP as patients on the other comparators.

In reality, best-supportive care is likely to consist of hydroxycarbamide in combination with blood transfusions and antibiotic treatment as required. As such, the potential cost-effectiveness of best-supportive care, consisting of hydroxycarbamide with additional costs, is considered in a sensitivity analysis. This comparator has not been included as a comparator in its own right owing to the lack of information on what exactly comprises best-supportive care, and the costs and efficacy associated with it.

7.2.6 **A table containing the following information and any additional features of the model not previously reported.**

Table B36: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (50 years)	CML is a chronic and terminal disease. The time horizon must be sufficiently long to incorporate all relevant benefits and costs. In the CP model, a time horizon that is too short will mean that patients who survive for longer periods do not experience AP and BP, which have high costs and low utilities. In the AP model, a time horizon that is too short will not have patients experiencing the low utility and high costs associated with BP. In the BP model, a time horizon that is too short will not have all patients experiencing death, which would underestimate both QALYs and costs.	This approach was also taken in TA241 and TA251 - other assessments in CML
Cycle length	1 month	A one month cycle is sufficient to allow for the fitting of survival data (typically given in years), and the incorporation of published cost data (frequently given in monthly costs).	
Half-cycle correction	No	Patients incur the costs of bosutinib and Stem Cell Transplant at the beginning of a cycle – these are the largest costs. In addition the inclusion of a half cycle correction would make no substantial difference to the ICER given that cycle length is very short compared to average survival, but would add spurious precision.	
Were health effects measured in QALYs; if not, what was used?	Yes	QALYs are used as per the NICE reference case.	
Discount of 3.5% for utilities and costs	Yes	Discounting was performed in line with the NICE methods guide (2008). Life Years were not discounted to allow easy comparison of survival estimates from published papers to results of the economic evaluations.	NICE (2008)
Perspective (NHS/PSS)	NHS	In this disease area there are not expected to be significant impacts on costs outside the NHS budget. Additionally the loss of working time is not expected to be a key issue given that much of the CML population is not working age, the median age at diagnosis is 59.1 years.[26]	
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Intervention and comparators in the model

As previously noted, there is no data specifically relating to the population covered by the licensed indication in Section 1.5 for bosutinib or for the comparators identified in this submission.

It is assumed that the data available is representative of this population and as such bosutinib and the comparators are considered to be implemented in the model as per the marketing authorisation. The explanation of these assumptions is explored further in Section 7.3.7.

Bosutinib: The recommended dose of bosutinib is 500mg per day. As noted in Section 1.10, according to the SPC, dose may be reduced in response to haematological and non-haematological events in 100mg decrements to 300mg. Dose may also be escalated to a maximum of 600mg in the case of a sub-optimal response.

In the base case of the model, it is assumed that all patients receive 500mg of bosutinib per day. The price of 400mg/day and 500mg/day is the same, but the cost of 300mg/day is cheaper and 600mg/day is marginally more expensive, as such the impact of dose intensity is explored in a sensitivity analysis.

Hydroxycarbamide: The recommended dose for hydroxycarbamide, according to the British National Formulary 64 is 20-30mg/kg daily or 80mg/kg every third day. The dosing for hydroxycarbamide is assumed to be 2g daily (assumes 25mg/kg daily for an average weight of 80kg), as considered by Loveman et al (2012).[85]

Interferon-alpha: The dosing for interferon-alpha is assumed to be 5 million units per square metre body surface area daily.[84] Assuming a body surface area of 1.73m^2, as Rogers et al (2012) did,[84] the daily dose is 8.65 million units. The recommended dose according to the summary of product characteristics is 4-5 million units per square metre body surface area daily.

Stem Cell Transplant: The assumptions relating to stem cell transplant (in resource use and costs) are detailed in a report by NHS Blood and Transplant, and are discussed in more detail in Section 7.4.21.

7.2.8 Has a treatment continuation rule been assumed?

In the SPC for bosutinib it is stated that “In clinical trials, treatment with bosutinib continued until disease progression or until it was no longer tolerated by the patient.”

Previous economic evaluations for the treatment of CML (TA241 and TA251) have recognised that patients do not remain on treatment indefinitely, and that duration of treatment is a key input for the costs of technologies.[84] Accordingly, in the base-case, patients in the CP model receive bosutinib only in CP (not in AP or BP), and patients in the AP model receive bosutinib only in AP (not in BP).

These economic evaluations provided parameters for treatment discontinuation in an imatinib-failure population (i.e. 2nd line) for interferon (mean of 0.5 years) and hydroxycarbamide (until death).

It was noted by both Rogers et al (2012)[84] and Loveman et al (2012)[85] that the use of PFS to represent time on treatment was inappropriate, as patients in practice do not stay on treatment until progression, but experience a time whilst in CP but no longer on active-treatment. This is particularly relevant given that most trial definitions of progression (including Study 200) generally include events such as loss of response, which do not necessarily correspond to an actual transformation from CP to AP.

Time to treatment discontinuation was recorded in Study 200, and so this data has been used to estimate time on treatment as the base-case in this model. The statistical

package R (R Foundation for Statistical Computing, Vienna, www.r-project.org) was used to fit parametric curves to the patient level data from Study 200. In the chronic phase, third-line population, the K-M curve for discontinuation [redacted] of patients remaining on treatment at 5 years, and only [redacted] of patients were censored.

Parametric curves were fitted to the data, and across all three cohorts (CP third-line, AP and BP) the log-normal curve was the best fitting according to the Akaike Information Criterion (AIC) and the Integrated Brier Score (IBS), and the loglogistic curve was the second best fitting.

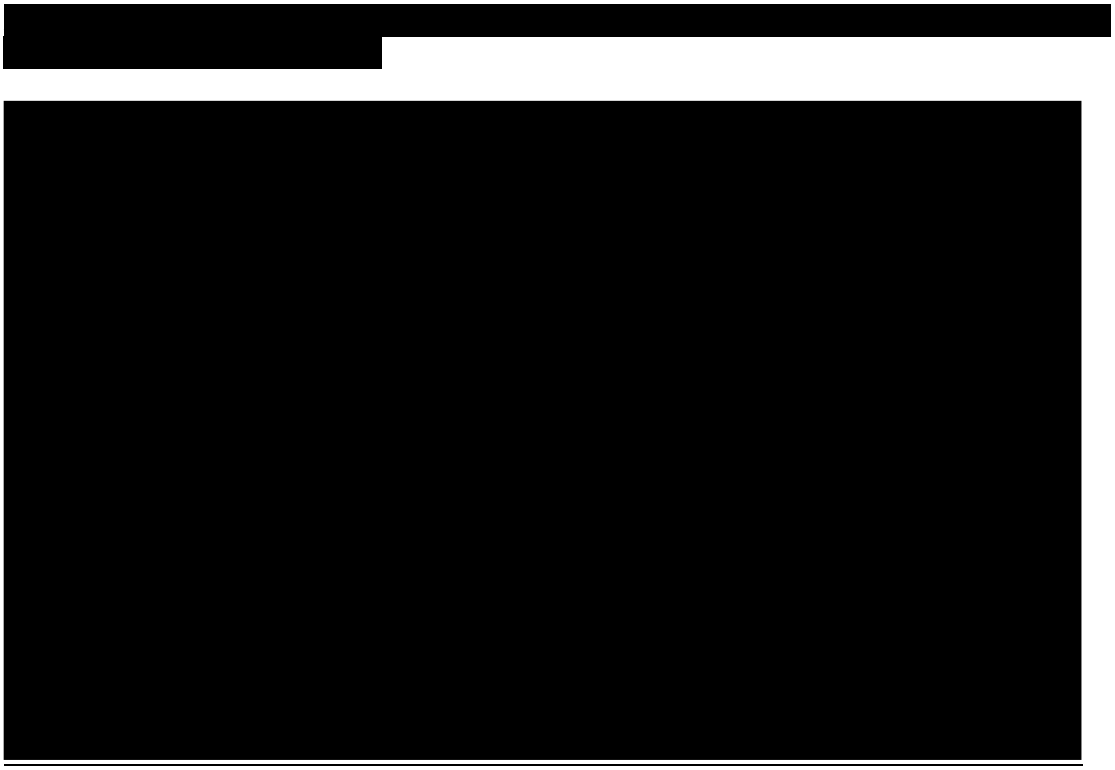
The curves for CP third-line are shown in Figure B14. The data is quite mature, and so the AIC is an appropriate method of determining the best fitting curve. Further details of the analysis of best-fitting parametric curves are provided in Appendix 10.18. Both the lognormal and loglogistic curves have a long tail, so using these curves accounts for those patients who may remain on bosutinib for a longer period of time. However, it should be noted that extrapolations based on the observed data are still associated with considerable uncertainty, particularly given the lack of external data to explore validity.

In the absence of direct evidence on treatment duration for the TKIs, Rogers et al (2012)[84] developed a method for estimating treatment duration, based on PFS from the TKI studies and clinical assumptions about the timing of premature discontinuation due to adverse events and progression post-TKI discontinuation (assumed to be equal to the progression associated with interferon). The method used by Rogers et al (2012)[84] is also shown in Figure B14, where it can be seen to overestimate the time on treatment for bosutinib. Further details of the analysis of best-fitting parametric curves to the CP, AP and BP cohorts are provided in Appendix 10.18.

In the base-case, treatment discontinuation is assumed to follow the lognormal curve for third-line CP patients in Study 200 (mean time on treatment [redacted], median time on treatment 0.97 years (the K-M estimate for median time on treatment in the third-line CP cohort of Study 200 was 9.0 months (0.75 years, [15 Feb 2012 snapshot]).

Scenario analysis is performed assuming that treatment discontinuation follows the loglogistic curve, the PFS curve from Study 200 and the curve fitted using the method by Rogers et al (2012)[84], all of which are shown in Appendix 10.18. [84]

Figure B14: Kaplan-Meier discontinuation from Study 200 with parametric fitted curves, and (CP only – not used in AP and



[redacted]

As previously described, it is assumed that patients who discontinue treatment with bosutinib receive hydroxycarbamide until death. Rogers et al (2012)[84] included an additional monthly cost for patients in the chronic phase off-treatment states, which incorporated costs that might be associated with patients discontinuing a second-line TKI (e.g. SCT, palliative care and further TKIs). Given the population being considered in this submission, it would not be appropriate to include this cost; however a scenario analysis is presented including higher costs in the off-treatment phase.

7.3 Clinical parameters and variables

7.3.1 Clinical data in the model

A) CHRONIC PHASE MODEL

Bosutinib

As previously described the third-line CP population for Study 200 is expected to be the most representative of the likely population in practice for bosutinib, and is therefore used in the base-case of the economic model. Patient level data on discontinuation, PFS and overall survival is taken from data snapshot 15 February 2012. MCyR data is taken from data snapshot 28 Mar 2011 as this represents minimum follow-up duration of 12 months, which corresponds to a similar time point for MCyR assessment as the studies used in TA241 on which the OS prediction was based.

As previously described, the full third-line cohort from Study 200 was chosen for the base-case in preference to the post-hoc population requested by the EMA of the 'unmet need' population. The EMA agreed that the full population is representative of the post-hoc population and was associated with similar efficacy. Indeed a comparison of the MCyR and CCyR rates for all third-line CP patients and those in the post-hoc analysis showed similar efficacy with overlapping confidence intervals. As such, the full study 200 cohort was felt to be more appropriate as the base case population because the sample size is larger and hence the uncertainty is smaller.

As described above, two approaches to estimating overall survival were considered, a 'surrogate-survival' approach and a 'direct OS' approach. These are discussed in more detail below.

Surrogate Survival approach

In this approach, overall survival was calculated using an established relationship based on MCyR described in the evaluation of TKIs in imatinib-failure population (i.e. 2nd line studies (Rogers et al, 2012)[84] This approach was compared to parametric curves fitted to the Kaplan-Meier data from Study 200, and found to be similar (see Figure B15).

The use of CCyR as a surrogate outcome as described by Hoyle et al, 2011a[80] in the appraisal of the TKIs in newly diagnosed CML (i.e. 1st line use) was also investigated. However, this approach was found to overestimate overall survival for bosutinib, as can be seen from Figure B15 below, and was therefore considered to be inappropriate as a base-case.

The details for these surrogate outcome relationships are discussed in Section 7.3.3.

Overall survival determined by parametric curve fitting

The statistical package R (R Foundation for Statistical Computing, Vienna, www.r-project.org) was used to fit parametric curves to the patient level data from Study 200.

In determining which curve best fit the OS data, it was not appropriate to rely solely on AIC and IBS. The OS data is not as mature as the discontinuation data, so the measures of goodness of fit are not as appropriate. In addition, these measures only provide an estimate of how well the curves fit the data available, and not necessarily which curves are most clinically plausible. For this reason, visual inspection and judgement played an important role in determining the most appropriate curves.

According to the AIC, the best-fitting curves for overall survival for the CP, AP and BP population are the log-normal and log-logistic curves, followed by the Weibull (and exponential and extreme value). The log-normal and log-logistic curves have long tails, so if they are used for overall survival, patients will remain alive for much longer than is realistic. The area under the curve for the Weibull is much greater than for the exponential (see Appendix 10.18), and this may not be clinically plausible, given the poor prognosis of these patients. Therefore, conservatively, the exponential curve is considered as the most appropriate, followed by the Weibull in scenario analyses.

As specified in the protocol of Study 200, patients who discontinued treatment with bosutinib only had to be followed up for survival for 2 years. As such, overall survival data from Study 200 is truncated at 2 years (following this point, only patients on treatment were followed, giving a biased sample for overall survival). Given that 2 years is premature to assess OS in a chronic phase population with over 90% of patients still surviving, and that the surrogate survival approach based on MCyR has been validated in a previous CML appraisal (TA241), the MCyR predicted OS was used in the base-case. The Study 200 OS data (truncated at 2 years) fitted a parametric curve is therefore considered in a scenario analysis.

Although OS data is only available for 2 years post-discontinuation, longer term study OS data is available for those who continued bosutinib treatment. The parametric curve for this data is shown in Figure B16 below. However, this analysis is not considered further in this submission due to the bias in the data and the fact that it therefore likely over-estimates the OS.

Figure B15: Approaches to survival modelling of Study 200 using MCyR and CCyR surrogate relationships, and best fitting parametric curves: 50 year horizon

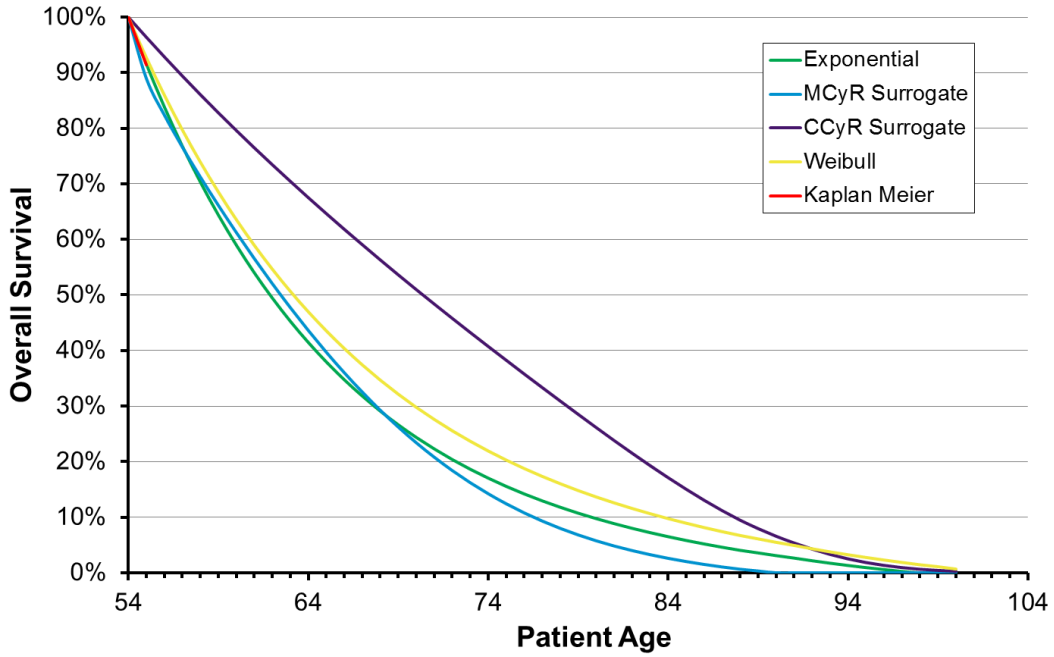
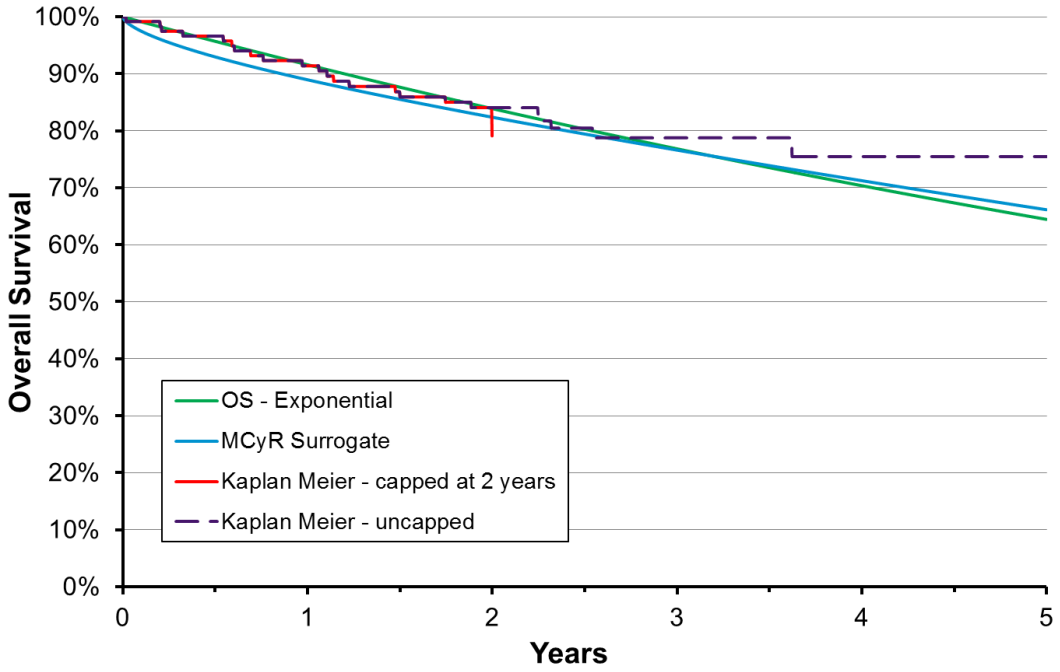


Figure B16: Approaches to survival modelling of Study 200 using MCyR surrogate relationship and best fitting parametric curve: 5 year horizon



Hydroxycarbamide

As noted in the systematic review in 6.9 (Comparator data section), limited data was found for hydroxycarbamide. Two studies were found that included patients treated with hydroxycarbamide, both in a second-line population. The first (Ibrahim 2011)[37] considered patients treated with hydroxycarbamide in an interferon-failure, TKI naive,

population. This was not considered as comparable because the license for bosutinib states that patients must have previously tried at least one TKI.

The second study (Kantarjian, 2007[36]) was the same as that used in both TA241 and TA251 and considered the use of hydroxycarbamide as one of several 'other treatments' in imatinib failure patients (n=12 out of 61 patients).

In both appraisals, exponential curves were fitted to estimates of time on treatment and overall survival based on clinical trial data for the 'other treatment' group in the Kantarjian study[85]. From this, estimates of 1.5 years for mean time on treatment and 3.5 years for mean overall survival were estimated for hydroxycarbamide.

The reason that estimates of overall survival have been used, rather than responses based on cytogenetic response (as for bosutinib) was due to the lack of data on these, as reported in Loveman et al. (2012)[85], page 50, here it is stated:

> *"owing to the lack of data for overall survival and major cytogenetic response for these comparators, we were unable to derive survival curves in this way and so have instead taken a simple pragmatic approach and selected an estimate for overall survival... In the model, an overall survival curve is derived from this overall survival estimate, by assuming a negative exponential distribution for mortality."*

In the absence of any other data, these estimates are also used as the efficacy input for the hydroxycarbamide arm. However, it should be noted that the data from Kantarjian et al (2007)[36] is for a second-line hydroxycarbamide population and therefore likely over-estimates the OS and PFS compared to a third-line population, as is the case for the base-case bosutinib population. As such, a sensitivity analysis is considered where a ratio is calculated for Study 200 second-line CP compared to the Study 200 third-line CP first with respect to OS and this is used to adjust the hydroxycarbamide OS data.

Interferon

As previously noted, no data was found for interferon in a second-line or later population. As such, the same approach to fitting time on treatment and overall survival curves for interferon as hydroxycarbamide, using estimates for the means 0.5 years and 3.6 years respectively (Loveman et al, 2012[85]). (Overall survival had previously been as high as almost 11 years using MCyR (Rogers et al, 2012)[84] and as low as 1-2 years according to clinician advice (Loveman et al, 2012)[85]).

Stem cell transplant

For SCT, the Jabbour 2011 study was selected for the base-case. This was because it was a full publication (rather than abstract), included the most comparable patient population (majority were third line) and presented OS curves. The only other full-publication that reported OS in a format that was useable for our economic evaluation was Oehler 2007, but this was in a second-line population only and therefore deemed to be less relevant. Nonetheless, this is considered in a sensitivity analysis.

The overall survival curve for the chronic phase patients who received SCT in Jabbour 2011[58] was digitized using GetData graph digitizer software (Sergey Federov, Russia, http://getdata-graph-digitizer.com). The patient level data was then reconstructed, and survival analysis was performed in R, as for the bosutinib data.

It was not possible to use the surrogate survival approach for SCT because response rates are not reported as SCT completely changes the course of the disease (it is effectively a cure if successful). As with the bosutinib data, the exponential curve was found to be the best fitting curve (see Appendix 10.18). This curve fitting is explored in sensitivity analysis, where the second best fit (according to the AIC), the Weibull, is used. In addition, a further sensitivity analysis is performed using figures from the other published studies identified in the systematic review.

Time in accelerated and blast phase in CP model

Rogers et al (2012)[84] and Loveman et al (2012)[85] assumed that patient spent 9.6 months in accelerated phase, and 13.1 months in blast crisis. Hoyle et al (2011a)[80] used the same assumption for accelerated phase, but decreased the time in blast crisis to 6 months in accordance with clinician advice.

Given that the Hoyle 2011a[80] evaluation for TA251 was conducted more recently (although published earlier) than the Rogers[84]/Loveman[85] appraisals for TA241, our model uses the assumptions from Hoyle 2011a[80] as this is more likely to reflect current thinking on the likely durations of AP and BP and seems more clinically plausible. As such, our model assumes that the 6 months prior to death will be spent in the blast crisis state, and that the 10 months prior to this (the model can only consider integer numbers of months due to model cycle) will be spent in the accelerated phase state. A sensitivity analysis is conducted using the figures from TA241 (Rogers 2012[84] and Loveman 2012[85]).

B) ADVANCED PHASE MODELS

As these models use the same methodology and data, the descriptions for how clinical data has been derived have been grouped together.

Bosutinib

As with the chronic phase model, the full accelerated phase cohort, rather than the EMA requested post-hoc 'unmet need' subpopulation is used as the base case population.

Patient level data for OS was from the more recent data snapshot of 15 February 2012 snapshot. Since this data has not been formally analysed, it is not able to be presented in Section 6.8.5. The K-M graphs of OS derived from the patient-level data are presented below.

Figure B17: Kaplan-Meier and parametric curves for AP – Overall Survival

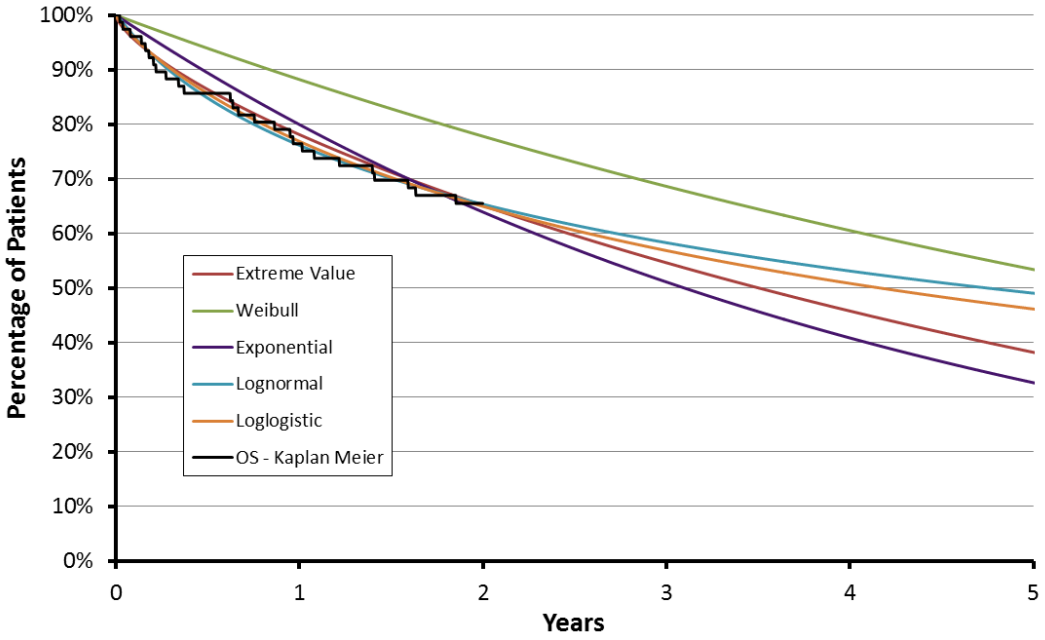
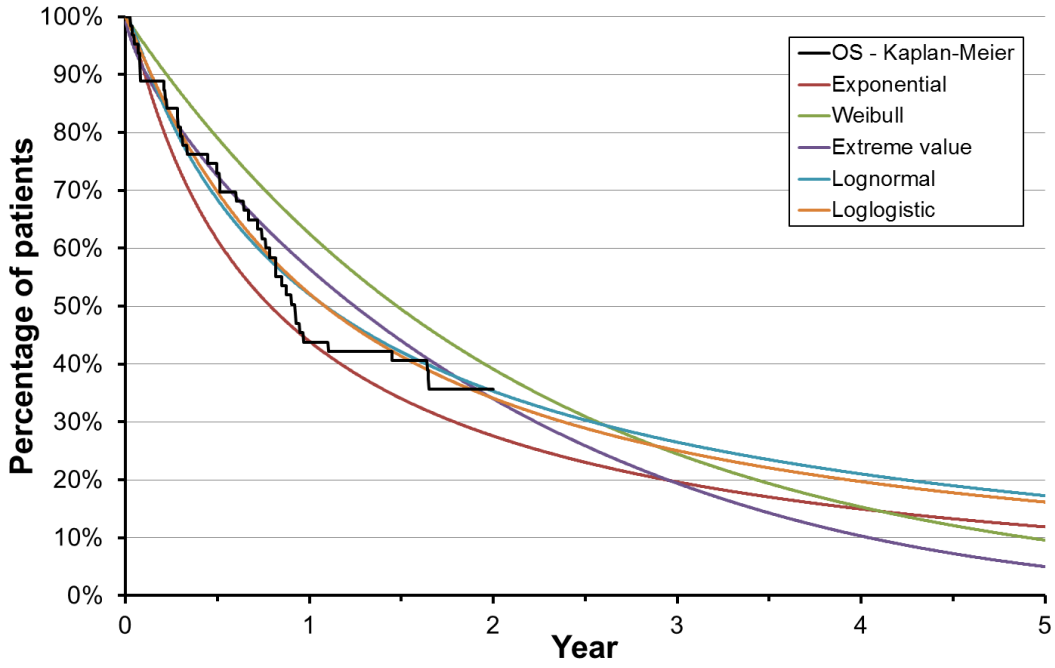


Figure B18: Kaplan-Meier and parametric curves for BP – Overall Survival



As previously noted, only the parametric curve fitting approach is considered for the AP and BP models, as surrogate outcomes are not validated for use in this population, and are likely to overestimate survival. Parametric curves were fitted in R, as for the chronic phase population. As in the CP model, the exponential curve is selected as the best-fitting curve and is used in the base-case for both the AP and BP models; the second best-fitting curve was the extreme value for the AP cohort and the Weibull in the BP cohort and these are considered in scenario analyses.

Total time in accelerated phase was determined by overall survival data from Study 200, less the fixed time in blast phase (6 months), instead of the fixed duration of 10 months used for hydroxycarbamide. The mean time in accelerated phase for bosutinib patients in the model is 4.03 years, substantially longer than the fixed period of 10 months.

Similarly, in the blast phase model, for patients receiving bosutinib, time in blast phase was be determined by Study 200 overall survival data directly, instead of the fixed duration of 6 months described in hydroxycarbamide. The mean time in blast phase for bosutinib patients in the model is 1.77 years, substantially longer than the fixed period of 6 months.

Stem cell transplant

For SCT in the advanced phases, although Oehler et al (2007) consider SCT in second-line patients, so less appropriate for this submission, OS curves are presented separately AP and BP. Conversely, in Jabbour et al (2011)[58], although the population is more appropriate (majority third-line), the overall survival curves is presented for a combined 'advanced phase' populations, consisting of 12 accelerated phase patients, 9 blast phase patients and 20 patients in second chronic phase.

Since it is anticipated that OS following SCT would be different for the AP and BP populations, it was felt to be more appropriate to use the Oehler 2007 data for the base-case. The AP and BP survival curves were digitized using GetData graph digitizer software (Sergey Federov, Russia, http://getdata-graph-digitizer.com). The patient level data was then reconstructed, and survival analysis was performed in R, as for the bosutinib data. The Jabbour 2011 'advanced phase' OS data is used in a sensitivity

analysis for the AP model as it contained a majority of AP and second-CP patients, who are expected to be similar to AP (N=32/41). For the BP model, a sensitivity analysis was conducted using OS data for the 'advanced phase' cohort from Saussele 2010 (majority second-line), as this contained a majority of blast phase patients (N=25/28).

Hydroxycarbamide

In the absence of any direct evidence on the survival of patients in accelerated phase who are treated with hydroxycarbamide, it is assumed that the mean survival is equal to the time spent in accelerated phase and blast phase from the chronic phase model (Section 7.3.1). This gives a mean survival of 16 months fixed duration (10+6), to which an exponential curve has been fitted.

7.3.2 **Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.**

In the CP model, the patient distribution each cycle is calculated using the following steps.

1. The proportion of patients in the death health state is calculated as 1 – the probability of overall survival.
2. Patients are assumed to spend the 6 months prior to death in the blast phase health state.
3. Patients are assumed to spend the 10 months before BP in the AP health state.
4. The proportion of patients in the CP off treatment state is calculated by subtracting the proportion of patients in the AP and BP states, and the probability of discontinuation, from the probability of overall survival. (For hydroxycarbamide and SCT, the probability of discontinuation is set to 0 at all time points, such that there are always 0 patients in the CP off treatment state.)
5. The proportion of patients in the CP on treatment state is calculated by subtracting the proportion of patients in the AP, BP and CP off treatment states from the probability of overall survival.

In the AP (and BP) model, the proportion of patients in the AP (BP) on and off treatment states is calculated in the same way as the CP on and off treatment states for the CP model. In the AP model, patients are assumed to spend the 6 months prior to death in the blast phase health state.

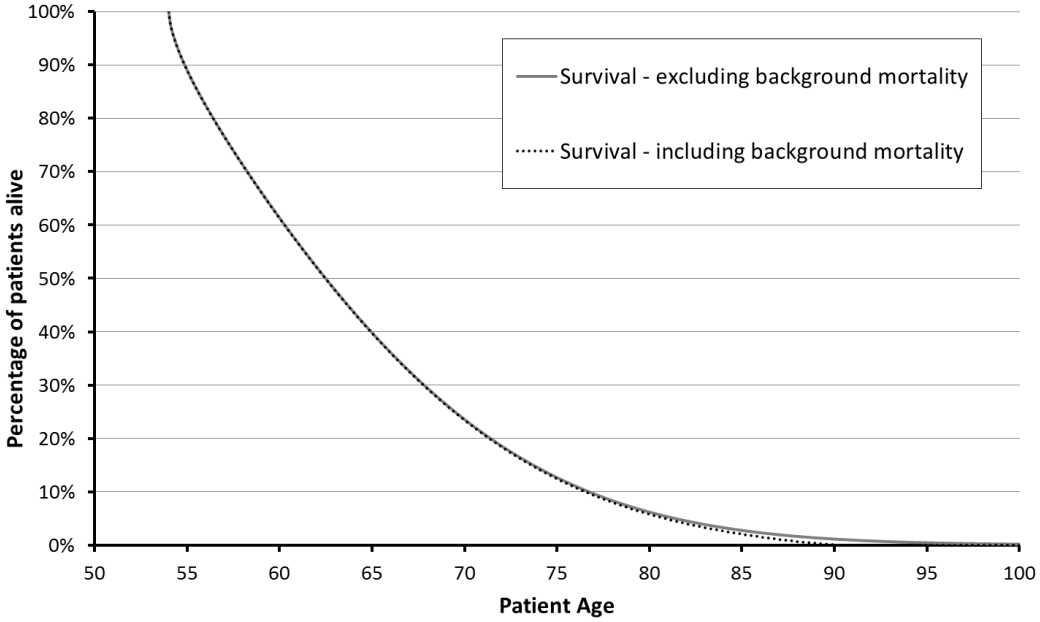
Death due to all cause mortality

For all three models, for all comparators, background mortality was incorporated into the model, to ensure that parametric curve fits did not over predict survival as patients aged.

Background mortality was applied in the model by subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200), and adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012). The starting age in the AP and BP models are 50 and 47 respectively, so these ages are used to adjust for background mortality.

As this component of mortality increases over time, it has the effect of ensuring survival curves do not asymptote to 0, estimating survival beyond what can be expected in clinical practice, where patients are likely to experience co-morbidities and competing risks. This is shown graphically in Figure B19.

Figure B19: OS for CP, excluding and including background mortality



7.3.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

As reported, the overall survival for the bosutinib patients in the chronic phase model was calculated using a relationship based on MCyR, as described by Rogers et al 2012[84] for TA241. This is described in detail below. As previously noted, this approach is not used in the AP and BP model, instead relying only on curves fitted to the empirical OS data from Study 200.

Jabbour et al [2008][87] present the overall survival for patients on high dose imatinib following the failure of standard dose imatinib. In this analysis, 35 of 84 patients are reported as experiencing MCyR within 12 months. Rogers et al [2012][84] report the hazard ratio between responders and responders as 0.37 (from a meta-analysis of three long-term studies for imatinib), and state that survival follows a Weibull distribution.

The hazard ratio from imatinib trials was considered appropriate for estimating overall survival for dasatinib and nilotinib because of their similar modes of action (Rogers et al, 2012)[84]. Our systematic review did not identify any long-term studies that reported MCyR, and the only bosutinib study identified was Study 200, so we had no direct evidence from which to estimate a hazard ratio. Since bosutinib is another TKI, we considered that the 0.37 hazard ratio would also be appropriate for our analysis.

The probability of overall survival at various time points was found by digitising the Kaplan Meier graph presented in Jabbour 2008[87] (figure 2, p. 2156), and using Solver in Microsoft Excel to find the parameters for the Weibull distribution (alpha 1.63, beta 178.7). We chose this study for the same reasons as Rogers et al (2012)[84] – that it is the most mature data available for overall survival in imatinib-refractory patients, and that the response rate is quoted in the study.

In the pre-specified analysis of MCyR, where patients who had a response at baseline and attained it were not counted as responders, the best-cumulative response was 32% at minimum follow up duration of 12 months (28 March 2012). Rogers et al (2012)[84] discuss the difficulty in deducing the direction of bias when considering MCyR status at

baseline, since prior response may increase the likelihood of response in the next line of therapy, or the patients may be in a more mature stage of CML progression. Nonetheless, the MCyR figures reported for the other TKIs appear to include those patients who had MCyR at baseline.

In our base-case, the MCyR in the third-line population used is 38.9%. As noted in section 6.8.5 this value is taken from Khoury 2012 publication (28 March 2012 snapshot) and corresponds to the best-cumulative response in patients who both maintained and attained a MCyR, at a minimum duration of follow-up at 12 months. This is consistent with the duration of minimum follow-up for the MCyR values selected for the TKIs in Rogers 2012[84]. With continued follow-up a slight improved in the MCyR is seen of 41%, data snapshot of 15 February 2012, which corresponds to 24 month minimum follow up data.

We also tested the relationship between CCyR and overall survival, using the explanation supplied by Hoyle et al (2011a).[80] The relationship between CCyR and overall survival was found from a meta-analysis of trials of imatinib 1st line (Hoyle et al, 2011a)[80]. This allowed the mortality due to CML-related causes and non-CML causes to be calculated for responders and non-responders. This was found to overestimate survival in this patient population (when compared to Study 200), and so was not used as it would have biased the results in favour of bosutinib (this relationship is shown in Section 7.3.1).

7.3.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[b]:

Section 7.8.1 describes the process used to validate the economic model and review assumptions used.

In all cases, assumptions were first made in a manner consistent with published literature and previous NICE appraisals wherever possible. Input was sought from one clinical expert. Clinical assumptions were presented in face-to-face meetings as well as telephone and email discussions arranged on an ad-hoc basis.

The clinical expert consulted was chosen based on their expertise as haematologist specialising in the treatment of CML in the UK setting and experience with previous HTA appraisals in CML.

Input was provided by the clinical expert to ensure assumptions were plausible. The expert in question examined utility estimates, model design and structure, and extrapolation of clinical data.

7.3.5 Summary of selected values

A list of the key parameters is given below. A full list of parameters, including confidence intervals, is given in the Appendix 10.19.

Table B37: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Age	54 years	Patient characteristics Section 6.8.3.2
Bosutinib monthly cost	£3,735.84	Intervention and comparator costs Section 7.4.21
Hydroxycarbamide monthly cost	£13	Intervention and comparator costs Section 7.4.21

[b] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Interferon monthly cost	£648	Intervention and comparator costs Section 7.4.21
Stem cell transplant month 0 cost	£76,560	Intervention and comparator costs Section 7.4.21
Stem cell transplant month 1-6 cost	£5,299	Intervention and comparator costs Section 7.4.21
Stem cell transplant month 7-12 cost	£3,231	Intervention and comparator costs Section 7.4.21
Stem cell transplant month 13-24 cost	£1,166	Intervention and comparator costs Section 7.4.21
Stem cell transplant month 25+ cost	£140	Intervention and comparator costs Section 7.4.21
Death cost	£6,004	NHS costs Section 7.4.16
CP cost per month	£385	Health state costs Section 7.4.22
AP/BP cost per month	£1,126	Health state costs Section 7.4.22
Time in AP on hydroxycarbamide	10 months	Clinical data in the model Section 7.3.1
Time in BP on hydroxycarbamide	6 months	Clinical data in the model Section 7.3.1
Hydroxycarbamide overall survival-mean	3.5 years	Clinical data in the model Section 7.3.1
Interferon overall survival-mean	3.6 years	Clinical data in the model Section 7.3.1
MCyR responders overall survival – alpha (Weibull)	1.63	Clinical data in the model Section 7.3.1
MCyR responders overall survival – beta (Weibull)	178.70	Clinical data in the model Section 7.3.1
Hazard ratio for non-MCyR-responders (Rogers 2012)[84]	0.37	Clinical data in the model Section 7.3.1
MCyR proportion-bosutinib	0.389	Clinical data in the model Section 7.3.1
SCT overall survival – CP - exponential parameter	1.89712	Clinical data in the model Section 7.3.1
Bosutinib treatment duration - CP– lognormal logscale	[redacted]	
Bosutinib treatment duration - CP – lognormal logshape	[redacted]	
Interferon treatment duration – mean	6 months	Clinical data in the model Section 7.3.1
Bosutinib treatment duration - AP– lognormal logscale	[redacted]	Clinical data in the model Section 7.3.1
Bosutinib treatment duration - AP – lognormal logshape	[redacted]	Clinical data in the model Section 7.3.1
Bosutinib treatment duration - BP– lognormal logscale	[redacted]	Clinical data in the model Section 7.3.1
Bosutinib treatment duration - BP – lognormal logshape	[redacted]	Clinical data in the model Section 7.3.1
Bosutinib overall survival – AP – exponential parameter	7.3986	Clinical data in the model Section 7.3.1
Bosutinib overall survival – BP – exponential parameter	6.4532	Clinical data in the model Section 7.3.1
SCT overall survival – AP - exponential parameter	1.0982	Clinical data in the model Section 7.3.1
SCT overall survival – BP -	0.9603	Clinical data in the model

exponential parameter		Section 7.3.1
FLAG-IDA cost (for blast phase model)	£29,212	NHS cost Section 7.4.16

7.3.6 Extrapolation of costs and clinical outcomes

Costs and clinical outcomes are extrapolated beyond the follow-up periods. The trial for bosutinib did not contain a comparator. As such, comparator efficacy has been taken from published clinical studies (in the case of stem cell transplant), and from distributions fitted to estimates from previous NICE technology assessments (in the case of interferon-alpha and hydroxycarbamide). Exponential curves have been used for bosutinib and all comparators and are shown in Section 7.3.1., fitted to Kaplan-Meier plots.

Key assumptions used in the model are presented in Section 7.3.7.

7.3.7 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table B38: Assumptions used in the de novo economic model

Assumption	Justification
Patients treated with bosutinib in clinical practice will be treated for the same period of time as in the 200 study	In TA241, an assumption was made that patients were treated based on PFS minus discontinuations due to adverse events. We have explored this in sensitivity analysis; however we have 5 years of patient-level discontinuation data from Study 200 to inform our assumption, which was unavailable for the drugs considered in TA241.
Following bosutinib treatment, all patients receive treatment with hydroxycarbamide	There is no consensus about what patients will receive following failure on bosutinib, but given that they are unsuitable for all other currently available TKIs, their options would be very limited. Whatever treatment is assumed for patients who discontinue on bosutinib would in theory be identical for hydroxycarbamide patients who fail treatment (e.g. SCT, hospitalisation or more intensive chemotherapy). As such, it was felt that the most appropriate post-bosutinib treatment was hydroxycarbamide to ensure a fair comparison of costs and effectiveness between bosutinib and hydroxycarbamide. This was the assumption made in TA241. Whilst BSC with hydroxycarbamide may be the 'base' treatment, Pfizer acknowledge that patients may incur other costs whilst on treatment with hydroxycarbamide. As such a sensitivity analysis is performed including additional costs for hydroxycarbamide. As there are no sources for these costs, a fixed cost is assumed per month.
The overall survival in study 200 is representative of the survival that would be seen in clinical practice with bosutinib	This assumption has been validated by comparing the data for the full population from Study 200 in CP, AP and BP with a post-hoc group of patients who were felt to be more representative of patients in clinical practice.
The overall survival experience of a cohort can be predicted as a function of MCyR rate and that this rate is the same regardless of	This assumption and the choice of a MCyR rate that includes maintainers and attainers of MCyR was used (and validated) in TA241. This assumption has also been validated in comparing the results seen to the predicted

Assumption	Justification
whether a patient receives a treatment in 1st, 2nd or later-lines of treatment.	overall survival from parametric curve fitting to empirical data from Study 200 data (7.3.1). The approach to predicting OS is tested in sensitivity analysis, with both trial based OS used, and the surrogate outcome of CCyR used (as in TA251). Whilst parametric curve fitting does provide similar results, on expert advice Pfizer have used the relationship with MCyR, as it has been validated in a larger cohort, and does not rely on extrapolation over a much larger time horizon than the original data.
The single arm studies used have patients with similar baseline demographics and risk factors, and are thus comparable	As no randomised or comparative clinical trials are available in this disease area for bosutinib, hydroxycarbamide, interferon, or stem cell transplant (at CP, AP or BP), the only data available is taken from single arm studies. However, the relevance of the studies included has been checked with a clinical expert.
In CP, patients treated with hydroxycarbamide exhibit overall survival as described by Loveman (2012)[85]	The assumption was taken from TA241, and is likely to be an overestimate of survival with hydroxycarbamide, as this estimate is from a second line therapy, whereas in the economic model is used as the survival for third line therapy line therapy. This assumption is tested in sensitivity analysis, where the survival is reduced by the ratio seen between OS for bosutinib treatment in second and third line therapy.
In CP, patients treated with interferon have survival in line with hydroxycarbamide, but experience adverse events associated with treatments (Loveman, 2012)	Clinicians do not view interferon as an active-treatment, although studies do report some efficacy benefit, with MCyR ranging from 0% to 54.5% (Garside et al, 2002).[88] However, given that these all relate to first-line studies, an assumption was used in TA241 that interferon would have similar efficacy as hydroxycarbamide and this was validated by clinicians. However, as noted in Rogers[84]/Loveman[85], interferon does cause patients to experience flu-like symptoms and is therefore associated with a utility decrement compared to other treatments in chronic phase. Interferon is not widely used in UK clinical practice. This assumption is explored in a sensitivity analysis.
In CP, patients treated with SCT have survival in line with that seen in Jabbour (2011)	Survival data for Stem Cell Transplant was taken from Jabbour (2011)[58]. This was a new study identified in our systematic review, not used in previous appraisals. It was selected as it represents the best clinical data available in a patient population most comparable to Study 200 and the licensed population (i.e. mixture of 3rd and 4th line patients in CP). This assumption was tested in sensitivity analysis, where data from another SCT study was considered.
In the CP model, following CP, all patients (irrespective of previous treatment) spend 10 months in AP, before progressing to BP.	This assumption was used in TA251, and validated by clinicians.
In the CP and AP models, following CP and AP, all patients (irrespective of previous	This assumption was used in TA251 and validated by clinicians. In TA241 (a later line of therapy) an alternative figure (13.12 months) was used. This is explored in the

Assumption	Justification
treatment) spend the final 6 months of life in blast crisis.	sensitivity analysis
In BP, patients who are to receive a Stem Cell Transplant are first treated with chemotherapy (the FLAG-IDA regimen) for 2 cycles prior to receiving SCT.	As identified in the scope, acute-style chemotherapy is used in blast-crisis phase patients prior to SCT. Clinical experts confirmed that FLAG-IDA is the most commonly used regimen for 2 cycles. As there is no data on what proportion of patients in blast-phase receive FLAG-IDA or SCT, it was deemed appropriate to assumed that all patients eligible for SCT would have previously received FLAG-IDA. A sensitivity analysis is conducted where this cost is not included
Patients treated with hydroxycarbamide receive hydroxycarbamide until death and hydroxycarbamide patients spend fixed durations of time in AP and BP of 6 and 10 months respectively irrespective of which phase hydroxycarbamide treatment was initiated in (i.e. this assumption is the same for the CP, AP and BP model).	This assumption was used in TA241 and TA251 and was validated by clinical experts during those appraisals.

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 **Please outline the aspects of the condition that most affect patients' quality of life.**

CML is a chronic disease and unless a patient is able to receive a SCT, patients remain on medication for many years. The estimated median survival with imatinib exceeds 25 years in patients with a median age of diagnosis of almost 60 years ([24, 32]). Quality of life is not significantly impaired in the chronic phase of CML compared to those of a similar age without CML, indeed approximately 40% of CP patients are asymptomatic and diagnosed as a result of a routine blood test.[18] For those that do experience symptoms in the chronic phase they tend to be mild and non-specific, such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss.[17]

Although quality of life is not assumed to be very different for CML patients on and off treatment, low grade chronic AEs can be debilitating, particularly if experienced over long periods of time, such as fatigue, oedema, muscle aches, rash or diarrhoea. Some more serious AEs may have a more significant impact on quality of life and may require intervention, for example a pleural effusion requiring steroids, pleural taps or pleural drains, PAOD requiring surgical bypass or balloon angioplasty or pulmonary HTN requiring cardiac catheterisation and medication.

Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising, bleeding and infections.[18] In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.[18, 19] For patients, symptoms such as breathlessness, tiredness, bleeding and infections can seriously affect patients' quality of life.

7.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition.**

Quality of life is expected to worsen as the disease progresses from chronic phase to accelerated phase and again to blast crisis phase.

In the chronic phase of the disease, previous studies have found that quality of life is not seriously impaired compared to those of a similar age without CML. In the advanced phases, HRQL is expected to be significantly worse. The utility associated with different phases of the disease are described in more detail in Section 7.4.7 below.

7.4.3 HRQL data from Study 200

HRQL was assessed using EQ-5D, the preferred utility measure in the reference case, in Study 200, as described in Section 6. The EQ-5D was valued using the UK tariff. Although this HRQL data is appropriate for the cost-effectiveness analysis, it is only available for bosutinib and has not been validated for use in comparators in CP, AP or BP CML. The EQ-5D data collected for the third-line CP and advanced phase CML population of Study 200 are presented below at each of the time-points it was collected.

Table B39: Summary of EQ-5D Results by Visit for third-line CP CML patients, n=118 (28 Mar 2011 snapshot)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]		

Table B40: Summary of EQ-5D Results by Visit for AP patients (28 Mar 2011 snapshot)

	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]					

Table B41: Summary of EQ-5D Results by Visit for BP patients (28 Mar 2011 snapshot)

[redacted]					

7.4.4 Mapping of HRQL

N/A

7.4.5 Systematic review of HRQL

A systematic search was conducted in October 2012 to identify HRQL data from studies that consider the broad patient group who have previously tried one or more TKI (i.e. 2nd line or later) across all 3 phases of CML. The same searches were run as described in Section 7.1.1, above (for full search strategies, please refer to Section 10.12.4).

The inclusion and exclusion criteria and the rationale for these were identical to the cost-effectiveness systematic review reported in Table B35, with the exception of study type and comparator. In this quality of life review, the study type that was included was any study that reported quality of life (measured on any scale) or utility data. Any comparator was acceptable and the results were not filtered by drug or comparator name.

Abstracts of citations found through the searches were assessed by two independent reviews for inclusion based on abstract and key words alone. Full-text copies of studies that potentially met the initial criteria were obtained and reviewed against the inclusion criteria by two independent reviewers. Studies that met the eligibility criteria after the second screening stage were extracted by a reviewer and checked by a second party.

The flow diagram of the studies included in this systematic review is shown in Figure B20 and described below:

- A total of 4,098 studies were identified from EMBASE, MEDLINE and MEDLINE In-Process and 776 from the Cochrane Library. 45 studies were identified from NHS EED, and 2 from EconLit.
- No additional articles that were not captured through the database searching were identified from the horizon scanning or congress report searches.
- Following deduplication of the database results, 2486 abstracts remained for review.
- In the first screening stage, 15 articles were identified as potentially relevant by two independent reviewers, and full texts were obtained for these.
- Of the full texts, 2 articles met the inclusion criteria for 2nd line CML treatment, and 0 for 3rd line CML treatment.

7.4.6 HRQL study details

New HRQL studies identified

Only 2 new studies of interest were identified in the systematic review that reported HRQL values from a previously treated CML population (Rea 2011[89] and Trask 2012[82].

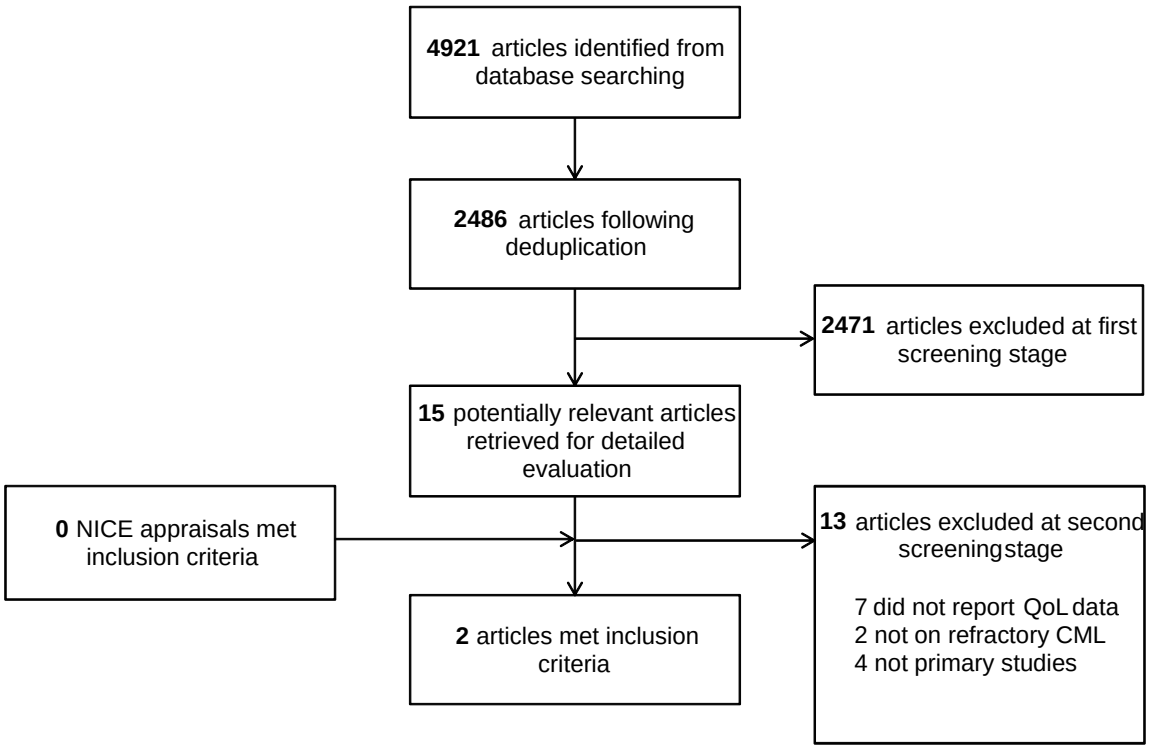
In addition, one systematic review was also identified, which included studies that looked at previously treated CML patients (Ferdinand 2012[90]). This review identified only 1 study that reported HRQL outcomes for a previously treated CML population (Trask 2011[91]). Trask 2011 was the congress abstract associated with the full Trask 2012 population and therefore has not been extracted separately.

Rea and colleagues (2011)[89] reported interim results from an observational study evaluating HRQL in patients with CML with resistance or intolerance to imatinib treated with second-line nilotinib. This study involved 145 patients from 30 sites in France, and HRQL was assessed using the EQ-5D questionnaire and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The authors did not provide details on the number of patients assessed for HRQL at the interim analysis. According to the EQ-5D questionnaire, the self-rated health index was stable over the first 6 months of follow-up (mean, 70.6 to 70.3). EORTC QLQ-C30 scores were also stable over time.

Trask and colleagues (2012)[82] reported a second-line study of bosutinib in imatinib-intolerant and imatinib-resistant patients and reported HRQL in terms of FACT-G and FACT-Leu in chronic CML patients only. Trask 2012[82] also reports that quality of life remained fairly consistent over the course of the trial, and was similar for imatinib-resistant and imatinib-intolerant cohorts.

Since HRQL measured by EQ-5D (NICE's preferred reference case) is available both from Study 200 and also from long-term studies of imatinib (as noted in TA241 and TA251), the full results of Rea[89] and Trask[82] are not reported below but can be found in Appendix 10.13.

Figure B20: Study flow diagram for HRQL Studies



Additional HRQL data from TA241 and TA251

Given the paucity of relevant HRQL data in a directly comparable population and that as noted above in section 7.4.2, HRQL is more driven by phase of CML than line of treatment, the results of both TA241 (reported in Loveman 2012[85] and Rogers 2012[84]) and the more recent TA251 (reported in Hoyle 2011a[80]) are considered relevant.

In both TA241 and TA251, the utility collected in the IRIS trial in patients taking imatinib (N=1,067) was selected, as reported by Reed and colleagues (2004)[92] and used by Dalziel 2004[93] in a previous HTA of imatinib for CML.

The utilities for accelerated and blast phase reported by Reed 2004[92] and colleagues are slightly different from those quoted by Dalziel 2004[93], although both are taken from the IRIS trial originally. In the Reed 2004[92] analysis, no difference was assumed between accelerated and blast phase since the observed difference in values was not statistically significant. Therefore, in both TA241 and TA251, the Assessment Group used the utility values cited by Dalziel[93] 2004 in order to distinguish between the two phases.

Due to the lack of data on utility values for patients receiving dasatinib and nilotinib in both TA241 and TA251, the utility values for these interventions was assumed to be equal to those for imatinib from the IRIS trial, based on clinical opinion and the similarity of the incidence of adverse events by treatment.

Similarly, no literature was identified on utilities for CML patients taking hydroxycarbamide and so in both TA241 and TA251, the utility when hydroxycarbamide is used in the chronic phase was assumed to be the same as the other TKIs used in chronic phase, regardless of line of treatment.

For patients undergoing SCT, previous NICE appraisals have reported a reduced quality of life compared to TKIs or hydroxycarbamide owing to the impact of post-transplant conditions such as graft-versus-host disease (GVHD). In TA251, utility decrements were taken from Lee et al. (1997)[94], which reported utility decrements for patients with chronic graft-versus-host disease undergoing SCT were applied to the general population for high and low-risk patients. In TA241, a fixed utility for SCT was assumed, which was taken as the mid-way value between utility values proposed by the BMS and Novartis submissions.

The full data extractions for the utility studies referenced in TA251 and TA241 can be found in Appendix 10.12. The key utility values are summarised in Table B42 below.

Table B42: Utility values used in TA251 and TA241

	TA251		TA241	
	Mean (se)	**Source**	**Mean (se)**	**Source**
Chronic phase				
dasatinib, nilotinib, imatinib (1st line in TA251; 2nd line in TA241)	0.85 (0.004) at diagnosis, mean age 50	Dalziel 2004[93]	0.85 (0.004)	Dalziel 2004[93]
SCT	75% patients (low risk group) utility equal to general population minus 0.041. 25% (high risk group) utility equal to general population minus 0.079	Lee 1997	0.71	An assumption based on mid-value between utility values stated in BMS (0.6) and Novartis (0.81) submissions [Loveman 2012][85]
Hydroxycarbamide	As dasatinib, nilotinib, imatinib 1st-line	Assumption	As dasatinib, nilotinib 2nd line	Assumption
Interferon	NR	NR	0.71 (0.008)	Reed 2004[92]
Accelerated phase				
Hydroxycarbamide	0.73 (0.06)	Dalziel et al (2004)[93]	NR	
Blast phase				
Hydroxycarbamide	0.52 (0.08)	Dalziel et al (2004)[93]	NR	
*Dalziel et al in turn cite unpublished IRIS study data contained in the 2003 submission to NICE				

Update to the TA251 systematic review

As noted above, TA251 represents the most recent systematic review of HRQL. As such, to ensure that we had not missed any relevant studies an update of the TA251 search was undertaken. This update identified a further 3 studies of potential interest (Guest 2012[95], Efficace 2011[96], and Aziz 2012[97]). However, none of these studies were felt to have more relevant HRQL data than either EQ-5D derived estimates from IRIS or Study 200 previously reported. Further details on these excluded studies can be found in the Appendix 10.12.8.

7.4.7 **Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.**

As noted above, a number of studies were identified that have considered utility in CML patients, however only those taken from the IRIS RCT, as reported in TA241 and TA251, consider trial-based utility collected using EQ-5D. As such, these are now compared to those reported in Study 200.

In the chronic phase of the disease, previous studies have found that quality of life is not seriously impaired compared to those of a similar age without CML. As reported in TA251 and TA241, the average utility (measured via EQ-5D) for patients taking imatinib in the imatinib newly diagnosed CML RCT (IRIS) was 0.85 (SE 0.004) at diagnosis at a median age of 50, taken from Reed 2004[92].

Despite being in a more refractory third-line chronic phase population, the quality of life measured in Study 200 provides similar quality of life estimates for CML patients. The mean utility (measured via EQ-5D) for the chronic phase, third-line patients across the trial was [redacted] for patients at a mean age of 51.50 years (utility during screening was [redacted]).

In the advanced phases, in TA241 and TA251, it was assumed that the utility of a patient in accelerated phase is 0.73 (SE 0.06) and for blast phase is 0.52 (SE 0.08) (based on IRIS RCT, Dalziel 2004[93]), also at a median age of 50. Similar values are seen in Study 200 (see Section 7.4.3 below); the average utility across the trial for patients is [redacted] and [redacted] respectively. The mean utility values at screening were [redacted] for AP and BP respectively.

Adverse events

7.4.8 **Please describe how adverse events have an impact on HRQL.**

The utility values that had been used for TKIs in previous assessments are used for bosutinib, as its adverse event profile was not considered sufficiently different to justify incorporating further impact on HRQL and because HRQL data from Study 200 was broadly comparable to the valuations used in previous assessments, which were preferred for reasons of consistency (Section 7.4.7).

Previous economic evaluations used lower utility values for interferon alpha and stem cell transplant than for TKIs, in order to capture the lower quality of life associated with adverse events from these treatments (Loveman et al, 2012[85] and Rogers et al, 2012[84]). In the absence of any new data identified in the HRQL systematic review for these interventions, these utility values have also been used in our model. The resulting values are shown in B44.

In order to explore the impact of these assumptions, two scenarios are presented in sensitivity analysis; firstly that utility falls when patients move in to an ‘off treatment’ state, as presumably their disease is less well controlled. As no data exists for this, a 5% decrease has been assumed. The second scenario explored is the removal of utility decreases for adverse events for patients treated with interferon, resulting in these patients having the same utility scores as bosutinib and hydroxycarbamide.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values**

obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

The values used in the base case of the economic model are shown in Table B43. Values used in previous appraisals (TA241 and TA251) were used over the results seen in Study 200.

Whilst values taken directly from the intervention clinical trial is often more appropriate, the values in previous appraisals are from the IRIS study. This study collected arrange of utilities, in a large cohort of patients, including the utility of patients who progressed to AP and BP whilst not on active treatment. These utilities, though vital for modelling, are not available from Study 200. In addition the use of the IRIS values provides consistency with previous technology appraisals.

For SCT, as noted above and confirmed with clinical experts in CML, HRQL post-transplant is worse than for TKIs or hydroxycarbamide, to account for the impact of conditions such as GVHD. In our base-case, a fixed utility is used, which corresponds to the mid-way value between the utility values proposed by the BMS and Novartis submissions, selected by the ERG in TA241.

The results of Study 200 are broadly in line with those used in TA241 and TA251, (CP of 0.81 vs 0.85), though higher in advanced and blast phases. A further weakness of the Study 200 data is that it contains only 'on treatment' utilities, which may be the reason the AP and BP utility values are in excess of those used in TA241 and TA251.

A sensitivity analysis is considered in which mean Study 200 utilities are used only when patients are treated with bosutinib and TA241/TA251 utilities otherwise. This was not considered to be appropriate for the base-case as the mix of different sources of data adds further uncertainty to the cost-effectiveness estimates.

Table B43: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
CP on treatment - bosutinib	0.85	(0.77 – 0.91)	Section 7.4.6	Assumed to be same as for other TKIs
CP off treatment - bosutinib	0.85	(0.77 – 0.91)		
AP - bosutinib	0.73	(0.64 – 0.81)		
CP - hydroxycarbamide	0.85	(0.77 – 0.91)		Used in previous economic evaluations [Hoyle et al, 2011a][80], [Loveman et al, 2012][85], [Rogers et al, 2012][84]
AP - hydroxycarbamide	0.73	(0.64 – 0.81)		
CP - SCT	0.71	(0.62 - 0.79)		
AP - SCT	0.71	(0.62 - 0.79)		
CP on treatment - interferon	0.71	(0.62 - 0.79)		
CP off treatment - interferon	0.85	(0.62 - 0.79)		
AP - interferon	0.73	(0.64 – 0.81)		
BP – all treatments	0.52	(0.42 – 0.62)		

Utility values presented are for a 56 year old patient.

7.4.10 Expert assessment of applicability of values

No utilities were estimated by experts. Section 7.8.1 details the validation used of the submission and modelling.

7.4.11 **Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

It is assumed that the HRQL depends only on disease state, treatment and age. This assumption was used in TA241 and TA251, as the health states contain patients who would be expected to be homogenous.

7.4.12 **Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?**

N/A

7.4.13 **If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?**

N/A

7.4.14 **Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.**

As described in Section 7.4.2, HRQL is assumed to worsen as the disease progresses from CP, to AP to BP. Additionally, HRQL is assumed to deteriorate over time, as the population ages. In TA251 the utilities in the model are adjusted for age using the formula by Ara & Brazier (2010). A similar approach to adjust utilities for age is taken in our model, using utility multipliers.

As previously described, patients in the chronic phase of CML experience minimal difference in HRQL compared to the general public. Accordingly, the utility for a CP patient at a mean age of 50, as described in TA251, is assumed to be 0.85 and according to Kind, 1999[98] the mean UK utility value for the general public at 50 years old is also 0.85 (assuming an equal male:female split). A utility multiplier is then calculated by dividing the utility values from TA251 reported in Table B43 above by 0.85, and the result of this is shown in Table B44. Example utility values are shown in Table B45.

Using the Ara & Brazier (2010) equation, the utility for the general population aged 50 (50:50 male to female) is 0.866, which is similar to the values calculated above. A sensitivity analysis is also conducted where utility is assumed not to decline as patients' age.

Table B44: Ratio of utility to general population utility

State	Utility multiplier value
CP on treatment - bosutinib	1.00
CP off treatment - bosutinib	1.00
AP - bosutinib	0.86
CP - hydroxycarbamide	1.00
AP - hydroxycarbamide	0.86
CP - SCT	0.84
AP - SCT	0.84
CP on treatment - interferon	0.84
CP off treatment - interferon	1.00
AP - interferon	0.86
BP – all treatments	0.61

Table B45: Example utilities including patient aging

Age	Average UK utility value	Utility of patients in BP on treatment with bosutinib
50	0.85	0.52

55	0.80	0.49
60	0.80	0.49
65	0.78	0.48
70	0.78	0.48
75	0.73	0.45
80	0.73	0.45

7.4.15 **Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

The values have been amended to account for patient aging (Section 7.4.14), but have otherwise not been altered.

Resource identification, measurement and valuation

7.4.16 **NHS costs**

Patients with CML will have regular outpatient appointments, some with a nurse and some with a haematologist. Since the patient has already tried at least one TKI, their appointment would be a follow-up appointment. Patients in AP and BP will also have occasional hospitalisations, consisting of ward days and intensive care unit days. The appropriate NHS reference costs are shown in Table B46.

Table B46: Healthcare unit costs used in the economic models

Type of resource	Cost	Code	Source	Note
Nurse-led outpatient appointment	£106	*370*	NHS Reference Costs 2011/12	Outpatient medical oncology - Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face
Haematologist-led outpatient appointment	£124	*370*	NHS Reference Costs 2011/12	Outpatient medical oncology - Consultant Led: Follow up Attendance Non-Admitted Face to Face
Inpatient Ward Day	£322	*SA17D/ SA17F*	NHS Reference Costs 2011/12	Average of excess bed day – Non-elective inpatient - Malignant Disorders of Lymphatic or Haematological Systems, with/without CC.
Inpatient ICU Day	£1,109	*SC01Z/ SC02Z/ SC03Z/ SC04Z/ SC05Z/ SC06Z/ SC07Z*	NHS Reference Costs 2011/12	Average of critical care unit costs – adult critical care

For all cost data taken from TA251, full details of how costs were derived are reported in Appendix 10.13.8.

There are additional costs for tests. In CP, this is £231 per month, and in AP and BP this is £377 per month, inflated from Hoyle et al (2011a)[80] using HCHS Pay and Price Index (Curtis, 2012). [54]

There is a cost of £6,004 associated with death. This is inflated from the cost of £5,401 reported by Addicott and Dewar [2008][99]. A cost of death was included in previous appraisals, based on assumed resource use. These alternative assumptions have been tested in sensitivity analysis, but were felt to be less appropriate than a published reference.

The cost of FLAG-IDA (in the blast phase model) is £29,212. The breakdown of this cost is provided in Appendix 10.20

7.4.17 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS Reference costs are appropriate in this condition due to the population treated being a relatively common form of leukaemia, and a population who would be expected to follow the same disease pathway i.e. there is no large variation in resource use.

Patients in this population are currently managed in secondary care and therefore the figures given in NHS reference costs for outpatient appointments are relevant.

7.4.18 Resource use systematic review

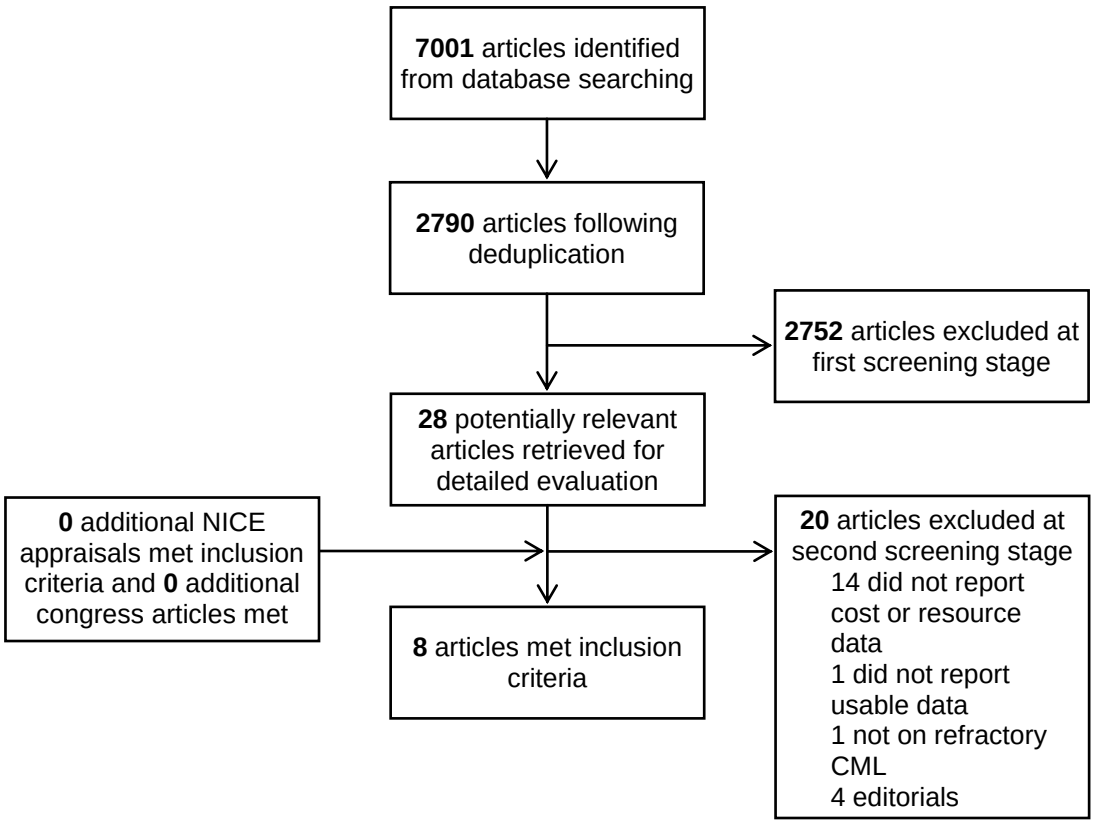
A systematic search was performed in October/November 2012 for relevant resource and cost data in the UK using the same search strategy, inclusion and exclusion criteria as previously described in Section 7.1.1, Table B35 with the exception of study type. In this cost and resource use review, the study type that was included was any study that reported cost or resource data from the UK.

Abstracts of citations found through the searches were assessed by two independent reviews for inclusion based on abstract and key words alone. Full-text copies of studies that potentially met the initial criteria were obtained and reviewed against the inclusion criteria by two independent reviewers. Studies that met the eligibility criteria after the second screening stage were extracted by a reviewer and checked by a second party.

The flow diagram of the studies included in this systematic review is shown in Figure B21, and described below:

- A total of 6303 studies were identified from EMBASE, MEDLINE and MEDLINE In-Process, 651 from the Cochrane Library, 45 studies from NHS EED and 2 from EconLit.
- No additional articles that were not captured through the database searching were identified from the horizon scanning or congress report searches.
- Following deduplication of the database results, 2790 abstracts remained for review.
- In the first screening stage, 28 articles were identified as potentially relevant by two independent reviewers, and full texts were obtained for these.
- Of the full texts, 8 articles met the inclusion criteria: 2 for 3rd line, and 6 for 2nd line CML treatment for data extraction. 3 of these were congress abstracts.

Figure B21: Study flow diagram for resource and cost studies



Results

Of the 8 articles that met the inclusion criteria, 3 related to the previous CML appraisal TA241 (reported in Rogers 2012[84], Loveman 2012[85] and Hoyle 2011b[86]).

Extraction tables for the studies identified in the systematic review are presented in Appendix 10.13. Since the relevant results presented in the Loveman 2012[85] and Hoyle 2011b[86] articles are encapsulated in the extraction of Rogers 2012[84], in order to avoid repetition, extraction tables for these two references are not provided. Therefore, extraction results for a total of 6 of the 8 identified articles are presented in Appendix 10.13, Table B91.

Following the lack of data identified by the resource use systematic review, resource use data from first-line studies was additionally sought. Hoyle 2011a[80] is the full PenTAG report of the first line NICE technology appraisal TA251 and represents the source of the TA251 resource use data presented below.

As with HRQL, resource use is expected to be driven primarily by phase of disease rather than line of treatment, and therefore the resource use and unit cost estimates from TA241 (Rogers 2012[84] and Loveman 2012[85]) and the more recent TA251 (Hoyle 2011a[80]) are felt to be the most relevant. The other identified studies, for which full results are less relevant and hence are not considered in detail, are summarised in Table B90 in Appendix 10.13.

Other medical management and monitoring

In TA251, medical management and monitoring costs were based on the mean frequency of hospital outpatient appointments and tests per month reported by the Oxford

Outcomes 2009 survey of six UK-based CML clinicians (conducted on behalf of BMS). Where PenTAG's clinical expert considered the frequency of tests from the Oxford Outcomes survey was unrealistic, these were adjusted (Hoyle et al, 2011a).[80]

In TA241, resource data is presented separately for the CP, AP and BP phases; however the source of these estimates is not given. The resource use assumptions from TA241 and TA251 are presented in Table B47 below.

Table B47: Resource utilisation from TA241 and TA251

	TA251		TA241		
Resource	CP (per patient/ month)	AP & BP (per patient/month)	CP	AP	BP
Nurse-led outpatient appointments	0.4	0.5	NR	NR	NR
Consultant-led outpatient appointments	0.9	1.3	4/yr	1/month	2/month
Hospital in patient-ward days	0.0	1.72	None	None	None
Hospital in patient - ICU days	0.0	0.10	N/A	N/A	N/A
BM tests*	N/A	N/A	2/yr (on-treatment only)	None	None
Radiography*	N/A	N/A	None	None	3/month
CT scans*	N/A	N/A	None	None	0.5/month
Blood transfusions	N/A	N/A	None	None	1/month
In TA251, the frequencies and cost of the following tests were included (based on the Oxford Outcomes 2009 clinician survey): complete blood count (CBC); cytogenetic analysis; bone marrow aspiration with biopsy; FISH; PCR; flow cytometry; cytochemistry analysis; blood film exam; chest X-ray; CT scan of chest; blood chemistry; C-reactive protein (CRP); EKG; upper endoscopy (EGD). NR = Not reported.					

In TA251, in addition to the quarterly care costs for advanced phase patients, additional costs were included for blast phase patients; a single death of an inpatient palliative care stay (£425) plus two non-medical specialist palliative care home visits (£72 each).

The unit costs used in TA241 (Rogers 2012)[84] and TA251 (Hoyle 2011a)[80] are summarised in Table B48 below. In both cases these were mostly sourced from the National Schedule of Reference Costs or the PSSRU Unit Costs of Health and Social Care.

Table B48: Summary of unit costs reported in TA241 and TA251

Resource	TA251 (£ 2009-10)	TA241 (£ 2009-10)
Nurse-led outpatient appointments	£100	N/A
Consultant-led outpatient appointments	£127	£121
Hospital in patient-ward days	£246	£119/day
Hospital in patient - ICU days	£1,219	N/A
BM tests*	N/A	£615/test
Radiography*	N/A	£29/visit
CT scans*	N/A	£103/scan
Blood transfusions	N/A	£400/transfusion

Cost of serious adverse events

In TA251, the Assessment Group estimated the cost of treating the following adverse events: neutropaenia, thrombocytopenia, anaemia and pleural effusion. The latter was included for dasatinib only, as it is a common although not serious event associated with this TKI. The source for the costs was a study by Oxford Outcomes, and the unit costs uprated from 2008 to 2011 are presented in Table B49.

In TA241, the cost of treating AEs is not included in the base-case for three reasons. First, the incidence of serious AEs on the TKIs appeared to be low. Second clinical opinion suggests the cost associated with treating AEs is also likely to be low. Third, given the substantial structural and parameter uncertainty, modelling treating costs associated with AEs may add spurious accuracy.

Table B49: Unit cost of treating the main serious adverse events

	TA251	TA241
	£2011 cost per AE	
Neutropaenia (Grade 3 & 4)	£497	The cost of treating AE was not included in TA241.
Thrombocytopenia (Grade 3 & 4)	£494	
Anaemia (Grade 3 & 4)	£340	
Pleural effusion (All grades)	£31	

Cost of stem cell transplant (2nd or 3rd line)

In TA251, the base case per patient cost estimate for an SCT was based on an unpublished September 2009 report by the London Specialised Commissioning Group.

The report gives a mean cost of transplant for phases 1 (decision to transplant and donor selection) through phase 4 (transplant inpatient admission) to phase 6 (day 100 post-transplant) of £47,500 (£, 2009) for related donor allografts and £79,600 for unrelated donor. The cost of transplant phases 1 to 6 was taken as the weighted average of these two costs based on an assumed 25%:75% split of related (usually sibling) vs. unrelated (volunteer) donor transplants, and inflated to 2011 costs

For the short-term cost of phases 7 and 8 (i.e. From 100+ days post-transplant to approximately 2 years), the costs of used antifungal drugs and repeat donor lymphocyte infusions were estimated from the 2009 London SCG analysis, but the mean per patient cost of donor lymphocyte infusions was based on three years of data relating to adult allogeneic stem cell transplants from University of Bristol Hospital.

In TA241, limited details are given to justify the value for SCT chosen in the model. Table B50 shows the estimation of the base case cost of SCT in TA251 and TA241.

Table B50: Per patient cost of a stem cell transplant

	TA251	TA241
Mean per patient cost of SCT	£81,600[a]	£80,000
Source	The figure for mean per patient cost of SCT was determined using costs presented in the London SCG[100], PSSRU – Curtis[101] and Ashfaq et al.[102]	The BMS submission in states that the cost of stem cell transplantation varies between £80,000 and £140,000 per person, the ERG used the value of £80,000
a Of UHB's related donor SCT recipients, 42% received at least 1 DLI (and of these 53% had 1, 32% had 2, 10% had 3, and 5% had 4. Of UHB's unrelated (volunteer) donor SCT recipients, 14% received		

at least 1 DLI (and of these 87% had 1 and 17% had 3.
b Rounded to the nearest £100.

In TA251, the cost of SCT was also estimated using an alternative method, using the National Schedule of Reference Costs HRG cost estimate for an inpatient stay for "peripheral blood STC in adults" alongside a table in the LSCG report which showed the percentage split of total costs across transplant phases, giving estimate of the total cost of phases 1, 2, 3, 5 and 6. The resulting estimate came out as £81,300.

Longer term costs following stem cell transplant

There was a considerable difference in the reported ongoing costs associated with SCT between TA251 and TA241.

In TA251, an estimated cost of £113 per month for patients suffering from Chronic Graft versus Host Disease (cGvHD) was included, which included the cost of quarterly specialist appointments with a clinical haematologist and the estimated cost of immunosuppressive drug therapies (Table B51).

In TA241, an estimated cost of £2400 per month was included, however no details as to how this calculated are provided.

Table B51: Estimation of on-going drug and monitoring costs after SCT

	TA251 (Hoyle 2011a)[80]	TA241 (Loveman 2012)[85]
Weighted mean cost per month:	£113[a]	£2400
Source	Based on unit costs of drugs from the NHS Drug Tariff (Mycophenolate Mofetil 500mg - £28.40 for 50 tablets; Prednisolone 5mg tablets £2.58 for 28 tablets) and the BNF 61 (Cyclosporin 50mg, £27.00 for 30 tablets).	Loveman 2012[85] reports that post-transplant treatment costs include costs associated with graft-versus-host disease, treatment of comorbidities, management of relapse and treatment of symptoms (chemotherapy, palliative regimens and lymphocyte infusions).

Cost of post-discontinuation in CP

As noted above, the estimates for OS are based on the empirical OS data from Jabbour looking at HDI in imatinib-failures, as per the approach described in TA241. In this Jabbour study, patients who discontinued treatment with HDI received life-prolonging therapies, and therefore the ERG estimated the potential costs associated with a disease phase analogous, based on the BMS/Oxford Outcomes Survey, as £1039.53 per month.

There is no such equivalent post-discontinuation cost included in TA251 as patients were assumed to receive hydroxycarbamide or SCT (and nilotinib in some patients) after failure of their 1st line TKI in chronic phase.

7.4.19 Resource use used in the economic evaluation

As described above, resource use was available from both TA241 and TA251. The source of the resource use in TA241 is not clear. In TA251, the more recent appraisal, the ERG (PenTAG) chose to use the results of UK survey conducted on behalf of BMS, to inform their resource use assumptions. Where the ERG's (PenTAG) clinical expert considered the frequency of tests from the survey was unrealistic, these were adjusted (Hoyle et al, 2011a)[80].

It has been suggested in previous CML appraisals that resource use, like HRQL, is more driven by phase than line of treatment and this assumption has been validated by clinical experts. In light of this, and the fact that the resource use assumptions in TA251 are more clearly referenced and more recent, it was felt to be more appropriate to use the values from TA251 (first-line CML) in our base-case. The resource use estimates from TA241 are explored in a sensitivity analysis. Monthly resource use from TA241 is described in Table B47 above.

The additional costs for blast phase patients of a single death of an inpatient palliative care stay (£425) plus two non-medical specialist palliative care home visits (£72 each) were also included in our base-case, as per TA251.

As noted above, in TA241, an additional cost is added post-discontinuation. However, this is not used in our base-case because it is assumed that all patients receive hydroxycarbamide. The impact of additional post-discontinuation costs is considered in a sensitivity analysis.

The costs associated with SCT and adverse events are explored in more detail below.

7.4.20 Clinical expert assessment of applicability of values

The applicability of the resource use has not been assessed by Pfizer, but has been used in previous economic evaluations where it has been considered applicable. (Hoyle et al, 2011a)[80].

7.4.21 Intervention and comparator costs

Bosutinib: Bosutinib is available in two strengths, 100mg and 500mg. The costs for bosutinib, as noted in Section 1.10, are:

- 100mg, 28 tablets: £859.17
- 500mg, 28 tablets: £3,436.67

As noted in Section 1.10 and Section □, the recommended daily dose of bosutinib is 500mg/day. At this daily dose (assuming 1 x 500mg tablet per day), the daily cost of bosutinib is £122.74, the monthly cost is £3,735.84 and the annual cost is £44,830.13. In the base case, it is assumed that all patients are managed at 500mg/day. The impact of dose intensity is examined in a sensitivity analysis.

Hydroxycarbamide: The cost of a 100 tab pack of 500mg hydroxycarbamide is £10.47 [British National Formulary 64]. This leads to a monthly cost of £13.

Interferon: The cost of one 0.5mL 9 million unit/mL vial of interferon is £21.29. 25% of patients require nurse assistance(Rogers 2012)[84], costing £39 per dose (district nurse visit, [Curtis 2012][54]) and the remaining patients self-inject. The monthly cost of interferon is therefore £648.

SCT: The cost for stem cell transplant in month 0 is £76,560 [NHSBT, 2010, inflated using Curtis [2012]].[54] Inflating the same source provides monthly cost for months 1-6 of £5,299, for months 7-12 of £3,231 and for months 13-24 of £1,166. In months 25 onwards, patients are assumed to receive 100mg of ciclosporin twice daily. A pack of 30 100mg Neoral (which accounts for over 90% of items in the UK based on Prescriptions Cost Analysis 2011) costs £69.11, giving a monthly cost of £140.

These costs for Stem Cell Transplant were preferred over those used in previous appraisals. Although they are approximately equal (£80,000 in Loveman, 2012[85]), the values used in our base-case are more fully referenced, and taken from an NHS Blood and Transplant costing study, whilst values from previous appraisals appear to be based on clinical opinion. A second reason to favour the NHS Blood and Transplant study is the

granularity of costs given for follow-up periods. These values have face validity as they capture the initially high costs of supporting patients (for example with tests for cytomegalovirus), which decline over time. Previous assessments appear to have used a monthly cost, which does not vary according to this expected cost profile – for example in Loveman [2012][85] this was assumed to be £2,400 per month.

Health-state costs

7.4.22 **Summary of costs included in each health state.**

Table B52 List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
Chronic Phase	Outpatient Appointments	£154	7.4.16
	Hospital Inpatient	£0	7.4.16
	Tests	£231	7.4.16
	Total	£385	7.4.16
Advanced Phase and Blast Phase	Outpatient Appointments	£214	7.4.16
	Hospital Inpatient	£665	7.4.16
	Tests	£377	7.4.16
	Total	£1,256	7.4.16

7.4.23 **Summary of adverse event costs**

Previous economic evaluations for TKIs have not included adverse events as it was considered that it may introduce spurious accuracy. However, in order to present a conservative estimate of the costs associated with bosutinib treatment, a per patient adverse event cost of £506 has been calculated for bosutinib, based on the costs of managing treatment-emergent adverse events of grade 3 or 4 that occurred in 5% or more of any of the subpopulations contained within the third-line cohort of Study 200 (see Table B27 in section 6 for further details).

Since the adverse events experienced in accelerated and blast phase are broadly similar to those in chronic phase, the same cost assumption is used in the AP and BP model. This represents a conservative approach, because many of the treatment-emergent AEs may not be specifically related to bosutinib treatment and may also occur with comparator treatments.

Table B53 List of adverse events and summary of costs included in the economic model

Adverse Event	Percentage of Patients (Study 200m CP third-line cohort)	Cost per Event	Cost source
Thrombocytopenia	25%	£504	Hoyle et al (2011a)[80]
Neutropaenia	14%	£506	Hoyle et al (2011a)[80]
Anaemia	5%	£347	Hoyle et al (2011a)[80]
Cardiac disorders	4%	£170	NHS reference costs 2011-12 Outpatient

			appointment, consultant led, non-admitted F2F 320
Gastrointestinal disorders	14%	£281	Erlotinib ERG report (from expert panel)
Hepatobiliary disorders	4%	£216	NHS reference costs 2011-12 Outpatient appointment, consultant led, non-admitted F2F 306
Infections and infestations	3%	£933	NHS reference costs 2011-12 – average of all infections costs
Investigations	9%	£31	NHS reference costs 2011-12 – average of WA20W and WA20Y
Metabolism and nutrition disorders	3%	£1,576	NHS reference costs 2011-12 – average of PA72Z and FZ49A/B/C
Musculoskeletal and connective tissue disorders	6%	£717	NHS reference costs 2011-12 – average of PA34A/B
Neoplasms benign, malignant and unspecified	3%	£1,570	NHS reference costs 2011-12 – average of all costs related to 'neoplasm'
Nervous system disorders	4%	£1,091	NHS reference costs 2011-12 average of PA01A/B
Respiratory, thoracic and mediastinal disorders	3%	£32	Hoyle et al (2011a)[80]
Skin and subcutaneous tissue disorders	2%	£139	Erlotinib ERG report (from expert panel)

Where available, adverse event costs have been taken from Hoyle et al (2011a)[80] and inflated using Curtis [2012].[54] The erlotinib ERG report[103] provided costs for diarrhoea and rash. All other adverse events were costed using the average NHS reference costs for the most appropriate items.

Miscellaneous costs

7.4.24 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

No additional costs have been included

Sensitivity analysis

7.4.25 Assessment of Structural uncertainty

See Section 7.5.2.

7.4.26 Which variables were subject to deterministic sensitivity analysis?

There are a number of uncertainties in the economic model for bosutinib. However, relatively few of these are parameter uncertainties, with the uncertainty relating to a structural assumption e.g. the appropriate utilities to use. The key sensitivity analyses are therefore grouped into categories (for example overall survival), and presented for each of the models as a series of scenario analyses.

Tornado diagrams are not presented, as the majority of important assumptions (approach used to overall survival, time on treatment assumptions, etc.) are not related to the value used, but the approach selected. A tornado diagram would be misleading, in omitting many of the more sensitive areas of the model.

Extensive scenario analyses are presented for each of the models.

7.4.27 Was PSA undertaken? If not, why not?

Probabilistic sensitivity analysis (PSA) has been implemented in the model, and is presented in the submission. It should be cautioned however that probabilistic analysis does not capture all of the uncertainty in the economic model.

The reason for this is that probabilistic sensitivity analysis conducted investigates only *parameter uncertainty*, and therefore underestimates the structural uncertainty in the model. We would therefore agree with the assessment of the Peninsula Technology Assessment Group in TA251, where it was felt that probabilistic analysis is less informative than scenario analysis.

An example of a parameter key to the model for which PSA is uninformative is that of OS on hydroxycarbamide. In the base case, this is set to 42 months, (as in TA241) but relates to second line treatment, which is likely to be an overestimate of survival in 3rd line treatment (which is varied in scenario analysis). The distribution around survival is again related to second line treatment, so the probabilistic analysis underestimates the true uncertainty in the model.

Results

As there are three models used in the submission, the results for these different models are presented separately, in

- Section 7.5: CP
- Section 7.6: AP
- Section 7.7: BP

7.5 Results – Chronic Phase (CP)

Clinical outcomes from the model

7.5.1 Comparison of outcomes from the trial and model.

As the study for bosutinib in this patient population (Study 200) is a single arm trial, comparative results are not available. Model outcomes are therefore compared to clinical trial outcomes for bosutinib only. The model results are very close to the clinical trial results.

Table B54 Summary of model results compared with clinical data

Outcome	Clinical trial result (data snapshot 15 Feb 2012)	Model result
Overall survival at year 1	91% [Khoury et al, 2012][48]	89%
Overall survival at year 2	83% [Khoury et al, 2012][48]	82%
Median time on treatment	0.75 years (8.6 months)	0.97 years

Overall survival is reported at year 2 for SCT in Jabbour et al (2011).[58] The model result is again close to the trial results.

Table B55: Summary of model results compared with clinical data - SCT

Outcome	Clinical trial result	Model result
Overall survival at year 2	72% [Jabbour et al, 2011]	69%

Overall survival data for interferon and hydroxycarbamide is informed by mean estimates from Rogers et al (2012)[84] rather than clinical trials. Therefore the mean survival from the model is compared to these mean estimates in Table B56. Again, they are close, and identical to 1 decimal place (as presented by Rogers et al (2012)[84].

Table B56: Summary of model results compared with means – interferon and hydroxycarbamide

Outcome	Rogers et al (2012)[84] mean estimate	Model result – life years
Overall survival – interferon	3.6 years	3.62 years
Overall survival – hydroxycarbamide	3.5 years	3.52 years

7.5.2 **Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.**

Figure B22 to Figure B25 present Markov traces of the proportion of patients in each health state for the comparator treatments. A tabulated Markov trace is available in Appendix 10.21.

Figure B22: Markov trace of bosutinib in the CP model (based on CP3L)

[redacted]

Figure B23: Markov trace of hydroxycarbamide in CP

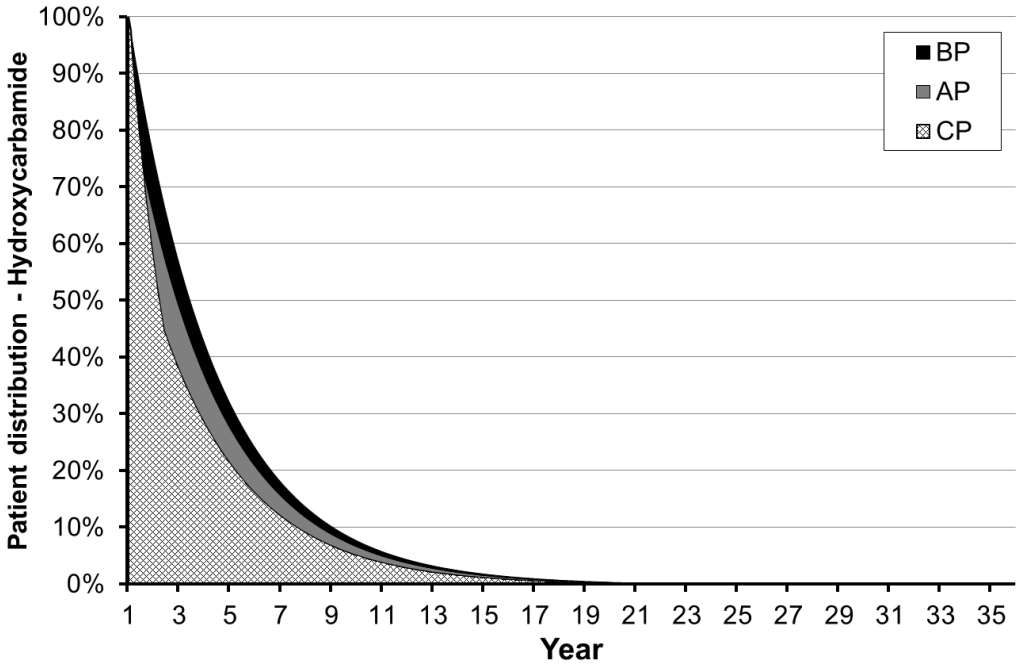


Figure B24: Markov trace of SCT in CP

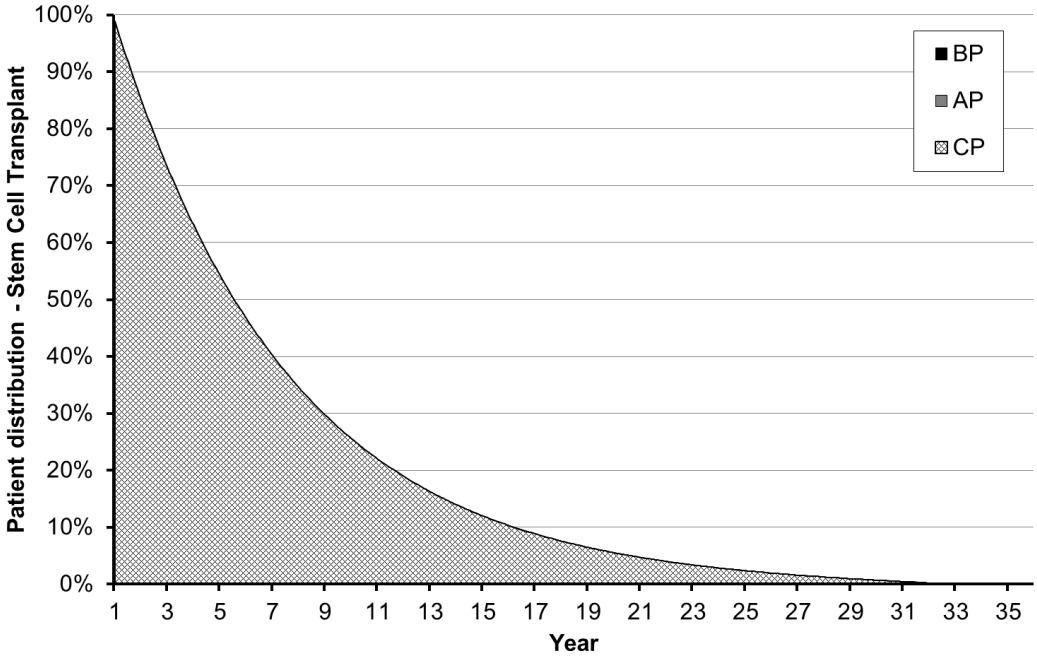
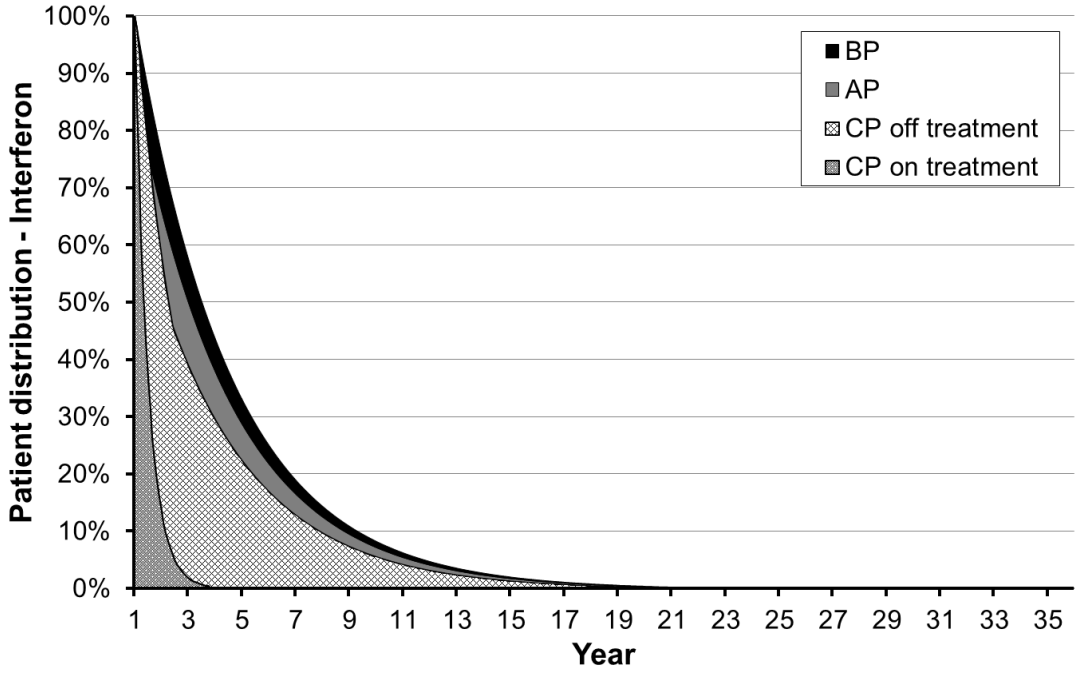


Figure B25: Markov trace of interferon in CP



7.5.3 **Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

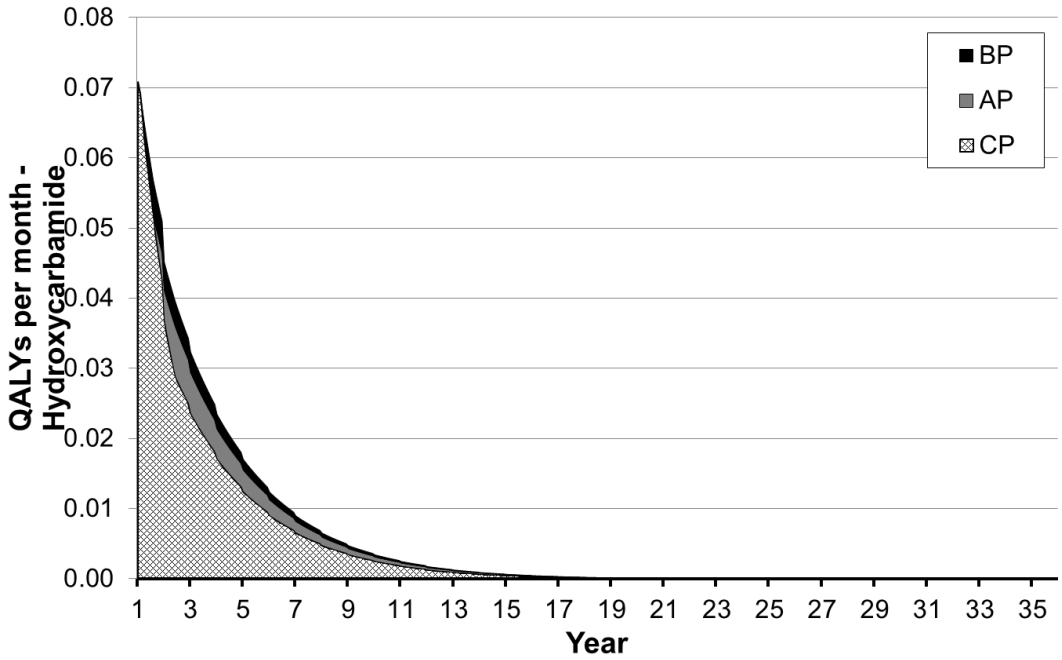
BOSUTINIB

Figure B26: QALYs accrued in the CP model – bosutinib

[redacted]

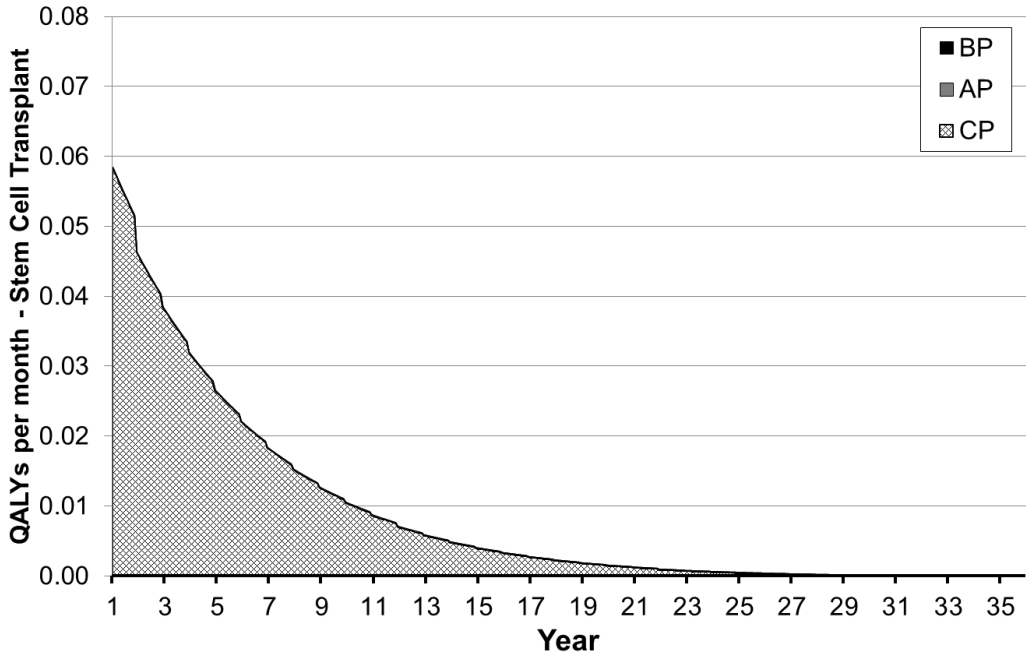
HYDROXYCARBAMIDE

Figure B27: QALYs accrued in the CP model – hydroxycarbamide



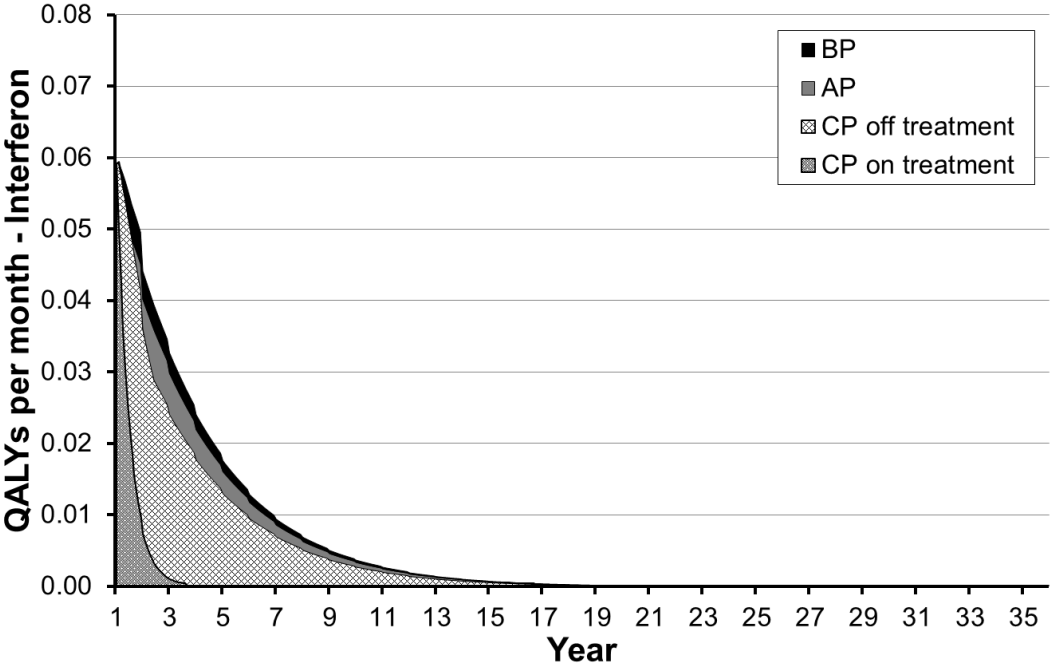
SCT

Figure B28: QALYs accrued in the CP model – SCT



INTERFERON

Figure B29: QALYs accrued in the CP model - Interferon



7.5.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a**

combination of other states, please present disaggregated results. For example:

Table B57 Model outputs by clinical outcomes in the CP model - bosutinib

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
[redacted]	[redacted]	[redacted]	[redacted]
Chronic Phase	9.13	5.75	[redacted]
Accelerated Phase	0.70	0.34	£7,544
Blast Phase	0.47	0.16	£5,156
Death	0	0	£4,443
Adverse Events	0.00		£506
Total	10.30	6.25	[redacted]
LY, life years; QALY, quality-adjusted life year			

Table B58: QALYs accrued in the CP model – Hydroxycarbamide - CP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Chronic Phase On Treatment	2.58	1.93	£11,283
Chronic Phase Off Treatment	0.00	0.00	£0
Chronic Phase	2.58	1.93	£11,283
Accelerated Phase	0.51	0.31	£6,815
Blast Phase	0.43	0.19	£5,940
Death	0	0.00	£5,436
Adverse Events	0.00		
Total	3.52	2.43	£29,473
LY, life years; QALY, quality-adjusted life year			

Table B59: Model outputs by clinical outcomes – SCT - CP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Chronic Phase On Treatment	6.60	3.70	£166,577
Chronic Phase Off Treatment	0.00	0.00	£0
Chronic Phase	6.60	3.70	£166,577
Accelerated Phase	0.00	0.00	£0
Blast Phase	0.00	0.00	£0
Death		0.00	£4,961
Adverse Events	0.00		
Total	6.60	3.70	£171,539
LY, life years; QALY, quality-adjusted life year			

Table B60: Model outputs by clinical outcomes – Interferon - CP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Chronic Phase On Treatment	0.54	0.38	£10,955
Chronic Phase Off Treatment	2.12	1.53	£9,064
Chronic Phase	2.67	1.92	£20,019
Accelerated Phase	0.52	0.31	£6,885
Blast Phase	0.44	0.19	£5,944
Death	0	0.00	£5,419
Adverse Events	0.00		
Total	3.62	2.42	£38,268
LY, life years; QALY, quality-adjusted life year			

7.5.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

Disaggregated costs and QALYs by health state are tabulated for each comparator in Section 7.5.4.

Table B61 Summary of predicted resource use by category of cost (discounted)

Item	Cost intervention (Bosutinib)	Cost comparator (Hydroxy-carbamide)	Cost comparator (Interferon)	Cost comparator (SCT)
Technology cost	[redacted]	£490	£8,461	£141,132
Mean total treatment cost	£857		£419	
Monitoring cost	£22,047	£13,195	£13,386	£10,163
Tests	£23,704	£10,352	£10,583	£15,283
Palliative care	£4,443	£5,436	£5,419	£4,961
Adverse Events	£506			
Total	[redacted]	£29,473	£38,268	£171,539

7.5.6 **Base-case ICERs**

Table B62 presents the base case results for the CP model. In calculations any dominated strategies are not included in incremental calculations e.g. the incremental cost of bosutinib is given as the incremental cost from hydroxycarbamide (the incremental cost of interferon is provided for information only).

This analysis demonstrates that bosutinib represents a cost-effective use of NHS resources compared to hydroxycarbamide, interferon and SCT, in CML patients previously treated with one or more TKI and for whom all currently available TKIs are not an option.

We believe the base-case presented represents the most plausible scenario for the cost-effectiveness of bosutinib in CP CML. In this analysis we have used the most relevant sources of information where possible, and where data has been lacking, appropriate conservative assumptions have been made. The key parameters used are:

- Overall survival on bosutinib is calculated using a published methodology, and validated using data from Study 200.
- Discontinuation is extrapolated directly from mature trial data (5 years, at which point [redacted] of patients had discontinued).
- Interferon and hydroxycarbamide efficacy is taken from a recent NICE appraisal in CML, but for a second-line population that is likely to have a better prognosis compared with the third-line patients from Study 200.
- SCT survival is taken from a study that was selected for having the most comparable patient population to Study 200 and the likely population in practice.
- Utilities and costs are also taken from previously validated economic evaluations (TA251), and the cost of SCT is taken from a recent NHS Blood and Transport report. Additionally, utilities are validated using EQ-5D data from Study 200.

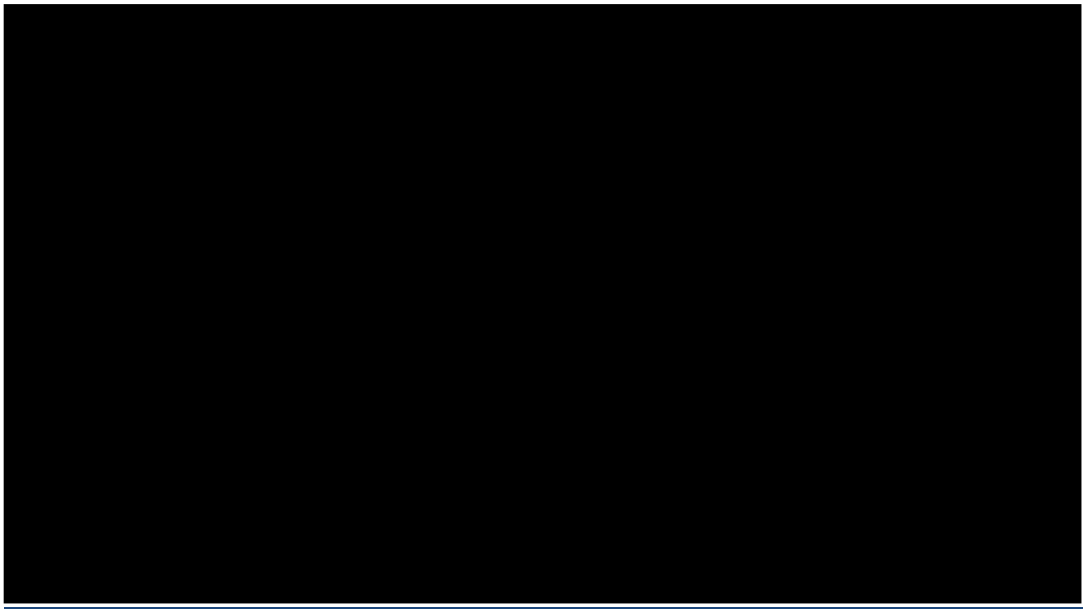
Table B62 Base-case results: CP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£111,511

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

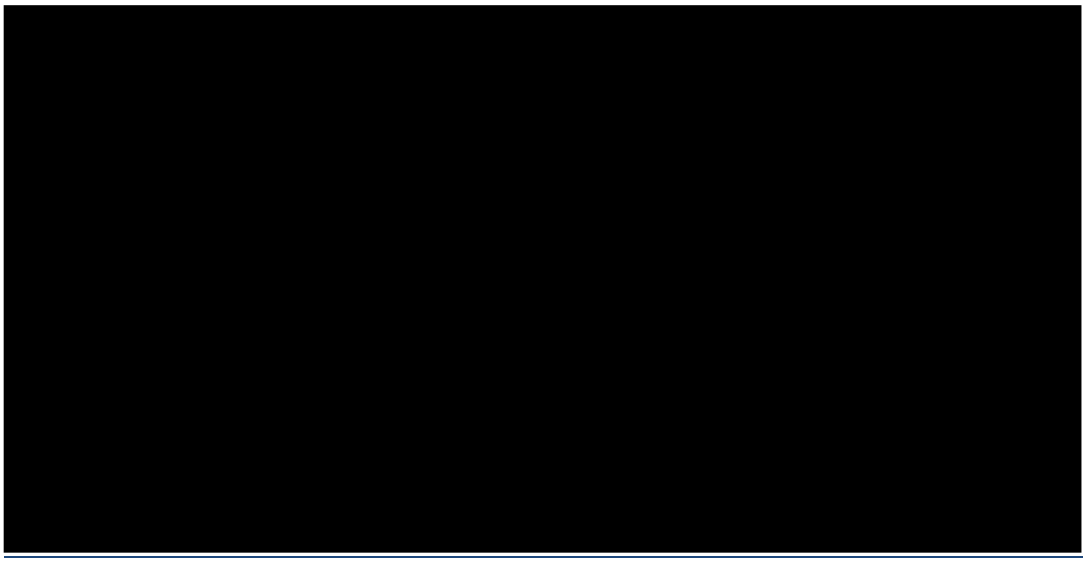
As there are 4 treatments, a cost-effectiveness plane is also given to show the results visually.

Figure B30: Cost-effectiveness plane: CP



The breakdown of the life years is also presented in a stacked bar chart.

Figure B31: Stacked bar chart of life years: CP



Sensitivity analyses

7.5.7 **Please present results of deterministic sensitivity analysis.**

Extensive sensitivity analyses are presented in Section 7.5.9, including deterministic and scenario analyses. Tornado diagrams are not presented due to limitations discussed in Section 7.4.26.

7.5.8 **Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.**

Probabilistic results are presented in Table B63, compared to deterministic results, based on 1,000 probabilistic simulations. The main differences are seen in the effectiveness of hydroxycarbamide and interferon, which are higher in the probabilistic estimate due to the distributions used.

Table B63: Deterministic vs Probabilistic point estimates

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		
Deterministic results						
Hydroxycarbamide	£29,473	2.43				
Interferon	£38,268	2.42	£8,795	-0.01	Dominated	Dominated
Bosutinib	[redacted]	6.25	[redacted]	3.82	[redacted]	[redacted]
SCT	£171,539	3.70	[redacted]	-2.55	Dominated	£111,511
Probabilistic results						
Hydroxycarbamide	£31,634	2.71				
Interferon	£43,904	3.29	£12,269	0.57	£21,357	£21,357
Bosutinib	[redacted]	6.22	[redacted]	2.93	[redacted]	[redacted]
SCT	£181,157	3.70	[redacted]	-2.51	Dominated	£151,056

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		

Costs and QALYs discounted at 3.5%. Dominated strategies not included in incremental calculations.

A probabilistic scatter plot is presented below and a cost-effectiveness acceptability curve in Figure B33.

Figure B32: Scatterplot of probabilistic sensitivity analysis, all strategies

Figure B33: Cost-effectiveness acceptability curve, all strategies

The most appropriate comparison, given the incremental ICERs (and lack of usage of interferon), is between hydroxycarbamide and the intervention of bosutinib. A pairwise comparison is therefore presented in Figure B34.

Figure B34: Pairwise comparison of hydroxycarbamide and bosutinib intervention

7.5.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis.**

Scenario analysis for the CP model is summarised in Table B64. As in the base-case, in most scenarios interferon is dominated by hydroxycarbamide and so these ICERs are not presented. The incremental ICER for bosutinib versus hydroxycarbamide is therefore presented in the first column below. SCT is in turn dominated by bosutinib in virtually all scenarios, and this ICER is not presented, instead the ICER for SCT versus hydroxycarbamide is presented for the sake of completeness.

In the few scenarios where interferon is not dominated by hydroxycarbamide and SCT is not dominated by bosutinib, the missing incremental ICERs are presented in brackets after the ICER versus hydroxycarbamide. Full descriptions of the scenarios and incremental results for all comparators are provided in Appendix 10.22

Table B64: Scenario analysis – CP model

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
Base case	N/A	N/A	[redacted]	£111,511
Patient population				
Bosutinib patient population	3rd line CP patient population from Study 200	Post-hoc analysis of 3rd line CP cohort to identify 'unmet need' subpopulation, as requested by the EMA	[redacted]	£111,511
		Full 2rd line CP patient population from Study 200	[redacted]	£111,511
		Combined analysis of patients identified in the post-hoc analysis of 2nd line cohort and 3rd line cohort from Study 200, as requested by the EMA	[redacted]	£111,511
Cohort starting age	54 years (Study 200)	49 years (-10%)	[redacted]	£107,849
		50 years (+10%)	[redacted]	£113,343
Overall survival				
Bosutinib overall survival	MCyR using hazard ratio for survival of 0.37 (Rogers (2012)[84])	MCyR using hazard ratio for survival of 0.156 (lower 95% of pooled estimate, Rogers (2012))	[redacted]	£111,511
		MCyR using hazard ratio for survival of 0.876 (upper 95% of pooled estimate, Rogers (2012))	[redacted]	£111,511
		OS estimated by fitting a parametric curve (exponential) to third-line CP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	£111,511
		Cumulative survival approach (OS = PFS [estimated by fitting a parametric curve to third-line CP cohort in Study 200] + 10 months AP + 6 months BP)	[redacted]	£111,511
Stem Cell Transplant overall survival	Exponential curve fitted to Jabbour (2011)	Weibull curve fitted to Jabbour (2011)	[redacted]	£49,625
		Exponential curve fitted to Oehler (2007)	[redacted]	£107,503
Hydroxycarbamide	Mean overall survival = 3.5	Mean OS for hydroxycarbamide is adjusted	[redacted]IFN vs hydroxy-	£96,437

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
overall survival	years (42 months) in **second-line** patients	by the ratio of 2nd and 3rd line OS from Study 200 to consider a more 'third-line' OS estimate for hydroxycarbamide. Mean OS for hydroxycarbamide = 2nd line LYs (11.51) divided by 3rd line LYs (10.30) multiplied by 42 = **38 months**	carbamide: £50,547 Bos vs IFN: [redacted]	
		Mean OS = 2 years (lower end of plausible range, Rogers (2012))	[redacted] IFN vs hydroxy-carbamide: £16,291 Bos vs IFN: [redacted]	£65,790
		Mean OS = 6.5 years (upper end of plausible range, Rogers (2012))	[redacted] Hydroxy-carbamide vs IFN: £1,041	Dominated
Transformation to AP and BP				
Time in blast phase	6 months	13 months (Rogers (2012))	[redacted]	£102,886
		3 months (assumption)	[redacted]	£116,795
Transformation following SCT	Patients cannot transform to AP or BP, but remain in CP	Patients transform to AP and BP for 10 months and 6 months respectively before death.	[redacted]	£125,553
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200	Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	£111,511
		Time on treatment equal to PFS minus discontinuation due to AEs (Rogers (2012))	[redacted]	£111,511
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial), the average cost per day for bosutinib is [redacted]	[redacted]	£111,511
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011a)[80]	Medical management resource use from TA241	[redacted]	£121,775
Cost of CP	Patients	Patients receive further	[redacted]	£88,362

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
off treatment health state	receive hydroxycarbamide, costing £12.75 per month	treatment post-discontinuation in CP (e.g. other TKIs or SCT) costing £1040 per month (similar approach to TA241).	Bos vs SCT: [redacted]	
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP £2,536/month (doubled)	[redacted]	£106,162
		BP £1,268/month(doubled)	[redacted]	£106,848
Cost of death	£6,004 - Dewer & Addicot	£569 – Hoyle (2011a)[80]	[redacted]	£111,848
Cost of best supportive care	Best supportive care = hydroxycarbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	£108,495
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	£108,495
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility at screening for CP third-line cohort from Study 200 used for all patients in CP on bosutinib and hydroxycarbamide	[redacted]	N/A
		Utility at screening for CP third-line cohort from Study 200 used for patients in CP on bosutinib only	[redacted]	£111,511
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011a)[80]	[redacted]	£82,290
Interferon on-treatment utility value	Decrement to HRQL from interferon treatment	No decrement to HRQL from interferon treatment	[redacted] IFN vs hydroxy-carbamide: £138,728 Bos vs IFN: [redacted]	£111,511
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	£103,577
Model Settings				
Time horizon	50 years	2 years	[redacted]	Dominated
		5 years	[redacted]	£431,170
		10 years	[redacted]	£168,277
		25 years	[redacted]	£112,781

* In these scenarios, interferon (IFN) is not dominated by hydroxycarbamide, therefore an incremental ICER is available for IFN versus hydroxycarbamide and for bosutinib versus interferon.

** In these scenarios, IFN is cheaper than hydroxycarbamide and therefore an incremental ICER for hydroxycarbamide vs IFN is available.
*** In these scenarios, SCT is cheaper than bosutinib and therefore an incremental ICER for bosutinib vs SCT is available

7.5.10 What were the main findings of each of the sensitivity analyses?

In all analyses, except when hydroxycarbamide patients receive high off-treatment costs and overall survival for hydroxycarbamide is 2 years, interferon is dominated by hydroxycarbamide. This is in keeping with clinical practice where clinicians do not believe interferon to be effective, but expect considerable adverse event rates.

- [redacted] When compared to hydroxycarbamide, bosutinib is always more expensive, and more effective, with ICERs ranging from approximately [redacted] per QALY.
  [redacted]

In the base case, the overall survival for hydroxycarbamide is taken from a second line study, where patients have a better prognosis than the third line population considered for bosutinib. When the second line population for bosutinib is considered and when the overall survival for hydroxycarbamide is reduced, there is a greater survival benefit for bosutinib treatment, and so the ICER decreases.

The resource use from TA241 is lower than that used in the base case, leading to lower costs in the health states and reducing the costs in both arms. However, as patients live longer in the bosutinib arm, the incremental costs decrease, leading to a lower ICER. The treatment line in TA241 is closer to the treatment line considered for bosutinib, and so the resource use may be more appropriate for this population. However, the resource use from TA251 was considered in the base-case. This is because TA251 is more recent and because the source of the resource use results from TA251 is known; for TA241 the source of the resource use results is not available.

In the majority of scenarios, stem cell transplant is the most costly intervention, and is frequently dominated by bosutinib treatment. Only if high costs are assigned to bosutinib treatment is stem cell transplant cheaper, although it remains less effective.

7.5.11 What are the key drivers of the cost-effectiveness results?

As stated in Section 7.2.2, the key drivers of cost-effectiveness in the economic model are the assumptions applied to overall survival, and time on treatment.

Whilst the model is not sensitive to reasonable changes, alternative approaches (for example patients remaining on treatment until progression with bosutinib) have the potential to radically alter results. Equally should patients survive for a shorter period of time with other treatments, bosutinib has the potential to be cost-effective.

7.6 Results: Accelerated Phase

Clinical outcomes from the model

7.6.1 Comparison of outcomes from the trial and model

As the study for bosutinib in this patient population (Study 200) is a single arm trial, comparative results are not available. Model outcomes are therefore compared to clinical trial outcomes for bosutinib only.

Table B65 Summary of model results compared with clinical data

Outcome	Clinical trial result (data snapshot 28 Mar 2011)	Model result
Overall survival at year 1	74%	80%
Overall survival at year 2	55%	65%
Median time on treatment	0.9 years (10.8 months)	0.79 years

7.6.2 **Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.**

Figure B35 to Figure B37 present Markov traces of the proportion of patients in each health state for the comparator treatments. A tabulated Markov trace is available in Appendix 10.21.

Figure B35: Markov Trace – Bosutinib - AP

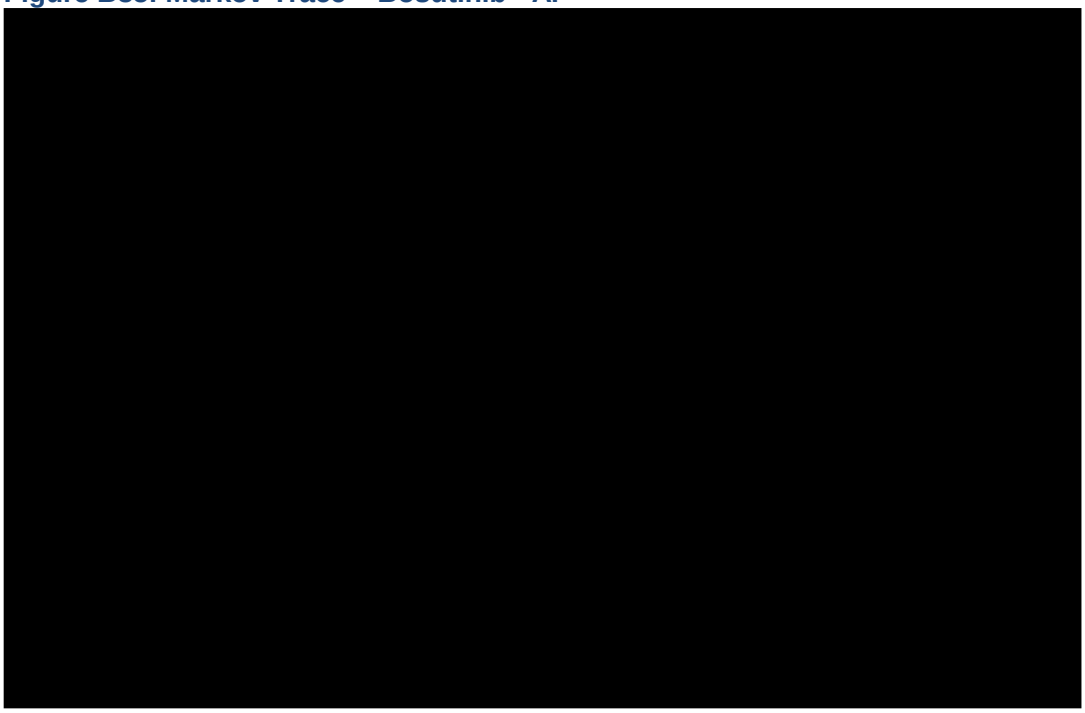


Figure B36: Markov Trace – SCT – AP

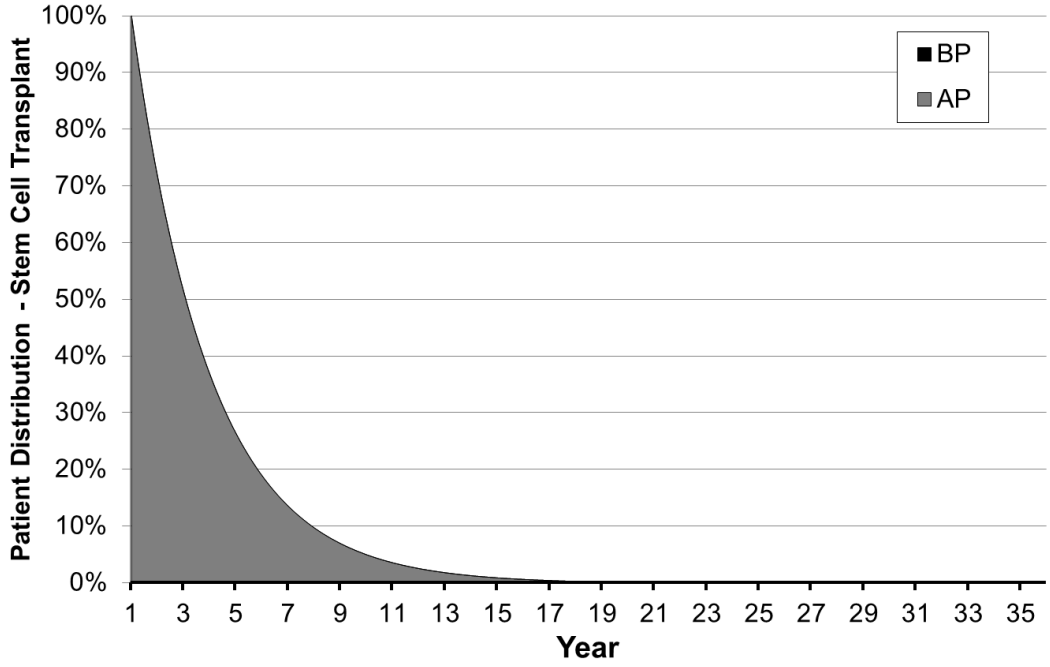
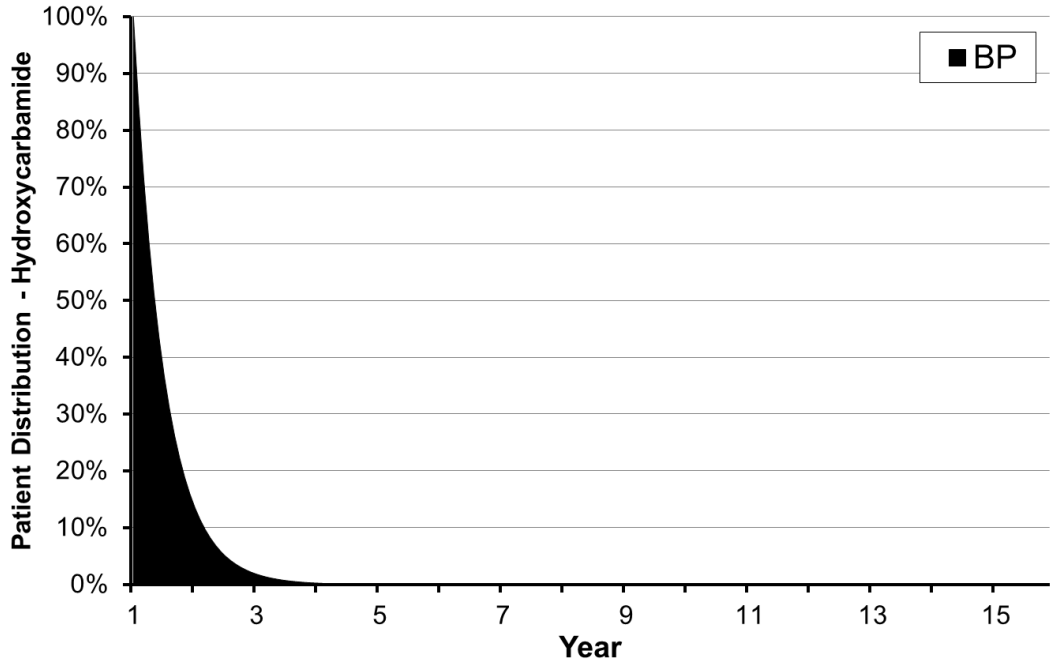


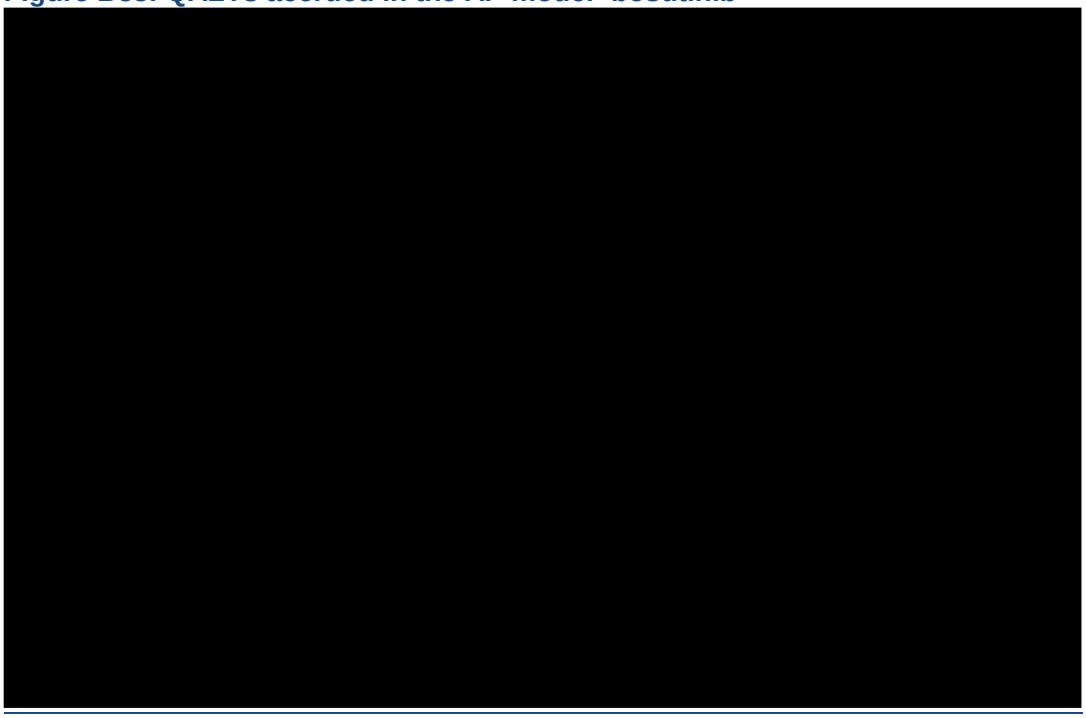
Figure B37: Markov Trace – Hydroxycarbamide – AP



7.6.3 **Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

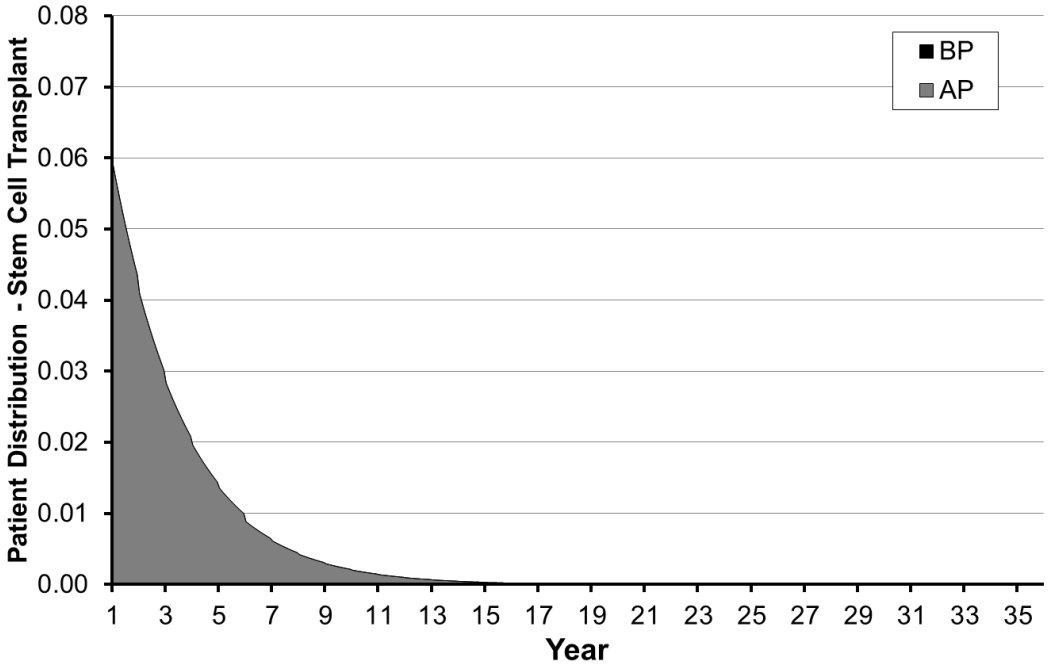
BOSUTINIB

Figure B38: QALYs accrued in the AP model- bosutinib



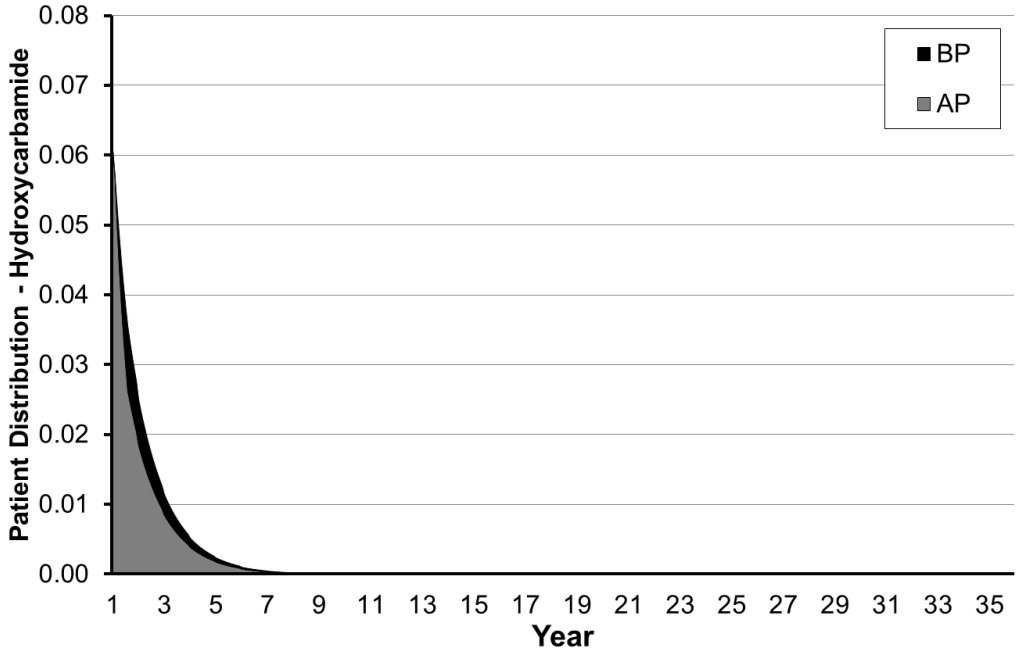
STEM CELL TRANSPLANT

Figure B39: QALYs accrued in the AP model- SCT



HYDROXYCARBAMIDE

Figure B40: QALYs accrued in the AP model- hydroxycarbamide



7.6.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:**

Table B66: Model outputs by clinical outcomes – Bosutinib - AP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Accelerated Phase	4.03	2.56	[redacted]
Blast Phase	0.45	0.20	£5,941
Death	0	0	£5,280
Adverse Events	0.00		£506
Total	4.48	2.76	[redacted]
LY, life years; QALY, quality-adjusted life year			

Table B67: Model outputs by clinical outcomes – SCT – AP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Accelerated Phase On Treatment	3.02	1.96	£172,572
Accelerated Phase Off Treatment	0.00	0.00	£0
Accelerated Phase	3.02	1.96	£172,572

Blast Phase	0.00	0.00	£0
Death	0	0	£5,520
Adverse Events	0.00		
Total	3.02	1.96	£178,093
LY, life years; QALY, quality-adjusted life year			

Table B68: Model outputs by clinical outcomes – Hydroxycarbamide - AP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Accelerated Phase On Treatment	1.02	0.72	£15,117
Accelerated Phase Off Treatment	0.00	0.00	£0
Accelerated Phase	1.02	0.72	£15,117
Blast Phase	0.35	0.18	£5,144
Death	0	0	£5,817
Adverse Events	0.00		
Total	1.37	0.90	£26,078
LY, life years; QALY, quality-adjusted life year			

7.6.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

Disaggregated costs and QALYs by health state are tabulated for each comparator in 7.6.4

Table B69: Summary of predicted resource use by category of cost (discounted)

Item	Cost intervention (Bosutinib)	Cost comparator (hydroxycarbamide)	Cost comparator (SCT)
Technology cost	[redacted]	£204	£130,528
Mean total treatment cost	£297		
Monitoring cost	£41,726	£14,032	£29,414
Tests	£17,916	£6,025	£12,630
Palliative care	£5,280	£5,817	£5,520
Adverse Events	£506		
Total	[redacted]	£26,078	£178,093

Base-case analysis

7.6.6 **Base-case ICERs- AP**

Table B70 presents the base-case results for the AP model.

Table B70 Base-case results

	Total	Incremental	ICER	ICER v

	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Hydroxyurea	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£142,982

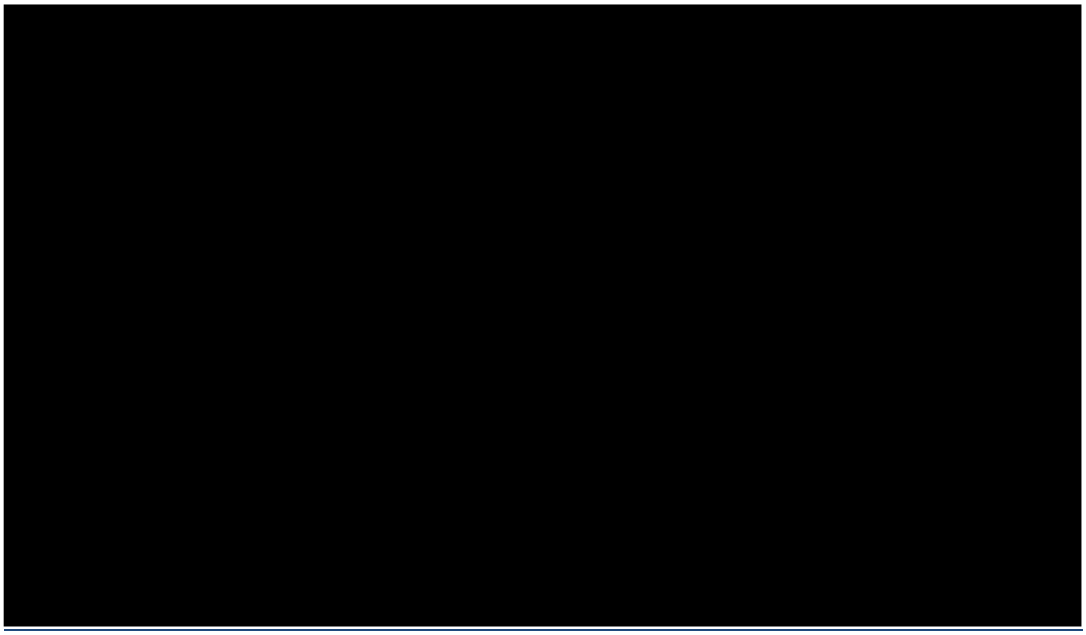
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

As there are 3 treatments, a cost-effectiveness plane is also given to show the results visually.

Figure B41: Cost-effectiveness plane: AP

The breakdown of the life years is also presented in a stacked bar chart.

Figure B42: Stacked bar chart of life years: AP



Sensitivity analyses

7.6.7 **Please present results of deterministic sensitivity analysis.**

Extensive sensitivity analyses are presented in Section 7.6.9 including one way and scenario analyses. Tornado diagrams are not presented due to limitations discussed in Section 7.4.26.

7.6.8 **Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.**

Probabilistic results are presented in Table B71, compared to deterministic results, based on 1,000 probabilistic simulations. The results are similar.

Table B71: Deterministic vs Probabilistic point estimates

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		
Deterministic results						
Hydroxyurea	£26,078	0.90				
Bosutinib	[redacted]	2.76	[redacted]	1.86	[redacted]	[redacted]
SCT	£178,093	1.96	[redacted]	-0.80	Dominated	£142,982
Probabilistic results						
Hydroxyurea	£26,095	0.91				
Bosutinib	[redacted]	2.75	[redacted]	1.84	[redacted]	[redacted]
SCT	£175,420	1.95	[redacted]	-0.80	Dominated	£143,454

Costs and QALYs discounted at 3.5%. Dominated strategies not included in incremental calculations.

A probabilistic scatter plot is presented in Figure B43, and a cost-effectiveness acceptability curve in Figure B44.

Figure B43: Scatterplot of probabilistic sensitivity analysis, all strategies

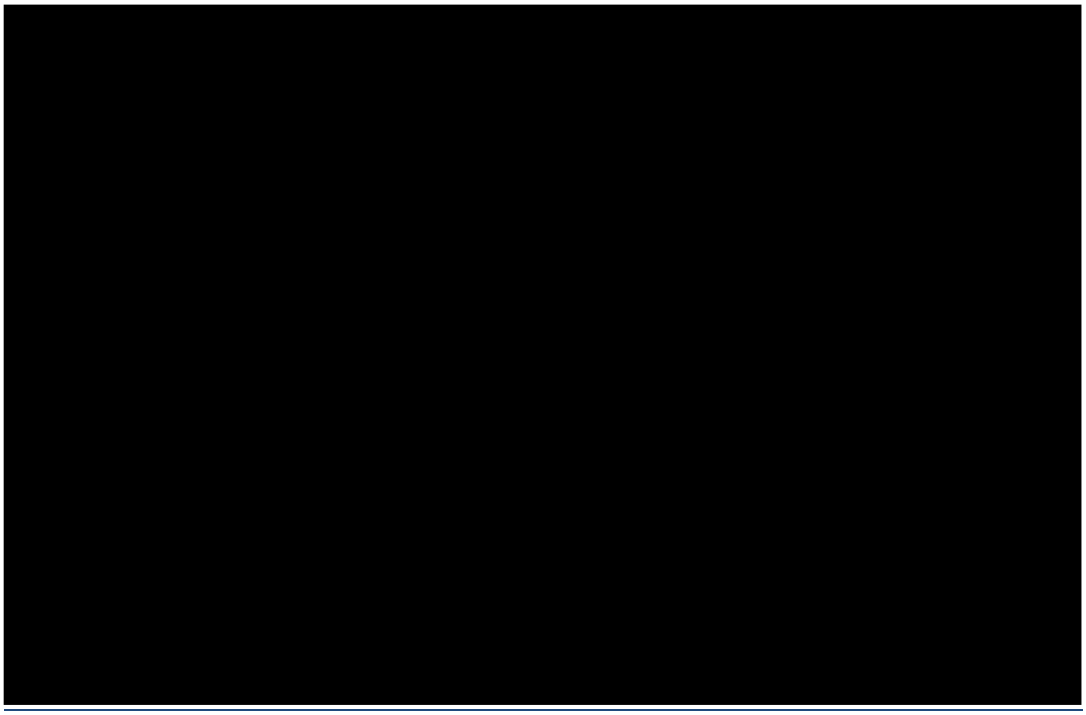
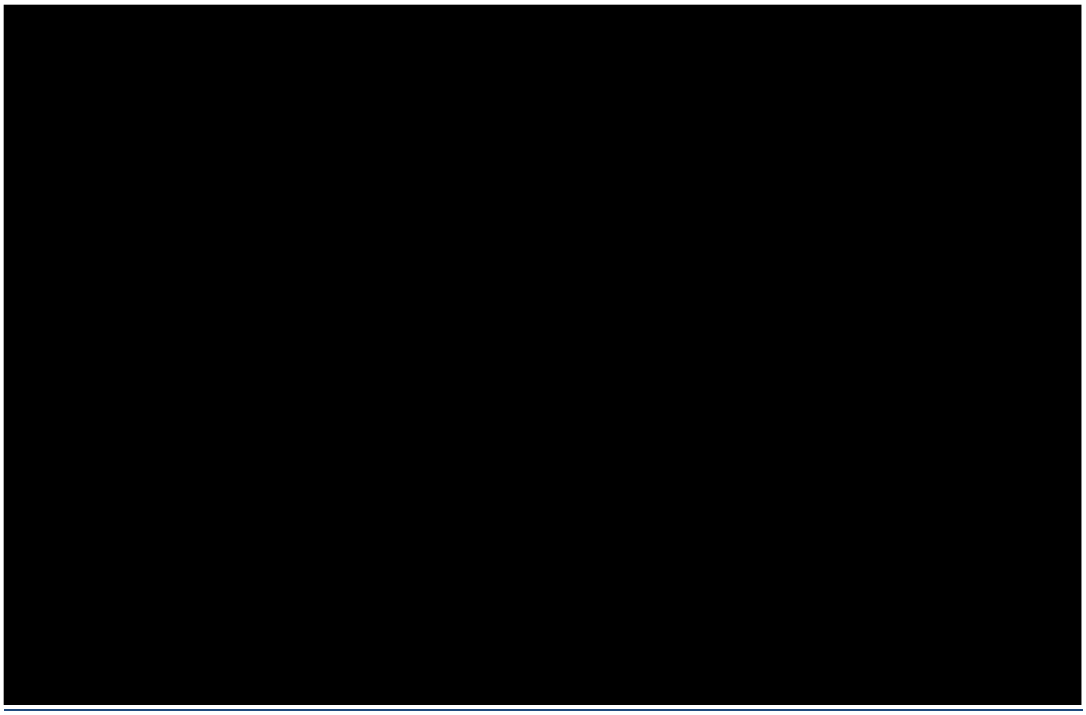


Figure B44: Cost-effectiveness acceptability curve, all strategies



The most appropriate comparison, given the incremental ICERs, is between hydroxycarbamide and the intervention of bosutinib. A pairwise comparison is therefore presented in Figure B45.

Figure B45: Pairwise comparison of hydroxycarbamide and bosutinib intervention

7.6.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis.**

Scenario analysis for the AP model is summarised in Table B72. As in the CP model, in the majority of scenarios, SCT is dominated by bosutinib. As such, the ICER for bosutinib versus hydroxycarbamide is presented in the first column and the ICER for SCT versus hydroxycarbamide is presented in the second. There is one scenario where SCT is not dominated by bosutinib, and this is noted in the table below. Full descriptions of the scenarios and incremental results for all comparators are provided in Additional Appendix 10.23.

Table B72: Scenario analysis – AP model

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib vs hydroxy-carbamide	SCT vs hydroxy-carbamide
Base case	N/A	N/A	[redacted]	£142,982
Patient population				
Cohort starting age	50 years (Study 200 – AP cohort)	45 years (-10%)	[redacted]	£140,888
		55 years (+10%)	[redacted]	£149,861
Overall survival				
Bosutinib overall survival	OS estimated by fitting exponential curve to AP cohort from Study 200	OS estimated by fitting 2nd best fitting curve (extreme value) to AP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	£142,982
Stem Cell Transplant	OS estimated by fitting	OS estimated by fitting 2nd best fitting curve	[redacted]	£165,173

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib vs hydroxy-carbamide	SCT vs hydroxy-carbamide
overall survival	exponential curve to AP cohort from Oehler (2007)	(Weibull) to Oehler (2007)		
		OS estimated based on curve (exponential) fitted to 'advanced phase' cohort from Jabbour (2011)	[redacted]	£98,279
Time spent in BP				
Time in blast phase	6 months	13 months (Rogers (2012)[84])	[redacted]	£195,626
		3 months (assumption)	[redacted]	£129,309
Transformation following SCT				
Transformation following SCT	Patients cannot transform to BP, but remain in AP	Patients transform to BP for 6 months before death.	[redacted]	£153,493
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from AP cohort in Study 200	Time on treatment equal to PFS from study 200 (AP to BP)	[redacted] Bos vs SCT: [redacted]	£142,982
		Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	£142,982
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial), the average cost per day for bosutinib is [redacted] for the AP cohort.	[redacted]	£142,982
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011a)[80]	Medical management resource use from TA241	[redacted]	£120,074
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP £2,536/month (doubled)	[redacted]	£136,703
		BP £1,268/month (doubled)	[redacted]	£138,144
Cost of death	£6,004 - Dewer & Addicot	£569 – Hoyle (2011a)[80]	[redacted]	£143,235
Cost of best supportive care	Best supportive care = hydroxycarbami	Additional cost of £100/month in hydroxycarbamide arm	[redacted]	£141,480

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib vs hydroxy-carbamide	SCT vs hydroxy-carbamide
	de, costing £12.75/month	only		
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	£141,480
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for AP and BP cohorts from Study 200 used for all patients in AP and BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	N/A
		Utility for AP in Study 200 only used for AP patients on bosutinib in the model (remainder as per base-case)	[redacted]	£142,982
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011a)[80]	[redacted]	£116,101
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	£140,682
Model Settings				
Time horizon	50 years	2 years	[redacted]	£417,691
		5 years	[redacted]	£183,409
		10 years	[redacted]	£147,725
		25 years	[redacted]	£142,982

* In this scenario SCT was cheaper than bosutinib and therefore the ICER for bosutinib vs SCT is also available

7.6.10 What were the main findings of each of the sensitivity analyses?

The key findings of the sensitivity analyses in accelerated phase were that in general the ICER for bosutinib remains between [redacted] per QALY compared to hydroxycarbamide and dominant compared to SCT. The ICER for SCT compared to hydroxycarbamide is similar to the ICER for bosutinib in every scenario.

The ICER increased most dramatically in two scenarios:

1. Varying the time on bosutinib treatment
2. Varying the cost of the AP health state (increasing resource use)

In both of these scenarios, the ICER increases as the additional survival benefit from bosutinib treatment remains the same, but the cost of keeping patients alive increases.

7.6.11 What are the key drivers of the cost-effectiveness results?

The key drivers of cost-effectiveness are the cost of bosutinib, cost of accelerated phase (i.e. resource utilisation), and the length of time patients remain on bosutinib treatment.

7.7 Results: Blast Phase

7.7.1 Clinical outcomes from the model

As the study for bosutinib in this patient population (Study 200) is a single arm trial, comparative results are not available. Model outcomes are therefore compared to clinical trial outcomes for bosutinib only.

Table B73 Summary of model results compared with clinical data

Outcome	Clinical trial result (data snapshot 28 Mar 2011)	Model result
Overall survival at year 1	42%	63%
Overall survival at year 2	35%	39%
Median time on treatment	0.23 years	0.27 years

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Figure B46 to Figure B48 present Markov traces of the proportion of patients in each health state for the comparator treatments. A tabulated Markov trace is available in Appendix 10.21.

Figure B46: Markov Trace – Bosutinib - BP

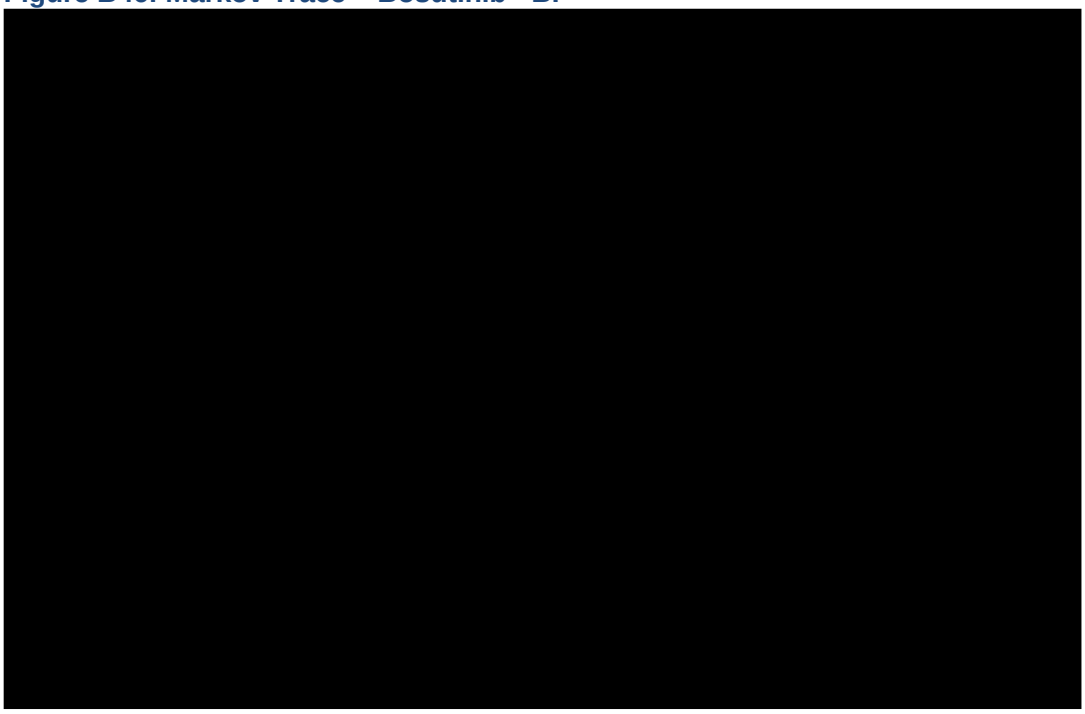


Figure B47: Markov Trace – SCT - BP

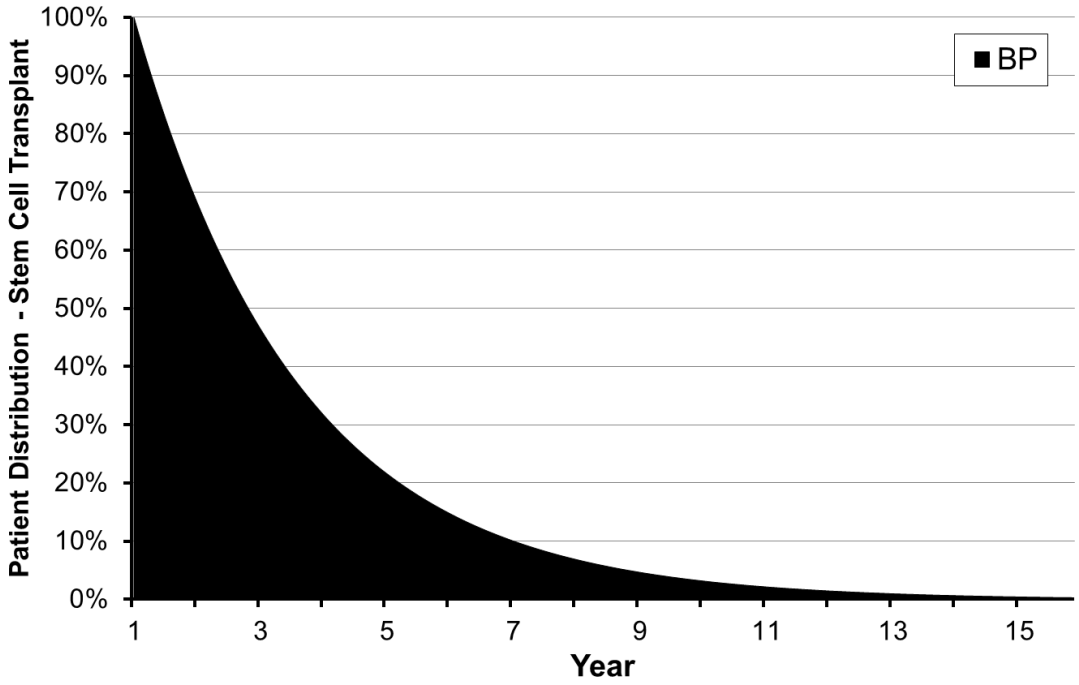
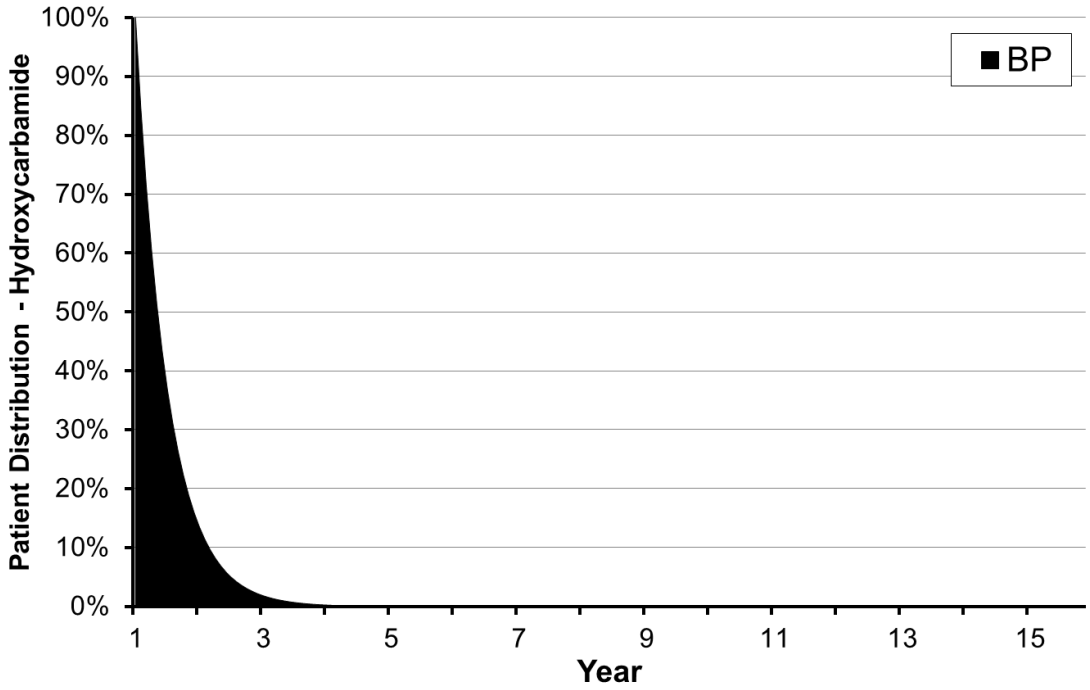


Figure B48: Markov Trace – Hydroxycarbamide - BP



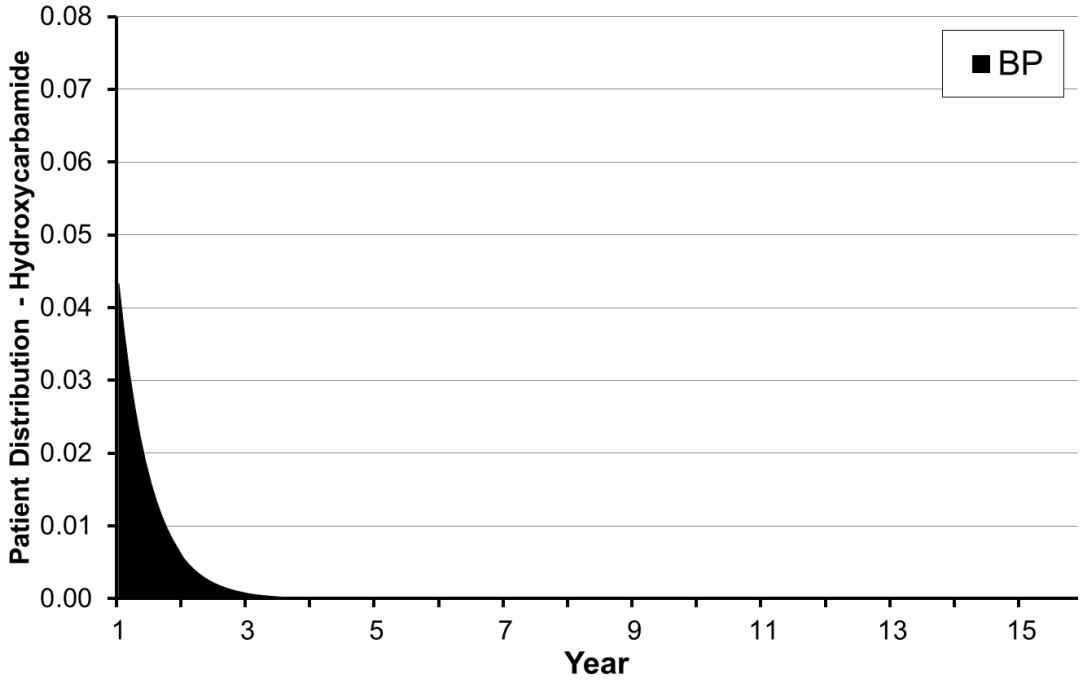
7.7.3 **Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

BOSUTINIB

Figure B49: Markov QALY Trace – Bosutinib - BP

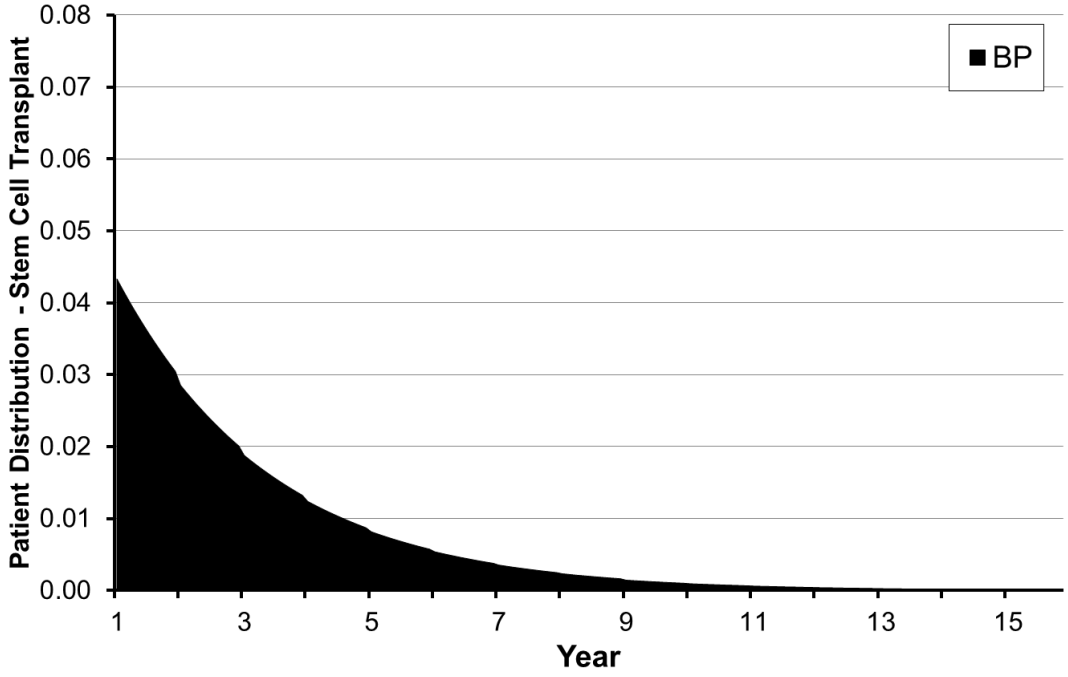
HYDROXYCARBAMIDE

Figure B50: Markov QALY Trace – Hydroxycarbamide - BP



SCT

Figure B51: Markov QALY Trace – SCT - BP



7.7.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator.**

Table B74: Model outputs by clinical outcomes- Bosutinib - BP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Blast Phase	1.77	0.54	[redacted]
Death	0	0	£5,743
Adverse Events	0.00		£506
Total	1.77	0.54	[redacted]
LY, life years; QALY, quality-adjusted life year			

Table B75: Model outputs by clinical outcomes- Hydroxycarbamide - BP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Blast Phase On Treatment	0.54	0.28	£8,203
Blast Phase Off Treatment	0.00	0.18	£0
Blast Phase	0.54	0.46	£8,203
Death	0	0	£5,967
Adverse Events	0.00		
Total	0.54	0.46	£14,170

LY, life years; QALY, quality-adjusted life year

Table B76: Model outputs by clinical outcomes- Stem Cell Transplant - BP

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Blast Phase On Treatment	2.64	1.28	£194,940
Blast Phase Off Treatment	0.00	0.00	£0
Blast Phase	2.64	1.28	£194,940
Death	0	0	£5,586
Adverse Events	0.00		
Total	2.64	1.28	£200,526
LY, life years; QALY, quality-adjusted life year			

7.7.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

Disaggregated costs and QALYs are presented by health state in 7.7.4 for each comparator.

Table B77: Summary of predicted resource use by category of cost (discounted)

Item	Bosutinib	Hydroxycarbamide	SCT
Technology cost	[redacted]	£82	£157,759
Mean total treatment cost	£169		
Monitoring cost	£17,935	£5,681	£26,011
Tests	£7,701	£2,439	£11,169
Palliative care	£5,743	£5,967	£5,586
Adverse Events	£506		
Total	[redacted]	£14,170	£200,526

Base-case analysis

7.7.6 **Base-case ICERs**

Table B78 Base-case results - BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£200,526	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£186,265

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

As there are 3 treatments, a cost-effectiveness plane is also given to show the results visually.

Figure B52: Cost-effectiveness plane: BP

The breakdown of the life years is also presented in a stacked bar chart.

Figure B53: Stacked bar chart of life years: BP

Sensitivity analyses

7.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

Extensive sensitivity analyses are presented in Section 7.7.9 . Tornado diagrams are not presented due to limitations discussed in Section 7.4.26 .

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic results are presented in Table B79, compared to deterministic results, based on 1,000 probabilistic simulations. The results are similar.

Table B79: Deterministic vs Probabilistic point estimates

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		
Deterministic results						
Hydroxycarbamide	£14,170	0.28				
Bosutinib	[redacted]	0.88	[redacted]	0.60	[redacted]	[redacted]
SCT	£200,526	1.28	[redacted]	0.40	[redacted]	£186,265
Probabilistic results						
Hydroxycarbamide	£15,262	0.32				
Bosutinib	[redacted]	0.89	[redacted]	0.57	[redacted]	[redacted]
SCT	£201,228	1.29	[redacted]	0.40	[redacted]	£192,016

Costs and QALYs discounted at 3.5%. Dominated strategies not included in incremental calculations.

A probabilistic scatter plot is presented in Figure B54, and a cost-effectiveness acceptability curve in Figure B55.

Figure B54: Scatterplot of probabilistic sensitivity analysis, all strategies

Figure B55: Cost-effectiveness acceptability curve, all strategies

The most appropriate comparison, given the incremental ICERs is between hydroxycarbamide and the intervention of bosutinib. A pairwise comparison is therefore presented in Figure B56.

Figure B56: Pairwise comparison of hydroxycarbamide and bosutinib intervention

7.7.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis.**

Scenario analysis for the BP model is summarised in Table B80. In the BP model, SCT is always more expensive than bosutinib with a similar or slightly higher effectiveness, as such in this table the incremental ICER for bosutinib versus hydroxycarbamide is presented first, followed by the ICER for SCT versus bosutinib. The ICER for SCT versus hydroxycarbamide is not included. Full descriptions of the scenarios and incremental results for all comparators are provided in Additional Appendix 10.24.

Table B80: Scenario analysis – BP model

Parameter	Base Case	Sensitivity Analysis	Incremental ICER	
			Bosutinib vs Hydroxy-carbamide	SCT vs bosutinib
Base case	N/A	N/A	[redacted]	[redacted]
Patient population				
Cohort starting age	47 years (Study 200 – AP cohort)	42 years (-10%)	[redacted]	[redacted]
		52 years (+10%)	[redacted]	[redacted]
Overall survival				
Bosutinib overall survival	OS estimated by fitting exponential curve to BP cohort from Study 200	OS estimated by fitting 2nd best fitting curve (Weibull) to BP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	[redacted]
Stem Cell Transplant overall survival	OS estimated by fitting exponential curve to BP cohort from Oehler (2007)	OS estimated by fitting 2nd best fitting curve (Weibull) to Oehler (2007)	[redacted]	[redacted]
		OS estimated based on curve (exponential) fitted to 'advanced phase' cohort from Saussele (2010)	[redacted]	[redacted]
Time spent in BP				
Time in blast phase	6 months	13 months (Rogers (2012))	[redacted]	[redacted]
		3 months (assumption)	[redacted]	[redacted]
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from BP cohort in Study 200	Time on treatment equal to PFS from study 200	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	[redacted]
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial), the average cost per day for bosutinib is [redacted] for the BP cohort.	[redacted]	[redacted]
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011a)[80]	Medical management resource use from TA241	[redacted]	[redacted]
Cost of AP and BP health states	BP £1,268/month	BP £1,268/month(doubled)	[redacted]	[redacted]
Cost of death	£6,004 - Dewer & Addicot	£569 – Hoyle (2011a)[80]	[redacted]	[redacted]
Cost of best supportive care	Best supportive care = hydroxycarbamide, costing	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	[redacted]

Parameter	Base Case	Sensitivity Analysis	Incremental ICER	
			Bosutinib vs Hydroxy-carbamide	SCT vs bosutinib
	£12.75/month	Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	[redacted]
Cost of SCT	All patients incur cost of FLAG-IDA at £29,212	FLAG-IDA cost removed	[redacted]	[redacted]
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility from BP cohort in Study 200 used for all patients in BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	N/A
		Utility from BP cohort in Study 200 only used for BP patients on bosutinib in the model (remainder as per base-case)	[redacted]	[redacted]
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011a)[80]	[redacted]	[redacted]
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	[redacted]
Model Settings				
Time Horizon	50 years	2 years	[redacted]	[redacted]
		5 years		
		10 years		
		25 years		

7.7.10 **What were the main findings of each of the sensitivity analyses?**

The key findings of the sensitivity analyses in blast phase were that in general the ICER for bosutinib remains between [redacted] per QALY compared to hydroxycarbamide. The ICER for SCT compared to hydroxycarbamide is consistently higher than the ICER for bosutinib.

The ICER increased most dramatically in two scenarios:

1. Varying the time on bosutinib treatment
2. Varying the cost of the BP health state (increasing resource use)

In both of these scenarios, the ICER increases as the additional survival benefit from bosutinib treatment remains the same, but the cost of keeping patients alive increases.

7.7.11 **What are the key drivers of the cost-effectiveness results?**

The key drivers of cost-effectiveness are the cost of bosutinib, cost of blast phase (i.e. resource utilisation), and the length of time patients remain on bosutinib treatment.

7.8 Validation

7.8.1 **Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-**

reference to evidence identified in the clinical, quality of life and resources sections.

Model design

At the design stage of the model, it was presented to a leading clinician currently treating CML patients in the UK (October 2012), in order to ensure the model has face validity, and matched clinical practice. The key issues around the economic modelling such as time horizon, comparators, survival analysis, adverse events, and utility measures were discussed with other experts using at an advisory meeting in December 2012.

The subsequent model design and shell were then presented to a senior UK economist (and former member of the NICE appraisal committee), whose comments were then incorporated. After this the full economic model was developed, and a first draft of the submission document produced.

Model accuracy and calculations

A number of steps were taken to validate the technical accuracy of the model and submission.

Firstly, estimates of time on treatment and overall survival from the final model were checked against values calculated in a separate spreadsheet – results were the same.

Secondly, extensive one-way sensitivity analyses were conducted on all model inputs and results were reviewed to ensure that changes in cost and effectiveness measures were consistent with expectations.

Thirdly, random checks were made on model inputs compared with source data.

As a last step in the model validation process, the model was reviewed by a senior health economist not involved with the project, using the Drummond checklist, as well as a proprietary internal checklist from BresMed (who developed the model). Following this review a report was produced, with discussions held and changes made to the model and documented accordingly

Finally, in terms of internal validity, as discussed in Section 7.2.2 the survival functions used to generate estimates of time on treatment and overall survival for bosutinib, hydroxycarbamide and stem cell transplant are very close to those obtained based on the empirical (Kaplan-Meier) survival distributions (see Section 7.3.1), and results seen in published NICE technology appraisals (TA241, TA251).

External review

Following the development of the model, the model and submission were reviewed by an independent UK economist not thus far involved with the project. This economist works in a department of a leading centre for health economics in the UK, and part of an Evidence Review Group. The economist reviewed the submission, highlighting areas for improvement and clarification, as well as any assumptions they did not agree with. Following this review, further changes were made (as well as amendments made to answers questions they raised), ahead of submission to NICE.

7.9 Subgroup analysis

7.9.1 **Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible,**

mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

Different patient populations are examined in sensitivity analysis (Section 7.5.9), and three different uses for bosutinib explored (CP, AP, and BP), however subgroups do not form a part of this submission.

7.9.2 **Please clearly define the characteristics of patients in the subgroup.**

N/A

7.9.3 **Please describe how the statistical analysis was undertaken.**

N/A

7.9.4 **What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).**

N/A

7.9.5 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.**

N/A

7.10 Interpretation of economic evidence

7.10.1 **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

The economic literature review did not find any papers in which the cost-effectiveness of bosutinib was investigated, however it should be noted the results of this evaluation for the comparators are consistent with those produced for previous NICE Technology Appraisals (TA241, TA251).

7.10.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?**

Three models have been developed to ensure that the economic evaluation is relevant to patients in all phases of CML, as defined by the license (CP, AP and BP). Additionally, the economic evaluation has included patients across a range of treatment lines, including second, third and fourth line, which is in line with the licensed population for bosutinib. Finally, sensitivity analyses were presented that considered a post-hoc analysis population, requested by the EMA, as being potentially representative of the 'unmet need' population in practice – i.e. those for whom imatinib, dasatinib and nilotinib are not suitable options. As noted in Appendix 10.16, the post-hoc analysis reported in the EMA addendum and the bosutinib SPC excluded fourth-line patients, although these patients would certainly be eligible for bosutinib.

7.10.3 **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

The strengths of the analysis include the transparent and robust economic modelling, along with extensive scenario analyses to explore alternative assumptions. Good data is also available from which to model parameters that have needed to be estimated in other appraisals (for example patient utility, and time on treatment).

However, there remain significant limitations in the evidence base in CML, particularly in the later stages of the disease. The absence of randomised controlled trials presents a major challenge of how best to interpret the evidence, and the appropriateness of naïve comparisons.

As a result of the evidence base, the submission requires a pragmatic approach to estimating the cost-effectiveness of bosutinib in the treatment of CML.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further information on the efficacy of bosutinib will become available due to the Pfizer post-marketing commitment to conduct a trial in the licensed population for bosutinib.

This trial will seek to validate the efficacy of bosutinib in the licensed population, however as it is only expected to be an observational trial, it will not provide any validation of the proposed superior efficacy of bosutinib over comparators such as hydroxycarbamide, interferon or SCT.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

In the costing template for TA241, it is stated that the prevalent population has been previously estimated at 2,660 in 2003, although no details are given for the source of this estimate. As noted in Section A, a French study has shown that the prevalence of CML has seen a mean annual increase of 9.3% from 2003 to 2007, since the introduction of imatinib (See Section 2.2).[27] This would therefore correspond to an estimated prevalence of 5,922 in 2012. It is challenging to estimate the proportion of the prevalent population that would be eligible for bosutinib treatment and therefore the likely eligible population has been calculated based on the number of newly diagnosed (incident) patients each year.

Approximately 596 and 35 patients were diagnosed with CML in England and Wales respectively in 2010 (see Table C1). According to a report from Cancer Research and the ONS, the incidence rate for leukaemia in the UK has largely stabilised in recent years and therefore, it is assumed that the average incidence of CML has remained stable and will continue to remain stable over the next 5 years[104] Around 90% of CML patients are diagnosed in the chronic phase of CML. It is therefore expected that of the estimated population eligible for bosutinib below, only 10% would be advanced phase patients.

Table C1: Estimated annual, incident population for bosutinib treatment in England and Wales

Population	Estimated incidence	Assumption	Reference
Cases of chronic myeloid leukaemia in England and Wales	631	596 people in England and 35 people in Wales diagnosed with CML in 2010. Assuming that incidence has been stable since 2010.	Office of National Statistics Cancer Statistics Registrations, England, 2010[105] Welsh Cancer Intelligence and Surveillance Unit, Annual Publication No. SA12/01[25]
People with Ph+ CML and treated with a 1st line TKI (imatinib)	599	95% of those diagnosed with CML are Ph+. All diagnosed patients are treated with a 1st line TKI (imatinib).	Goldman, 2009[4] Assumption
People for whom 1st line imatinib treatment is unsuccessful and are treated with a 2nd line TKI	234	39% of 1st line patients discontinued imatinib (excluding those who discontinued due to mortality or receipt of a SCT) and all are treated with a 2nd line TKI (usually nilotinib)	Deininger, 2009[32] Assumption

Population	Estimated incidence	Assumption	Reference
2nd line patients for whom current 2nd line TKIs are inappropriate options and therefore **eligible for bosutinib at 2nd line**	12	5% of imatinib-resistant patients from Study 200 may have been unsuitable for treatment with nilotinib and dasatinib at 2nd line, due to the presence of mutations conferring resistance or co-morbidities (See Appendix 10.16).	Draft EPAR
Patients for whom 2nd line TKI treatment is unsuccessful and are treated with a 3rd line TKI	107	48% of 2nd line patients discontinued nilotinib due to lack of efficacy (progression) or intolerance (adverse events) and treated with a 3rd line TKI	Kantarjian (2011)[34]
3rd line patients whom the remaining TKI is not an appropriate option and therefore **eligible for bosutinib at 3rd line**	19	18% of third-line patients from Study 200 may have been unsuitable for treatment with nilotinib or dasatinib at third-line (depending on previous treatment), due to the presence of mutations conferring resistance or co-morbidities, and therefore may be eligible for bosutinib at 3rd line. (See Appendix 10.16).	Draft EPAR
Patients for whom all currently available TKIs have been unsuccessful at 3rd line and are therefore **eligible for bosutinib at 4th line**	49	56% of 3rd line patients (nilotinib and dasatinib) discontinue treatment excluding those discontinued due to mortality or receipt of a SCT) and have therefore exhausted all TKI options currently available.	Garg (2009)[106]
Total incident population eligible to receive bosutinib under its proposed licensed indication	**80**	**80 patients per year may be eligible for bosutinib.**	

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

In the above calculations, it was assumed that all newly diagnosed CML patients are treated with a 1st line TKI (usually imatinib). At 1st line, alternative non-TKI treatments such as SCT or cytotoxic drugs, such as interferon or hydroxycarbamide would not be considered.

For those who discontinue 1st line TKI treatment (except those who die or receive a SCT), it is assumed that all of them will be treated with a different TKI at 2nd line (usually nilotinib).

There are no 3rd line drugs specifically recommended by NICE in the UK, however as described by its license, bosutinib may only be considered in those who are unsuitable for imatinib, nilotinib and dasatinib. Although dasatinib is not recommended by NICE in the UK, clinicians have confirmed that it is used in a 3rd line setting, accessed either through the CDF or through IFRs. As such, it is assumed that patients who discontinue 2nd line treatment (excluding those who die or receive a SCT) do receive a 3rd line TKI (either nilotinib or dasatinib).

It is assumed that all patients who have previously failed on all three TKIs, either due to lack of efficacy or intolerance, would be eligible for bosutinib at 4th line. Additionally, as previously described there will be a small number of 2nd line and 3rd line patients for whom imatinib, dasatinib and nilotinib are all unsuitable options because they have mutations or co-morbidities that make current TKIs inappropriate.

No data was found on the uptake of SCT versus hydroxycarbamide (BSC) in the patient population under consideration in this license. Clinical experts have estimated that only 30% of this population would be eligible for SCT given the strict eligibility criteria and availability of donors, it is assumed that the rest will receive hydroxycarbamide.

8.3 What assumption(s) were made about market share (when relevant)?

The uptake assumptions above would therefore result in the following patients annually eligible for SCT or hydroxycarbamide (BSC) (see Table C2). As per the economic evaluation described in section 7, it is assumed that hydroxycarbamide patients are treated until death with hydroxycarbamide and therefore these patients accrue over the 5 year period.

Table C2: Total number of patients receiving SCT or hydroxycarbamide

	Year 1	Year 2	Year 3	Year 4	Year 5
Total for whom imatinib, nilotinib and dasatinib are inappropriate	80	80	80	80	80
SCT	24	24	24	24	24
Hydroxycarbamide (BSC)	56	56	56	56	56
Total Hydroxycarbamide (BSC) patients (assuming treatment until death)	*56*	*112*	*168*	*224*	*280*

Since SCT is the only 'cure' for CML and its uptake is largely defined by the eligibility of patients and the availability of matched donors, it is assumed that the uptake of SCT will not change with the introduction of bosutinib. As such, the potential impact on SCT is not considered in this assessment.

However, given the step-change in efficacy and quality of life associated with bosutinib over hydroxycarbamide for this CML population with high unmet needs, it is assumed that bosutinib will take the majority of market share from hydroxycarbamide in these patients (see Table C3 below).

Table C3: Total number of new bosutinib patients each year

	Year 1	Year 2	Year 3	Year 4	Year 5
Bosutinib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New patients receiving bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients receiving bosutinib (assuming time on treatment of [redacted] years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New patients receiving hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients receiving hydroxycarbamide (assuming treatment until death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As previously described, bosutinib patients are expected to come from different lines of treatment (i.e. second line or later) and from different phases. As shown in section 7, time on treatment decreases as patients move through lines of treatment and phases of the disease. In the base-case model, time on bosutinib was estimated by fitting a parametric curve to the discontinuation data from Study 200 (data snapshot 15 Feb 2012). For the third-line CP cohort, the mean time on bosutinib was estimated at [redacted] years (the median duration of treatment from Study 200 is 8.6 months). This value is likely to over-estimate time on treatment in practice, as it does not include fourth-line patients, which are expected to be the majority of bosutinib patients or advanced phase patients.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The following cost estimates take into account the full range of direct NHS costs associated with the introduction of bosutinib into the NHS, including drug costs, costs of routine medical management, and adverse event management, as detailed in Section 7.4.21 to Section 7.4.23 above.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

All cost estimates included in this section are based on the inputs of the economic model described in Section 7 and in Table C4 below. This calculation is based on the total number of patients expected to receive bosutinib and hydroxycarbamide and the average time on treatment for bosutinib presented above.

As described in Section 7, patients who discontinue bosutinib are assumed to be treated with hydroxycarbamide. As such, the costs post-bosutinib are expected to be equal to the ongoing costs of patients treated with hydroxycarbamide and therefore the budget impact for patients after year 1 are not considered in this assessment.

The cost of managing AEs associated with bosutinib are considered in this analysis (see table below), but the additional resource use costs for all patients in chronic phase are not considered as these are expected to be similar whether the patient is on hydroxycarbamide or bosutinib.

The total budget impact over 5 years in a scenario where bosutinib is introduced is compared to a scenario where bosutinib is not introduced.

Table C4: Monthly and annual costs considered in budget impact assessment

	Monthly cost	Annual cost
Acquisition cost of bosutinib	£3,733	£44,799
Cost of managing AEs associated with bosutinib	N/A	£506
Acquisition cost of hydroxycarbamide	£13	£156

8.6 Were there any estimates of resource savings? If so, what were they?

There are no resource savings estimated within this budget impact.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Based on the assumptions described above the following budget impact has been calculated for the NHS in England and Wales (Table C5).

Table C5: Incremental budget impact if bosutinib introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide (if bosutinib introduced)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide (if bosutinib not introduced)	£8,736	£17,472	£26,208	£34,944	£43,680
Incremental cost if bosutinib is introduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Additional costs associated with hydroxycarbamide

In our economic model, only the acquisition costs of hydroxycarbamide have been included. In practice, according to clinical opinion, it is likely that patients will receive other interventions such as blood transfusions or antibiotics, on top of hydroxycarbamide. The use of bosutinib is expected to significantly reduce the need for these interventions, however given that there is a lack of evidence on this, these costs have not been incorporated into our budget impact assessment.

Aside from drug costs, the majority of high-cost resource use is actually incurred in the more advanced phases as shown in Section 7. Therefore, over a short time-frame (e.g. 5 years) some cost-offsets may be expected because bosutinib will delay progression compared to hydroxycarbamide. However, in the long-term (e.g. 10 years), all patients (except those who die of non-CML causes) will eventually progress to the advanced phases.

Additional costs associated with SCT

As shown above, bosutinib is more cost-effective than SCT in virtually all scenarios considered. Nonetheless, SCT remains the only ‘cure’ for CML and bosutinib is not expected to replace SCT for the minority of patients who are eligible to receive a SCT and who have a match. However, in practice the impact of introducing another effective TKI option may result in a reduction in the numbers of SCT since patients or clinicians may prefer to try another TKI before or instead of SCT given the considerable cost, morbidity and mortality impact associated with SCT.

In addition to the high cost of SCT, for patients in the advanced phases, prior treatment with an acute-leukaemia style chemotherapy regimen, such as FLAG-IDA is typical and costly (around £29,000 per patient for 2 cycles of treatment, see Appendix 10.20, Section 10.20, for calculation). It is likely that many patients will incur the cost of FLAG-IDA but

not go on to benefit from SCT. The introduction of bosutinib as another option may therefore reduce the need for this expensive chemotherapy regimen and result in additional resource savings that have not been included in this assessment.

Costs associated with TKI use in 'non-responding' patients

Finally, according to our clinical advisors, for patients who have failed on all 3 TKI treatments currently available, clinicians may keep patients on 'active' treatment rather than resort to hydroxycarbamide, even if patients are not responding. Alternatively, clinicians may try increased doses of TKIs such as imatinib or dasatinib, which significantly increases cost (Table C6) but has limited evidence of improved efficacy, as noted in TA241. There is no evidence on the number of patients remaining unnecessarily on normal or high-dose TKIs despite lack of efficacy, but the introduction of bosutinib may result in considerable cost-offsets compared to keeping patients on TKIs unnecessarily.

Table C6: Additional costs not considered in budget impact assessment

	Annual cost per patient
Costs of SCT in year 1	£127,740
Costs of SCT in year 2	£13,992
Costs of SCT for year 3 onwards	£1,680
Costs of FLAG-IDA	£29,212
Cost of managing patients in advanced phases	£13,512
Cost of dasatinib (80-180mg qd)	£30,477 - £61,000
Cost of imatinib (400-800mg qd)	£20,980 - £41,960
Cost of nilotinib (300-400mg bd)	£31,714

9 References

1. O'Brien S, Berman E, Borghaei H, et al. NCCN clinical practice guidelines in oncology: chronic myelogenous leukemia. J Natl Compr Canc Netw 2009;7:984-1023.
2. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340:1330-40.
3. Cortes J. Natural history and staging of chronic myelogenous leukemia. Hematol Oncol Clin North Am 2004;18:569-84, viii.
4. Goldman JM. Chronic Myeloid Leukaemia. Medicine 2009;37:195-197.
5. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.
6. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. Blood 2008;112:4808-17.
7. Imatinib (Glivec) SPC- Latest update, European Medicines Agency. 2012.
8. Nilotinib (Tasigna) SPC- Latest update, European Medicines Agency. 2012.
9. Dasatinib (Sprycel) SPC- Latest update, European Medicines Agency. 2012.
10. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164-72.
11. Ren R. Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukaemia. Nat Rev Cancer 2005;5:172-83.
12. Steelman LS, Pohnert SC, Shelton JG, et al. JAK/STAT, Raf/MEK/ERK, PI3K/Akt and BCR-ABL in cell cycle progression and leukemogenesis. Leukemia 2004;18:189-218.
13. Van Etten RA. Mechanisms of transformation by the BCR-ABL oncogene: new perspectives in the post-imatinib era. Leuk Res 2004;28 Suppl 1:S21-8.
14. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2292-302.
15. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 2006;108:1809-20.
16. Cancer Research UK, http://www.cancerresearchuk.org/cancer-help/type/cml/about/the-blood-and-chronic-myeloid-leukaemia. [Accessed November 28th 2012].
17. Cancer Research UK, http://www.cancerresearchuk.org/cancer-help/type/cml/about/symptoms-of-chronic-myeloid-leukaemia. [Accessed November 28th 2012].
18. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance TA241. http://guidance.nice.org.uk/TA241. January 2012.
19. Aleem A, Siddiqui N. Chronic myeloid leukemia presenting with extramedullary disease as massive ascites responding to imatinib mesylate. Leuk Lymphoma 2005;46:1097-9.
20. Deremer DL, Katsanevas K, Ustun C. Critical appraisal of nilotinib in frontline treatment of chronic myeloid leukemia. Cancer Manag Res 2011;3:65-78.
21. Homewood J, Watson M, Richards SM, et al. Treatment of CML using IFN-alpha: impact on quality of life. Hematol J 2003;4:253-62.
22. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
23. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-8.
24. Office for National Statistics. Cancer statistics registrations. Registrations of cancer diagnosed in 2009, England. 7 Sept 2011;MB1 40.
25. Welsh Cancer Intelligence and Surveillance Unit. Cancer Incidence in Wales, 2005-2009. 27 Jan 2011;SA11/01.
26. Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011;105:1684-92.

27. Corm S, Micol J, Leroyer A, et al. Kinetic of chronic myeloid leukaemia (CML) prevalence in Northern France since the introduction of imatinib. J Clin Oncol 2008;26.
28. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance TA70. Guidance on the use of imatinib for chronic myeloid leukaemia. http://www.nice.org.uk/ta70. Oct 2003.
29. Baccarani M, Dreyling M. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v165-7.
30. Goldman JM. Initial treatment for patients with CML. Hematology Am Soc Hematol Educ Program 2009:453-60.
31. Westin. Treatment of chronic myelogenous leukemia as a paradigm for solid tumours: how targeted agents in newly diagnosed disease transformed outcomes.
32. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. American Society of Hematology 51st Annual Conference, New Orleans, USA. 5-8 December 2009.
33. Botteman. Long-term estimatee of quality-adjusted life expectancy for nilotinib and imatinib as first-line treatment for newly diagnosed patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia in chronic phase CML (CML-CP).
34. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood 2011;117:1141-5.
35. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance TA251. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. http://guidance.nice.org.uk/TA251. Apr 2012.
36. Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer 2007;109:1556-60.
37. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. Haematologica 2011;96:1779-82.
38. Hehlmann R. How I treat CML blast crisis. Blood 2012;120:737-47.
39. National Institute for Health and Clinical Excellence. NICE Cancer Service Guidance: Improving outcomes in haematological cancers. October 2003.
40. Jain N, van Besien K. Chronic myelogenous leukemia: role of stem cell transplant in the imatinib era. Hematol Oncol Clin North Am 2011;25:1025-48, vi.
41. Irvine DA, Heaney NB, Holyoake TL. Optimising chronic myeloid leukaemia therapy in the face of resistance to tyrosine kinase inhibitors--a synthesis of clinical and laboratory data. Blood Rev 2010;24:1-9.
42. London CDF-. London Cancer Drugs Fund- Drug List.
43. Szydlo R, Goldman JM, Klein JP, et al. Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings. J Clin Oncol 1997;15:1767-77.
44. Goldman JM, Szydlo R, Horowitz MM, et al. Choice of pretransplant treatment and timing of transplants for chronic myelogenous leukemia in chronic phase. Blood 1993;82:2235-8.
45. Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet 1998;352:1087-92.
46. Milojkovic D, Ibrahim A, Reid A, et al. Efficacy of combining dasatinib and FLAG-IDA for patients with chronic myeloid leukemia in blastic transformation. Haematologica 2012;97:473-4.

47. Appendix D- Response to consultee and commentator comments on the draft scope and provisional matrix (NICE STA Bosutinib for previously treated chronic myeloid leukaemia). 2013.
48. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403-12.
49. European LeukemiaNet Update. Recommendations from the European LeukemiaNet for the Management of chronic myeloid leukemia (CML). ASCO Annual Meeting 2010.
50. Anthony Nolan Trust. Press release, 28th October 2011, Comedian Hardeep Singh fronts charity campaign to get young men on donor register, http://www.anthonynolan.org/Media/press-releases/Comedian-Hardeep-Singh-fronts-charity-campaign-to-.aspx.
51. NHS blood and transplant. News Release: NHS Blood and Transplant and Anthony Nolan welcome publication of stem cell strategy report. http://www.nhsbt.nhs.uk/news/2010/newsrelease011210.html 01 December 2010.
52. Stein AS, Fung HC, Sahebi F, et al. Reduced intensity allogeneic stem cell transplantation (alloSCT) for patients ≥ 60 years old with advanced hematologic malignancy 2003 ASCO Annual Meeting 2003.
53. National Cancer Action Team: Cancer Drugs Fund Bulletin- August 2012. 2013.
54. Curtis L. Unit Costs of Health & Social Care 2012. PSSRU 2012.
55. Khoury HJ, Gambacorti-Passerini C, Kantarjian H, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Failure with Imatinib Plus Dasatinib and/or Nilotinib: 24-month Minimum Follow-up Update, In 54th Annual Meeting of the American Society of Hematology, 2012.
56. Study 200 Clinical Study Report, Pfizer, Data on File.
57. Schleuning M, Scholten M, van Biezen A, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia after prior treatment with nilotinib or dasatinib, In 52nd Annual Meeting of the American Society of Hematology, 2010.
58. Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-7.
59. Cortes J, Kantarjian H, Kim DW, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib: 36-month Minimum Follow-up Update, In 54th Annual Meeting of the American Society of Hematology, 2012.
60. Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-5.
61. Weisser M, Schleuning M, Haferlach C, et al. Allogeneic stem-cell transplantation provides excellent results in advanced stage chronic myeloid leukemia with major cytogenetic response to pre-transplant imatinib therapy. Leuk Lymphoma 2007;48:295-301.
62. Holroyd A, Phillips E, Szydlo R, et al. Response to tyrosine kinase inhibitor therapy in patients undergoing allogeneic hematopoietic stem cell transplantation for advanced phase chronic myeloid leukemia, In 52nd Annual Meeting of the American Society of Hematology, 2010.
63. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol 2009;62:1253-1260 e4.
64. Haematology BCfSi. Recommendations for the Management of BCR-ABL-positive Chronic Myeloid Leukaemia.
65. Group CELS. Website- Ongoing Management http://www.cml-info.com/de/healthcare-professionals/about-cml/ongoing-management.html. [Accessed November 28th 2012].
66. Cortes J, Quintas-Cardama A, Kantarjian HM. Monitoring molecular response in chronic myeloid leukemia. Cancer 2011;117:1113-22.

67. Milojkovic D, Nicholson E, Apperley JF, et al. Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Haematologica 2010;95:224-31.
68. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11:1029-35.
69. Cella D, Jensen SE, Webster K, et al. Measuring Health-Related Quality of Life in Leukemia: The Functional Assessment of Cancer Therapy - Leukemia (FACT-Leu) Questionnaire. Value Health 2012;15:1051-8.
70. Euroqol, http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d/who-is-using-eq-5d.html. [Accessed 30/01/2013].
71. EMA Clinical Overview Addendum. 2012.
72. Bornhauser M, Kroger N, Schwerdtfeger R, et al. Allogeneic haematopoietic cell transplantation for chronic myelogenous leukaemia in the era of imatinib: a retrospective multicentre study. Eur J Haematol 2006;76:9-17.
73. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. Cancer 2007;110:340-4.
74. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-9.
75. Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after Bcr-Abl kinase mutation-related imatinib failure. Blood 2006;108:1421-3.
76. Markiewicz M, Dzierzak-Mietla M, Wisniewska-Piaty K, et al. The favorable results of allo-HSCT in TKI-resistant CML, In 53rd Annual Meeting of the American Society of Hematology, 2011.
77. Benedicte D, Emmanuel B, Nicole R, et al. Impact of prior second-generation tyrosine kinase inhibitors on the outcome of hematopoietic stem cell transplantation for chronic myeloid leukemia In 52nd Annual Meeting of the American Society of Hematology, 2010.
78. Radich JP, Olavarria E, Apperley JF. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia. Hematol Oncol Clin North Am 2004;18:685-702, x.
79. National Cancer Institute, http://www.meb.uni-bonn.de/Cancernet/CDR0000062876.html. 2012.
80. Hoyle M, Pavey T, Ciana O, et al. Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. 2011.
81. Baccarani M, Pileri S, Steegmann JL, et al. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii72-7.
82. Trask PC, Cella D, Besson N, et al. Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia. Leukemia Research 2012;36:438-42.
83. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27:6041-51.
84. Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:1-410.
85. Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation. Health Technology Assessment 2012;16:1-137.
86. Hoyle M, Rogers G, Moxham T, et al. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. Value Health 2011;14:1057-67.

87. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 2009;113:2154-60.
88. Garside R, Round A, Dalziel K, et al. The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review. Health Technol Assess 2002;6:1-162.
89. Rea D, Maloisel F, Huguet F, et al. EOSTA: An observational study on the compliance and quality of life (QoL) of chronic myeloid leukemia (CML) patients treated with second line nilotinib (Tasigna): Interim results at 6 months of follow-up. Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH 2011 San Diego, CA United States. Conference Start: 20111210 Conference End: 20111213. Conference Publication: (var.pagings). 118 (21) , 2011. Date of Publication: 18 Nov 2011. 2011.
90. Ferdinand R, Mitchell SA, Batson S, et al. Treatments for chronic myeloid leukemia: a qualitative systematic review. J Blood Med 2012;3:51-76.
91. Trask PC, Cella D, Besson N, et al. Health-related quality of life (HRQoL) of bosutinib (SKI-606) in imatinib-resistant (IM-R) or imatinib-intolerant (IM-I) chronic phase chronic myeloid leukemia (CP CML). Journal of Clinical Oncology. Conference: ASCO Annual Meeting 2011 Chicago, IL United States. Conference Start: 20110603 Conference End: 20110607. Conference Publication: (var.pagings). 29 (15 SUPPL. 1) , 2011. Date of Publication: 20 May 2011. 2011.
92. Reed SD, Anstrom KJ, Ludmer JA, et al. Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2004;101:2574-83.
93. Dalziel K, Round A, Stein K, et al. Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technol Assess 2004;8:iii, 1-120.
94. Lee SJ, Kuntz KM, Horowitz MM, et al. Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: a decision analysis. Ann Intern Med 1997;127:1080-8.
95. Guest JF, Naik N, Sladkevicius E, et al. Utility values for chronic myelogenous leukemia chronic phase health states from the general public in the United Kingdom. Leuk Lymphoma 2012;53:928-33.
96. Efficace F, Baccarani M, Breccia M, et al. Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. Blood 2011;118:4554-60.
97. Aziz Z, Iqbal J, Aaqib M, et al. Assessment of quality of life with imatinib mesylate as first-line treatment in chronic phase-chronic myeloid leukemia. Leuk Lymphoma 2011;52:1017-23.
98. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D, Discussion Paper 172. 1999.
99. Addicott R, Dewar S. Improving choice at end of life: A descriptive analysis of the impact and costs of the Marie Curie Delivering Choice Programme in Lincolnshire. King's Fund 2008.
100. Millen M, Phennah D. Adult BMT costing and pricing model workshop. London Specialised Commissioning Group; 2009. 2009.
101. Curtis L. Unit Costs of Health & Social Care 2010. PSSRU 2010.
102. Ashfaq K, Yahaya I, Hyde C, et al. Clinical effectiveness and cost-effectiveness of stem cell transplantation in the management of acute leukaemia: a systematic review. Health Technol Assess 2010;14:iii-iv, ix-xi, 1-141.
103. Erlotinib ERG Report, http://www.nice.org.uk/nicemedia/pdf/Lungcancer_erlotinib_ERGreport.pdf.
104. Cancer Research UK, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/leukaemia/incidence/uk-leukaemia-incidence-statistics.
105. Office for National Statistics. Cancer statistics registrations. Registrations of cancer diagnosed in 2010, England. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-262496. 2010;MB1 40.
106. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood 2009;114:4361-8.

107. Ghatnekar O, Hjalte F, Taylor M. Cost-effectiveness of dasatinib versus high-dose imatinib in patients with Chronic Myeloid Leukemia (CML), resistant to standard dose imatinib a Swedish model application. Acta Oncologica 2010;49:851-858.
108. Asano E, Nita M, Moellmann-Coelho A, et al. Cost-utility analysis of dasatinib in patients with imatinib-resistant chronic myeloid leukemia (CML) on chronic (CP), accelerated (AP) and blast (BP) phases in Brazil. Value in Health Conference: ISPOR 12th Annual European Congress Paris France Conference Start 2009;12:A280-A281.
109. Gaultney JG, Sanhueza E, Janssen JJ, et al. Application of cost-effectiveness ana lysis to demonstrate the potential value of companion diagnostics in chronic myeloid leukemia. Pharmacogenomics 2011;12:411-421.
110. Juarez-Garcia A, Uc-Coyoc R, Hernandez-Rivera G, et al. The cost and cost effectiveness of dasatinib (SPRYCEL) 100 MG therapy for the management of imatinib resistant and intolerant patients in chronic phase with chronic myeloid leukemia (CML) in Mexico. Value in Health Conference: ISPOR 12th Annual European Congress Paris France Conference Start 2009;12.
111. Ko BS, Tang JL, Kuo MC, et al. Pharmacoeconomic evaluation of nilotinib in treating Taiwan patients with chronic myeloid leukemia (CML). Value in Health Conference: ISPOR 4th Asia Pacific Conference Phuket Thailand Conference Start 2010;13:A514-A515.
112. Kuznetzov S, Mungapen LJ, Samyshkin Y, et al. Cost-utility analysis of dasatinib as a second-line treatment in the chronic phase of chronic myeloid leukaemia in Russia. Value in Health Conference: ISPOR 13th Annual European Congress Prague Czech Republic Conference Start 2010;13.
113. Niu X, Hay J. Cost-effectiveness analysis of nilotinib versus dasatinib in patients with imatinib-resistant or imatinib-intolerant chronic myeloid leukemia (CML). Value in Health Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012;15:A209-A210.
114. Orozco Giraldo JJ, Valencia JE, Garrido Lecca S, et al. Economic evaluation of dasatinib in chronic myelogenous leukaemia patients resistant to imatinib in peru, compared to nilotinib and high doses of imatinib. Value in Health Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011;14.
115. Ramirez De Arellano A, Sbarigia U, Taylor MJ, et al. Cost-effectiveness analysis of dasatinib 100 mg vs. imatinib 800 mg in patients with imatinib-resistant chronic myeloid leukemia in Spain. Value in Health Conference: ISPOR 13th Annual European Congress Prague Czech Republic Conference Start 2010;13.
116. Taylor MJ, Saxby RC, Davis C. An economic evaluation of dasatinib for the treatment of imatinib-resistant patients with chronic myelogenous leukaemia. Blood Conference: 51st Annual Meeting of the American Society of Hematology, ASH New Orleans, LA United States Conference Start 2009;114.
117. Taylor M, Saxby R, Davis C. Using short-term response to predict long-term outcomes in patients with imatinib-resistent or imatinib-intolerant chronic myeloid leukaemia. Value in Health. Conference: ISPOR 14th Annual International Meeting Orlando, FL United States. Conference Start: 20090516 Conference End: 20090520. Conference Publication: (var.pagings). 12 (3) (pp A50), 2009. Date of Publication: May 2009. 2009.
118. Taylor M, Mealing S, Scott D, et al. A UK based cost-effectiveness analysis of dasatinib (sprycel) 100mg daily compared to imatinib (glivec) 600/800mg daily as therapy for imatinib failing chronic myeloid leukemia (CML). Value in Health Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012;15.
119. Valencia Zapata JE, Orozco GJJ, Ribon GG, et al. Economic evaluation of dasatinib for the treatment of chronic myelogenous leukaemia in patients resistant to imatinib in colombia and venezuela. Value in Health Conference: 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2010;13.
120. Warren E, Ward S, Gordois A, et al. Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. Clinical Therapeutics 2004;26:1924-1933.

121. Taylor M, Lewis L, Lebmeier M, et al. An economic evaluation of dasatinib for the treatment of imatinib resistant patients with advanced phase chronic myelogenous leukaemia. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2011;14:A167.
122. Taylor M, Lewis L, Lebmeier M, et al. An economic evaluation of dasatinib for the treatment of imatinib reistant patients with chronic myelogenous leukaemia. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2011;14:A166-A167.
123. Darba J, Kaskens L. Cost-effectiveness analysis of dasatinib versus high-dose imatinib in the treatment of chronic myeloid leukemia in patients resistant to standard doses of imatinib. Pharmacoeconomics Spanish Research Articles 2012;9:63-71.
124. Szabo SM, Levy AR, Davis C, et al. A multinational study of health state preference values associated with chronic myelogenous leukemia. Value Health 2010;13:103-11.
125. Szabo SM, Davis C, Sidhu S, et al. Characterizing resource use and treatment costs for chronic myelogenous leukemia (CML) in the UK (UK). Value in Health Conference: ISPOR 12th Annual European Congress Paris France Conference Start 2009;12.
126. Curtis L. Unit Costs of Health and Social Care 2009, PSSRU, http://www.pssru.ac.uk/archive/pdf/uc/uc2009/uc2009.pdf. 2009.
127. Institute NC. Common Terminolgy Criteria for Adverse Events v3.0 (CTCAE). August 2006.
128. Pastore D, Specchia G, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed acute myeloid leukemia: single-center experience. Ann Hematol 2003;82:231-5.
129. Mean patient weight - Health Survey for England 2011 Adult Trend Tables. http://www.ic.nhs.uk/article/2021/Website-Search?productid=10152&q=health+survey+for+england&sort=Relevance&size=10&page=1&area=both#top. 2011.
130. Sacco JJ, Botten J, Macbeth F, et al. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One 2010;5:e8933.
131. Steinmetz HT, Schulz A, Staib P, et al. Phase-II trial of idarubicin, fludarabine, cytosine arabinoside, and filgrastim (Ida-FLAG) for treatment of refractory, relapsed, and secondary AML. Ann Hematol 1999;78:418-25.
132. Prescription Cost Analysis for England 2011. Health and Social Care Information Centre PaPCS.
133. Joint Formulary Committee, British National Formulary (online) London: BMJ Grop and Pharmaeutical Press. 2012.
134. NHS National Schedule of Reference Costs 2011-2012.

10 Appendices

10.1 Appendix 1

10.1.1 **SPC/IFU, scientific discussion or drafts.**

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

10.2.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following electronic databases were searched:

- Medline (R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE (R) 1946 to present (via OVID)
- EMBASE, 1980 to present (via OVID)
- The Cochrane Library (via OVID), searching the following databases:
    - The Cochrane Central Register of Controlled Trials (CENTRAL)
    - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
    - The Database of Abstracts of Reviews of Effects (DARE)
    - The Health Technology Assessment Database (HTA)

In addition, the following conference proceedings were searched (2010-2012):

- American Society of Haematology (ASH)
- American Society of Clinical Oncology (ASCO)
- European Haematology Association (EHA)

10.2.2 **The date on which the search was conducted.**

All databases were accessed on 21st January, 2013.

10.2.3 **The date span of the search.**

The searches spanned the following dates:

- Embase was searched from 1974 to January 18th 2013
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid Medline(R) were searched from 1946 to Present (accessed January 21st 2013)
- Cochrane Central Register of Controlled Trials December 2012
- Cochrane Database of Systematic Reviews 2005 to December 2012
- EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2012,
- Health Technology Assessment 4th Quarter 2012
- NHS Economic Evaluation Database 4th Quarter 2012

10.2.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH)**

and the relationship between the search terms (for example, Boolean).

The search strings used for each electronic database are detailed in the tables below.

Embase 1974 to January 18th 2013: accessed January 21st 2013

# ▲	Searches	Results
1	exp chronic myeloid leukemia/	28150
2	exp myeloid leukemia/	94931
3	chronic.mp. or exp CHRONIC DISEASE/	1137090
4	2 and 3	37637
5	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	36017
6	1 or 4 or 5	40870
7	imatinib.mp. or exp IMATINIB/	25210
8	(gleevec or glivec).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	7043
9	(STI-571 or STI571 or CGP-57148B or CGP57148B).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3450
10	imatinib mes?late.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3959
11	7 or 8 or 9 or 10	25381
12	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1825148
13	11 and 12	8632
14	((second or third or fourth) adj2 line).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18247
15	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20661
16	exp hydroxycarbamide/	18838
17	exp stem cell transplantation/	73805

18	(HSCT or SCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	16373
19	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	80164
20	(best adj2 support*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2980
21	BSC.mp.	1903
22	exp alpha interferon/	42290
23	("roferon-a" or "intron-a").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4127
24	(interferon adj2 alpha).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	58762
25	exp bosutinib/	768
26	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	785
27	13 or 14	26479
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	164462
29	exp Meta Analysis/	68526
30	((meta adj analy$) or metaanalys$).tw.	64279
31	(systematic adj (review$1 or overview$1)).tw.	49775
32	or/29-31	126912
33	cancerlit.ab.	667
34	cochrane.ab.	29194
35	embase.ab.	26182
36	(psychlit or psyclit).ab.	960
37	(psychinfo or psycinfo).ab.	6477
38	(cinahl or cinhal).ab.	8859
39	science citation index.ab.	1924
40	bids.ab.	426

41	or/33-40	44645
42	reference lists.ab.	8707
43	bibliograph$.ab.	13958
44	hand-search$.ab.	4023
45	manual search$.ab.	2311
46	relevant journals.ab.	733
47	or/42-46	26833
48	data extraction.ab.	10705
49	selection criteria.ab.	19538
50	48 or 49	28886
51	review.pt.	1927821
52	50 and 51	17160
53	letter.pt.	810639
54	editorial.pt.	423694
55	animal/	1814965
56	human/	14033665
57	55 not (55 and 56)	1358614
58	or/53-54,57	2579283
59	32 or 41 or 47 or 52	158341
60	59 not 58	152465
61	Clinical trial/	880466
62	Randomized controlled trial/	338298
63	Randomization/	60597
64	Single blind procedure/	16904
65	Double blind procedure/	115252
66	Crossover procedure/	36027
67	Placebo/	224651
68	Randomi?ed controlled trial$.tw.	83038
69	Rct.tw.	10825

70	Random allocation.tw.	1244
71	Randomly allocated.tw.	18468
72	Allocated randomly.tw.	1879
73	(allocated adj2 random).tw.	797
74	Single blind$.tw.	13248
75	Double blind$.tw.	140106
76	((treble or triple) adj blind$).tw.	322
77	Placebo$.tw.	189572
78	Prospective study/	223692
79	or/61-78	1323025
80	Case study/	18387
81	Case report.tw.	246829
82	Abstract report/ or letter/	874710
83	or/80-82	1135017
84	79 not 83	1286701
85	Clinical study/	89188
86	Case control study/	73451
87	Family study/	9857
88	Longitudinal study/	57858
89	Retrospective study/	305071
90	Prospective study/	223692
91	Randomized controlled trials/	25395
92	90 not 91	222997
93	Cohort analysis/	138791
94	(Cohort adj (study or studies)).mp.	93662
95	(Case control adj (study or studies)).tw.	66302
96	(follow up adj (study or studies)).tw.	43659
97	(observational adj (study or studies)).tw.	50576
98	(epidemiologic$ adj (study or studies)).tw.	70019

99	(cross sectional adj (study or studies)).tw.	68258
100	or/85-89,92-99	1060706
101	60 or 84 or 100	2135162
102	6 and 27 and 28 and 101	634

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed January 21st 2013

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	14336
2	exp Leukemia, Myeloid/	73716
3	exp Chronic Disease/ or chronic.mp.	866224
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	22855
5	2 and 3	21552
6	1 or 4 or 5	26689
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9340
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1329087
9	7 and 8	3386
10	((second or third or fourth) adj2 line).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	12295
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9716
12	exp Hydroxycarbamide/	6966
13	exp Hematopoietic Stem Cell Transplantation/	24548

14	(HSCT or SCT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9314
15	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	52708
16	("roferon-a" or "intron-a").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	602
17	(interferon adj2 alpha).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	34862
18	exp Interferon-alpha/	22848
19	(best adj2 support*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1940
20	BSC.mp.	1393
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	159
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	101858
23	9 or 10	15527
24	Randomized controlled trials as Topic/	82308
25	Randomized controlled trial/	337940
26	Random allocation/	75868
27	Double blind method/	117051
28	Single blind method/	16860
29	Clinical trial/	472870
30	exp Clinical Trials as Topic/	259509
31	or/24-30	838537
32	(clinic$ adj trial$1).tw.	186641
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	118891
34	Placebos/	31156
35	Placebo$.tw.	144503

36	Randomly allocated.tw.	14961
37	(allocated adj2 random).tw.	690
38	or/32-37	374411
39	31 or 38	967127
40	Case report.tw.	185707
41	Letter/	775875
42	Historical article/	288376
43	Review of reported cases.pt.	0
44	Review, multicase.pt.	0
45	or/40-44	1239238
46	39 not 45	940466
47	Epidemiologic studies/	5506
48	exp case control studies/	577770
49	exp cohort studies/	1213923
50	Case control.tw.	66232
51	(cohort adj (study or studies)).tw.	68832
52	Cohort analy$.tw.	3047
53	(Follow up adj (study or studies)).tw.	34614
54	(observational adj (study or studies)).tw.	35931
55	Longitudinal.tw.	121664
56	Retrospective.tw.	236529
57	Cross sectional.tw.	139952
58	Cross-sectional studies/	148552
59	or/47-58	1671329
60	Meta-Analysis as Topic/	12349
61	meta analy$.tw.	47037
62	metaanaly$.tw.	1193
63	Meta-Analysis/	36590
64	(systematic adj (review$1 or overview$1)).tw.	39507

65	exp Review Literature as Topic/	6473
66	or/60-65	95085
67	cochrane.ab.	22972
68	embase.ab.	20860
69	(psychlit or psyclit).ab.	844
70	(psychinfo or psycinfo).ab.	8116
71	(cinahl or cinhal).ab.	7677
72	science citation index.ab.	1607
73	bids.ab.	331
74	cancerlit.ab.	546
75	or/67-74	38173
76	reference list$.ab.	7893
77	bibliograph$.ab.	10357
78	hand-search$.ab.	3325
79	relevant journals.ab.	572
80	manual search$.ab.	1965
81	or/76-80	21577
82	selection criteria.ab.	16585
83	data extraction.ab.	8165
84	82 or 83	23449
85	Review/	1735402
86	84 and 85	15340
87	Comment/	518398
88	Letter/	775875
89	Editorial/	318524
90	animal/	4993336
91	human/	12521330
92	90 not (90 and 91)	3656512
93	or/87-89,92	4819761

94	66 or 75 or 81 or 86	121442
95	94 not 93	113116
96	46 or 59 or 95	2475570
97	6 and 22 and 23 and 96	198

EBM Reviews - Cochrane Central Register of Controlled Trials December 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2012, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2012, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2012: accessed January 21st 2012

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ ?	243
2	exp Leukemia, Myeloid/ ?	1243
3	exp Chronic Disease/ or chronic.mp. ?	55159
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	663
5	2 and 3 ?	322
6	1 or 4 or 5 ?	711
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	398
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	66651
9	7 and 8 ?	119
10	((second or third or fourth) adj2 line).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	1784
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	602

12	exp Hydroxycarbamide/ ?	289
13	exp Hematopoietic Stem Cell Transplantation/ ?	779
14	(HSCT or SCT).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	538
15	(stem adj2 cell adj2 transplant*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	2329
16	("roferon-a" or "intron-a").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	258
17	(interferon adj2 alpha).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	4044
18	exp Interferon-alpha/ ?	2264
19	(best adj2 support*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	437
20	BSC.mp. ?	175
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	3
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ?	7700
23	9 or 10 ?	1896
24	6 and 22 and 23 ?	26

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches were conducted

10.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria are detailed in Section

Table B1

10.2.7 **The data abstraction strategy.**

Results from database searches were downloaded into a bespoke Access® database, which was used to manage citation screening. Following full-text review and identification of studies to be included, data was extracted into a Data Extraction Table (DET). The DET included, but was not limited to, the following column headings:

- Country
- Study design
- Number of patients
- Key inclusion and exclusion criteria including subgroups
- Baseline characteristics
- Outcomes reported as summarised on page 6
- Likelihood of bias (quality components)

This data extraction was performed by one reviewer and verified by a second party.

Table B81: Chambers criteria for quality assessment of non-RCTs

Criteria used for quality assessment
1 Were selection/eligibility criteria adequately reported?
2 Was the selected population representative of that seen in normal practice?
3 Was an appropriate measure of variability reported?
4 Was loss to follow-up reported or explained?
5 Were at least 90% of those included at baseline followed-up?
6 Were patients recruited prospectively?
7 Were patients recruited consecutively?
8 Did the study report relevant prognostic factors?

Using the above criteria, a study's quality could be scored as good, satisfactory or poor; good, if the answer is 'yes' to all of criteria 1 to 8; satisfactory, if the answer is 'yes' to criteria 2 and 4-7; poor, if the answer is not 'yes' to one or more of the criteria listed for 'satisfactory'.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 **A suggested format for the quality assessment of RCT(s) is shown below.**

No RCTs evaluating the intervention (bosutinib) were identified by the systematic review and hence Appendix 10.3 is not relevant to this submission

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

All studies identified in the systematic review were of an uncontrolled, single-arm design, therefore no indirect comparison or network meta-analysis was possible since there is no connected network with one or more common comparator(s). Appendix 10.4 is therefore not relevant to this submission.

10.4.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

N/A

10.4.2 **The date on which the search was conducted.**

N/A

10.4.3 **The date span of the search.**

N/A

10.4.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

N/A

10.4.5 **Details of any additional searches (for example, searches of company databases [include a description of each database]).**

N/A

10.4.6 **The inclusion and exclusion criteria.**

N/A

10.4.7 **The data abstraction strategy.**

N/A

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 **A suggested format for the quality assessment of RCT(s) is shown below.**

No comparator RCTs were identified by the systematic review and hence Appendix 5 is not relevant to this submission.

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

See Appendix 10.2

10.6.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

N/A

10.6.2 **The date on which the search was conducted.**

N/A

10.6.3 **The date span of the search.**

N/A

10.6.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

N/A

10.6.5 **Details of any additional searches (for example, searches of company databases [include a description of each database]).**

N/A

10.6.6 **The inclusion and exclusion criteria.**

N/A

10.6.7 **The data abstraction strategy.**

N/A

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 **Please tabulate the quality assessment of each of the non-RCTs identified.**

The quality assessment of non-RCTs was performed according to the Chambers et al, 2009 criteria. These criteria are detailed in Table B82.

Table B82: Chambers criteria for quality assessment of non-RCTs

Criteria used for quality assessment
1 Were selection/eligibility criteria adequately reported?
2 Was the selected population representative of that seen in normal practice?
3 Was an appropriate measure of variability reported?
4 Was loss to follow-up reported or explained?
5 Were at least 90% of those included at baseline followed-up?
6 Were patients recruited prospectively?
7 Were patients recruited consecutively?
8 Did the study report relevant prognostic factors?

Using the above criteria, a study's quality could be scored as good, satisfactory or poor; good, if the answer is 'yes' to all of criteria 1 to 8; satisfactory, if the answer is 'yes' to criteria 2 and 4-7; poor, if the answer is not 'yes' to one or more of the criteria listed for 'satisfactory'.

The results of the quality assessment of non-RCTs identified by the systematic review and the Study 200 CSR are detailed in Table B83.

Table B83: Quality assessment of non-RCTs identified by the systematic review and Study 200

Study	Eligibility criteria adequately reported?	Study population representative of a normal population?	An appropriate measure of variability reported?	Loss to follow-up reported or explained?	At least 90% included at baseline followed-up?	Were patients recruited prospectively?	Were patients recruited consecutively?	Did the study report relevant prognostic factors?	Quality score
Bosutinib studies									
Bosutinib, advanced disease study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 2nd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 3rd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Comparator studies									
Benedicte 2010	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor
Bornhäuser 2006	Yes	No[†]	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Holroyd 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ibrahim 2011	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor
Jabbour 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jabbour 2007[73]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jabbour 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kantarjian 2007	Yes	Yes	Yes	Yes	No[‡]	No	Yes	Yes	Poor
Markiewicz 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Oehler 2007	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor
Saussele 2010	Yes	Yes	Yes	Yes	Yes[§]	Yes	Yes	Yes	Good
Schleuning 2010	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor
Weisser 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

[†]>50% of patients (n=32) were at high risk for transplant-related deaths (Gratwold scores of 5–7)

[‡]Of the 574 patients analysed, the outcome of 127 could not be retrieved in detail in relation to subsequent therapies or survival. The next analysis concentrated only on patients in whom imatinib therapy was discontinued for either clear cut resistance or recurrence (n=374) or for imatinib toxicities (n=46).

[§]Follow-up was reported in the 84 patients who underwent transplantation.

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

See Appendix 10.2

10.8.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

N/A

10.8.2 **The date on which the search was conducted.**

N/A

10.8.3 **The date span of the search.**

N/A

10.8.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

N/A

10.8.5 **Details of any additional searches (for example, searches of company databases [include a description of each database]).**

N/A

10.8.6 **The inclusion and exclusion criteria.**

N/A

10.8.7 **The data abstraction strategy.**

N/A

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

See Appendix 10.7

10.9.1 **Please tabulate the quality assessment of each of the non-RCTs identified.**

N/A

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

10.10.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The databases searched were as follows:

- Medline (OVID Interface)
- Embase (OVID Interface)
- Medline In-Process (OVID Interface)
- EconLIT (OVID Interace)
- NHS EED (Searched via the Cochrane Library and also via Centre for Reviews and Dissemination)
- Cochrane Library

10.10.2 **The date on which the search was conducted.**

The search was conducted on 02/10/12

10.10.3 **The date span of the search.**

The search date span was from database inception to 02/10/12

10.10.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

Ovid Interface

1. “myeloid* leukemia*”[tw]
2. “myeloid* leukaemia*”[tw]
3. Leukemia, Myeloid[MeSH:NoExp]
4. CML[tw]
5. leukemia, myeloid, chronic-phase[MeSH:NoExp]
6. leukemia, myeloid, chronic, atypical, bcr-abl negative[MeSH:NoExp]
7. leukemia, myelogenous, chronic, bcr-abl positive[MeSH]
8. “myelogenous* leukemia*”[tw]
9. “myelogenous* leukaemia*”[tw]
10. “myelocytic* leukemia*”[tw]
11. “myelocytic* leukaemia*”[tw]
12. leukemia, myelomonocytic, chronic[MeSH:NoExp]
13. “major cytogenetic response”[tw]
14. “major molecular response”[tw]
15. Or/1- 14
16. Philadelphia Chromosome[MeSH:NoExp]
17. Philadelphia[tw] AND Chromosome[tw]
18. (PH1[tw] OR “PH 1”[tw]) AND Chromosome[tw]
19. Or/16-18
20. 15 OR 19
21. costs and cost analysis[MesH] OR health care costs[MeSH]

22. economics[MeSH]
23. value of life[MeSH]
24. burden[tw] AND (disease[tw] OR illness[tw])
25. economic*[tw] OR expenditure*[tw] OR price*[tw] OR pricing[tw] OR pharmacoeconomic*[tw]
26. budget*[tw] OR fiscal[tw] OR funding[tw] OR financial[tw] OR finance*[tw]
27. resource[tw] AND (allocation*[tw] OR utili*[tw] OR use[tw])
28. Socioeconomic factors[MeSH:NoExp]
29. Cost-benefit analysis[MeSH]
30. Health expenditures[MeSH:NoExp]
31. Capital expenditures[MeSH:NoExp]
32. Financial management, hospital[MeSH:NoExp]
33. cost[tw] AND (estimat*[tw] OR variable*[tw] OR unit[tw])
34. Models, statistical[MeSH]
35. decision trees[MeSH]
36. decision making, computer assisted[MeSH]
37. theoretical model[MeSH]
38. markov chains[MeSH:NoExp]
39. Monte Carlo Method[MeSH:NoExp]
40. Decision Theory[MeSH]
41. (healthcare[tw] OR health-care[tw]) AND cost*[tw]
42. Computer simulation[MeSH]
43. Models, Theoretical[MeSH]
44. Patient Simulation[MeSH]
45. pharmacoeconomic*[tw] OR pharmaco-economic*[tw]
46. “cost* effective*”[tw] or “cost* utilit*” or “cost* benefit*”[tw] or “cost* minimi*”[tw] or CEA[tw] or CUA[tw] or CMA[tw]
47. “incremental cost effectiveness ratio*”[tw] OR icer*[tw]
48. “decision* tree*”[tw] OR “decision* analy*”[tw] OR “decision* model*”[tw] OR “markov model*”[tw]
49. “Quality-Adjusted Life Years”[MeSH]
50. “Quality-adjusted life year*”[tw] OR QALY*[tw]
51. OR/21-50
52. 20 AND 51

Cochrane library

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. Philadelphia Chromosome
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. MeSH descriptor **Leukemia, Myeloid**, this term only
13. MeSH descriptor **leukemia, myeloid, chronic-phase**, this term only
14. MeSH descriptor **leukemia, myeloid, chronic, atypical, bcr-abl negative**, this term only
15. MeSH descriptor **leukemia, myelogenous, chronic, bcr-abl positive**, explode all trees
16. MeSH descriptor **leukemia, myelomonocytic, chronic**, this term only
17. MeSH descriptor **Philadelphia Chromosome**, this term only
18. #12 OR #13 OR #14 OR #15 OR #16 OR #17

19. #11 OR #18
20. MeSH descriptor **costs and cost analysis**, explode all trees
21. MeSH descriptor **health care costs**, explode all trees
22. MeSH descriptor **economics**, explode all trees
23. MeSH descriptor **value of life**, explode all tree
24. Burden of disease* OR disease burden OR burden of illness
25. Cost* OR economic* OR expenditure* OR price* OR pricing OR pharmacoeconomic*
26. Budget* OR fiscal OR funding OR financial OR finance*
27. Resource allocation OR resource use OR resource utili*
28. MeSH descriptor **financial management, hospital,** this term only
29. MeSH descriptor **cost of illness**, this term only
30. MeSH descriptor **employer health costs**, this term only
31. MeSH descriptor **health expenditures**, this term only
32. MeSH descriptor **capital expenditures**, this term only
33. Low cost* OR high cost*
34. Healthcare cost* OR health care cost*
35. Cost estimat*
36. Cost variable
37. Unit cost*
38. Cost* effective* OR cost* utility* OR cost* benefit* OR cost* minimi* OR CEA OR CUA OR CMA
39. MeSH descriptor **models, statistical**, explode all trees
40. MeSH descriptor **computer simulation**, explode all trees
41. MeSH descriptor **models, theoretical**, explode all trees
42. #39 OR #40 OR #41
43. MeSH descriptor **patient simulation**, explode all trees
44. MeSH descriptor **decision trees**, explode all trees
45. Incremental cost effectiveness ratio* or icer*
46. MeSH descriptor **Monte Carlo Method**, this term only
47. MeSH descriptor **Decision Theory**, explode all trees
48. Decision* tree* or decision* analy* or decision* model* or markov model*
49. MeSH descriptor exp **Quality-Adjusted Life Years**, explode all trees
50. Quality-adjusted life year* or QALY*
51. #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50
52. #19 AND #51

NHS EED, via CRD

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. Philadelphia Chromosome
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

Search results were also filtered by the following terms:

- Dasatinib *or* BMS-354825 *or* Sprycel®
- Nilotinib *or* AMN107 *or* Tasigna®
- Imatinib *or* imatinib mesilate or STI571 *or* Gleevec® *or* Glivec®

- Bosuntinib *or* SKI-606 *or* Bosulif®
- Stem-cell *or* stem cell
- Hydroxycarbamide *or* hydrocarbamide *or* Droxia® *or* Hydrea®
- Interferon *or* IFN *or* Roferon®
- Standard of care *or* standard care *or* placebo *or* supportive care

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Horizon scans for relevant articles were performed using the Google search engine using the key words: CML, chronic myeloid leukaemia, combined with cost-effectiveness, cost-utility, model.

ISPOR, ASCO, ESMA, ICLLM and ASH congress abstracts/posters were also searched for any relevant articles not picked up by the search in 10.10.4. NICE HTAs were also searched.

10.11 Appendix 11: Quality assessment and extracted results of cost-effectiveness studies (Section 7.1)

Cost-effectiveness studies in refractory CML for interventions other than bosutinib

One article, Loveman et al. (2012)[85], was an update of Rogers et al. 2012[84], which was also captured. This contained data from 4 studies/models: Ghatnekar et al. (2010)[107], the BMS model, the Novartis Model, and the PenTAG model (from Rogers et al. (2012)[84]). Extraction grids were therefore provided for each of these 4 sources.

Table B84: Summary List of Other Cost-Effectiveness Evaluations

Study information	
Study Title	Cost-utility analysis of dasatinib in patients with imatinib-resistant chronic myeloid leukemia (CML) on chronic (CP), accelerated (AP) and blast (BP) phases in Brazil
First author	E. Asano[108]
Date of study	2009
Country(ies) where study was performed	Brazil
Funding source	Not stated, however authors are from BMS and National Institute of Cancer, Brazil
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the value of dasatinib vs imatinib >400 mg for treatment of imatinib-resistant CML patients
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	NR
Interventions assessed (including dose)	For chronic phase: Dasatinib 100 mg Imatinib 600 mg For accelerated phase and blast phase:

	Dasatinib 140 mg Imatinib 800 mg
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	5.0% annual discount for both costs and effects
Time horizon	Lifetime horizon
Perspective	Brazilian Health Care System (SUS)
Source(s) of effectiveness data	Best treatment response rates taken from dasatinib clinical trials.
Source(s) of utility data	Estimated from published literature.
Source(s) of cost data	Drug costs were obtained according to official prices and standard government discounting procedures. Since nilotinib does not have a published price in Brazil, the lowest international price found on the internet was used. Resource utilisation was based on clinical survey.
Were indirect costs included?	Not clear
Main assumptions used in model	NR
Relevance of study to England and Wales	NR
Patient population	
Disease description (eg. stage)	All CML phases – separate evaluations for CP, AP and BP
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	NR
Costs (currency and base year)	NR
Base case cost results (intervention and comparator)	NR
Base case ICER (per QALY gained)	For dasatinib compared to imatinib: CP: dasatinib dominant vs both imatinib >400 mg and nilotinib AP: approx. 52,000/QALY (Brazilian currency) BP: approx. 51,000/QALY (Brazilian currency)
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Deterministic and probabilistic

Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	'Robustness was assessed' – outcomes not stated beyond 'pharmaceutical costs are the most important driver of the result'
Brief summary of author's conclusions	Compared to imatinib >400 mg and nilotinib, dasatinib is associated with increased QALYs in all phases and lower overall costs in CP. So dasatinib is the dominant strategy for the treatment of chronic phase CML patients resistant to imatinib, and since clinical outcomes for imatinib 800 mg for advanced phases are unsatisfactory, dasatinib 140 mg is a reasonable option for imatinib-resistant CML patients in accelerated and blast phases.
Study information	
Study Title	Application of cost-effectiveness analysis to demonstrate the potential value of companion diagnostics in chronic myeloid leukemia
First author	J. Gaultney[109]
Date of study	March 2011
Country(ies) where study was performed	Netherlands
Funding source	PamGene
Summary of model	
What are the stated objectives of the evaluation?	To assess the potential value of companion diagnostics in supporting treatment decisions for dasatinib and nilotinib in chronic myeloid leukaemia. This was carried out by assessing the potential cost savings and health gains of treating according to the results of a companion diagnostic in CML.
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness analysis
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Decision tree model
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase resistant CML -> 1. response testing with companion diagnostic/ 2. no testing: dasatinib for all with further branches for each: 1. – optimal response with dasatinib - Optimal response with nilotinib - Respond to both dasatinib and nilotinib - Respond to neither 2. – reponse to dasatinib - No response to dasatinib (administer nilotinib as third line treatment) Each broken down further into disease progression/ no progression etc.
Interventions assessed (including dose)	Second-line treatment with dasatinib during the first year, and a switch to nilotinib during the second year if failing to respond. Or: companion diagnostic strategy, whereby

	treatment decisions were made on the basis of the patient's response profile as depicted by biomarker-based testing. Four categories: optimal responder to dasatinib, optimal responder to nilotinib, optimal responder to both (treated with dasatinib), and optimal responder to neither (alternative treatments in CML, such as allogeneic stem cell transplant if eligible and/or IFNa plus low dose arabinosylcytosine)
Was a no-treatment/supportive care strategy included?	No – but as this study is regarding the effectiveness of a companion diagnostic strategy there is a no-testing strategy: based on treatment recommendations for the target patient population as described by the Dutch handbook for treatment of haematological disorders.
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	Costs: 4% Effects: 1.5%
Time horizon	2 year
Perspective	Healthcare sector of the Netherlands
Source(s) of effectiveness data	Clinical trial results were used to estimate the proportion of patients who will and will not respond to dasatinib and nilotinib. Sources: Kantarjuan et al 2007, Giles et al 2006, Quintas-Carmadas et al 2007 Progression-free life years were calculated using progression-free survival estimates from the literature
Source(s) of utility data	From literature: Reed et al, 2003
Source(s) of cost data	Medical costs amassed by the hospital and/or healthcare insurer relevant to the comparator strategies were identified and valued. Unit costs for dasatinib and nilotinib were taken from the Dutch Healthcare Insurance Board of the Netherlands. The cost of SCT and FISH testing were taken from the Dutch Healthcare Authority. The costs of the companion diagnostic were assumed to be €3026 based on the cost estimate for a companion diagnostic for breast cancer. Costs of adverse events were not included in the study since the safety profiles of the drugs do not generally differ. Unit prices were taken from the year 2008 and inflated to represent the cost in the year 2009.
Were indirect costs included?	None reported
Main assumptions used in model	Assumed that in no-testing strategy patient population was treated as described in the Dutch handbook for treatment of haematological disorders ie dasatinib first

	administered to imatinib-resistant patients, followed by treatment with nilotinib if no response to dasatinib. Assumed that the performance of the test achieved a sensitivity and specificity approximating 100%. Cost of companion diagnostic assumed to be €3026 based on the cost estimate for a companion diagnostic for breast cancer.
Relevance of study to England and Wales	NR
Patient population	
Disease description (eg. Stage)	Chronic phase CML patients eligible for second-line therapy with TKIs, who failed to respond to high-dose imatinib, and who lacked the T315I mutation.
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	Lacking T315I mutation
Results	
Effectiveness measure (eg. QALY)	QALYs and PFLYs
Base case effectiveness results (intervention and comparator)	Companion diagnostic strategy: - 1.63 QALYs or 1.84 PFLYs No testing strategy: - 1.61 QALYs or 1.74 PFLYs
Costs (currency and base year)	€ Unit prices were taken from the year 2008 and inflated to represent the cost in the year 2009
Base case cost results (intervention and comparator)	Companion diagnostic strategy: - €89,000 No testing strategy: - €101,500
Base case ICER (per QALY gained)	Companion diagnostic strategy is 'dominant'
Types and description of sensitivity analysis performed (eg. One-way sensitivity analysis, probabilistic sensitivity analysis)	Time-to-progression Comparative effectiveness
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	No differences unless time-to-progression was changed from 6 months (base case) to 11 months for both responders and non-responders, resulting in very high ICERs ($128,474/496,038)
Brief summary of author's conclusions	A companion diagnostic strategy in CML offers the potential to improve both the effectiveness and costs of second-line treatment at a time horizon of 2 years. Patients are treated with the most effective TKI or diverted to more effective alternative treatments at an earlier moment in treatment than currently implemented in usual care.
Study information	
Study Title	Cost-effectiveness of dasatinib versus high-dose imatinib in patients with Chronic Myeloid

	Leukemia (CML), resistant to standard dose imatinib a Swedish model application
First author	O. Ghatnekar[107]
Date of study	2010
Country(ies) where study was performed	Sweden
Funding source	BMS
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the cost-effectiveness of dasatinib treatment vs high-dose imatinib (800 mg) in CP-CML patients resistant to standard dose imatinib in Sweden.
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Four health states: CP, AP, BP, death
Interventions assessed (including dose)	Dasatinib 140 mg/day Imatinib 800 mg/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3% for both
Time horizon	Lifetime
Perspective	Societal
Source(s) of effectiveness data	Clinical trials: response to treatment data from Kantarjian et al, 2003. Progression data taken from: Aoki et al 2005, Kantarjian et al, 2002, Holowiecki et al, 2006, Silver et al, 2004
Source(s) of utility data	Quality of life data: published sources Utility weights for each health state were elicited with a time-trade-off (TTO) technique using the EQ-5D instrument among 100 lay persons in the UK. In sensitivity analysis utility weights provided for a NICE appraisal of imatinib were used.
Source(s) of cost data	Resource utilisation: expert opinion (two Swedish clinical haematologists at the same facility) Unit prices: official price lists
Were indirect costs included?	Yes - production loss estimated using average monthly salaries
Main assumptions used in model	All patients assumed to start treatment in CP Assumed identical utilities for both study medications, which may not be the case given potential differences in for example adverse event profiles or maintenance of response Assumed 85% work force participation among CML patients

Relevance of study to England and Wales	Model based on Sweden but some relevance can be assumed
Patient population	
Disease description (eg. stage)	Chronic phase CML
Previous treatments	Imatinib
Average age in years	Starting age of 60
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALYs
Base case effectiveness results (intervention and comparator)	Dasatinib: 5.19 Imatinib: 4.57
Costs (currency and base year)	Euro, 2008
Base case cost results (intervention and comparator)	Total societal cost Dasatinib: €504,532 Imatinib: €500,281
Base case ICER (per QALY gained)	€6880 (including indirect costs) €7207 (direct costs only)
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Several one-way sensitivity analyses are performed (base case in parenthesis): 1. time horizon 10 years (lifetime), 2. discount rate 0% (3%), 3. inclusion of adverse event (AE) costs (not included), 4. patients intolerant to imatinib (patients resistant to imatinib), and 5. utility weights provided for a NICE appraisal of imatinib (TTO among CML-patients)
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Dasatinib generates more health in terms of QALYs, but it is uncertain whether this comes at an extra cost or if it generates cost savings. All observations fall below the derived willingness-to-pay for a QALY in Sweden.
Brief summary of author's conclusions	Dasatinib is a cost-effective treatment option compared to imatinib (800 mg/day) for CML patients resistant to standard dose imatinib in Sweden, as previously shown for Scotland, Austria and Spain using the same model.
Study information	
Study Title	Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia
First author	M. Hoyle[86]
Date of study	2011b
Country(ies) where study was performed	UK
Funding source	UK NHS HTA
Summary of model	
What are the stated objectives of the evaluation?	To estimate the cost-effectiveness of dasatinib and nilotinib compared with high-dose imatinib for people with chronic phase chronic myeloid leukemia, which are resistant to normal-dose imatinib and compared with

	interferon-α for people intolerant to imatinib, from the perspective of the UK National Health Service.
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Area under the curve partitioned survival Markov-type model
What are the main components of the model (e.g. health states within a Markov model)?	Five health states: - Chronic phase on second line treatment - Chronic phase on third line treatment - Accelerated phase - Blast crisis - Death Two separate models implemented: - One simulating a cohort of people *resistant* to normal-dose imatinib - One simulating people *intolerant* to imatinib *please note that third line treatments are only implicitly, not explicitly, modelled due to lack of data.
Interventions assessed (including dose)	Dasatinib: 100 mg once per day Nilotinib: 400 mg twice per day High-dose imatinib: 400 mg twice per day Interferon-α target dose: 5 million units per square meter body surface area per day. Cytarabine (used with interferon-α) – 20mg per square meter body per day for 10 days per month
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5% per year for both costs and benefits
Time horizon	44 year (until age 100)
Perspective	UK NHS
Source(s) of effectiveness data	Major cytogenic response rates: clinical trials identified by a systematic review Treatment duration: NICE submissions/clinical trial data
Source(s) of utility data	From literature review Used those collected during IRIS trial and used in a previous assessment of imatinib for CML
Source(s) of cost data	2nd line drug costs: British national formulary Medical management/3rd line drug costs: various sources including NHS trusts and PCTs combined, survey of UK clinicians by BMS
Were indirect costs included?	No
Main assumptions used in model	Male to female ratio 1:1

	People assumed to start second-line treatment aged 56 Assumed a constant hazard ratio between survival curves Utility values for people taking dasatinib and nilotinib in chronic phase are not cited in literature so these were set to values equal to the value for high-dose imatinib in chronic phase Assumptions for resource use were based on expert opinion The progression-free survival (PFS) curve for people who stopped treatment due to serious adverse events was assumed to follow the modelled overall PFS for interferon-α, where we assumed that interferon-α delays progression only slightly compared with no drug treatment. Assumed that patients would stop drug treatment mostly due to serious adverse events at 3 months. Time spend in accelerated phase and blast crisis were assumed independently of treatment arm. In the base case, the costs of treating adverse events, and the disutility associated with their incidence are not explicitly included, except via a lower utility while on treatment with interferon-α compared with the other drugs.
Relevance of study to England and Wales	Directly relevant
Patient population	
Disease description (eg. stage)	Patients starting second-line treatment in *chronic phase* CML who are either resistant or intolerant to normal-dose imatinib
Previous treatments	Normal-dose imatinib
Average age in years	Assumed to start at age 56
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	*Imatinib resistant:* total QALYs (mean, discounted): Dasatinib: 7.846 Nilotinib: 7.63 High-dose imatinib: 7.311 *Imatinib intolerant:* total QALYs (mean, discounted): Dasatinib: 8.463 Nilotinib: 7.406 Interferon-α: 6.229
Base case effectiveness results (intervention and comparator)	*Imatinib resistant:* Nilotinib dominates high-dose imatinib; nilotinib is expected to yield 0.32 more quality-adjusted life years (QALYs) at £11,100 (pound sterling) less per patient.

	Dasatinib is predicted to provide 0.53 more QALYs than high-dose imatinib at substantially greater cost (£48,900), yielding a very high incremental cost-effectiveness ratio (ICER) of £91,500 QALY. Dasatinib is predicted to provide 0.22 more QALYs than nilotinib at substantially greater cost (£60,000), yielding a very high ICER of £277,700 QALY. *Imatinib intolerant:* Compared with interferon-α, nilotinib is expected to yield 1.2 more QALYs at £123,000 more per patient, yielding a very high ICER of £104,700 QALY Dasatinib is expected to yield 2.2 more QALYs at £185,000 more per patient, also yielding a very high ICER of £82,600 QALY Dasatinib is expected to yield 1.1 more QALYs than nilotinib at £61,300 more per patient, also yielding a high ICER of £58,000 QALY.
Costs (currency and base year)	£, mostly from 2009 inflated to 2010. One cost (single district nurse visit) from 2006/7 inflated to 2009/10.
Base case cost results (intervention and comparator)	*Imatinib resistant:* Nilotinib - £161,300 Dasatinib - £221,325 High-dose imatinib - £172,415 *Imatinib intolerant:* Nilotinib - £222,092 Dasatinib - £283,441 Interferon-α - £98,818
Base case ICER (per QALY gained)	*Imatinib resistant:* Nilotinib vs high-dose imatinib: dominates Dasatinib vs high-dose imatinib: £91,500 Dasatinib vs nilotinib: £277,700 *Imatinib intolerant:* Nilotinib vs interferon-α: £104,700 Dasatinib vs interferon-α: £82,600 Dasatinib vs nilotinib: £58,000
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way sensitivity analyses and probabilistic sensitivity analyses were performed by varying effectiveness, utility, and cost parameters.

Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	*Imatinib resistant:* One-way analysis: The ICER for dasatinib versus high-dose imatinib remains above £30,000 QALY in all but one sensitivity analysis. In particular, when PFS for dasatinib is set equal to that for nilotinib or high-dose imatinib, dasatinib then dominates high-dose imatinib. Probabilistic analysis: At a willingness-to-pay threshold of £30,000 QALY, nilotinib provides the best value for money in virtually all simulations. When PFS for nilotinib=dasatinib, high-dose imatinib is expected to provide best value for money for willingness-to-pay thresholds up to £100,000 QALY. *Imatinib intolerant:* One-way analysis: Although ICERs were sensitive to method of estimating inputs such as overall survival, hazard ratio and PFS curve, none of the parameter variations on their own resulted in drops below £48,000/QALY. Probabilistic analysis: In virtually all simulations both dasatinib and nilotinib incur greater lifetime costs and benefits than interferon-α
Brief summary of author's conclusions	Whilst clinical data remains immature, the cost-effectiveness of dasatinib and nilotinib for imatinib-resistant people is highly uncertain. Both nilotinib and dasatinib are highly unlikely to be cost-effective versus interferon-α for people intolerant to imatinib. We recommend that the structure of our model be re-used when higher quality data becomes available.
Study information	
Study Title	The cost and cost effectiveness of dasatinib (SPRYCEL) 100 MG therapy for the management of imatinib resistant and intolerant patients in chronic phase with chronic myeloid leukemia (CML) in Mexico
First author	A. Juarez-Garcia[110]
Date of study	2009
Country(ies) where study was performed	Mexico
Funding source	Authors from BMS
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the cost-effectiveness of dasatinib compared to nilotinib for the management of imatinib resistant patients with CML in the chronic phase
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision	Markov

tree, discrete event simulation, decision analytic model)	
What are the main components of the model (e.g. health states within a Markov model)?	Not stated – but CP, AP, BP included
Interventions assessed (including dose)	Dasatinib 100 mg Nilotinib 800 mg
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	Costs – 5%, no reported discount rate for effects
Time horizon	Lifetime
Perspective	Mexican healthcare perspective
Source(s) of effectiveness data	Initial best response: defined by the START studies. As researchers did not identify any clinical trials that compared dasatinib directly with the comparator, an indirect comparison was performed using all the relevant published efficacy literature Transition probabilities and QALYs were estimated from published international literature
Source(s) of utility data	QALYs were estimated using published international literature
Source(s) of cost data	Costs of drugs and other healthcare treatments were primarily obtained from IMSS published information
Were indirect costs included?	NR
Main assumptions used in model	NR
Relevance of study to England and Wales	Mexican study therefore not very relevant
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	Imatinib resistant
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib vs nilotinib Dasabinib more effective, QALY difference of 0.2
Costs (currency and base year)	US Dollars, year not stated
Base case cost results (intervention and comparator)	Dasatinib less costly than nilotinib -US$41,329 difference
Base case ICER (per QALY gained)	NR
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Deterministic sensitivity analysis

Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Robust
Brief summary of author's conclusions	In Mexico, dasatinib is a cost-effective therapy for the management of imatinib resistant patients with CML in the chronic phase.
Study information	
Study Title	Pharmacoeconomic evaluation of nilotinib in treating Taiwan patients with chronic myeloid leukemia (CML)
First author	B-S. Ko[111]
Date of study	September 2010
Country(ies) where study was performed	Taiwan
Funding source	Unclear
Summary of model	
What are the stated objectives of the evaluation?	To assess the lifetime clinical outcomes and economic impacts for high-dose imatinib (HDI) vs nilotinib for patients in chronic phase CML using a simulation model
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	6 health states: - Chronic phase patients initiating therapy - Chronic phase - Death (non-CML causes) - Advanced phase - Death (CML causes) - Blast crisis phase
Interventions assessed (including dose)	Imatinib 600 mg/day Imatinib 800 mg/day Nilotinib 400 mg/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	Tertiary medical centres which are the major haematology disease treatment centres in Taiwan
Discount rates (same for costs and effects?)	3.5% for both
Time horizon	Unclear – length of treatment? Mean of 250-978 days for different treatments
Perspective	Unclear
Source(s) of effectiveness data	For HDI: retrospective chart review of patients treated in two centres in Taiwan Nilotinib: a phase II study of imatinib-resistant CML patients
Source(s) of utility data	QALYs were generally assumed to be the same for nilotinib and HDI. Review of literature was undertaken for health utility

	values in Ph+ CML
Source(s) of cost data	Costs were taken from list of reimbursement rates of the Bureau of National Health Insurance (BNHI) in Taiwan
Were indirect costs included?	Unclear. Costs given are medication costs and costs of drug-related adverse events
Main assumptions used in model	Utility assumed to be the same for both HDI and nilotinib
Relevance of study to England and Wales	Unclear
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Resistance and/or intolerance to standard dose (400 mg/day) imatinib
Average age in years	HDI: 42.3 Nilotinib: 56.6
Other important population characteristics	Ph+ CML
Results	
Effectiveness measure (eg. QALY)	Base case discounted QALYs
Base case effectiveness results (intervention and comparator)	HDI: 7.47 years Nilotinib: 9.6 years
Costs (currency and base year)	N. T. Dollars; unclear which year
Base case cost results (intervention and comparator)	HDI: 8,734,055 Nilotinib: 11,417,691
Base case ICER (per QALY gained)	ICER not given Costs per QALY (NTD/year): HDI: 1,169,547 Nilotinib: 1,189,150
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	None given
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	NR
Brief summary of author's conclusions	Under the assumption of similar drug price for nilotinib and HDI, using this model is clear benefit for nilotinib as better clinical outcome achieved in terms of lower adverse event rate, better QALY, with acceptable economic impact. The decision to shift therapy from HDI to nilotinib in Ph+ CML-CP patients with resistance to standard dose imatinib is a reasonable option.
Study information	
Study Title	Cost-utility analysis of dasatinib as a second-line treatment in the chronic phase of chronic myeloid leukaemia in Russia
First author	L. Mungapen[112]
Date of study	2010
Country(ies) where study was	Russia

performed	
Funding source	BMS
Summary of model	
What are the stated objectives of the evaluation?	To estimate the ICER of dasatinib (100 mg/day) in chronic phase CML patients resistant to imatinib 400 mg compared with imatinib 800 mg and nilotinib 800 mg in the Russian setting
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Deterministic Markov model
What are the main components of the model (e.g. health states within a Markov model)?	CP, AP, BP, death
Interventions assessed (including dose)	Dasatinib 100 mg/day Imatinib 800 mg Nilotinib 800 mg
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	Not stated – but were applied as it was mentioned they were changed in sensitivity analyses
Time horizon	Lifetime
Perspective	NR
Source(s) of effectiveness data	Clinical inputs came from multicentric RCTs published in international reviews and including Russian CML patients
Source(s) of utility data	NR
Source(s) of cost data	Resource use data were obtained through interviews with local specialists in Russia conducted in three different regions. The model was adapted to the Russian setting in terms of unit costs (ie hospitalisation, costs of side effects, drug costs)
Were indirect costs included?	NR
Main assumptions used in model	Patient population characteristics are based on multicentric RCT publications. This model assumes that the trial population characteristics are equivalent in Russia.
Relevance of study to England and Wales	NR
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Imatinib
Average age in years	56
Other important population characteristics	50% male, 55 months since diagnosis
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results	*Dasatinib vs imatinib in CP imatinib resistant*

(intervention and comparator)	*patients only, response rates reported at 3 months in trials:* Dasatinib 100 mg: 4.81 Imatinib 800 mg: 4.63 Incremental: +0.17 *Dasatinib vs nilotinib in CP all patients, response rates reported at 24 months in trials:* Dasatinib 100 mg: 5.24 Nilotinib 800 mg: 5.02 Incremental: +0.22
Costs (currency and base year)	RUB, base year not stated – assume 2010?
Base case cost results (intervention and comparator)	*Dasatinib vs imatinib in CP imatinib resistant patients only, response rates reported at 3 months in trials:* Dasatinib 100 mg: 12,225,105 RUB Imatinib 800 mg: 13,589,325 RUB Incremental: -1,364,220 RUB *Dasatinib vs nilotinib in CP all patients, response rates reported at 24 months in trials:* Dasatinib 100 mg: 13,293,653 RUB Nilotinib 800 mg: 14,072,274 RUB Incremental: -1,339,200
Base case ICER (per QALY gained)	Dasatinib dominant compared to imatinib or nilotinib
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way sensitivity analyses
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Variations in starting age, discounting rates and time horizon did not impact on the overall conclusion, demonstrating the robustness of the model. Results are mostly sensitive to drug costs in the comparison with both nilotinib and imatinib in the chronic phase. Time horizon had an important impact in the chronic phase comparison with imatinib, with a shorter time horizon resulting in a lower ICER.
Brief summary of author's conclusions	Dasatinib was found to be a cost saving and effective strategy in second line chronic patients compared to high-dose imatinib or nilotinib. This is consistent with results from a cost per responder study on second line CML therapy in Russia.
Study information	
Study Title	Cost-effectiveness analysis of nilotinib versus dasatinib in patients with imatinib-resistant or imatinib-intolerant chronic myeloid leukemia (CML)
First author	X. Niu[113]
Date of study	2012
Country(ies) where study was	USA

performed	
Funding source	Not stated – authors from University of Southern California
Summary of model	
What are the stated objectives of the evaluation?	To compare the economic impact from a US societal perspective of nilotinib and dasatinib in second-line therapies in treatment of CML patients with imatinib resistance
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase, progressive phase, death
Interventions assessed (including dose)	Nilotinib 800 mg/day Dasatinib 100 mg/day (chronic phase) Dasatinib 140 mg/day (advanced phase)
Was a no-treatment/supportive care strategy included?	Yes
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	
Discount rates (same for costs and effects?)	Costs – 3% per year Not mentioned for effects
Time horizon	20 years
Perspective	US societal perspective
Source(s) of effectiveness data	Clinical efficacy evidence was obtained from a head-to-head comparative clinical trials of two agents and discounted into three month cycles
Source(s) of utility data	Obtained from a study using the time trade off (TTO) technique with an interview administered survey from a convenience sample in US laypersons
Source(s) of cost data	Obtained from published literature and government and organisation websites
Were indirect costs included?	Yes
Main assumptions used in model	Efficacy data used was based on a relatively short term follow-up clinical trial
Relevance of study to England and Wales	Mentions that results in terms of QALYs gained are slightly different from a recently published similar study from the perspective of the UK NHS (Hoyle et al, 2011b)[86]
Patient population	
Disease description (eg. stage)	All
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	20 years Nilotinib: 4.47

	Dasatinib: 3.83 Incremental: 0.64 10 years Nilotinib: 3.97 Dasatinib: 3.50 Incremental: 0.47
Costs (currency and base year)	US $ in 2011
Base case cost results (intervention and comparator)	Per 3 months Chronic phase: Nilotinib: $2,870 Dasatinib: $21,596 Progressive phase: Nilotinib: $34,467 Dasatinib: $33,050 Best supportive care: $37,022 Overall Results 20 years Nilotinib: $156,085 Dasatinib: $126,926 Incremental: $45,682 10 years Nilotinib: $138,523 Dasatinib: $114,762 Incremental: $23,761
Base case ICER (per QALY gained)	ICER for nilotinib vs dasatinib = $45,682
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way sensitivity analyses
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Parameters are relatively insensitive to the changes in efficacy, unit price, dose and utility value
Brief summary of author's conclusions	Based on a willingness-to-pay threshold of $120-150,000/QALY, nilotinib treatment in CML patients who were resistant or intolerant to imatinib is a cost-effective treatment. However, the results may be less applicable to high-risk patients, the elderly, children and those less eligible for bone marrow transplantation.
Study information	
Study Title	Economic evaluation of dasatinib in chronic myelogenous leukaemia patients resistant to imatinib in Peru, compared to nilotinib and high doses of imatinib
First author	J. J. Orozco Giraldo[114]
Date of study	2011
Country(ies) where study was performed	Peru
Funding source	Not stated but authors from BMS

Summary of model	
What are the stated objectives of the evaluation?	To compare the costs and cost-effectiveness ratios of using 100 mg/day and 140 mg/day doses of dasatinib with the use of 800 mg/day doses of nilotinib or an increased dose of imatinib (800 mg/day) for each phase of CML in patients who developed resistance to habitual doses of imatinib.
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	NR
Interventions assessed (including dose)	Dasatinib 100 mg/day Dasatinib 140 mg/day Nilotinib 800 mg/day Imatinib 800 mg/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	
Discount rates (same for costs and effects?)	3.5% for both
Time horizon	Lifetime horizon
Perspective	NR
Source(s) of effectiveness data	NR
Source(s) of utility data	NR
Source(s) of cost data	NR
Were indirect costs included?	NR
Main assumptions used in model	NR
Relevance of study to England and Wales	NR
Patient population	
Disease description (eg. stage)	All three phases
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib 100 mg/day in chronic phase QALY=6.62, this was the highest but others not given
Costs (currency and base year)	Peruvian Soles, 2010
Base case cost results (intervention and comparator)	NR
Base case ICER (per QALY gained)	No values given. CP: Dasatinib 100 mg/day yielded highest amount of QALYs and the lowest cost-effectiveness ratio AP: Dasatinib 140 mg/day showed lowest

	cost-effectiveness compared to nilotinib and imatinib BP: Dasatinib showed lower cost-effectiveness ratio than imatinib
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	NR
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	NR
Brief summary of author's conclusions	Dasatinib 100mg/day showed the lowest cost-effectiveness ratios than doses of 800 mg/day of Nilotinib and imatinib 800 mg for the treatment of patients with CML resistant to usual imatinib doses in the chronic phase, as well as in the accelerated and blast phases. Although there was an overall cost increase, especially due to the cost of Dasatinib in 140 mg/day doses, this fact was explained by the increase in life years gained and, consequently, the use of medical resources and drugs.
Study information	
Study Title	Cost-effectiveness analysis of dasatinib 100 mg vs. imatinib 800 mg in patients with imatinib-resistant chronic myeloid leukemia in Spain
First author	A. Ramirez de Arellano[115]
Date of study	2010
Country(ies) where study was performed	Spain
Funding source	Not stated – but authors affiliated with BMS and BCN Health
Summary of model	
What are the stated objectives of the evaluation?	To assess the cost-effectiveness relationship of dasatinib in comparison to high dose imatinib in the treatment of imatinib-resistant CML in Spain.
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Four health states: chronic phase, accelerated phase, blast phase, death
Interventions assessed (including dose)	Dasatinib High-dose imatinib
Was a no-treatment/supportive care strategy included?	No

Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5% for both
Time horizon	Lifetime
Perspective	Spanish health system
Source(s) of effectiveness data	Estimated from a direct comparison derived from the clinical trial BMS 017
Source(s) of utility data	NR
Source(s) of cost data	Healthcare resource use set up by a Spanish clinical expert
Were indirect costs included?	NR
Main assumptions used in model	NR
Relevance of study to England and Wales	NR
Patient population	
Disease description (eg. stage)	All stages
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib higher level of effectiveness, 0.19 QALY gained
Costs (currency and base year)	Euros, 2009
Base case cost results (intervention and comparator)	Dasatinib potential cost saving of €56,995
Base case ICER (per QALY gained)	Dasatinib is dominant
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Deterministic
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	These results indicate that dasatinib remains as a dominant alternative in front of the changes in the most relevant variables: costs, utility values, age at the start of the treatment, time horizon, and discount rate.
Brief summary of author's conclusions	Compared to imatinib, dasatinib shows a slower disease progression with relatively lower direct medical costs. Dasatinib can be regarded as a dominant treatment option in patients with imatinib-resistant CML in the Spanish Health System.
Study information	
Study Title	An economic evaluation of dasatinib for the treatment of imatinib-resistant patients with chronic myelogenous leukaemia
First author	M. Taylor[116]
Date of study	2009
Country(ies) where study was performed	Not stated – assume UK? Costs in £
Funding source	Not stated- authors from York Health Economics Consortium and BMS

Summary of model	
What are the stated objectives of the evaluation?	To estimate the lifetime costs and health outcomes associated with the use of dasatinib in the treatment of imatinib-resistant CML patients
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov model
What are the main components of the model (e.g. health states within a Markov model)?	NR
Interventions assessed (including dose)	Dasatinib 100 mg Imatinib 800 mg Nilotinib 800 mg
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	Results discounted at 3.5%, no rate given for costs
Time horizon	Lifetime
Perspective	NR
Source(s) of effectiveness data	From existing clinical trials
Source(s) of utility data	Obtained through a survey
Source(s) of cost data	Unit costs were drawn from national databases, and were multiplied by resource use (dependent upon a patient's current health state and response level) to estimate total costs
Were indirect costs included?	NR
Main assumptions used in model	NR
Relevance of study to England and Wales	Relevant
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	Imatinib resistant
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib: 5.70 Imatinib: 5.56 Dasatinib produced additional 0.30 QALY vs nilotinib
Costs (currency and base year)	£, base year not stated
Base case cost results (intervention and comparator)	Dasatinib: £260,866 Imatinib: £311, 685 Dasatinib £2,546 more expensive than nilotinib
Base case ICER (per QALY gained)	Dasatinib is dominant vs imatinib Dasatinib vs nilotinib: £8,554

Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Probabilistic sensitivity analysis
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	NR
Brief summary of author's conclusions	Dasatinib is cost-effective compared to both imatinib and nilotinib in the treatment of imatinib-resistant patients with chronic-phase CML.
Study information	
Study Title	Using short-term response to predict long-term outcomes in patients with imatinib-resistant or imatinib-intolerant chronic myeloid leukaemia
First author	M. Taylor[117]
Date of study	2009
Country(ies) where study was performed	Not stated – authors from UK and US
Funding source	Not stated – authors affiliated with University of York and BMS
Summary of model	
What are the stated objectives of the evaluation?	To use outputs from recent clinical trials evaluating TKIs to predict the long-term economic and cost outcomes associated with different levels of best response
Type of evaluation (eg. cost-utility, cost-benefit)	Not clear – estimates costs and health outcomes (QALYs) separately
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Not stated – possibly 'no response, complete haematological response, partial cytogenetic response and complete cytogenetic response' but not explicitly stated that these are the states
Interventions assessed (including dose)	Not stated – mentions imatinib and other TKIs 'such as dasatinib and nilotinib' but does not clearly state which are being compared
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	NR
Time horizon	Lifetime
Perspective	NR
Source(s) of effectiveness data	Recent clinical trials
Source(s) of utility data	NR
Source(s) of cost data	NR
Were indirect costs included?	NR

Main assumptions used in model	NR
Relevance of study to England and Wales	NR
Patient population	
Disease description (eg. stage)	NR
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Accelerated phase (QALYs) No response: 0.71 Complete haematological response: 1.70 Partial cytogenetic response: 1.57 Complete cytogenetic response: 4.10 Blast phase (QALYs) No response: 0.18 Complete haematological response: 0.41 Partial cytogenetic response: 0.63 Complete cytogenetic response: 1.46
Costs (currency and base year)	NR
Base case cost results (intervention and comparator)	Accelerated phase (lifetime costs) No response: <=35,273 Complete haematological response: <=35,850 Partial cytogenetic response: <=35,886 Complete cytogenetic response: <= 51,693 Accelerated phase (lifetime costs) No response: <=13,252 Complete haematological response: <=7,109 Partial cytogenetic response: <=10,993 Complete cytogenetic response: <= 25,501
Base case ICER (per QALY gained)	NR
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	NR
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	NR
Brief summary of author's conclusions	There is a strong apparent relationship between short-term response to treatment and long-term outcomes in CML. These findings are likely to be useful in assessing the cost-effectiveness of existing treatments, whose short-term response is known, but where long-term data are currently unavailable.
Study information	
Study Title	A UK based cost-effectiveness analysis of

	dasatinib (Sprycel) 100mg daily compared to imatinib (glivec) 600/800mg daily as therapy for imatinib failing chronic myeloid leukemia (CML)
First author	M. Taylor[118]
Date of study	2012
Country(ies) where study was performed	UK
Funding source	BMS
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the cost-effectiveness of dasatinib vs imatinib as therapy for imatinib-failing chronic CML patients
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Partitioned survival/costing model
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase second line treatment, progressed disease, death
Interventions assessed (including dose)	Dasatinib 100 mg/day Imatinib 600 mg/day Imatinib 800 mg/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5% for both
Time horizon	Lifetime
Perspective	UK health service
Source(s) of effectiveness data	Based on published RCTs – Kantarjian et al, 2009, Jabbour et al, 2009, Shah et al, 2010
Source(s) of utility data	Szabo et al, 2010
Source(s) of cost data	Recent UK-based studies and appropriate national databases, BNF
Were indirect costs included?	NR
Main assumptions used in model	NR
Relevance of study to England and Wales	Directly relevant – UK study
Patient population	
Disease description (eg. stage)	Not stated – likely to be chronic phase
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	Imatinib-failing
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib: 5.73 Imatinib 600 mg: 2.73 Imatinib 800 mg: 5.25
Costs (currency and base year)	£, base year not stated but BNF 2011 used
Base case cost results (intervention	Dasatinib: £276,000

and comparator)	Imatinib 600 mg: £207,700 Imatinib 800 mg: £286,800
Base case ICER (per QALY gained)	Dasatinib vs imatinib 600 mg: £22,800 Dasatinib vs imatinib 800 mg: dominant
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Probabilistic sensitivity analysis
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	At a threshold of £30,000/QALY gained, dasatinib had a 98.1% probability of being cost-effective Deterministic analysis showed that the model was sensitive to changes in 12 month response probabilities and drug costs. It was robust to changes in adverse event rates/costs and to utility estimates.
Brief summary of author's conclusions	Dasatinib has been shown to be clinically superior to imatinib in CML patients who have failed imatinib treatment and, on the basis of this analysis, is also a cost-effective alternative to imatinib dose escalation in this patient group.
Study information	
Study Title	Economic evaluation of dasatinib for the treatment of chronic myelogenous leukaemia in patients resistant to imatinib in Colombia and Venezuela
First author	J. J. Orozco [119]
Date of study	2010
Country(ies) where study was performed	Colombia and Venezuela
Funding source	Not stated – author affiliations: CES University, Colombia, and Bristol-Myers Squibb
Summary of model	
What are the stated objectives of the evaluation?	To perform an economic evaluation of dasatinib compared with nilotinib and imatinib at high dose for the treatment of CML in imatinib-resistant patients treated in Colombia and Venezuela.
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov model
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase, accelerated phase, blast phase, death
Interventions assessed (including dose)	Dasatinib 100 mg/day Dasatinib 140 mg/day Nilotinib 800 mg/day Imatinib 800 mg/day
Was a no-treatment/supportive care strategy included?	No

Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5% for both
Time horizon	Lifetime
Perspective	NR
Source(s) of effectiveness data	Each country's specific mortality rate used
Source(s) of utility data	Utilities from a previous BMS study were assumed
Source(s) of cost data	Drug costs: retail current maximum price reports in Colombia and Venezuela in 2009 Costs of medical interventions: Colombia – a decree of the then Ministry of Health, which is a referent for negotiations between health providers and insurers Venezuela – costs in Class A and C private institutions were used as reference based on Covenin standards
Were indirect costs included?	Possibly – costs listed include follow-up (generally medicine, specialised consultation, interconsultation, in-hospital visits), tests (x-ray, CAT, bone marrow, cytogenetic, antibiotics), and other (blood transfusion, palliative care, bone marrow transplant)
Main assumptions used in model	Absence of data about resource use in countries assessed, probability and frequency in use of resources expressed in the original model (BMS study presented by the York Consortium) were used. Same assumptions as this report: utility values, 56 years starting age, 10,000 patients, lifetime horizon. Only SAEs include.
Relevance of study to England and Wales	The guidelines for CML management does not differ significantly between the UK and Colombia and Venezuela
Patient population	
Disease description (eg. stage)	All three stages evaluated: chronic, accelerated, blast phases
Previous treatments	Standard dose imatinib
Average age in years	56 at start of treatment
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	*Chronic phase:* Colombia: Dasatinib 100 mg/day – 6.88 Dasatinib 140 mg/day – 6.33 Nilotinib 800 mg/day – 6.03 Venezuela: Dasatinib 100 mg/day – 6.54 Dasatinib 140 mg/day – 6.03 Nilotinib 800 mg/day – 5.73

	Imatinib 800 mg/day – 4.10 *Accelerated phase:* Colombia: Dasatinib 140 mg/day – 2.89 Nilotinib 800 mg/day – 2.03 Imatinib 800 mg/day – 0.83 Venezuela: Dasatinib 140 mg/day – 2.78 Nilotinib 800 mg/day – 1.97 Imatinib 800 mg/day – 0.83 *Blast phase:* Colombia: Dasatinib 140 mg/day – 0.47 Imatinib 800 mg/day – 0.14 Venezuela: Dasatinib 140 mg/day – 0.47 Imatinib 800 mg/day – 0.14
Costs (currency and base year)	Colombian pesos 2009 Venezuela – Bolivares Fuertes (BsF) 2009
Base case cost results (intervention and comparator)	*Chronic phase:* Colombia: Dasatinib 100 mg/day – 987,893,242 Dasatinib 140 mg/day – 963,976,565 Nilotinib 800 mg/day – 945,459,343 Venezuela: Dasatinib 100 mg/day – 1,256,253 Dasatinib 140 mg/day – 1,264,644 Nilotinib 800 mg/day – 1,402,205 Imatinib 800 mg/day – 1,250,793 *Accelerated phase:* Colombia: Dasatinib 140 mg/day – 595,171,509 Nilotinib 800 mg/day – 459,787,593 Imatinib 800 mg/day – 283,191,292 Venezuela: Dasatinib 140 mg/day – 957,770 Nilotinib 800 mg/day – 838,442 Imatinib 800 mg/day – 517,995 *Blast phase:* Colombia: Dasatinib 140 mg/day – 123,667,068 Imatinib 800 mg/day – 75,604,913 Venezuela: Dasatinib 140 mg/day – 202,422 Imatinib 800 mg/day – 132,334
Base case ICER (per QALY gained)	No ICERs given but cost-effectiveness ratios are listed below: *Chronic phase:* Colombia:

	Dasatinib 100 mg/day – 143,589,134 Dasatinib 140 mg/day – 152,286,977 Nilotinib 800 mg/day – 156,792,594 Venezuela: Dasatinib 100 mg/day – 192,087 Dasatinib 140 mg/day – 209,725 Nilotinib 800 mg/day – 244,712 Imatinib 800 mg/day – 305,071 *Accelerated phase:* Colombia: Dasatinib 140 mg/day – 205,941,699 Nilotinib 800 mg/day – 226,496,351 Imatinib 800 mg/day – 341,194,328 Venezuela: Dasatinib 140 mg/day – 344,522 Nilotinib 800 mg/day – 425,605 Imatinib 800 mg/day – 624,090 *Blast phase:* Colombia: Dasatinib 140 mg/day – 263,121,421 Imatinib 800 mg/day – 540,035,093 Venezuela: Dasatinib 140 mg/day – 430,685 Imatinib 800 mg/day – 945,241
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Sensitivity analysis made with a potential 5% increase in the price of dasatinib in both countries. Dasatinib continued to have a preferred cost-effectiveness ratio versus imatinib and nilotinib, with the exception of CML in its chronic phase in Colombia for dasatinib 140 mg/day vs nilotinib.
Brief summary of author's conclusions	Dasatinib, both in 100 mg/day and 140 mg/day doses, showed the best average cost-effectiveness compared to imatinib and nilotinib, both at 800 mg/day, to treat the three phases of CML, both for Colombia and Venezuela.
Study information	
Study Title	Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase
First author	E. Warren[120]
Date of study	2004
Country(ies) where study was performed	UK
Funding source	Novartis
Summary of model	
What are the stated objectives of the evaluation?	To estimate the incremental cost-utility of imatinib compared with hydroxycarbamide in

	patients with chronic phase CML for whom first-line treatment with interferon-a failed to produce a response
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Chronic state, accelerated phase, blast phase, death
Interventions assessed (including dose)	Imatinib 400 mg/day Hydroxycarbamide 2 g/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	Hydroxycarbamide administered on an outpatient basis, no details given for imatinib
Discount rates (same for costs and effects?)	Costs: 6% QALYs:1.5%
Time horizon	Lifetime
Perspective	Costs from perspective of UK NHS. No further details on perspective given
Source(s) of effectiveness data	Clinical trials Probability of patient entering accelerated/blast crisis stage: panel of 6 UK clinicians Transition probabilities: phase II trial 12 month results Rate of disease progression after 12 months: data from Italian Cooperative Study Group on CML trial
Source(s) of utility data	No quality of life data collected in UK trials so utilities estimated using a panel of UK clinicians deriving values for each health state in the model based on their perception of a typical patient in that subgroup. The mean of all responses was taken as the baseline utility weight for each subgroup.
Source(s) of cost data	Direct costs incurred by NHS, validated by clinicians currently providing care for CML patients in the UK. Assumed that the cost of home palliative care was 0 as all costs were assumed to have been incurred by the individual and/or family/friends.
Were indirect costs included?	NR
Main assumptions used in model	Assumed that imatinib was administered at standard registration trial dosages, and hydroxycarbamide was always administered on an outpatient basis with no supplementary treatment, regardless of response. Visit intervals assumed. Bone marrow tests every 6 months for imatinib patients. Rate of disease progression after 12 months

	for patients responding to imatinib would be the same as that for patients receiving interferon-a therapy. Assumed that monthly rate of progression after year 10 was the same as monthly rate of progression during year 10. Assumed that at the time of disease progression, 70% patients entered accelerated phase and 30% progressed into blast crisis.
Relevance of study to England and Wales	Directly relevant
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Interferon-α (non-responders)
Average age in years	53
Other important population characteristics	1000 hypothetical patients
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Imatinib: 5.95 Hydroxycarbamide: 3.49
Costs (currency and base year)	£; 2001 values
Base case cost results (intervention and comparator)	Imatinib: £110,103 Hydryoxyurea: £15,566
Base case ICER (per QALY gained)	£38,468
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Univariate sensitivity analysis
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	ICER for imatinib in chronic phase interferon-a therapy failures varied from £14,195 to £62,745 when underlying modelling assumptions were varied. The sensitivity analyses indicate that imatinib's cost-effectiveness was sensitive to its price and to changes in the discount rate. The ICER was insensitive to assumptions regarding the costs of palliative care in advanced CML, the utility estimates, and the assumption regarding the discontinuation of treatment for imatinib mesylate non-responders at 3 months.
Brief summary of author's conclusions	The present model analysis found that imatinib as a second-line treatment for patients with chronic phase CML was found to offer considerable health benefits to patients, but at a cost to the payer. The ICER was £38,468 (year 2001 values).
Study information	
Study Title	An economic evaluation of dasatinib for the treatment of imatinib reistant patients with advanced chronic myelogenous Leukaemia
First author	M. Taylor[121]
Date of study	2011

Country(ies) where study was performed	UK
Funding source	Not stated- authors from York Health Economics Consortium and BMS
Summary of model	
What are the stated objectives of the evaluation?	To estimate the lifetime costs and health outcomes associated with dasatinib in the treatment of imatinib-resistant CML patients who have the accelerated or blast stages of the disease
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	No response, complete haematological, partial cytogenic, complete cytogenetic, molecular
Interventions assessed (including dose)	Imatinib 600mg Imatinib 800mg Dasatinib Nilotinib (accelerated phase only) BMT
Was a no-treatment/supportive care strategy included?	NR
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	NR
Time horizon	Lifetime
Perspective	NR
Source(s) of effectiveness data	NR
Source(s) of utility data	NR
Source(s) of cost data	National Databases
Were indirect costs included?	NR
Main assumptions used in model	NR
Relevance of study to England and Wales	High
Patient population	
Disease description (eg. stage)	Advanced (Accelerated and Blast Phases)
Previous treatments	Imatinib
Average age in years	NR
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Accelerated Phase Dasatinib: 2.603 Imatinib 600mg: 0.583 Imatinib 800mg: 0.583 Nilotinib: 1.697 BMT: 2.861 Blast Phase

	Dasatinib: 0.485 Imatinib 600mg: 0.240 Imatinib 800mg: 0.240 BMT: 1.757
Costs (currency and base year)	GBP; N/A
Base case cost results (intervention and comparator)	Per patient: Accelerated Phase Dasatinib: £170,478 Imatinib 600mg: £88,949 Imatinib 800mg: £96,552 Nilotinib: £141,128 BMT: £230,277 Blast Phase Dasatinib: £105,103 Imatinib 600 mg: £108,306 Imatinib 800 mg: £115,123 BMT: £173,892
Base case ICER (per QALY gained)	Dasatinib vs. comparators: Imatinib 600mg: dominant Imatinib 800mg: dominant BMT: £54,093
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Univariate and probabilistic sensitivity analyses
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	NR
Brief summary of author's conclusions	In imatinib-resistant AP CML, dasatinib was more effective than imatinib 600mg, 800mg and nilotinib, and less costly than BMT. In BP CML, dasatinib was more effective than imatinib 600mg and 800mg and less costly than imatinib 600mg, 800mg, nilotinib and BMT. Dasatinib is, therefore, cost-effectiveness when compared against other pharmacological interventions in the treatment of advanced stages of CML
Study information	
Study Title	An economic evaluation of dasatinib for the treatment of imatinib reistant patients with chronic myelogenous Leukaemia
First author	M. Taylor[122]
Date of study	2011
Country(ies) where study was performed	UK
Funding source	Not stated- authors from York Health Economics Consortium and BMS
Summary of model	
What are the stated objectives of the evaluation?	To estimate lifetime costs and health outcomes associated with initiating dasatinib treatment in the chronic-phase of imatinib-resistant CML

Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Chronic Phase, Progressed, Dead
Interventions assessed (including dose)	Dasatinib 100mg Imatinib 600mg Imatinib 800mg Nilotinib 800mg Exploratory analyses also included for imatinib 400mg; interferon-a; bone marrow stem cell transplant
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	NR
Time horizon	Lifetime (40 years)
Perspective	UK National Health Service
Source(s) of effectiveness data	Trial data: Dasatinib 100mg: Shah et al. 2010 Imatinib 600mg: Kantarjian et al. 2009 Imatinib 800mg: Jabbour et al. 2009 Nilotinib 800mg: Kantarjian et al. 2009
Source(s) of utility data	Taken from Szabo (2010), Pallua (2010), and converted to utilities using algorithm from McKenzie (2009). Long-term survival data for BMSCT taken from Gratwohl (2006)
Source(s) of cost data	Unit costs from National Databases (British National Formulary, Personal Social Services Research Unit Costs, NHS Reference Costs) multiplied by resource use (driven by disease state and response level)
Were indirect costs included?	Yes: hospitalisations, staff time, administration, and the management of SAEs
Main assumptions used in model	Extrapolated from 48 month follow up to 40 year time horizon, assuming that monthly rate of progression was equal to that observed during the final year of the published follow-up Prognosis is assumed to depend on the initial best response achieved regardless of the treatment
Relevance of study to England and Wales	Highly (UK data)
Patient population	
Disease description (eg. stage)	Chronic-phase
Previous treatments	Imatinib
Average age in years	NR

Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib: 6.425 Imatinib 400mg: 1.485 Imatinib 600mg: 2.394 Imatinib 800mg: 5.910 Nilotinib: 6.235 Interferon-a:1.664 BMSCT: 4.738
Costs (currency and base year)	GBP/N/A
Base case cost results (intervention and comparator)	Dasatinib: £314,413 Imatinib 400mg: £135,326 Imatinib 600mg: £173,705 Imatinib 800mg: £350,365 Nilotinib: £318,978 Interferon-a: £129,292 BMSCT: £324,234
Base case ICER (per QALY gained)	Imatinib 400mg: £36,251 Imatinib 600mg: £34,907 Imatinib 800mg: dominant Nilotinib: dominant Interferon-a: £38,877 BMSCT: dominant
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way, univariate and probabalistic

Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Results from the one-way sensitivity analysis showed that key impact factors in the model include: utility of responders, starting age and time horizon. Comparison with BMSCT, key impact factors include: initial cost of BMSCT, all resource use costs and post-BMSCT utility. Demonstrated that the model's findings were relatively robust to changes in the key parameters of the model Results from the probabilistic sensitivity analysis demonstrated that greater survival is usually associated with greater cost. The ratio of costs to benefits remained relatively stable, despite variations in costs and benefits. The PSA showed that for a willingness-to-pay per QALY gained of £30,000, the likelihood of dasatinib being cost-effective against BMSCT was 81%. The cost of comparators was a major driver of the model's results. For pharmaceutical therapies it can be argued that cost is relatively stable, but there is a substantial amount of uncertainty around the cost of BMSCT
Brief summary of author's conclusions	Dasatinib results in more QALYs gained than the comparators in the treatment of chronic-phase imatinib-resistant patients with CML. Dasatinib is estimated to be less costly than imatinib 800mg, nilotinib and BMSCT. Dasatinib is therefore a cost-effective treatment option Comparisons against imatinib 400mg, interferon-a and BMSCT are based on tentative data and should be treated with caution
Study information	
Study Title	Cost-effectiveness analysis of dasatinib versus high-dose imatinib in the treatment of chronic myeloid leukemia in patients resistant to standard doses of imatinib
First author	J. Darba[123]
Date of study	2012
Country(ies) where study was performed	NR
Funding source	BMS
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the cost effectiveness of dasatinib 100mg/day compared with imatinib 800mg/day in the treatment of imatinib-resistant CML patients
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov

What are the main components of the model (e.g. health states within a Markov model)?	Chronic Phase, Accelerated Phase, Blast Phase, Death
Interventions assessed (including dose)	Dasatinib 100mg/day Imatinib 800mg/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5%
Time horizon	Lifetime (resistance onset to death)
Perspective	Public health system
Source(s) of effectiveness data	Clinical trials BMS 017 and BMS 034
Source(s) of utility data	UK Study (Levy 2007)
Source(s) of cost data	Direct medicals costs in € 2009 were determined by taking into account daily dose, and type and amount of health care resources used per month. Calculated from Base Spanish Medicines Data), and direct health costs were obtained from the literature and a panel of experts.
Were indirect costs included?	No
Main assumptions used in model	Assumes that the CML stages are consecutive, that any stage can lead to death, and that patients can return to the chronic phase from other stages of the disease
Relevance of study to England and Wales	Some relevance. UK utility data, but Spanish cost data.
Patient population	
Disease description (eg. stage)	Chronic Phase, Accelerated Phase, Blast Phase, Death
Previous treatments	Imatinib 400mg/day
Average age in years	Assumed to have started treatment at 56 years
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY
Base case effectiveness results (intervention and comparator)	Dasatinib: 5.70 Imatinib 800mg/day: 5.57
Costs (currency and base year)	€ 2009
Base case cost results (intervention and comparator)	Dasatinib: 359,883 Imatinib 800mg/day: 422,494
Base case ICER (per QALY gained)	Dasatinib vs Imatinib 800mg/day: dominant
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Deterministic sensitivity analysis

Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Generally did not differ substantially from the base case analysis. Some variation in the chronic phase case, with a base value of 0.68 that varied between 0.54 and 0.82 for no response, and from 0.68 to 1 in the case of response (base case 0.85)
Brief summary of author's conclusions	Treatment with dasatinib should have a higher priority than treatment with high doses of imatinib in patients with CML resistant to standard doses of imatinib
Study information	
Study Title	Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: A systematic review and economic evaluation
First author	G. Rogers[84]
Date of study	April 2012
Country(ies) where study was performed	UK
Funding source	HTA
Summary of model	
What are the stated objectives of the evaluation?	To estimate the cost-effectiveness, in terms of ICER per QALY of dasatinib and nilotinib against relevant comparators for: 1. People in CML-CP who develop resistance to imatinib, dasatinib or nilotinib compared with HDI 2. People in CML-CP who are intolerant of imatinib, dasatinib or nilotinib compared with IFN
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility and cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Survival model
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase on treatment Chronic phase following discontinuation of treatment under simulation Accelerated phase Blast phase Death
Interventions assessed (including dose)	Dasatinib, nilotinib, high-dose imatinib, interferon
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5% per annum for costs and benefits
Time horizon	44 years
Perspective	NHS/PSS
Source(s) of effectiveness data	Various studies for each comparator
Source(s) of utility data	Estimated from the IRIS study (Reed et al (2008))

Source(s) of cost data	British National Formulary
Were indirect costs included?	No
Main assumptions used in model	• Overall survival is predicted on the basis of major cytogenetic response and the relationship between major cytogenetic response and overall survival is the same for all treatments, and not affected by the timing, duration and depth of CyR. The hazard ratio for the overall survival for the major cytogenetic response versus non-major cytogenetic response groups is based upon first-line therapy and is still valid for second-line treatments, and is constant over time. • Duration of treatment is estimated on the basis of progression-free survival with a deduction to account for premature discontinuations. • Times spent in accelerated phase and blast-crisis phases is independent of chronic-phase treatment, i.e. is identical across comparators. • Treatment-related AEs incur no utility decrement and no additional costs. • Duration of chronic phase (no treatment) is estimated by deducting time spent in chronic phase (treatment), accelerated-phase and blast-crisis-phase states from overall survival.
Relevance of study to England and Wales	High
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Standard-dose imatinib
Average age in years	Assumed age of 56 years
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	LYs, QALYs
Base case effectiveness results (intervention and comparator)	LYs Dasatinib: 9.57 Nilotinib: 9.32 Imatinib 800mg: 8.95 QALYs Dasatinib: 7.85 Nilotinib: 7.63 Imatinib 800mg: 7.31
Costs (currency and base year)	£, Inflated to 2009-10
Base case cost results (intervention and comparator)	Dasatinib: 5080 Imatinib: 6505 Nilotinib: 5286 IFN-a: 1486
Base case ICER (per QALY gained)	ICER for nilotinib vs IFN-a: 44,616

	Nilotinib dominates HDI ICER for dasatinib vs nilotinib: 277,698
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way deterministic sensitivity analysis performed by varying single parameters. Probabalistic sensitivity analysis were run with 1000 Monte Carlo simulations. A cost-effectiveness acceptability curve was constructed to show the probability that each treatment would be considered to most cost-effective, for a range of WTPs thresholds.
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Deterministic sensitivity analysis: the base-case conclusion for dasatinib is not affected by changes to the parameter values except for changing the treatment duration to be the same as for either high-dose imatinib or nilotinib. In these cases, dasatinib becomes cost-effective compared with these treatments. Probabalistic sensitivity analysis: at a conventional WTP threshold of 30,000 per QALY, the PenTAG AR2 model estimates the probability of interferon alfa providing optimal cost–utility at 97%, with corresponding likelihoods for nilotinib, high-dose imatinib and dasatinib of 3%, 0% and 0%, respectively. At a WTP threshold of around 45,000 per QALY, nilotinib is predicted to be the optimal choice. The model predicts that it is unlikely that dasatinib would be considered the best option; even when WTP approaches 150,000 per QALY, the probability of dasatinib being most cost-effective is < 20%.
Brief summary of author's conclusions	Deterministic and probabilistic results make it appear unlikely that dasatinib would be considered to provide an acceptable cost–utility balance
Study information	
Study Title	Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation
First author	O. Ghatnekar[85]
Date of study	2010
Country(ies) where study was performed	Sweden
Funding source	BMS AB, Sweden
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the cost-effectiveness of dasatinib treatment vs. HDI in patients with CP-CML who are resistant to standard-dose imatinib in Sweden
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility and cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation,	Markov with patients starting in chronic phase

decision analytic model)	
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase, accelerated phase, blast phase, death (can progress from chronic phase to accelerated phase after 12 weeks)
Interventions assessed (including dose)	Dasatinib 140mg/day Imatinib 800mg/day
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3%
Time horizon	Lifetime
Perspective	Societal
Source(s) of effectiveness data	A 12-week head-to-head clinical trial of dasatinib vs. high-dose imatinib (Kantarjian et al (2007))
Source(s) of utility data	Elicited from a time trade-off technique using the EQ-5D instrument among 100 laypersons in the UK and applied to both the dasatinib and imatinib arms by Levy et al (2007)
Source(s) of cost data	Resource use per patient and month in each health state elicited from two Swedish clinical haematologists Direct health care-related costs taken from published Swedish statistics Cost of thrombocyte transfusion based on a regional cost-per-patient study, inflated to year 2008 Indirect costs in terms of production lost estimated using the human capital approach
Were indirect costs included?	Yes (production lost)
Main assumptions used in model	• The better the initial response to treatment, the slower the expected cohort disease progression. • It is not possible to move from chronic phase to blast-crisis phase directly; the probability of CML-related death is dependent on the health state and the treatment response of the patient. • Utilities are assumed to be the same for both study groups. • Adverse event rates are limited to the first month only; no disutility weights are used for AEs and patients are assumed to continue with study medication. • Patients are treated until disease progression.
Relevance of study to England and Wales	Unclear
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	≤600mg imatinib

Average age in years	Median age of 51 years
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY and life years
Base case effectiveness results (intervention and comparator)	Dasatinib: 5.19 Imatinib: 5.57
Costs (currency and base year)	€ 2008
Base case cost results (intervention and comparator)	Total direct costs Dasatinib: 350,960 Imatinib: 346,507 Total societal costs Dasatinib: 504,532 Imatinib: 500,281
Base case ICER (per QALY gained)	6880 per QALY gained (societal) 7207 per QALY gained (direct) Indirect costs of production losses and increased public consumption almost cancel out
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One-way sensitivity analysis Probabalistic sensitivity analysis
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Dasatinib is a dominant treatment option in a 10-year time horizon. Probabalistic sensitivity analysis results fall below the derived willingness to pay for a QALY in Sweden
Brief summary of author's conclusions	The authors conclude that dasatinib is a cost-effective treatment among imatinib-resistant patients with CML in Sweden compared with imatinib 800 mg/day
Study information	
Study Title	Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation
First author	Novartis[85]
Date of study	2012
Country(ies) where study was performed	UK
Funding source	Novartis
Summary of model	
What are the stated objectives of the evaluation?	To evaluate the cost-effectiveness of nilotinib for the treatment of adult patients with CML who are resistant to prior standard-dose imatinib therapy in the CP
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility and cost-effectiveness
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of	Hypothetical cohort of 1000 patients in CP

the model (e.g. health states within a Markov model)?	who progress to AP, then BC, then death
Interventions assessed (including dose)	Nilotinib 800mg/day Imatinib 800mg/day SCT: SCT as third-line therapy if appropriate HU: 2g/day as third-line therapy SCT/HU second-line exploratory analysis
Was a no-treatment/supportive care strategy included?	No
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5%
Time horizon	Lifetime
Perspective	UK NHS and Personal Social Services perspective
Source(s) of effectiveness data	Overall survival estimated from the clinical study CAMN107A2101 at 24 months' follow up. Long-term survival extrapolated from the study data. Overall survival and TTD data taken from Kantarjian et al (2009) for high-dose imatinib.
Source(s) of utility data	Derived from Reed et al (2004); Reed et al (2008)
Source(s) of cost data	NHS reference costs 2006/7 British National Formulary 2010 (except high-dose imatinib, which used a cost that reflected a future cost increase) Clinical experts where published data were not available
Were indirect costs included?	No
Main assumptions used in model	• All patients in either the nilotinib arm or high-dose imatinib arm are assumed to receive treatment until treatment failure, when it is assumed they receive allo-stem cell transplantation as a third-line option, if eligible, otherwise hydroxycarbamide; this is assumed to occur before progression to accelerated phase. Patients in both arms who progress to accelerated phase or blast crisis receive hydroxycarbamide. • All patients are assumed to have died of CML or other causes by the age of 100 years. • Patients may stop taking nilotinib prior to progression to the next phase of treatment, so TTD of treatment is used in the model, rather than progression-free survival, to provide an estimate of time on nilotinib. • It was assumed that 10% of patients who discontinued treatment owing to

	AEs would progress from chronic phase to accelerated phase. • Utilities were assumed to be independent of drug therapy and time; also utility values for • accelerated phase and blast-crisis phase were assumed to be the same.
Relevance of study to England and Wales	High
Patient population	
Disease description (eg. stage)	Chronic phase
Previous treatments	Standard-dose imatinib
Average age in years	Patients enter the model at 57 years
Other important population characteristics	NR
Results	
Effectiveness measure (eg. QALY)	QALY and LYG
Base case effectiveness results (intervention and comparator)	QALYs High-dose imatinib: 4.28 Nilotinib: 4.51 SCT/HU: 3.18
Costs (currency and base year)	£ 2009-2010
Base case cost results (intervention and comparator)	High-dose imatinib: 146,234 Nilotinib: 139,216 SCT/HU: 80,933
Base case ICER (per QALY gained)	High-dose imatinib vs. nilotinib: -30,513 per QALY gained High-dose imatinib vs. SCT/HU: 36,748 per QALY gained
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	One way sensitivity analyses and PSAs

Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	Deterministic sensitivity analyses: most ICERs are close to the base-case result of -30,000, except for the 5-year time horizon, which gives an ICER of -82,000 (due to delayed treatment benefit), and for extending high-dose imatinib TTD from 14 months to 19.4 months, which gives an ICER of 201,871 (higher costs of high-dose imatinib treatment with marginal QALY gain for high-dose imatinib vs nilotinib). Probabilistic sensitivity analysis: undertaken to explore the impact of joint uncertainty in all model parameters on the cost-effectiveness results. Results give an ICER of -86,413 per QALY gained. From cost-effective acceptability curves nilotinib is predicted to be cost-effective at a threshold of over £10,000 per QALY.
Brief summary of author's conclusions	Nilotinib represents a clinically effective and cost-effective treatment option for patients with CP-CML, who are resistant to standard-dose imatinib (From exploratory analyses reported only in an appendix, when compared with SCT/HU, the cost per QALY gained for nilotinib in CP is £44,028)
Study information	
Study Title	Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation
First author	BMS[85]
Date of study	2012
Country(ies) where study was performed	UK
Funding source	BMS
Summary of model	
What are the stated objectives of the evaluation?	To appraise the clinical effectiveness and cost-effectiveness of dasatinib, nilotinib and HDI compared with standard-dose imatinib, SCT, HU, IFN-α, acute leukaemia-style chemotherapy and best supportive care, for patients with CML who are resistant to imatinib
Type of evaluation (eg. cost-utility, cost-benefit)	Cost-utility
Type of model (eg. Markov, decision tree, discrete event simulation, decision analytic model)	Markov
What are the main components of the model (e.g. health states within a Markov model)?	Chronic phase and accelerated both consisted of three health states: stable disease, progressed disease and death. Blast phase consisted of two health states: stable disease and death.

Interventions assessed (including dose)	Dasatinib: CP 100mg/day; AP/BC 140mg/day Nilotinib: 800mg/day Imatinib: doses incr4eased to 800mg/day in the absence of SAE
Was a no-treatment/supportive care strategy included?	No. Bone marrow/SCT, IFN-a
Institutional setting: where is/are the intervention(s) being evaluated usually provided?	NR
Discount rates (same for costs and effects?)	3.5% for costs and benefits
Time horizon	40 years
Perspective	NHS/PSS
Source(s) of effectiveness data	Various studies for each intervention Progression-free survival rates from BMS 034 trial
Source(s) of utility data	Cross-sectional study (Szabo et al (2010))
Source(s) of cost data	NHS Reference costs 2006/7 British National Formulary 2010 (high dose imatinib used a cost that reflected a future cost increase) Clinical expert advice sought where published data not available
Were indirect costs included?	No
Main assumptions used in model	• Response to treatment is assessed in the initial period; after that, it is assumed to remain at the same level until disease progression. • The efficacy of 800 mg imatinib is equivalent to 600 mg in accelerated phase and blast-crisis phases. • The efficacy of standard-dose imatinib and interferon-a is zero. • Patients cannot return to the chronic phase from advanced phases of CML. • The probability of progressing to the next CML phase and death was estimated from the progression-free survival and overall survival data for patients in a dasatinib trial (i.e. BMS trial 034).22 The probability of progression or death was (other than by response) independent of treatment. • Beyond the trial period, progression rates were assumed to remain constant, at a rate equal to that during the final year of follow-up. • After failing imatinib, dasatinib or nilotinib, patients receive post-failure treatment (PFT). • Progression rates and other input parameters for patients receiving PFT are assumed equal to those used for non-responders.

	• Patients receiving PFT incur the cost, but not the utility benefits. • Utility values do not change over time, as long as the patient remains in the same health state. • Where utility estimates for serious adverse events (SAEs) were not available from the non-CML literature a 5% (–0.05) decrement was assumed. • Where resource use associated with an AE was not known, a cost of £100 was assumed. • Monthly cost of bone marrow stem cell transplantation is based on an aggregate figure to reflect the average costs for different prognoses post stem cell transplantation. • Different utility values were used for response and no response groups.			
Relevance of study to England and Wales	High			
Patient population				
Disease description (eg. stage)	Chronic phase, accelerate phase and blast phase			
Previous treatments	Imatinib			
Average age in years	CP: 56 years AP: 56 years BC: 48 years			
Other important population characteristics	NR			
Results				
Effectiveness measure (eg. QALY)	QALYs, PFS, LYs			
Base case effectiveness results (intervention and comparator)		QALYS	PFS	LYs
	Dasatinib	6.425	10.720	11.764
	Imatinib 400mg	1.485	2.094	3.557
	Imatinib 600mg	2.394	4.606	3.155
	Imatinib 800mg	5.910	11.013	9.938
	Nilotinib	6.235	10.368	11.435
	IFN-a	1.664	2.094	3.557
	Bone marrow SCT	4.738	11.563	11.982
Costs (currency and base year)	£ 2009			
Base case cost results (intervention and comparator)	Dasatinib: 314,413 Imatinib 400mg: 135,326 Imatinib 600mg: 173,705 Imatinib 800mg: 350,365 Nilotiinib: 318,978 IFN-a: 129,292 Bone Marrow SCT: 324,234			
Base case ICER (per QALY gained)	Dasatinib vs.:			

	Imatinib 400mg: 36,251 Imatinib 600mg: 34,907 Imatinib 800mg: dominant Nilotinib: dominant IFN-a: 38,877 Bone Marrow SCT: dominant
Types and description of sensitivity analysis performed (eg. one-way sensitivity analysis, probabilistic sensitivity analysis)	Deterministic and PSAs Parameters used in the model were varied in the deterministic sensitivity analysis, including costs, utilities, starting age, time horizon and discounting
Summary of sensitivity analysis results (did they differ substantially from the base case analysis? If so, what were the suggested causes?)	The key impact factors include the utility of responders, starting age, and time horizon of the model. The sensitivity analyses were not presented in the normal way and are difficult to interpret The PSA showed the probability of dasatinib being cost-effective compared with bone marrow SCT of 81%. Cost-effectiveness acceptability curves were not presented for all possible drugs together, and results were not shown for the probability that dasatinib was cost-effective compared with its alternatives
Brief summary of author's conclusions	Dasatinib is more clinically effective than HDI and cost-effective compared with HDI which BMS3 considers the appropriate comparator
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)	

A complete quality assessment of cost-effectiveness studies is provided in Table B85.

Table B85: Quality Assessments of Cost-Effectiveness Studies

Study name	**Asano et al. 2009[108]** **Cost-utility analysis of dasatinib in patients with imatinib-resistant chronic myeloid leukemia (CML) on chronic (CP), accelerated (AP) and blast (BP) phases in Brazil**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Not clear	Implied in research question and perspective (Brazilian health care system)
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	No further information beyond conclusion statement
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?		Drugs and doses given, no further information

6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate	Yes	

stated?		
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Not clear	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name	**Gaultney et al. 2011[109]** **Application of cost-effectiveness analysis to demonstrate the potential value of companion diagnostics in chronic myeloid leukemia**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the	Yes	

analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Not clear	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key	No	

parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Ghatnekar et al. 2010[107]** **Cost-effectiveness of dasatinib versus high-dose imatinib in patients with Chronic Myeloid Leukemia (CML), resistant to standard dose imatinib a Swedish model application**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question	Yes	

stated?		
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		Implicit in conclusion
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	

20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Hoyle et al. 2011b[86]** **Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**

Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	It is however acknowledged that this is only an exploratory analysis due to immature clinical data
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Not clear	Dasatinib /nilotinib only briefly described and no distinguishing characteristics mentioned
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	n/a	
16. Were quantities of resources reported separately from their unit cost?	Yes	

17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Juarez-Garcia et al. 2009[110]** **The cost and cost effectiveness of dasatinib (SPRYCEL) 100 MG therapy for the management of imatinib resistant and intolerant patients in chronic phase with chronic myeloid leukemia (CML) in Mexico**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?		Implicit in perspective
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		Implicit in conclusion
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Not clear	
5. Were the alternatives being compared clearly described?		Only drug and dose
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	No	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were	No	

obtained given?		
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?		Only for costs
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	No	No explanation for lack of benefit discount
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions	No	

accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Ko et al. 2010[111]** **Pharmacoeconomic evaluation of nilotinib in treating Taiwan patients with chronic myeloid leukemia (CML)**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Not clear	Mentions 'economic impacts of treatment' in objectives
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	No	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Not clear	'literature research was undertaken'
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other	No	

benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	Markov model and transition probabilities described but choice of model is not justified
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	No	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study	Yes	

question given?		
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Mungapen et al. 2010[112]** **Cost-utility analysis of dasatinib as a second-line treatment in the chronic phase of chronic myeloid leukaemia in Russia**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		Not beyond results of study
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?		Only drugs and doses
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Only stated 'from published RCTs'
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic	Yes	

evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Only for drug costs
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as	Yes	

well as aggregated form?		
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Niu et al. 2012[113]** **Cost-effectiveness analysis of nilotinib versus dasatinib in patients with imatinib-resistant or imatinib-intolerant chronic myeloid leukemia (CML)**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	Drug and dose
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of	No	

effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?		Only for costs, none reported for benefits
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	

31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Orozco-Giraldo et al. 2011[114]** **Economic evaluation of dasatinib in chronic myelogenous leukaemia patients resistant to imatinib in Peru, compared to nilotinib and high doses of imatinib**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Not clear	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Only in conclusion	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?		Only drug names and doses given
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	No	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were	N/A	

appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Ramirez de Aerellano et al. 2010[115]** **Cost-effectiveness analysis of dasatinib 100 mg vs. imatinib 800 mg in patients with imatinib-resistant chronic myeloid leukemia in Spain**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Not explicitly	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Only in conclusion	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	No – no dose	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the	No	

parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Taylor et al. 2009[116]** **An economic evaluation of dasatinib for the treatment of imatinib-resistant patients with chronic myelogenous leukaemia**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Only in conclusion
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Only in title
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of	Yes	

effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	For results only, no mention of cost discounting
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity	Yes	

analysis described?		
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Taylor et al. 2012[118]** **A UK based cost-effectiveness analysis of dasatinib (sprycel) 100mg daily compared to imatinib (glivec) 600/800mg daily as therapy for imatinib failing chronic myeloid leukemia (CML)**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Only in title

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?		Yes for treatment events quantities but not the associated costs
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Not clear	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Orozco et al. 2010[119]** **Economic evaluation of dasatinib for the treatment of chronic myelogenous leukaemia in patients resistant to imatinib in Colombia and Venezuela**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Not explicitly stated	Implied through study of costs for countries involved
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	

5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Not explicitly	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	Based on previous study but few justifications given
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate	No	

justified?		
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Warren et al. 2004[120]** **Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative	Yes	

programmes or interventions compared?		
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	

23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	Only justified for costs, not for QALYs
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Study name	**Taylor et al. 2011[121]** **An economic evaluation of dasatinib for the treatment of imatinib reistant patients with advanced chronic myelogenous Leukaemia**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	

4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	No	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	

Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Taylor et al. 2011[122]** **An economic evaluation of dasatinib for the treatment of imatinib reistant patients with chronic myelogenous Leukaemia**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	

2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	

20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Darba et al. 2012[123]** **Cost-effectiveness analysis of dasatinib versus high-dose imatinib in the treatment of chronic myeloid leukemia in patients resistant to standard doses of imatinib**	

Study question	Grade (yes/no/not clear/N/A)	Comments
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	

18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Rogers et al. 2012[84]**	

	Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: A systematic review and economic evaluation	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	

16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Loveman et al. 2012[85]** **Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation (Ghatnekar study)**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	

33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Loveman et al. 2012[85]** **Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation (Novartis Model)**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Study name	**Loveman et al. 2012[85]** **Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation (BMS Model)**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	

27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

10.12.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The databases searched were as follows:

- Medline (OVID Interface)
- Embase (OVID Interface)
- Medline In-Process (OVID Interface)
- EconLIT (OVID Interace)
- NHS EED (Searched via the Cochrane Library and also via Centre for Reviews and Dissemination)

- Cochrane Library

10.12.2 **The date on which the search was conducted.**

The search was conducted on 02/10/12

10.12.3 **The date span of the search.**

The search date span was from database inception to 02/10/12

10.12.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

Ovid Interface
1. myeloid$ leuk?emia$.mp.
2. Leukemia, Myeloid/
3. (CML).tw.
4. leukemia, myeloid, chronic-phase/
5. leukemia, myeloid, chronic, atypical, bcr-abl negative/
6. exp leukemia, myelogenous, chronic, bcr-abl positive/
7. myelogenous$ leuk?emia$.mp.
8. myelocytic$ leuk?emia$.mp.
9. leukemia, myelomonocytic, chronic/
10. major cytogenetic response.ti,ab.
11. major molecular response.ti,ab.
12. Or/1- 11
13. Philadelphia Chromosome/
14. (Philadelphia adj1 Chromosome).mp.
15. (PH1 or PH 1 adj3 Chromosome).mp.
16. Or/13-15
17. 12 or 16
18. Quality of Life/
19. ((quality adj3 life) or life quality or QoL).ti,ab.
20. (HRQL or HRQoL or HRQoL).ti,ab.
21. (value adj2 life).ti,ab. or Value of Life/
22. (life adj2 qualit$3).tw.
23. (quality-adjusted life year$1 or QALY or QALYs).ti,ab. or Quality-Adjusted Life Years/
24. daly.ti,ab.
25. (disabilit$3 adj2 life).ti,ab.
26. Health Status Indicators/
27. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.
28. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
29. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.
30. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
31. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.
32. (euroQoL or euro QoL or eq5d or eq 5d).tw.
33. (hye or hyes or health$ year$ equivalent$).tw.
34. hui$1.tw.

35. rosser.tw.
36. (willing$ adj2 pay).tw.
37. willing$ adj2 accept.tw.
38. standard gamble$.tw.
39. (health adj3 (utilit$3 or value$2 or preference$2)).tw.
40. (visual analog$3 scale or VAS).tw.
41. patient preference$2.tw.
42. (person$ trade-off or person$ trade off or (PTO)).ti,ab.
43. (Contingent value or contingent valuation).ti,ab.
44. (discrete choice).ti,ab.
45. (health status).ti,ab. or Health Status/
46. ((quality adj3 (wellbeing index)) or QWB).ti,ab.

Cochrane library

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. Philadelphia Chromosome
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. MeSH descriptor Leukemia, Myeloid, this term only
13. MeSH descriptor leukemia, myeloid, chronic-phase, this term only
14. MeSH descriptor leukemia, myeloid, chronic, atypical, bcr-abl negative, this term only
15. MeSH descriptor leukemia, myelogenous, chronic, bcr-abl positive, explode all trees
16. MeSH descriptor leukemia, myelomonocytic, chronic, this term only
17. MeSH descriptor Philadelphia Chromosome, this term only
18. #12 OR #13 OR #14 OR #15 OR #16 OR #17
19. #11 OR #18
20. MeSH descriptor Quality of Life, this term only
21. life qualit* OR QoL OR quality of life
22. HRQL OR HRQoL OR HRQoL
23. MeSH descriptor Value of Life, this term only
24. Value of life
25. Life quality
26. quality-adjusted life year* OR quality adjusted life year* OR QALY OR QALYs
27. MeSH descriptor Quality-Adjusted Life Years, this term only
28. Daly
29. disabilit* adjusted life year*
30. MeSH descriptor Health Status Indicators, this term only
31. sf36 OR sf 36 OR short form 36 OR shortform 36 OR sf thirtysix OR sf thirty six OR sf thirty-six OR shortform thirtysix OR shortform thirty six OR shortform thirty-six OR short form thirty six OR short form thirtysix OR short form thirty-six
32. sf6 OR sf 6 OR short form 6 OR shortform 6 OR sf six OR sfsix OR shortform six OR short form six
33. sf12 OR sf 12 OR short form 12 OR shortform 12 OR sf twelve of sftwelve OR shortform twelve OR short form twelve
34. sf16 OR sf 16 OR short form 16 OR shortform 16 OR sf sixteen OR sfsixteen OR shortform sixteen OR short form sixteen

35. sf20 OR sf 20 OR short form 20 OR shortform 20 OR sf twenty of sftwenty OR shortform twenty of short form twenty
36. euroQoL OR euro QoL OR eq5d OR eq 5d
37. hye OR hyes OR health* year* equivalent*
38. hui*
39. rosser
40. willing* to pay
41. willing* to accept
42. standard gamble
43. health utilit* OR health value* OR health preference*
44. visual analog* scale OR VAS
45. patient preference*
46. person* trade-off OR person* trade off OR PTO
47. Contingent value OR contingent valuation
48. discrete choice
49. health status
50. MeSH descriptor Health Status, this term only
51. quality of wellbeing index OR QWB OR quality of wellbeing score*
52. health utilities index
53. time trade off OR time trade-off OR TTO
54. utility OR utilities
55. disutil*
56. disability
57. wellbeing OR well-being OR well being OR qwb
58. quality of well being
59. quality of wellbeing
60. Or (#20-#59)
61. 19 and 60

NHS EED, via CRD

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. Philadelphia Chromosome
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Horizon scans for relevant articles were performed using the Google search engine using the key words: CML, chronic myeloid leukaemia, combined with cost-effectiveness, cost-utility, model.

ISPOR, ASCO, ESMA, ICLLM and ASH congress abstracts/posters were also searched for any relevant articles not picked up by the search in 7.4.5. NICE HTAs were also searched.

10.12.6 **The inclusion and exclusion criteria.**

See main body of submission

10.12.7 **The data abstraction strategy.**

For the 11 articles, data and methods were extracted by one reviewer, and checked by another independent reviewer. Extractions were carried out to fill the following table:

Study information	
Study Title	
First author	
Date of study	
Funding source	
Population in which health effects were measured	
Size of population	
Nationality	
Information on recruitment (ie. how was the sample selected)	
Response rate to questionnaire	
General public or patient group?	
Description of health states or adverse events	
Previous treatments	
Current treatments	
Average age in years	
Other important population characteristics	
Method of elicitation	
Method of elicitation	
Method of valuation	
Was mapping used?	
Summary of results	
Results with confidence intervals	
Applicability	
Applicability to UK population	
Appropriateness of health states given condition and treatment pathway	
Consistency with reference case (eg. EQ-5D?)	
Other points on	

appropriateness for cost-effectiveness analysis	
Other	
Any other comments on methodology, results or applicability	
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)	

10.12.8 Results of HRQL data extractions

Table B86: Summary of identified HRQoL Studies (Previously Treated)

Study information	
Study Title	EOSTA: An observational study on the compliance and quality of life (QoL) of chronic myeloid leukemia (CML) patients treated with second line nilotinib (Tasigna): Interim results at 6 months of follow-up
First author	D. Rea[89]
Date of study	2011
Funding source	NR
Population in which health effects were measured	
Size of population	145
Nationality	France
Information on recruitment (ie. how was the sample selected)	NR
Response rate to questionnaire	NR
General public or patient group?	Patient group
Description of health states or adverse events	N/A
Previous treatments	Imatinib and dasatinib (22%)
Current treatments	Nilotinib
Average age in years	57.5
Other important population characteristics	NR
Method of elicitation	
Method of elicitation	EQ-5D and QLQ-C30
Method of valuation	NR
Was mapping used?	NR
Summary of results	
Results with confidence intervals	EVA stable over first 6 months (70.6 to 70.3) QLQ-C30 scores showed good global health status (mean 69, 33 to 100), good functional score (mean 80, 37 to 100) and poor symptom score (mean 20, 0 and 85). Results were stable over time regardless of duration of previous nilotinib treatment
Uncertainty around	NR

values	
Applicability	
Applicability to UK population	Applicable-Western European country
Appropriateness of health states given condition and treatment pathway	NR
Consistency with reference case (eg. EQ-5D?)	EQ-5D
Other points on appropriateness for cost-effectiveness analysis	NR
Other	
Any other comments on methodology, results or applicability	'Overall, QoL was not impaired despite some issues on mobility, usual activities, pain/discomfort and anxiety/depression'
Study information	
Study Title	Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia
First author	P. C. Trask[82]
Date of study	2012
Funding source	Pfizer
Population in which health effects were measured	
Size of population	288
Nationality	NR
Information on recruitment (ie. how was the sample selected)	NR
Response rate to questionnaire	Baseline HRQoL data was available for 84% (167/200) of the IM-resistant and 91% (80/88) of the IM-intolerant patients. For the IM-resistant group completion rates were 77% (154/200), 77% (152/197), 71% (136/192), 62% (117/190), and 54% (88/163) at weeks 4, 12, 24, 48, and 96, respectively. For the IM-intolerant group, data was available at weeks 4, 12, 24, 48, and 96 for 76% (66/87), 73% (63/86), 62% (52/84), 58% (49/84), and 51% (40/78) of the subjects.
General public or patient group?	Patient group
Description of health states or adverse events	Chronic Phase
Previous treatments	Imatinib
Current treatments	Bosutinib
Average age in years	Imatinib-resistant (IM-R): 50 Imatinib-intolerant (IM-I):54
Other important population characteristics	NR
Method of elicitation	

Method of elicitation	44-Item Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)							
Method of valuation	Scale of 0-4							
Was mapping used?	NR							
Summary of results								
Results with confidence intervals	**FACT-Leu Scale**	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 96**
	IM resistant	n=148	n=144	n=143	n=130	n=126	n=108	n=77
	Physical Well-being	-0.81*	0.17	0.76*	0.66*	0.81*	0.23	1.11**
	Social/Family Well-being	-0.32	-0.32	-0.59	-0.63	-0.51	-0.34	-1.20**
	Emotional Well-being	0.99+	1.01+	0.94+	1.30+	1.18+	0.79*	1.43+
	Functional Well-being	-0.56	0.02	-0.01	-0.11	0.36	0.37	-0.09
	Leukemia-specific subscale	0.72	1.27	2.02+	2.49+	2.51+	2.17+	3.26+
	FACT-General	-0.70	0.88	1.11	1.19	1.90	1.05	1.18
	FACT-Leukemia Total	-0.12	2.04	3.07**	3.67**	4.31+	3.21	4.30**
	FACT-Trial Outcome Index	-0.70	1.44	2.75+	3.04**	3.62+	2.75*	4.19+
	IM intolerant	n=65	n=66	n=63	n=51	n=48	n=48	n=40
	Physical Well-being	-0.79	0.37	0.11	1.11	1.69+	1.66+	1.69*
	Social/Family Well-being	-0.90	-0.56	-0.91	-0.49	0.75	0.57	0.41
	Emotional Well-being	1.16*	1.09**	0.95	1.55+	*2.60+*	*2.45+*	*2.46+*
	Functional Well-being	-1.64**	-0.68	-0.25	0.29	1.13	1.15	0.70
	Leukemia-specific subscale	1.20	1.30	1.78	3.03**	*4.46+*	*3.94+*	*4.35+*
	FACT-General	-2.31	0.34	-0.10	2.46	*6.17+*	*5.83+*	*5.15***
	FACT-Leukemia Total	-1.41	1.69	1.68	5.50*	*10.63+*	*9.56+*	*9.31+*
	FACT-Trial Outcome Index	-1.50	1.13	1.64	4.44*	*7.27+*	*6.52+*	*6.74+*
	FACT, Functional Assessment of Cancer Therapy; IM, imatinib; MID, minimally important differences. MIDs: Physical Well-being, 2-3 points; Social/Family Well-being, not available; Emotional Well-being, 2 points; Functional Well-being, 2-3 points; Leukemia-specific subscale, 4-7 points; FACT-General, 3-7 points; FACT-Leukemia Total, 6-12 points; and FACT-Trial Outcome Index, 5-6 points.							

	Negative changes reflect a reduction in health-related quality of life. Text in bold italics denotes a change in excess of the MID, indicating not only a statistical significance but also clinical significance (degree of change that is noticeable to the patient). *p<0.05 **p≤0.01 + p<0.005
Uncertainty around values	NR
Applicability	
Applicability to UK population	NR
Appropriateness of health states given condition and treatment pathway	NR
Consistency with reference case (eg. EQ-5D?)	No
Other points on appropriateness for cost-effectiveness analysis	NR
Other	
Any other comments on methodology, results or applicability	Table 2 gives mean FACT-Leu change from baseline scale scores over time.
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)	

HRQL in newly diagnosed CML patients

TA251 represents the most recent systematic review of HRQL. As such, to ensure that we had not missed any relevant studies an uptate of the TA251 search was undertaken. This update identified a further 3 studies of potential interest (Guest 2012[95], Efficace 2011[96], and Aziz 2012[97]).

- **Guest 2012[95]:** This study used the TTO technique and standard gamble (SG) to elicit utility values for the chronic phase health states: hematologic response, cytogenetic response and molecular response. These were obtained from members of the British public (n=241). Direct TTO and SG as used here are the most highly reliable methods of utility estimation and therefore provide useful utility estimations. **The study only presents utlity per response type rather than across all CP patients and does not give utilities for the accelerated or blast phases.**

- **Efficace 2011[96]:** This study obtained SF-36 scores from Italian CML patients and a matched control group (n=448) to investigate whether patients with CML in treatment with long-term therapy imatinib have a different HRQoL profile compared with the general population. **The study does not report actual utility values, and is not in a UK population.**

- **Aziz 2011[97]:** This study aimed to assess the QoL by using FACT-BRM scores of 90 patients in Pakistan with newly diagnosed CP-CML being treated with first-

line imatinib. The primary endpoint was the Trial Outcome Index (TOI) which was used as a measure of physical function and well-being. **No utility values were reported, and its applicability to UK patients is limited.**

Given the limitations of the above first-line studies and the availability of HRQL taken directly from CML patients in trials and measured by EQ-5D, the results of these studies are not reported below, however the full results can be found in Appendix 10.12.

As discussed, the most relevant results for this submission are deemed to be those presented in TA241 and TA251. Therefore, full results for the 2 studies (Rea 2011[89]; Trask 2012[82]) identified in the original systematic review, the 3 studies (Szabo 2010[124]; Reed 2004[92]; Dalziel 2004[93]) identified as part of the TA251 systematic review and the 3 further studies (Guest 2012[95]; Efficace 2011[96]; Aziz 2011[97]) identified by the update to the TA251 systematic review are not presented in this submission. These studies and the results that they present are instead summarised briefly in Table B87, below, and full extraction details can be found in Appendix 10.12.

Table B87: Summary of identified studies for which full results are not relevant for inclusion

Study identified	Country	Summary of HRQL results presented	Justification for exclusion
D. Rea, 2011[89]	France	EQ-5D QLQ-C30	TA241 and TA251 provide long-term EQ-5D data (the reference case) which is more relevant than the HRQL data reported in D. Rea, 2011
P. C. Trask, 2012[82]	NR	44-Item Functional Assessment of Cancer Therapy-Leukemia (FACT-LEU)	TA241 and TA251 provide long-term EQ-5D data (the reference case) which is more relevant than the HRQL data reported in P. C. Trask, 2012
S. M. Szabo, 2010[124]	Canada, UK, US and Australia	Age- and sex-adjusted TTO utilities for seven CML-related heath states	The Assessment group for TA251 decided to use utilities from the IRIS study over those reported in Szabo, 2010 as these values were derived from a larger population
S. D. Reed, 2004[92]		Mean utility weights calculated from EQ-5D scores	Only the most relevant utility results, which are those used in TA251 and presented in Table B42 were extracted from this study
K. Dalziel, 2004[93]	NR	EQ-5D (also measured Functional Assessment of Cancer Therapy-Biological Response Modifier [FACT-BRM] and Global Rating of Change [GRC], but these results	Only the most relevant utility results, which are those used in TA251 and presented in Table B42 were extracted from this study

		were not extracted	
J. F. Guest, 2012[95]	UK	Mean utilities estimated by time trade-off and standard gamble	The study only presents utlity per response type rather than across all CP patients and does not give utilities for the accelerated or blast phases.
F. Efficace, 2011[96]	Italy	SF-36	The study does not report actual utility values, and is not in a UK population
Z. Aziz, 2011[97]	Pakistan	FACT-BRM	No utility values were reported, and its applicability to UK patients is limited.

NR = not reported

Table B88: Summary of identified HRQL Studies (Newly Diagnosed)

Study information	
Study Title	Utility values for chronic myelogenous leukemia chronic phase health states from the general public in the United Kingdom
First author	J. F. Guest[95]
Date of study	2012
Funding source	Novartis
Population in which health effects were measured	
Size of population	241
Nationality	British
Information on recruitment (ie. how was the sample selected)	Randomly selected members of the public from various locations in the UK
Response rate to questionnaire	NR
General public or patient group?	General public
Description of health states or adverse events	Chronic phase CML untreated; hematologic response; cytogenetic response; molecular response
Previous treatments	None
Current treatments	Not specified
Average age in years	45.3
Other important population characteristics	51% female, £21,800 mean annual salary, 7% had any cancer at time of interview, 84% new individuals with cancer
Method of elicitation	
Method of elicitation	Time trade off and standard gamble
Method of valuation	NR
Was mapping	No

used?					
Summary of results					
Results with confidence intervals	Mean utilities (95% CI) for CML chronic phase-related health states, stratified by respondents' cancer status				
		Untreated	Hematologic Response	Cytogenic Response	Molecular Response
	Utilities elicited using TTO				
	Whole cohort	0.72 (0.69; 0.75)	0.80 (0.79; 0.82)	0.89 (0.87; 0.90)	0.94 (0.94; 0.95)
	Those with cancer	0.65 (0.51; 0.79)	0.72 (0.62; 0.83)	0.83 (0.74; 0.92)	0.89(0.82; 0.96)
	Those without cancer	0.73 (0.70; 0.75)	0.81 (0.79; 0.83)	0.89 (0.88; 0.90)	0.95 (0.94; 0.96)
	Utilities elicited using SG				
	Whole cohort	0.39 (0.36; 0.41)	0.44 (0.41; 0.46)	0.61 (0.59; 0.64)	0.80 (0.78; 0.82)
	Those with cancer	0.35 (0.25; 0.45)	0.39 (0.30; 0.48)	0.54 (0.42; 0.66)	0.74 (0.62; 0.86)
	Those without cancer	0.39 (0.37; 0.42)	0.44 (0.41; 0.46)	0.62 (0.60; 0.65)	0.80 (0.78; 0.82)
	TTO, time trade-off; SG, standard gamble				
Applicability					
Applicability to UK population	Applicable as utilities derived from members of the UK general public				
Appropriateness of health states given condition and treatment pathway	Appropriate and accurately described, howeverno health states for accelerated or blast phase given and utilities only reported stratified by response status, not for the whole population, which does not correspond to the approach considered in our model.				
Consistency with reference case (eg. EQ-5D?)	Not EQ-5D, but direct TTO and SG are reliable methods of utility estimation				
Other points on appropriateness for cost-effectiveness analysis	Does not give utilities for the accelerated or blast phases. The study does report utilities by different socio-demographic parameters if a specific population is required for the model				
Other					
Any other comments on methodology, results or applicability	NR				
Study information					
Study Title	Health-related quality if life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population				
First author	F. Efficace[96]				
Date of study	2011				
Funding source	Novartis				
Population in which health effects were measured					
Size of population	448				
Nationality	Italy				

Information on recruitment (ie. how was the sample selected)	CML patients were enrolled in a multicentre cross-sectional study including 26 centres. Patients were identified through hospital medical records and were invited to participate by their own treating physician in the hospital	
Response rate to questionnaire	94%	
General public or patient group?	Patient group	
Description of health states or adverse events	Chronic phase CML patients receiving imatinib and matched control group	
Previous treatments	None	
Current treatments	Imatinib	
Average age in years	57	
Other important population characteristics	Patient had to be at least in completed cytogenetic response at the time of study entry Patients who had received any type of previous treatment were not eligible	
Method of elicitation		
Method of elicitation	SF-36	
Method of valuation	NR	
Was mapping used?	NR	
Summary of results		
Results with confidence intervals	**SF-36 Scales**	**CML patients, mean (SD)**
	Physical health	
	Physical functioning	76.8 (24.8)
	Role physical	61.6 (42.2)
	Bodily pain	70.4 (26.2)
	General health	52.7 (22.6)
	PCS	46.0 (9.6)
	Mental Health	
	Vitality	56.2 (21.2)
	Social functioning	73.9 (22.7)
	Role emotional	64.5 (40.7)
	Mental health	67.1 (19.8)
	MCS	49.3 (9.8)
	CML indicates chronic myeloid leukemia; PCS, physical component summary; MCS, mental component summary; SD, standard deviation; and CI, confidence interval.	
Uncertainty around values	SD values reported above	
Applicability		
Applicability to UK population	Some (European Country)	
Appropriateness of health states given condition and treatment pathway	Only one health state measured (chronic phase patients receiving imatinib)	
Consistency with reference case (eg. EQ-5D?)	Not EQ-5D	
Other points on appropriateness for cost-effectiveness analysis	No QoL scores for accelerated or blast phases	
Other		

Any other comments on methodology, results or applicability	NR

Study information	
Study Title	Assessment of quality of life with imatinib mesylate as first-line treatment in chronic phase-chronic myeloid leukemia
First author	Z. Aziz[97]
Date of study	2011
Funding source	NR
Population in which health effects were measured	
Size of population	90
Nationality	Pakistan
Information on recruitment (ie. how was the sample selected)	Enrolment through the Imatinib Expanded Access Program between May 2009 and April 2010 at a single centre
Response rate to questionnaire	100%
General public or patient group?	Patient
Description of health states or adverse events	Chronic phase patients receiving imatinib
Previous treatments	None
Current treatments	Imatinib mesylate
Average age in years	38
Other important population characteristics	Chemotherapy naive
Method of elicitation	
Method of elicitation	FACT-BRM
Method of valuation	Trial outcome index (TOI) created as a measure of physical function and well-being
Was mapping used?	NR

Summary of results

Results with confidence intervals — Trial Outcome Index (TOI) mean scores in assessment of QoL with imatinib mesylate in CP-CML*

TOI Scale	Total Score	Baseline	3 Months	6 Months	Mean	p-value
DFWB†	32	13.5	28.47	30.3	+16.4	<0.0001
Fatigue‡	12	11.1	6.1	4.7	-6.2	<0.0001
ECF‡	16	9.9	6.1	4.9	-4.9	<0.0001
Side ‡effects	28	24.1	9.8	7.7	+16.1	<0.0001

*Estimates calculated by repeated measures analysis of variance (ANOVA)
†A high score in DFWB scale represents a high/healthy quality of life. A decrease of 5 or more considered a clinically significant improvement
‡A low score in fatigue, ECF, and side-effects scale represents a high/healthy quality of life. A decrease of 5 or more is considered a clinically significant improvement
DFWB, daily functioning and well-being; ECF, emotional and cognitive function

Uncertainty around values	NR
Applicability	
Applicability to UK population	Low
Appropriateness of health states given condition and treatment pathway	Only one health state measured (chronic phase patients receiving imatinib)
Consistency with reference case (eg. EQ-5D?)	No
Other points on appropriateness for cost-effectiveness analysis	No QoL scores for accelerated or blast phases

Other								
Any other comments on methodology, results or applicability	NR							
Study information								
Study Title	A multinational study of patient preference values for health states for chronic myelogenous leukemia							
First author	S. M. Szabo[124]							
Date of study	2010							
Funding source	BMS							
Population in which health effects were measured								
Size of population	339 (97 from the UK)							
Nationality	Drawn from Canada, the United Kingdom, the United States and Australia							
Information on recruitment (ie. how was the sample selected)	Interviewer administered survey							
Response rate to questionnaire	NR							
General public or patient group?	General Public							
Description of health states or adverse events	Chronic phase, responder (CR) Chronic phase, non-responder (CNR) Accelerated phase, responder (AR) Accelerated phase, non-responder (ANR) Blast phase, responder (BR) Blast phase, non-responder (BNR) Withdrawal of treatment due to serious AEs							
Previous treatments	NR							
Current treatments	NR							
Average age in years	44.9 (43.2 for UK)							
Other important population characteristics	NR							
Method of elicitation								
Method of elicitation	Preference for CML-related health states							
Method of valuation	Individual health state preference values were calculated by dividing the number of years the respondent would live in full health by the ten year time horizon							
Was mapping used?	NR							
Summary of results								
Results with confidence intervals	Age- and sex-adjusted TTO utilities (05% CI) for 339 layperson respondents for seven CML-related health states according							
		Health state						
	Respondents	CR	CNR	AR	ANR	BR	BNR	SAEs
	All	0.91 (0.87, 0/93)	0.73 (0.66, 0.79)	0.78 (0.71, 0.83)	0.49 (0.41, 0.56)	0.48 (0.39, 0.56)	0.22 (0.15, 0.29)	0.58 (0.50, 0.65)
	UK	0.85 (0.61, 0.94)	0.68 (0.48, 0.81)	0.79 (0.62, 0.88)	0.50 (0.33, 0.63)	0.50 (0.31, 0.63)	0.31 (0.14, 0.44)	0.48 (0.25, 0.64)
Uncertainty around values	NR							
Applicability								
Applicability to UK population	High (contains UK patients)							
Appropriateness of health states given condition and treatment pathway	Appropriate							

Consistency with reference case (eg. EQ-5D?)	Not EQ-5D, but direct TTO
Other points on appropriateness for cost-effectiveness analysis	NR
Other	
Any other comments on methodology, results or applicability	NR
Study information	
Study Title	Cost-effectiveness of imatinib versus interferon-a plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia
First author	S. D. Reed[92]
Date of study	2004
Funding source	Novartis
Population in which health effects were measured	
Size of population	NR
Nationality	UK
Information on recruitment (ie. how was the sample selected)	Patients from the IRIS study
Response rate to questionnaire	NR
General public or patient group?	Patient
Description of health states or adverse events	Chronic phase (CP), accelerated phase (AP) and blast crisis (BP)
Previous treatments	None: newly diagnosed CML
Current treatments	Imatinib or IFN+LDAC
Average age in years	NR
Other important population characteristics	NR
Method of elicitation	
Method of elicitation	Mean utility weights calculated from EQ-5D scores
Method of valuation	N/A
Was mapping used?	No
Summary of results	
Results with confidence intervals	Mean utility weights: CP: 0.854 AP: 0.595 BP: 0.595
Uncertainty around values	CP: 0.004 (SE) AP: 0.077 (SE) BP: 0.077 (SE)
Applicability	
Applicability to UK population	Study on UK patients, so highly applicable

Appropriateness of health states given condition and treatment pathway	Appropriate
Consistency with reference case (eg. EQ-5D?)	EQ-5D
Other points on appropriateness for cost-effectiveness analysis	Utility weights for AP and BP were calculated from pooled data from IRIS patients in either of the clinical phases, regardless of their initial treatment assignment due to the small number of patients progressing to advanced phases of CML
Other	
Any other comments on methodology, results or applicability	Utilities were assumed to be independent of drug therapy and time
Study information	
Study Title	Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis
First author	K. Dalziel[93]
Date of study	2004
Funding source	Novartis
Population in which health effects were measured	
Size of population	1106
Nationality	NR
Information on recruitment (ie. how was the sample selected)	NR
Response rate to questionnaire	1067 patients were included in the QoL assessment, as Danish participants and Flemish-speaking patients in Belgium were excluded
General public or patient group?	Patient group
Description of health states or adverse events	Chronic phase, accelerated phase and blast phase for each treatment. No detailed description of states given
Previous treatments	87% patients of total population (N=1106) had previously taken hydroxycarbamide
Current treatments	Imatinib (N=553) or IFNα + Ara-C (N=553)
Average age in years	51
Other important population characteristics	59% male Median 1.97 months since diagnosis
Method of elicitation	
Method of elicitation	EQ-5D (also measured Functional Assessment of Cancer Therapy–Biological Response Modifier [FACT-BRM] and Global Rating of Change [GRC], but these results were not extracted)
Method of valuation	N/A

Was mapping used?	No		
Results with confidence intervals	**Health States**	**Utility values (SD)**	**Source**
	CP: imatinib treatment	0.8539 (0.1925)	IRIS study 2002, Novartis data on file
	CP: imatinib treatment after loss of CR	0.8539 (0.1925)	IRIS study 2002, Novartis data on file
	CP: IFN-a treatment	0.7104 (0.2658)	IRIS study 2002, Novartis data on file
	CP: IFN-a treatment after loss of CR	0.7104 (0.2658)	IRIS study 2002, Novartis data on file
	CP hydroxycarbamide treatment	0.9 (0.2[a])	Kattan et al., 1996
	CR: imatinib treatment	0.8539 (0.1925)	IRIS study 2002, Novartis data on file
	CR: IFN-a treatment	0.7104 (0.2658)	IRIS study 2002, Novartis data on file
	AP: imatinib treatment	0.729 (0.204)	IRIS study 2002, Novartis data on file
	AP: IFN-a treatment	0.729 (0.204)	IRIS study 2002, Novartis data on file
	AP: hydroxycarbamide treatment	0.729 (0.204)	IRIS study 2002, Novartis data on file
	BP: mercaptopurine	0.524 (0.424)	IRIS study 2002, Novartis data on file
	[a]Estimated		
Uncertainty around values	SD values given above		
Applicability			
Applicability to UK population	Unclear, as no break-down of nationality		
Appropriateness of health states given condition and treatment pathway	Very appropriate		
Consistency with reference case (eg. EQ-5D?)	Used EQ-5D, therefore consistent with reference case		
Other points on appropriateness for cost-effectiveness analysis	None		
Other			
Any other	Patient estimates, and are likely to capture preference for the treatment as		

comments on methodology, results or applicability	well as a preference for being in a particular health state Utilities were assumed to be independent of drug therapy and time

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

10.13.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

- Medline (OVID Interface)
- Embase (OVID Interface)
- Medline In-Process (OVID Interface)
- EconLIT (OVID Interace)
- NHS EED (Searched via the Cochrane Library and also via Centre for Reviews and Dissemination)
- Cochrane Library

10.13.2 **The date on which the search was conducted.**

The search was conducted on 2/10/2012

10.13.3 **The date span of the search.**

The date span of the search was from database inception to 2/10/2012

10.13.4 **The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).**

Ovid Interface

1. “myeloid* leukemia*”[tw]
2. “myeloid* leukaemia*”[tw]
3. Leukemia, Myeloid[MeSH:NoExp]
4. CML[tw]
5. leukemia, myeloid, chronic-phase[MeSH:NoExp]
6. leukemia, myeloid, chronic, atypical, bcr-abl negative[MeSH:NoExp]
7. leukemia, myelogenous, chronic, bcr-abl positive[MeSH]
8. “myelogenous* leukemia*”[tw]
9. “myelogenous* leukaemia*”[tw]
10. “myelocytic* leukemia*”[tw]
11. “myelocytic* leukaemia*”[tw]
12. leukemia, myelomonocytic, chronic[MeSH:NoExp]

13. “major cytogenetic response”[tw]
14. “major molecular response”[tw]
15. Or/1- 14
16. Philadelphia Chromosome[MeSH:NoExp]
17. Philadelphia[tw] AND Chromosome[tw]
18. (PH1[tw] OR “PH 1”[tw]) AND Chromosome[tw]
19. Or/16-18
20. 15 OR 19
21. costs and cost analysis[MesH] OR health care costs[MeSH]
22. economics[MeSH]
23. value of life[MeSH]
24. burden[tw] AND (disease[tw] OR illness[tw])
25. economic*[tw] OR expenditure*[tw] OR price*[tw] OR pricing[tw] OR pharmacoeconomic*[tw]
26. budget*[tw] OR fiscal[tw] OR funding[tw] OR financial[tw] OR finance*[tw]
27. resource[tw] AND (allocation*[tw] OR utili*[tw] OR use[tw])
28. Socioeconomic factors[MeSH:NoExp]
29. Cost-benefit analysis[MeSH]
30. Health expenditures[MeSH:NoExp]
31. Capital expenditures[MeSH:NoExp]
32. Financial management, hospital[MeSH:NoExp]
33. cost[tw] AND (estimat*[tw] OR variable*[tw] OR unit[tw])
34. Models, statistical[MeSH]
35. decision trees[MeSH]
36. decision making, computer assisted[MeSH]
37. theoretical model[MeSH]
38. markov chains[MeSH:NoExp]
39. Monte Carlo Method[MeSH:NoExp]
40. Decision Theory[MeSH]
41. (healthcare[tw] OR health-care[tw]) AND cost*[tw]
42. Computer simulation[MeSH]
43. Models, Theoretical[MeSH]
44. Patient Simulation[MeSH]
45. pharmacoeconomic*[tw] OR pharmaco-economic*[tw]
46. “cost* effective*”[tw] or “cost* utilit*” or “cost* benefit*”[tw] or “cost* minimi*”[tw] or CEA[tw] or CUA[tw] or CMA[tw]
47. “incremental cost effectiveness ratio*”[tw] OR icer*[tw]
48. “decision* tree*”[tw] OR “decision* analy*”[tw] OR “decision* model*”[tw] OR “markov model*”[tw]
49. “Quality-Adjusted Life Years”[MeSH]
50. “Quality-adjusted life year*”[tw] OR QALY*[tw]
51. OR/21-50
52. 20 AND 51

Cochrane library

1. CML
2. myeloid* leukaemia*
3. myeloid* leukemia*
4. myelogenous* leukemia*
5. myelogenous* leukaemia*
6. myelocytic* leukemia*
7. myelocytic* leukaemia*
8. major cytogenetic response
9. major molecular response
10. Philadelphia Chromosome
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

12. MeSH descriptor **Leukemia, Myeloid**, this term only
13. MeSH descriptor **leukemia, myeloid, chronic-phase**, this term only
14. MeSH descriptor **leukemia, myeloid, chronic, atypical, bcr-abl negative**, this term only
15. MeSH descriptor **leukemia, myelogenous, chronic, bcr-abl positive**, explode all trees
16. MeSH descriptor **leukemia, myelomonocytic, chronic**, this term only
17. MeSH descriptor **Philadelphia Chromosome**, this term only
18. #12 OR #13 OR #14 OR #15 OR #16 OR #17
19. #11 OR #18
20. MeSH descriptor **costs and cost analysis**, explode all trees
21. MeSH descriptor **health care costs**, explode all trees
22. MeSH descriptor **economics**, explode all trees
23. MeSH descriptor **value of life**, explode all tree
24. Burden of disease* OR disease burden OR burden of illness
25. Cost* OR economic* OR expenditure* OR price* OR pricing OR pharmacoeconomic*
26. Budget* OR fiscal OR funding OR financial OR finance*
27. Resource allocation OR resource use OR resource utili*
28. MeSH descriptor **financial management, hospital,** this term only
29. MeSH descriptor **cost of illness**, this term only
30. MeSH descriptor **employer health costs**, this term only
31. MeSH descriptor **health expenditures**, this term only
32. MeSH descriptor **capital expenditures**, this term only
33. Low cost* OR high cost*
34. Healthcare cost* OR health care cost*
35. Cost estimat*
36. Cost variable
37. Unit cost*
38. Cost* effective* OR cost* utility* OR cost* benefit* OR cost* minimi* OR CEA OR CUA OR CMA
39. MeSH descriptor **models, statistical**, explode all trees
40. MeSH descriptor **computer simulation**, explode all trees
41. MeSH descriptor **models, theoretical**, explode all trees
42. #39 OR #40 OR #41
43. MeSH descriptor **patient simulation**, explode all trees
44. MeSH descriptor **decision trees**, explode all trees
45. Incremental cost effectiveness ratio* or icer*
46. MeSH descriptor **Monte Carlo Method**, this term only
47. MeSH descriptor **Decision Theory**, explode all trees
48. Decision* tree* or decision* analy* or decision* model* or markov model*
49. MeSH descriptor exp **Quality-Adjusted Life Years**, explode all trees
50. Quality-adjusted life year* or QALY*
51. #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50
52. #19 AND #51

NHS EED, via CRD

12. CML
13. myeloid* leukaemia*
14. myeloid* leukemia*
15. myelogenous* leukemia*
16. myelogenous* leukaemia*

17. myelocytic* leukemia*
18. myelocytic* leukaemia*
19. major cytogenetic response
20. major molecular response
21. Philadelphia Chromosome
22. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

Search results were also filtered by the following terms:

- Dasatinib *or* BMS-354825 *or* Sprycel®
- Nilotinib *or* AMN107 *or* Tasigna®
- Imatinib *or* imatinib mesilate or STI571 *or* Gleevec® *or* Glivec®
- Bosuntinib *or* SKI-606 *or* Bosulif®
- Stem-cell *or* stem cell
- Hydroxycarbamide *or* hydrocarbamide *or* Droxia® *or* Hydrea®
- Interferon *or* IFN *or* Roferon®
- Standard of care *or* standard care *or* placebo *or* supportive care

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Horizon scans for relevant articles were performed using the Google search engine using the key words: CML, chronic myeloid leukaemia, combined with cost-effectiveness, cost-utility, model.

ISPOR, ASCO, ESMA, ICLLM and ASH congress abstracts/posters were also searched for any relevant articles not picked up by the search in 7.5.3. NICE HTAs were also searched.

10.13.6 The inclusion and exclusion criteria.

See main body of submission

10.13.7 The data abstraction strategy.

For the identified articles, data and methods were extracted by one reviewer, and checked by another independent reviewer. Extractions were carried out to fill the following table:

Table B89: Example extraction grid used to abstract relevant data from identified studies

Study information	
Study Title	
First author	
Date of study	
Country(ies) where study was performed	
Currency	
Funding source	
Applicability to UK clinical practice	
Summary of resource use	
Resource use items measured (eg. hospitalisations, GP visits etc.)	

Resource use items suitable for use in the economic analysis (give brief results)	
Summary of costs	
Items costed (if different from resource use list above)	
Resource Use Costs	
Technology costs	
Other	
Any other comments on methodology, results or applicability	
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)	

Table B90: Summary of identified studies for which full results are not relevant for inclusion

Study identified	Country	Summary of relevant resource use and costs	Justification for exclusion
J. Darba, 2012[123]	UK/Spain	Resource use Special visit, day hospital visit, chest x-ray, PCR, cytogenetic testing, transfusion Costs Same as resource use. Additionally, monthly costs of dasatinib 100 mg/day and imatinib 800 mg/day	Resource use/cost data from a Spanish population (although utility data is from a UK study)
S. M. Szabo, 2009[125]	UK	Resource use Outpatient visits, laboratory tests, interventions and hospitalization Costs Costs of response and no-response to treatment in CP, AP and BP	Only abstract available
M, Taylor, 2009[117]	UK	Resource use None Costs Lifetime cost of treatment of CP CML patients with dasatinib 100 mg, imatinib 800 mg and nilotinib 800 mg (versus dasatinib)	
M. Taylor, 2009b[116]	UK	Resource use None	Only abstract available

		Costs Cost associated with different phases of CML to achieve 'no response', 'complete haematological response' (CHR), 'partial cytogenic response' (PHR) and 'complete cytogenic response' (CCR) in the chronic, accelerated and blast phases.	
E. Warren, 2004[120]	UK	Resouce use Palliative care per day, outpatient visit, bone marrow test, blood transfusion, radiology tests, nurse home visit, GP home visit, conventional chemotherapy Costs Imatinib mesylate per month, hydroxycarbamide per month	

As discussed in Section 7.4.18, full extraction results for 6 of the 8 articles identified by the resource use systematic review are presented in Table B136. The extraction results for Loveman 2012[85] and Hoyle 2011a[80] are not provided, since these articles report on the Rogers 2012[84] results and hence the relevant extraction results from these articles is already captured under Rogers 2012[84] in Table B91.

Table B91: Summary of Identified Resource and Cost Studies

Study information							
First author	J. Darba[123]						
Date of study	2012						
Country(ies) where study was performed	UK/Spain						
Currency	Euro						
Funding source	BMS						
Applicability to UK clinical practice	Some – Spanish cost/resource data						
Summary of resource use							
Resource use items measured (eg. hospitalisations, GP visits etc.)	Special visits, day hospital visits, chest x-ray, PCR, cytogenic testing, transfusion. All given as resource use per month						
Resource use items suitable for use in the economic analysis (give brief results)		**Chronic Phase**		**Accelerated Phase**		**Blast Phase**	
	Resource	**Response**	**No Response**	**Response**	**No Response**	**Response**	**No Response**
	Special Visit	0.5	1	1	2	2	4
	Day Hospital Visit	0	0	1	2	1	2
	Chest x-ray	0	0	0	1	3.5	3.5
	PCR	0.5	1	1	2	2	4

	Cytogenic Testing	0.17	0.33	0.33	0.33	0.33	0.33
	Transfusion	0	0	0.5	0.63	1	2

Summary of costs	
Items costed (if different from resource use list above)	As above. Additionally, monthly costs of dasatinib 100mg/day and imatinib 800mg/day
Resource Use Costs	Special visits: €59.98 Day hospital visits: €193.53 Chest x-ray: €6.83 PCR: €260.03 Cytogenic Testing: €154.46 Transfusion: €231.11
Technology costs	Dasatinib 100mg/day: €4,082 Imatinib 800mg/day: €5,001
Other	
Any other comments on methodology, results or applicability	Spanish cost/resource data, but study uses utility data from a UK study
Study information	
First author	M. Hoyle (b)[86]
Date of study	July 2011
Country(ies) where study was performed	UK
Currency	Pounds
Funding source	NR
Applicability to UK clinical practice	UK study
Summary of resource use	
Resource use items measured (eg. hospitalisations, GP visits etc.)	Consultant outpatient visits, bone marrow tests, x-rays, CT scans, blood transfusions, third line treatment, inpatient terminal care
Resource use items suitable for use in the economic analysis (give brief results)	Consultant outpatient visits: CP treated: 4 visits/year CP not treated: 4 visits/year AP: 1 visit/month BP: 2 visits/month Bone marrow tests: CP treated: 2 visits/year CP not treated: none AP: none BP: none X-rays: CP treated: none CP not treated: none AP: none BP: 3 month CT scans: CP treated: none CP not treated: none AP: none BP: 0.5/month Blood transfusions CP treated: none CP not treated: none AP: none BP: none Third line treatment: CP treated: none

	CP not treated: continuously AP: none BP: none Inpatient terminal care: CP treated: none CP not treated: none AP: none BP: 1 stay/month, each stay 3 days		
Summary of costs			
Items costed (if different from resource use list above)	Second line 2-month cycle drug costs (dasatinib, nolitinib, high-dose imatinib, inferferon-α and cytarabine)		
Resource Use Costs	Consultant outpatient visits: £121/visit Bone marrow tests: £615/test X-rays: £29/visit CT scans: £103 per scan Blood transfusions: £490/transfusion Third line treatment: £2,079 per 2 months Inpatient terminal care: £119/day		
Technology costs	2-month cycle drug costs: Dasatinib: £5,080 Nilotinib: £5,286 High dose imatinib: £6,505 Interferon-α: £2,643 Cytarabine (with Interferon-α): £28		
Other			
Any other comments on methodology, results or applicability	NR		
Study information			
First author	G. Rogers[84]		
Date of study	April 2012		
Country(ies) where study was performed	UK		
Currency	Pounds		
Funding source	NR		
Applicability to UK clinical practice	Very applicable-health technology assessment for NICE		
Summary of resource use			
Resource use items measured (eg. hospitalisations, GP visits etc.)	Drug administration, monitoring outpatient appointment, bone marrow tests, radiography, CT scans, Blood transfusions, post discontinuation treatment, inpatient palliative care		
Resource use items suitable for use in the economic analysis (give brief results)	**Item**	**Population**	**Frequency**
	Consultant Outpatient Visits	CP treated	Four visits/year
		CP post-doscontinuation	Four visits/year
		AP	One visit/month
		BC	Two visits/month
	BM tests	CP treated	Two tests/year
		CP post-doscontinuation	None
		AP	None
		BC	None
	Radiography	CP treated	None

		CP post-doscontinuation	None
		AP	None
		BC	Three/month
	CT scans	CP treated	None
		CP post-doscontinuation	None
		AP	None
		BC	0.5/month
	Blood transfusions	CP treated	None
		CP post-doscontinuation	None
		AP	None
		BC	One/month
	Inpatient terminal care	CP treated	None
		CP post-doscontinuation	None
		AP	None
Summary of costs			
Items costed (if different from resource use list above)	NR		
Resource Use Costs	Consultant outpatient visits: £121 per visit BM tests: £615 per test Radiography: £29 per visit CT scans: £103 per scan Blood transfusions: £490 per transfusion Inpatient terminal care: £119 q.d.		
Technology costs	Imatinib-resistant CML Dasatinib drug cost: £161,432 Nilotinib drug cost: £70,143 High dose imatinib drug cost: £6597 IFN drug cost: : £15,936 Imatinib-intolerant CML Dasatinib drug cost: £244,926 Nilotinib drug cost: £169,771 IFN drug cost: : £15,936		
Other			
Any other comments on methodology, results or applicability	NR		
Study information			
First author	S. M. Szabo[125]		
Date of study	2009		
Country(ies) where study was performed	UK		
Currency	Pounds		
Funding source	Not stated		
Applicability to UK clinical practice	Very applicable		
Summary of resource use			
Resource use items measured (eg. hospitalisations, GP visits etc.)	Outpatient visits, laboratory tests, interventions and hospitalization		

Resource use items suitable for use in the economic analysis (give brief results)	Not stated
Summary of costs	
Items costed (if different from resource use list above)	3 month cost of treatment for patients in each phase
Resource Use Costs	Total Costs Responding to treatment: Chronic phase: £730 Accelerated phase: £867 Blast phase: £2659 Not responding to treatment: Chronic phase: £901 Accelerated phase: £1012 Blast phase: £4486
Technology costs	NR
Other	
Any other comments on methodology, results or applicability	Abstract only available. Presented at ISPOR 12th Annual European Congress Paris
Study information	
First author	M. Taylor[117]
Date of study	2009a
Country(ies) where study was performed	UK
Currency	Pounds
Funding source	Not stated
Applicability to UK clinical practice	Applicable
Summary of resource use	
Resource use items measured (eg. hospitalisations, GP visits etc.)	None
Resource use items suitable for use in the economic analysis (give brief results)	NR
Summary of costs	
Items costed (if different from resource use list above)	Lifetime cost of treatment of patients in chronic-phase CML taking dasatinib 100 mg, imatinib 800 mg and nilotinib 800 mg (vs dasatinib)
Resource Use Costs	NR
Technology costs	Dasatinib: £260,866 Imatinib: £311,685 Dasatinib produced an increased cost of £2,546 when compared against nilotinib
Other	
Any other comments on methodology, results or applicability	Lifetime QALYs also included
Study information	
First author	M. Taylor[116]
Date of study	2009b
Country(ies) where study was performed	UK
Currency	Pounds
Funding source	Not stated
Applicability to UK clinical practice	Should be applicable
Summary of resource use	
Resource use items measured (eg. hospitalisations, GP visits etc.)	None
Resource use items suitable for use in the	NR

economic analysis (give brief results)	
Summary of costs	
Items costed (if different from resource use list above)	Cost associated with different phases of CML to achieve 'no response', 'complete haematological response' (CHR), 'partial cytogenic response' (PHR) and 'complete cytogenic response' (CCR) in the chronic, accelerated and blast phases.
Resource Use Costs	Lifetime costs Chronic Phase No response: £57,867 CHR: £62,617 PCR: £66,499 CCR: £67,117 Accelerated Phase No response: £35,273 CHR: £35,850 PCR: £35,886 CCR: £51,693 Blast Phase No response: £13,252 CHR: £7,109 PCR: £10,993 CCR: £25,501
Technology costs	NR
Other	
Any other comments on methodology, results or applicability	Abstract only available. Presented at ISPOR 14th Annual International Meeting Orlando.
Study information	
First author	E. Warren[120]
Date of study	2004
Country(ies) where study was performed	UK
Currency	Pounds
Funding source	Not stated
Applicability to UK clinical practice	Applicable
Summary of resource use	
Resource use items measured (eg. hospitalisations, GP visits etc.)	Pallative care per day, Outpatient visit, Bone marrow test, Blood Transfusion, Radiology tests, Nurse home visit, GP home visit, Conventional chemotherapy
Resource use items suitable for use in the economic analysis (give brief results)	NR
Summary of costs	
Items costed (if different from resource use list above)	Imatinib mesylate per month, Hydroxyura per month
Resource Use Costs	Imatinib treatment Pallative care per day: £181 (remain there for the duration of their time in that health state) Outpatient visit: £60 (at beginning, Weeks 1, 2, 4 and every 8 weeks after) Bone marrow test: £60 (2/year and at time of disease progression) Blood Transfusion: £3243 (incurred immediately at progression to advanced disease states) Radiology tests: £94 Nurse home visit: £19 GP home visit: £45

	Conventional chemotherapy: £575 Hydroxycarbamide Pallative care per day: £181 (remain there for the duration of their time in that health state) Outpatient visit: £60 (every 4 weeks) Bone marrow test: £60 (at time of progression) Blood Transfusion: £3243 (incurred immediately at progression to advanced disease states) Radiology tests: £94 Nurse home visit: £19 GP home visit: £45 Conventional chemotherapy: £575
Technology costs	Imatinib mesylate per month: £1581 Hydroxycarbamide per month: £15
Other	
Any other comments on methodology, results or applicability	Resource costs taken from: British National Formulary; Chartered Institute of Public Finance and Accountancy; NHS; Personal Social Services Research Unit, University of Kent; National Blood Donor Registry
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); CP, chronic phase; AP, accelerated phase; BP, blast phase/crisis; CHR, complete haematological response; PHR, partial cytogenic response; CCR, complete cytogenic response	

10.13.8 Full cost calculations from TA251

Details of the full cost calculations giving rise to the costs presented in Section 7.4.18 are provided below.

Table B92: Full cost calculations for Table B49: Unit cost of treating the main serious adverse events

	Cost of treating if hospitalised	Cost of treating if not hospitalised	% that would be hospitalised	£ 2008 cost per AE	£ 2011 cost per AE
Neutropenia (Grade 3 & 4)	£1,668	£279	14.0%	£473	£497
Thrombocytopenia (Grade 3 & 4)	£1,234	£467	0.5%	£471	£494
Anaemia (Grade 3 & 4)	£324	£324	0.7%	£324	£340
Pleural effusion (All grades)		£30	0%	£30	£31
Source: Oxford Outcomes					

Table B93: Additional cost information from TA251 – costs of the main serious adverse events (during the first year after starting treatment)

	1st line treatment			2nd line treatment
	Dasatinib	**Nilotinib (300mg)**	**Imatinib[a]**	**Nilotinib (400mg)**
Neutropenia	£104	£59	£99	£144
Thrombocytopenia	£94	£50	£46	£144
Anaemia	£34	£11	£21	£11
Pleural effusion	£47	-	-	-
Total annual cost:	£280	£119	£166	£299
[a]based on weighted annual incidence from imatinib arm of DASISION and ENESTnd trials				

Table B94: Full cost calculations for Table B48: Summary of unit costs reported in TA241 and TA251

	Frequency (per month)a	Unit cost (£ 2009)c	Monthly cost (£ 2010)
Chronic phase:			
Nurse-led outpatient appointments	0.4	£100	40.00
Haematologist/Oncologist-led outpatient appointments	0.9	£127	114.30
Tests (various)b	See note[b]	Various	216.07
Hospital in patient – ward days	0	£246	0
Hospital in patient – ICU days	0	£1,219	0
Chronic phase total:		370	
Advanced phase:			
Nurse-led outpatient appointments	0.5	£100	50.00
Haematologist/Oncologist-led outpatient appointments	1.3	£127	165.10
Tests (various)b	See note[b]	Various	352.45
Hospital in patient – ward days	1.72	£246	423.83
Hospital in patient – ICU days	0.1	£1,219	121.90
Advanced phase total:			1,113

a frequencies as reported in Table 30 (p.56) of BMS"s submission to NICE
b The frequencies and cost of the following tests were included (based on the Oxford Outcomes 2009 clinician survey): complete blood count (CBC); cytogenetic analysis; bone marrow aspiration with biopsy; FISH; PCR; flow cytometry; cytochemistry analysis; blood film exam; chest X-ray; CT scan of chest; blood chemistry; C-reactive protein (CRP); EKG; upper endoscopy (EGD).
C See unit costs used by BMS (Table 39, p.65 of their submission) mostly sourced from the National Schedule of Reference Costs or the Unit Costs of Health and Social Care (Curtis 2009)[126], except: correction to the unit cost of a nurse-led and consultant-led haematology or oncology outpatient appointment – used NSRC 2009-10 estimates for face to face non-admitted outpatient appointments.

Table B95: Full cost calculations for Table B50: Per patient cost of a stem cell transplant

Related donor	Unrelated donor	Source and notes	
Cost for phases 1- 6 (£ 2009)	£47,500	£79,600	London SCG140
Inflated to 2011 (i.e. 2 years)	£49,115	£82,306	PSSRU – Curtis 2009[126]
% split of related vs unrelated:	25%	75%	Ashfaq et al
Weighted average:		£74,008	
PLUS cost of antifungal drugs	£5,369	London SCG140 (weighted average)	
PLUS donor lymphocyte infusions	£2,225	London SCG140 (weighted average, also using University Hospital Bristol dataa on % of related and unrelated donor patients receiving different numbers of DLIs)	

Mean per patient cost of SCT	£81,600b
a Of UHB's related donor SCT recipients, 42% received at least 1 DLI (and of these 53% had 1, 32% had 2, 10% had 3, and 5% had 4. Of UHB's unrelated (volunteer) donor SCT recipients, 14% received at least 1 DLI (and of these 87% had 1 and 17% had 3. b Rounded to the nearest £100.	

Table B96: Full cost calculations for Table B51: Estimation of on-going drug and monitoring costs after SCT

Immunosuppressive regime	Drug costs[a]	Quarterly appointments		% split	
Cyclosporin (50mg bd) plus Prednisolone (20mg od)	£65.96	£42	£107.62	60%	£64.57
Mycophenolate (1g bd) plus Prednisolone (20mg od)	£80.32	£42	£121.97	40%	£48.79
Weighted mean cost per month:	£113				
a Based on unit costs of drugs from the NHS Drug Tariff (Mycophenolate Mofetil 500mg - £28.40 for 50 tablets; Prednisolone 5mg tablets £2.58 for 28 tablets) and the BNF 61 (Cyclosporin 50mg, £27.00 for 30 tablets).					

ADDITIONAL APPENDICES

10.14 Appendix 14: Study 200 Definitions

Table B97 and Table B97 provide details of the definitions or resistance and intolerance, and of outcomes used in Study 200, referred to in Section 6.8.3.

Table B97: Definitions of resistance and intolerance used in Study 200

Term	Definition
Resistance	Resistance could be in the form of primary resistance or acquired resistance, as defined below. Resistance could also be as a result of a Bcr-Abl mutation
Primary resistance	Failure to achieve or maintain any of the following: • Haematological improvement within 4 weeks • Complete haematological response (CHR) after 12 weeks • Any cytogenetic response by 24 weeks • MCyR by 12 months
Acquired resistance	Loss of MCyR or any haematological response

Intolerance	An inability to take the TKI because of: • Drug-related grade 4 haematological toxicity lasting more than 7 days • Drug-related grade 3 or 4 non-haematological toxicity • Persistent grade 2 toxicity not responding to dose reduction and medical management • Loss of previously attained response on lower-dose TKI therapy with an inability to receive a higher dose due to a previous toxicity thought to be due to the prior TKI

Table B98: Definitions of outcomes used in Study 200

Outcome	Description/details
Cytogenetic Response	At least 20 metaphases were required for post-baseline assessment. If fewer than 20 metaphases were available, fluorescence in situ hybridisation (FISH) analysis of bone marrow aspirate for the presence of Bcr-Abl fusion protein could be used, provided ≥200 cells were analysed. Cytogenetics were performed within 14 days of registration and every 3 months thereafter. After 2 years, assessments were performed every 6 months. For CP patients, disease status was assessed at baseline and every 12 weeks during the first 2 years of treatment, every 24 weeks thereafter, and at the time of treatment completion. For advanced phase patients, cytogenetic assessments were performed monthly until week 12, or until the patient's status returned to chronic phase (whichever came first) and at week 24
Major cytogenetic response (MCyR)	0%—35% Ph^+ metaphases (0%—35% positive cells by FISH) MCyR = CCyR + PCyR
Complete cytogenetic response (CCyR)	0% Ph^+ metaphases (<1% positive cells by FISH)
Partial cytogenetic response (PCyR)	1%—35% Ph^+ metaphases (1%—35% positive cells by FISH)
Minor Cytogenetic Response (MiCyR)	36%—65% Ph^+ metaphases (36%—65% positive cells by FISH)
Minimal Cytogenetic Response	66%—95% (66%—95% positive cells by FISH)
No Cytogenetic Response	>95% positive cell (>95% positive cells by FISH)

Outcome	Description/details
Haematological Response	Haematological responses were based upon peripheral blood assessments (complete blood count, including 5-part differential, platelet count, absolute neutrophil count), bone marrow assessments (differential, clonal evolution) and clinical assessments of extramedullary disease. Peripheral blood assessments were performed at screening, weeks 1, 2, 3, 4, 8, 12, every 12 weeks during the first 2 years of treatment, every 24 weeks beginning with the third year of treatment and at the final visit
Complete haematological response (CHR)	For a patient to be deemed to possess a CHR, they must have fulfilled all of the following haematological criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in blood • White blood cell count (WBC) ≤ institutional ULN • Platelets <450 x 10^9/L • <20% basophils in blood • No extramedullary involvement (including hepato- or splenomegaly) • Platelets ≥100 x 10^9/L (only applicable to advanced phase) • Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (only applicable to advanced phase) • ≤5% bone marrow blasts (only applicable to advanced phase)
Overall haematological response (OHR)	A patient was defined as having an OHR if they met the criteria for any one of: CHR, no evidence of leukaemia (NEL) or return to chronic phase (RCP). <u>CHR</u> See above for criteria <u>NEL</u> A patient was defined as having NEL if they met all of the following criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in the blood • WBC ≤ institutional ULN • 450 x 10^9/L> platelets ≥20 x 10^9/L • ANC ≥0.5 x 10^9/L • <20% basophils in blood • No extramedullary involvement • ≤5% bone marrow blasts (only applicable to advanced phase) <u>RCP</u> To be defined as having achieved RCP, a patient had to meet all of the below criteria, with the exception of patients with CP CML who were not required to have post-baseline bone marrow samples taken. Disappearance of features defining accelerated and blast phases, but still in chronic phase as noted by: • <15% blasts in both peripheral blood and bone marrow • <30% blasts and promyelocytes in both peripheral blood and bone marrow • <20% basophils in both peripheral blood and bone marrow • No extramedullary involvement other than liver/spleen

Outcome	Description/details
Major haematological response (MHR)	A patient was defined as having a MHR if they met the criteria for either a CHR or NEL (see above)
Molecular Response	Assessed with non-nested RT-PCR for the BcrAbl transcript performed at a central laboratory (Quest Diagnostics) monthly for the first 3 months, every 3 months through 2 years and every 6 months thereafter
Major molecular response (MMR)	≥ 3 log reduction from standardised baseline (baseline based upon the PCR data of 120 previously untreated CML patients) in ratio of Bcr-Abl to Abl transcripts
Complete molecular response (CMR)	Undetectable Bcr-Abl transcript, with a PCR sensitivity of ≥5 log
Progression-free survival (PFS)	Within Study 200, PFS was calculated as the time from start of bosutinib therapy to disease progression (as assessed by an investigator), treatment discontinuation due to death or death within 30 days of the last dose. For patients who were last known to be alive and without progression, censoring was performed using the last date at which the patient was known to be progression free. Progression was defined by possession of any of the following criteria: • Entry in CP and clear progression to AP within the first 4 weeks of therapy (early progressor). To be considered a progressor to AP, a patient must have had an absolute increase of at least 10% in the count(s) qualifying the patient for accelerated phase • Evolution from initial CP, or from CP to which the patient returned, to AP or BP (evolution had to be measured on at least 2 consecutive assessments, at least 1 week apart) • Doubling of white blood cell count over at least 1 month with a second count >20 x 10^9/L confirmed at least 1 week later • Loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss • Loss of MCyR with an increase of ≥30% in Ph^+ metaphases
Overall survival (OS)	Overall survival was taken as the interval from the date of the first dose of bosutinib to the date of death, due to any cause. Patients who were not recorded as dead at the end of the study were censored at the last date at which they were known to be alive. The Study 200 protocol only required patients who discontinued treatment to be followed up for 24 months. It should therefore be noted that overall survival is truncated at 24 months for these patients and that this may bias the analysis with regards to this outcome

Outcome	Description/details
AP/BP Transformation Rate	Patients were considered to have undergone transformation if they experienced an evolution of disease from CP at study entry to AP or BP, or from AP at study entry to BP. This measure of transformation had to be present on 2 consecutive post-baseline assessments at least 1 week apart. In cases where the last haematological assessment did not confirm AP or BP status, then treatment discontinuation due to disease progression and death, or death within 30 days of last dose was considered a confirmation of transformation
FACT-Leu	The FACT-Leu is a 44-item, self-reported, reliable and valid assessment of health-related quality-of-life in patients with leukaemia. The FACT-Leu measures leukaemia specific health related quality of life and consists of 4 domains (27 items): • Physical well being (PWB) • Social well being (SWB) • Emotional well being (EWB) • Functional well being (FWB) The FACT-leu also measures a leukaemia subscale (LEUS) of additional concerns (17 items)
EQ-5D	EQ-5D is a patient-reported outcome which was obtained at screening, weeks 4, 8 and 12, every 12 weeks thereafter and at the end of treatment visit in countries where appropriate translations were available. EQ-5D assessments were also administered at the time of disease progression, grade 3 or 4 toxicitiy or at the time of early withdrawal. EQ-5D is a 5-item validated assessment of patient utility, consisting of: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Where each item takes an integral value from 1 (“no problems”) to 3 (“extreme problems”). The scores on these 5 items are summarised to create a single summary score. Since the questions may be answered differently in different countries/regions, for example due to different societal perspectives or customs, different weightings or tarrifs may be applied to the summary score. Study 200 EQ-5D data presented in this submission uses the UK summary score, such that the evidence is most relevant to the patient population covered in this submission i.e.patients in England and Wales. In addition, the EQ-5D has a general health visual anaolog scale (VAS): scores range from 0 to 100, where 0 is equivalent to the worst imaginable health state and 100 is equivalent to the best imaginable health state.
Adverse events (AEs)	Incidence and severity of AEs were reported at each study visit through 30 days after the last dose of bosutinib. Graded by use of the National Cancer Institute Common

Outcome	Description/details
	Terminology for Adverse Events Version 3.0[127]
Grade 3/4 adverse event	Unique clinical descriptions dictate the grading of each AE, but generally grade 3/4 AEs are considered severe (grade 3) or life-threatening or disabling (grade 4)

10.15 Appendix 15: The second-line CP CML population

The second-line CP CML patient population was considered of lesser relevance to this submission, as the majority of patients in UK clinical practice will be eligible to receive nilotinib as a second-line therapy. Therefore the details of this patient population and the clinical efficacy and safety results are presented as part of this additional appendix.

Table B99 provides an overview of the data sources used for the presentation of data for the second-line CP CML patient population from Study 200.

Table B99: Data sources for the second-line CP CML patient population

Second-line CP CML population
Data snapshot 28th March 2011 (24 month minimum follow-up): • Cortes et al, 2011 publication[5] • CSR[56] **Data snapshot 15th May 2012 (36 month minimum follow-up update):** • Cortes et al, ASH 2012 poster.[59] This source is in the form of a poster presented at the 54th ASH Annual Meeting and Exposition, December 8-11, 2012

The Cortes et al, 2011 publication[5] reports a subpopulation analysis of 288 patients with imatinib-resistant or imatinib-intolerant CP Ph^+ CML (ie. second-line CP CML patients). Within the second-line population, a small subpopulation may have been unsuitable for dasatinib and nilotinib, for example due to their mutation or co-morbidity profile. Therefore, this study is representative of and includes patients from the licensed patient population for bosutinib. This publication presents data from a June 2010 snapshot. The evidence in this publication has since been updated by data from a 28th March 2011 snapshot (24-month minimum follow-up), which is presented in the CSR[56] and a 15th May 2012 snapshot (36-month minimum follow-up) presented in the Cortes et al, ASH 2012 poster.[59] Given the availability of this more recent data, the Cortes et al, 2011 publication will not be the focus of this submission and the majority of the data considered as the evidence base for the second-line CP CML population will come from the CSR and the Cortes et al, ASH 2012 poster.

Characteristics of the second-line CP CML patient population

The second-line CP CML patient population comprised of 288 adult patients with imatinib-intolerant or imatinib-resistant Ph^+ CP CML and no other previous TKI exposure

Study design

The majority of the aspects of the Study 200 design for the second-line CP CML reference population were shared with the other patient populations and hence are presented in Table B5. Those aspects specific to the second-line CP CML patient population are presented in Table B100.

Table B100: Design aspects of Study 200 specific to the second-line CP CML population

Parameter	Second-line CP CML population
Duration of follow-up	Patients remain in the trial until death or lost to follow-up Cortes et al, 2011[5] presents data from a 3rd June 2010 data snapshot The Study 200 CSR is based on a 28th March 2011 data snapshot, which corresponds to 24 months minimum follow-up Cortes et al, December 2012 presents data from a 15th May 2012 data snapshot, which corresponds to 36 months minimum follow-up[59] Where 2nd line patient level data is used in the economic model, this is based on data snapshot 15 Feb 2012. No further statistical analysis of this data has been performed and therefore the results from this data snapshot are not presented in section 6.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint of the study was rate of MCyR by 24 weeks
Secondary outcomes (including scoring methods and timings of assessments)	Other outcomes reported for this population were: • Further response rates for efficacy endpoints: CCyR, CHR, MMR and CMR • Median duration of MCyR and CHR • Median time to MCyR and CHR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • Transformation Rate • FACT-Leu • EQ-5D Safety outcomes were also considered: • Incidence rate of any AEs

Eligibility criteria for the second-line CP CML patient population

In addition to the general eligibility criteria presented in Table B6, the following eligibility criteria applied to the second-line CP CML patient population:

- Imatinib-resistant or imatinib-intolerant CP Ph^+ CML
- QTc interval <470 msec at screening

Patient characteristics at baseline

Patient characteristics at baseline for the second-line CP CML population (n=288) are presented in Table B101.

Table B101: Baseline characteristics for the second-line CP CML population

Characteristic	Imatinib-resistant (n=200)	Imatinib-intolerant (n=88)	Total
Age, y			
Median	51.0	54.5	53.0
Range	18-86	23-91	18-91
Sex, n (%)			
Female	84 (42%)	50 (57%)	134 (47%)
Male	116 (58%)	38 (43%)	154 (53%)
Haematological analysis, 10^9/L			
White blood cell count			
Median	6.7	5.9	6.5
Range	2.1-151	2.1-160.7	2.1-151
Platelet count			
Median	261.5	202.5	237.5
Range	47-2436	48-2251	47-2436
Duration of disease, y			
Median	4.0	2.8	3.6
Range	0.1-15.1	0.1-13.6	0.1-15.1
Treatment history			
No. of previous therapies*, n (%)			
1	131 (66%)	65 (74%)	196 (68%)
2	69 (35%)	23 (26%)	92 (32%)
Previous IFN	69 (35%)	23 (26%)	92 (32%)
Previous SCT	6 (3%)	2 (2%)	8 (3%)
Features of imatinib treatment			
Duration of previous imatinib treatment, y			
Median	2.6	1.5	2.2
Range	0.4-8.8	<0.1-8.3	<0.1-8.8
Previous CHR with imatinib, n (%)	164 (82%)	55 (63%)	219 (76%)
Reason for stopping imatinib, n (%)			
Adverse event (intolerance)†	1 (1%)	86 (98%)	87 (33%)
Disease progression	163 (92%)	1 (1%)	164 (62%)
Regimen completed	7 (4%)	0 (0%)	8 (3%)
Other	7 (4%)	1 (1%)	7 (3%)
Missing‡	22	0	22
1 or more Bcr-Abl mutations detected§	57/83 (69%)	8/32 (25%)	65/115 (57%)

*Includes previous tyrosine kinase inhibitor therapies. Percentages may not total 100% because of rounding

†Patients simultaneously meeting the protocol definitions for imatinib resistance and imatinib intolerance are categorized as having imatinib resistance

‡The reason for stopping imatinib was not reported

§Total of 83 imatinib-resistant and 32 imatinib-intolerant patients assessed for mutation status at baseline

Statistical analyses

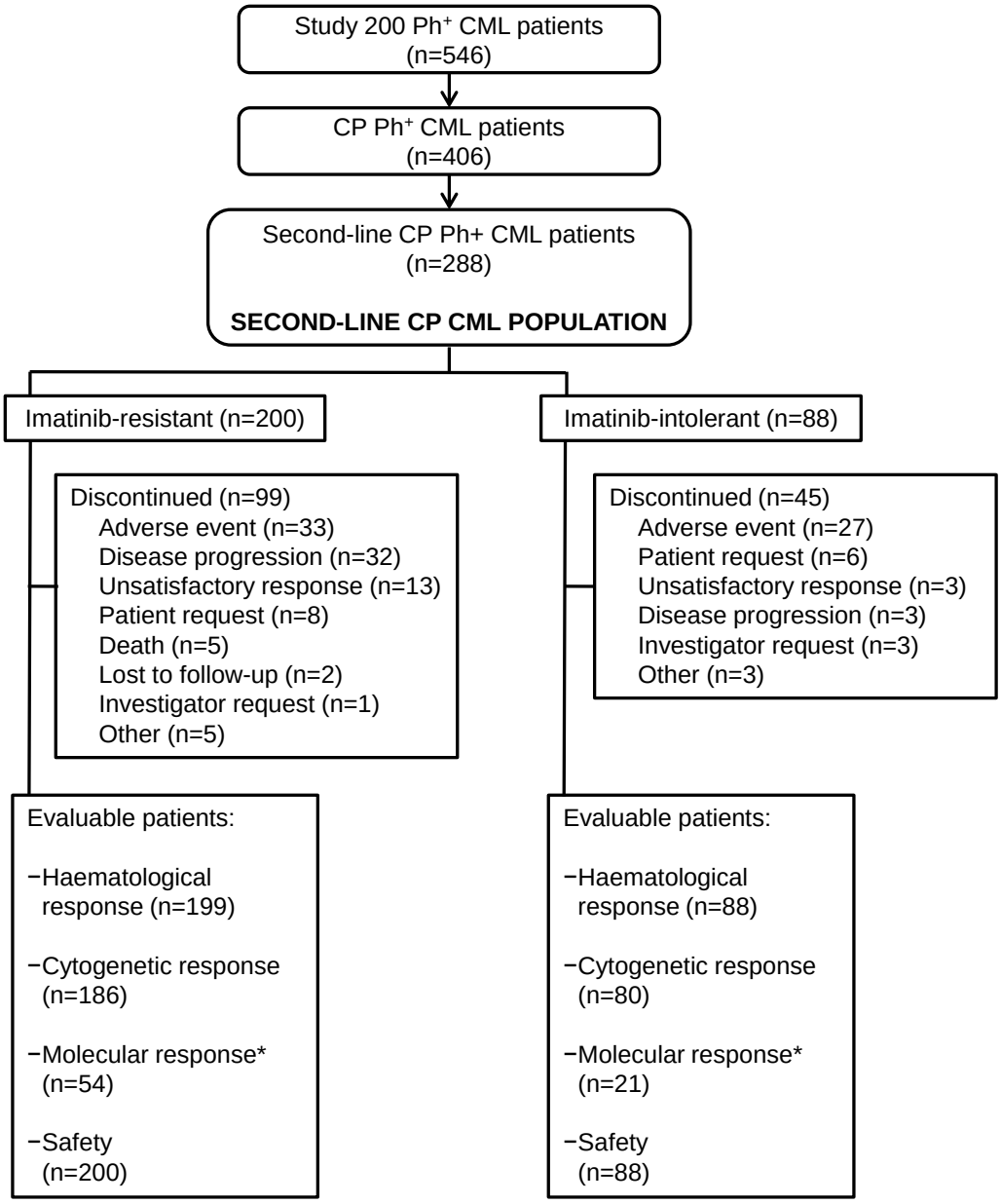
The second-line CP CML patient population was comprised of patients with imatinib resistance and patients with imatinib intolerance. The details of the statistical analyses for these patient groups are presented in Table B102.

Table B102: Statistical analysis details for the second-line CP CML population

TKI exposure history	Stastical analysis details
CP CML patients resistant to imatinib and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a MCyR rate at 24 Weeks of 0.33 is of interest. Taking the interesting and uninteresting rates for MCyR rate at 24 Weeks to be p1=0.33 and p0=0.23, respectively, it was desired to test the null hypothesis of H0: p≤0.23 against the 1-sided alternative H1: p>0.23 Power calculation The hypothesis test was performed with a type I error rate of 0.05 and 80% power at p=0.33 Sample size calculation The design of the primary cohort incorporated a 4-stage group sequential design , requiring a maximum sample size of 167 evaluable patients, with a sample size of 82 expected under the null hypothesis, and a sample size of 115 expected when the true MCyR rate was p=0.33. Statistical analyses The test statistic, standardized using the empirical variance estimate, was assessed for efficacy at an overall 1-sided significance level of 0.05, and assessed for futility at an overall 1-sided significance level of 0.20. The decisions concerning stopping for efficacy or futility were based on the error spending functions at the actual number of enrolled patients at the interim analyses.
CP CML patients intolerant to imatinb and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a 73% MCyR rate at 24 Weeks was of interest. Taking the interesting and uninteresting MCyR rates at 24 Weeks to be p1=0.73 and p0=0.56, respectively, the null hypothesis H0: p ≤p0 was tested against the alternative H1: p≥p1. Sample size calculation The optimum Simon 2-stage design for alpha=0.05, beta=0.20, required a maximum of n=55 patients with 16 in the first stage. If the response rate was no greater than 9/16=0.56 at stage 1, consideration was given to early termination. The expected sample size under the null was 31.5 and probability of early termination under the null was 0.60.

Figure B57 shows the flow of participants for the second-line CP CML population.

Figure B57: Patient flow for the second-line CP CML population



*Due to logistical constraints, patients from sites in China, India, Russia and South Africa were not assessed for Molecular Response

SECOND-LINE CP CML POPULATION CLINICAL RESULTS

Summary of efficacy: Second-line CP CML population

- Bosutinib is associated with high rates of cytogenetic and molecular response, long duration of responses and high rates of PFS and OS. This efficacy was observed in both the imatinib-resistant (IM-R) and imatinib-intolerant (IM-I) sub-populations and across all Bcr-Abl mutations, except for T315I.

- **High response rates**
  - The primary endpoint of MCyR at 24 weeks was met by 31% of second-line

CP CML patients (33% of IM-R patients; 27% of IM-I patients).
    - At a minimum follow-up duration of 36 months (12 May 2012 snapshot), cumulative MCyR was 59% in the evaluable population.

- **Durable clinical response**
    - At a minimum follow-up duration of 36 months (12 May 2012 snapshot), the K-M estimate of retaining MCyR at 3 years was 76% for the total second-line CP CML population

- **High levels of survival**
    - Durable responses are reflected in high rates of PFS and OS and low rates of transformation
    - At 2 years, PFS for the whole second-line CP CML population was 79% at a minimum follow-up duration of 24 months (28 Mar 2011 snapshot).
    - At 2 years, OS was 92% (89% for IM-R patients; 98% at IM-I patients) at a minimum follow-up duration of 24 months (28 Mar 2011 snapshot)
    - The cumulative incidence of transformation to AP/BP was 5% (95% CI, 3-9) for IM-R patients and 2% (95% CI, 1-9) for IM-I patients, at a minimum follow-up of 36 months (12 May 2012 snapshot).

Data Sources

The second-line CP CML population of Study 200 provides clinical evidence for the efficacy and safety of bosutinib as a second-line therapy for CP Ph^+ CML patients. This population consisted of 288 adult patients with imatinib-intolerant or imatinib-resistant CP Ph^+ CML and no other previous TKI exposure.

A publication of the second-line CP population, at data snapshot 03 Jun 2010, is available (Cortes et al, 2011 publication)[5], which corresponds to a median follow-up duration of 24.2 months. An analysis from data snapshot 28 Mar 2011 is presented in the CSR[56] and represents a minimum follow-up duration of 23.3 months and a median duration of follow-up of 31.79 months.

Results from the 15 May 2012 snapshot, corresponding to a minimum follow-up time of 36 months, are also provided in a poster that was presented at ASH in 2012 (Cortes et al, 2012 ASH poster).[59] Two patients from the original second-line CP CML population of 288 patients were lost to the 36 month follow-up such that the total population for this update analysis consisted of 286 patients.

With the exception of the primary endpoint of MCyR at 24 weeks, no data from the Cortes et al, 2011 publication (03 Jun 2010 snapshot) is presented in this submission, because more recent analyses with longer follow-up durations are available. In addition, two sub-populations were analysed within the second-line CP population, imatinib-resistant and imatinib-intolerant patients. The primary endpoint is reported by subpopulation and overall, however for all secondary and other efficacy endpoints, only the full second-line population results are presented.

Primary Endpoint: MCyR at Week 24

As of 28 Mar 2011, the primary endpoint for the second-line CP CML population, MCyR at 24 weeks, was met. The MCyR rate at Week 24 in the primary cohort (imatinib-resistant patients) for the evaluable population (n=186) was 35.5% (90% CI: [29.7, 41.7]), with a 24.2% (90% CI: [19.1, 29.9]) CCyR rate. In the per protocol (PP) analysis (n=162), 39.5% had a MCyR (90% CI: [33.1, 46.2]), with 26.5% (90% CI: [20.9, 32.9]) having a CCyR. In the all-treated analysis (n=200) 33.0% of imatinib-resistant subjects (90% CI: [27.5, 38.9]) had a MCyR, with 22.5% (90% CI: [17.7, 27.9]) having CCyR.

For the full second-line CP CML population (all treated analysis, n=288), 31% (95% CI, 26%-37%) achieved MCyR at 24 weeks overall.

Table B103 presents cytogenetic response rates at 24 weeks for thefull second-line CP CML population.

Table B103: MCyR response rate at 24 weeks for second-line CP CML (03 Jun 2010 snapshot)

Response	IM-R		IM-I		Total	
	N	%	N	%	N	%
All treated patients*	200		88		288	
MCyR†	66	33	24	27	90	31
CCyR	45	23	20	23	65	23

*Patients without a baseline or week 24 assessment were counted as non-responders
†Major cytogenetic response = complete + partial cytogenetic response
IM-R = imatinib resistant; IM-I = imatinib intolerant
Cortes et al (2010), 03 Jun 2010 snapshot.

Response rates

Results of an analysis of the best cumulative response, in the evaluable population, to bosutinib at 23.3 month (28 Mar 2011) and 36 month (15 May 2012) minimum follow-up are presented in Table B104.

Table B104: Summary of response rates for the second-line CP CML evaluable population

Response, n (%) [95% CI]	28 Mar 2011 Snapshot	15 May 2012 Snapshot
Median follow-up (range), mo	31.79 (0.6 to 66.0)	41.7 (0.6-78.5)
Cytogenetic Response		
Evaluable[a]	266	264
MCyR	142 (53.4) [47.2,59.5]	155 (59) [53-65]
CCyR	114 (42.9) [36.8, 49.0]	130 (49) [43-55]
Haematological Response		
Evaluable[a]	288	285
CHR	244 (85.0) [80.4, 88.9]	244 (85) [81-90]
Molecular Response		
Evaluable[a]	200	
MMR	69 (34.5)[a] [27.9,41.5]	N/A
CMR	55 (27.5)[a] [21.4,34.2]	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.

Duration of response

As of the 28 Mar 2011 snapshot, the K-M estimate of retaining MCyR at 1 year and 2 years was 73.7% (95% CI, 65.0,80.5) and 73.7% (95% CI, 65.0,80.5) respectively, for the total evaluable second-line CP population. The K-M estimate of retaining CHR at 1 year and 2 years was 84.6% (79.0,88.8) and 72.1% (65.2,77.8) respectively.

As of the 15 May 2012 snapshot, the K-M estimate of retaining MCyR at 3 years was 76% (95% CI, 68-83) for the total second-line CP CML population. The K-M estimate of

retaining CHR at 3 years was 70% (95% CI, 63-76) for the total second-line CP CML population.

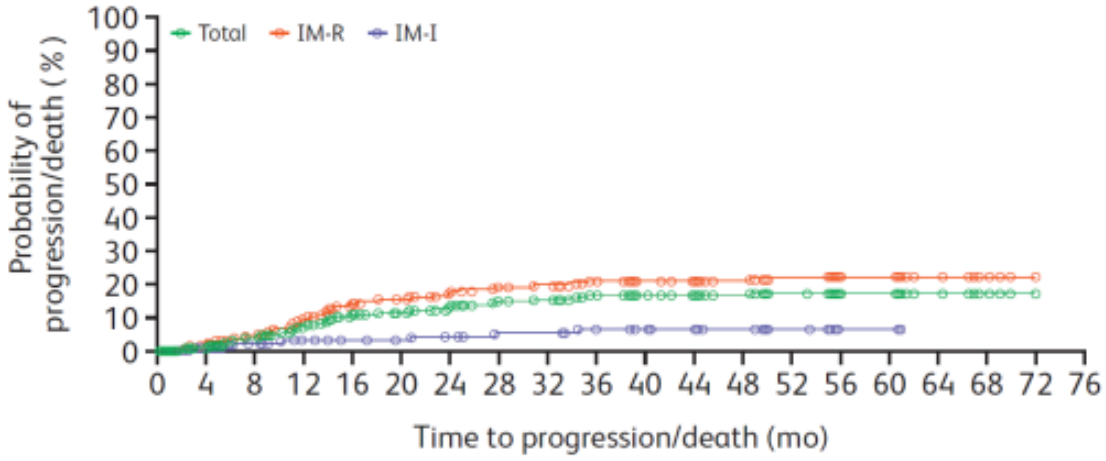
Progression-free survival (PFS)

At 1 year, the PFS rate (see Table B98 for the definition of PFS) for the population as a whole (n=288) was 91%, including 89% of imatinib-resistant patients and 91% of imatinib-intolerant patients. At 2 years, PFS rate for the population as a whole was 79%, including 73% of imatinib-resistant and 95% of imatinib-intolerant patients.

As of data snapshot 28 Mar 2011, the K-M estimates of PFS in the all-treated population at Year 1 and Year 2 were 91.3% (95% CI: [86.8, 94.3]) and 80.6% (95% CI: [74.3, 85.4]) respectively. The K-M median PFS has not been reached.

For the 36 month minimum follow-up analysis (Cortes et al, 2012 ASH poster), PFS is not presented as defined by the original protocol; however the cumulative incidence of on-treatment progression or death is presented. The cumulative incidence of on-treatment progression or death at 3 years was 17% (95% CI, 13-22) for the second-line CP CML population overall (Figure B58).

Figure B58: Cumulative incidence of on-treatment progression or death in the second-line CP CML population (15 May 2012 snapshot)



Transformation

As of the 28 Mar 2011 snapshot, of the 288 subjects in the second-line CP CML all-treated population, 11 subjects (3.8%;95% CI: [1.9, 6.7]) had confirmed disease transformation to AP or BP while on treatment with bosutinib.

As of the 15 May 2012 snapshot, of the 286 subjects in the second-line CP CML all-treated population, the cumulative incidence of on-treatment transformation to AP/BP CML was 5% (95% CI, 3-9) for IM-R patients and 2% (95% CI, 1-9) for IM-I patients at 3 years.Of all patients, 54% discontinued treatment without transformation.

Overall survival

As of the 28 Mar 2011 snapshot, the K-M estimate of OS in the all-treated population at Year 1 was 96.8% (95% CI: [94.0, 98.3]) and 90.6% (95% CI: [86.5, 93.5]) at Year 2, with the K-M median OS yet to be reached.

K-M estimates of OS at 3 years are not provided, since the study protocol specified following patients for only 2 years after bosutinib discontinuation, which could therefore render OS results beyond 2 years as unreliable. However, as of the most recent snapshot (15 May 2012), a total of 34 deaths (12% of patients) occurred during the study. Of these, 5 deaths occurred within 30 days after the last study dose.

The most common reason for death was disease progression (6%), followed by AEs unrelated to bosutinib (4%). One treatment-related death occurred during the study. This was a result of febrile neutropaenia and occurred 78 days after the last dose of bosutinib.

Response by baseline mutation status

The second-line CP CML population was assessed for CHR and MCyR, stratified by baseline mutation status. As of the most recent analysis (15 May 2012), of 210 patients assessed for baseline mutation status, 78 (37%) had ≥1 of 42 unique Bcr-Abl kinase domain mutations, including 9 (4%) with the T315I mutation (Table B105).

Responses to bosutinib were observed across different baseline Bcr-Abl mutations, including those which confer clinical resistance to other tyrosine kinase inhibitors, but were low (22% for both CHR and MCyR) among patients with the T315I mutation.

When patients with the T315I mutation (n=9) are excluded from the analysis, rates of response were 93% for CHR and 62% for MCyR among remaining patients with ≥1 baseline mutation.

Table B105: Response by baseline mutation status in the second-line CP evaluable population (15 May 2012 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)	
		CHR	MCyR
No mutation	132	119/132 (90)	70/120 (58)
≥1 mutation	78	65/77 (84)	44/77 (57)
≥2 mutations	11	8/11 (73)	3/10 (30)
Most common individual mutations[b]			
T315I[c,d]	9	2/9 (22)	2/9 (22)
M351T	9	9/9 (100)	8/9 (89)
F359V[d]	9	8/9 (89)	4/9 (44)
G250E	6	5/6 (83)	3/5 (60)
M244V	6	6/6 (100)	3/6 (50)
L248V	5	5/5 (100)	3/5 (60)
F317L[c]	4	4/4 (100)	3/4 (75)
E255K[d]	3	0/2	2/3 (67)
Y253H[d]	2	2/2 (100)	2/2 (100)
E255V[d]	2	2/2 (100)	1/2 (50)
F311I	2	2/2 (100)	1/2 (50)
F311L	2	2/2 (100)	2/2 (100)
E355G	2	2/2 (100)	1/2 (50)
H396P	2	2/2 (100)	2/2 (100)
H396R	2	1/2 (50)	0/2

[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint
[b] Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib

Treatment discontinuation

As of 12 May 2012, a total of 166 patients (58%) discontinued treatment with bosutinib during the study. The reasons for discontinuation are summarised for both the 28 Mar 2011 snapshot and the more recent 12 May 2012 snapshot in Table B106.

Table B106: Treatment discontinuation in the second-line CP CML population

Reason for discontinued treatment	28 Mar 2011 Snapshot (n=288)	12 May 2012 Snapshot (n=286)
Discontinued treatment, n (%)	159 (55.2)	166 (58)
AE	64 (22.2)	66 (23)

Reason for discontinued treatment	28 Mar 2011 Snapshot (n=288)	12 May 2012 Snapshot (n=286)
Disease progression	41 (14.2)	41 (14)
Lack of efficacy	21 (7.3)	24 (8)
Patient request	18 (6.3)	17 (6)
Death	7 (2.4)	6 (2)
Investigator Request	5 (1.7)	2 (1)
Lost to follow-up	2 (0.7)	2 (1)
Other	1 (0.3)	8 (3)

Patient-reported Outcomes

FACT-LEU

Health-related quality-of-life (HRQOL) was assessed through the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale.

At baseline, second-line CP CML subjects reported that their physical well being (PWB) and functional well being (FWB), components of the FACT-Leu, showed little impairment.

During treatment, a statistically significant deterioration was seen in FACT-Leu at the Week 4 assessment, a change that was likely due to side effects of treatment and reflected in a question around “are you bothered by the side effects of treatment”. Nonetheless, although not statistically significant, numerical improvements in PWB, EWB, LEUS, and summary scales occurred over the course of therapy.

Since EQ-5D was also captured in Study 200 and this represents the preferred utility measure for the NICE reference case, the full FACT-Leu results are not reported here. However, further details of the HRQOL in the second-line CP population, as measured by FACT-Leu, can be found in the publication by Trask and colleagues (2011), identified by the systematic review.[82]

EQ-5D

Improvements in overall health status as assessed by the EQ-5D were observed for second-line CP patients over the course of treatment, as of 28 Mar 2011 snapshot.

Imatinib-resistant subjects experienced a significant improvement in overall health status from baseline starting at Week 8 ($p<0.05$) and continuing at each subsequent assessment until Week 48 (all $p<0.001$). Imatinib-intolerant subjects experienced significant improvement from baseline by Week 24 ($p<0.001$) that continued until Week 48 ($p<0.001$).

The mean and median EQ-5D scores, and the number of patients with an EQ-5D score at each observation is summarised in Table B107.

Table B107 Summary of EQ-5D Results by Visit for second-line CP patients, n=288 (28 Mar 2011 snapshot)

[redacted]					
[redacted]					

SECOND-LINE CP CML POPULATION

Summary of safety: Second-line CP CML population

- The most common nonhaematological TEAEs of any grade in the overall population at a minimum follow-up of 36 months were:
  - Diarrhoea (85% of IM-R patients; 87% of IM-I patients)
  - Nausea (43% of IM-R patients; 52% of IM-I patients)
  - Rash (32% of IM-R patients; 44% of IM=I patients)
  - Vomiting (36% of IM-R patients; 39% of IM-I patients).
- In the majority of cases, these common nonhaematological TEAEs were of grade 1/2 severity. The most common grade 3/4 nonhaematological TEAEs in the overall population were:
  - Diarrhoea (9% of IM-R patients; 11% of IM-I patients)
  - Rash (8% of IM-R patients; 12% of IM-I patients)
  - Vomiting (2% of IM-R patients; 9% of IM-I patients)
  - Elevated ALT (7% of IM-R patients; 9% of IM-I patients).

The second-line CP CML population of Study 200 provides clinical evidence for the efficacy and safety of bosutinib as a second-line therapy for CP Ph^+ CML patients. This population consisted of 288 adult patients with imatinib-intolerant or imatinib-resistant CP Ph^+ CML and no other previous TKI exposure. Data demonstrating the clinical efficacy of

bosutinib in this patient population have been presented in Section 6.8.4. Safety data for this patient population are provided by Cortes et al, December 2012, which presents safety and tolerability data for the second-line CP CML population at a minimum follow-up of 36 months.[59]

Most common non-haematological TEAEs: ≥20% of patients

Table B108 presents the rates at which all non-haematological TEAEs reported in ≥20% of patients occurred.

Table B108: Rates of most common (≥20%) adverse events in the second-line CP CML population

AE[a], n (%)	IM-R (n=195)		IM-I (n=91)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhoea	165 (85)	18 (9)	79 (87)	10 (11)
Nausea	83 (43)	1 (1)	47 (52)	3 (3)
Rash	63 (32)	16 (8)	40 (44)	11 (12)
Vomiting	70 (36)	3 (2)	35 (39)	8 (9)
Pyrexia	57 (29)	1 (1)	16 (18)	1 (1)
Fatigue	47 (24)	1 (1)	23 (25)	2 (2)
Abdominal pain	46 (24)	2 (1)	24 (26)	2 (2)
Cough	44 (23)	0	17 (19)	0
Elevated ALT	41(21)	14 (7)	22 (24)	8 (9)
Upper abdominal pain	40 (21)	1 (1)	17 (19)	0
Elevated AST	36 (19)	7 (4)	19 (21)	5 (6)
Headache	34 (17)	0	18 (20)	0

IM-R = imatinib-resistant; IM-I = imatinib-intolerant; ALT = alanine aminotransferase; AST = aspartate aminotransferase

[a]AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

The most common TEAE was diarrhoea, reported by 85% of imatinib-resistant patients and by 87% of imatinib-intolerant patients. However, for the majority of patients the diarrhoea experienced was of only Grade 1 or 2 severity, with grade 3/4 diarrhoea reported in only 9% and 11% of imatinib-resistant and imatinib-intolerant patients, respectively. Furthermore, only 5 patients (2%) discontinued treatment due to diarrhoea. Diarrhoea was typically first experienced early during treatment, with a median of 2.0 days (range, 1—1,330 days) to the first diarrhoea AE. Diarrhoea AEs were relatively short, with a median duration of 1.0 days (range 1—830 days) and were managed with concomitant antidiarrhoeal medication in the majority (68%) of cases and less commonly with bosutinib dose interruption (16%) or reduction (6%).

Liver-related AEs (primarily aminotransferase elevations) were reported in 85 (30%) patients, including 10% of all patients who experienced a maximum event severity of grade 3 and 1% of patients who experienced a grade 4 event. Liver-related AEs had a median duration of 22.0 days (range, 1—803 days), although median event durations were shorter for grade 3 (15.0 days [range, 2—88 days]) and grade 4 (10.0 days [range, 8-13 days]) events. Patients with liver-related AEs were primarily managed with dose interruption (40%) and dose reduction (24%), while 18% of patients received concomitant medication for these AEs.

AEs led to treatment discontinuation in 32 (16%) of imatinib-resistant patients and 37 (41%) of imatinib-intolerant patients, with the most common AE to cause treatment discontinuation being thrombocytopaenia (2% of imatninib resistant patients, 11% of imatinib-intolerant patients).

10.16 Appendix 16: The post-hoc unmet clinical need subpopulation

10.16.1 Eligibility criteria for the post-hoc unmet clinical need subpopulation

As discussed in Section 6.8.3.5, following consultation with the EMA and healthcare professionals working in CML, a subpopulation of patients from the Study 200 trial was identified who possessed a significant unmet clinical need and who matched the proposed indication for bosutinib.

For a patient to be eligible for inclusion in the unmet clinical need subpopulation, it was required that they were adults with CP, AP or BP Ph^+ CML previously treated with one or more tyrosine kinase inhibitors and for who nilotinib or dasatinib are not considered appropriate treatment options, in line with the proposed indication for bosutinib.

All patients within Study 200 had been previously treated with one or more TKIs: all patients had been previously treated with imatinib as required by the overall Study 200 eligibility criteria presented in Table B6, whilst some patients (the third-line CP CML population and the multi-TKI group of the advanced phase CML population) had additionally received dasatinib and/or nilotinib.

To identify those patients within Study 200 for who nilotinib or dasatinib are not considered appropriate treatment options, a post-hoc selection algorithm was used to review the Study 200 patient population, based on the following clinical features:

- Presence of a Bcr-Abl kinase domain mutation that would be reasonably expected to confer resistance to dasatinib or nilotinib and expected to have sensitivity to bosutinib
- Presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatnib therapy. Prior toxicities relevant in this setting were selected on the basis of adverse drug reactions associated with treatment with other TKIs

Further specific details of Bcr-Abl kinase domain mutations, medical conditions and prior toxicities that were considered to render nilotinib or dasatinib an inappropriate treatment option for a patient are displayed in Table B109.

Table B109 Summary of mutations and medical conditions defining inappropriateness of nilotinib and dasatinib

	Nilotinib	Dasatinib
Mutation	Y253 E255 F359	F317 E255
Medical history or evidence of prior TKI intolerance	Coronary artery occlusion, coronary arterial stent insertion, arterial occlusive disease, coronary artery disease, arteriosclerosis, glucose tolerance impairment, coronary angioplasty, coronary artery bypass, hyperglycaemia, hypertriglyceridaemia, diabetes, pancreatitis	Pleural effusion, blood pressure increase, interstitial lung disease, chronic obstructive pulmonary disease, bronchitis chronic, pulmonary hypertension, pulmonary fibrosis, pulmonary oedema, emphysema, hypertension (Grade 3 or 4), cardiomyopathy, cardiac

		failure, ventricular failure, ventricular dysfunction, myocardial infarction., myocardial ischaemia, respiratory disorder

10.16.2 Patient flow in the unmet clinical need subpopulation

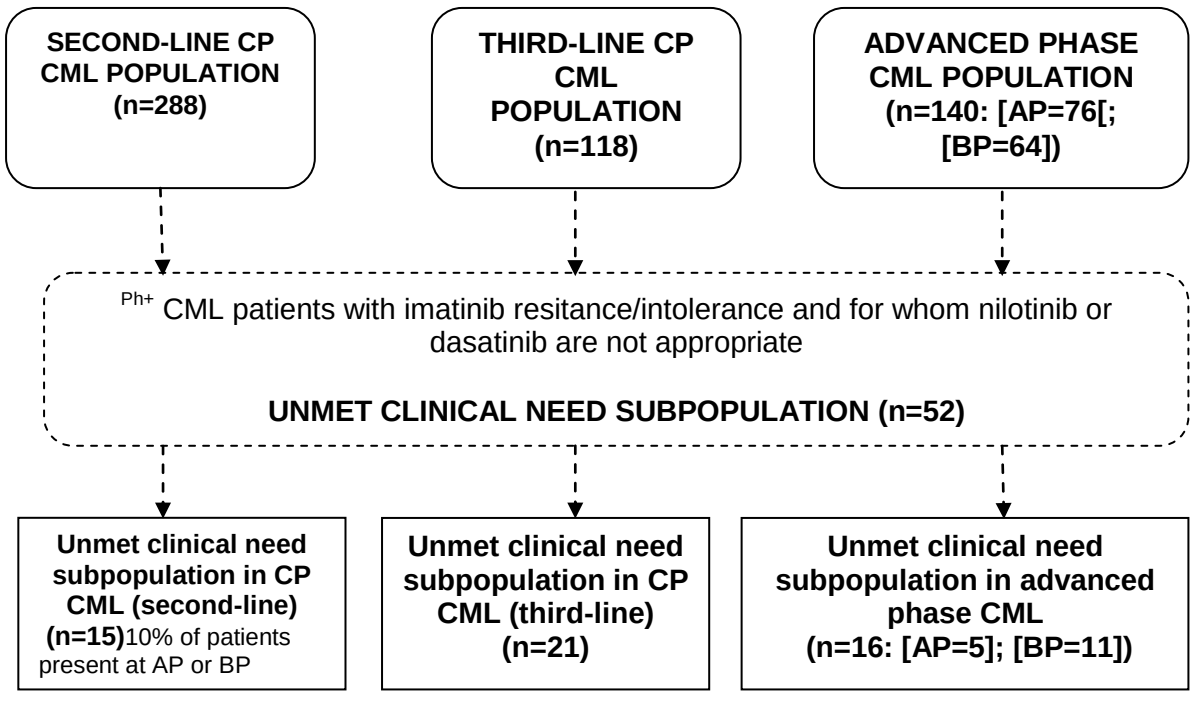
In line with the eligibility criteria described in Section 10.14.2, patients included in the post-hoc unmet clinical need subpopulation could be drawn from any of the Study 200 populations, as described below:

- **Second-line CP CML population:** some patients in this population might be eligible for inclusion in the post-hoc analysis if, after unsuccessful treatment with imatinib, both dasatinib and nilotinib are not considered to be appropriate treatment options as a result of a Bcr-Abl mutation, a prior toxicity or a medical condition as described in Table B109
- **Third-line CP CML population:** some patients in this population might be eligible for inclusion in the post-hoc analysis if, after unsuccessful treatment with imatinib followed by dasatinib and/or nilotinib, the remaining TKI is not considered to be an appropriate treatment option as a result of a Bcr-Abl mutation, a prior toxicity or a medical condition as described inTable B109
- **Advanced phase CML population:** This population consisted of a group of patients whose prior TKI exposure comprised of either imatinib only, or imatinib followed by dasatinib and/or nilotinib (multi-TKI group). Therefore patients in this population might be eligible for inclusion in the post-hoc analysis as described above for the second-line CP CML population (imatinib-only group) or the third-line CP CML population (multi-TKI group).

The identified post-hoc unmet clinical need subpopulation comprised of a total of 52 patients identified from the Study 200 populations as described above.

Figure B59 presents the patient flow from the Study 200 populations into this unmet clinical need subpopulation.

Figure B59 Patient flow for the unmet clinical need subpopulation



As can be seen in Figure B59, the unmet clinical need subpopulation (n=52) is comprised of the following:

- 15 patients drawn from the second-line CP CML population. These represent CP Ph^+ CML patients who failed treatment with imatinib only and had no other previous TKI exposure and for whom nilotinib or dasatinib are not appropriate treatment options
- 21 patients drawn from the third-line CP CML population. These represent CP Ph^+ CML patients who failed treatment with imatinib followed by dasatinib and/or nilotinib and for whom treatment with the remaining TKI was considered unsuitable
- 16 patients drawn from the advanced phase CML population. There represent advanced phase Ph^+ CML patients who failed treatment with imatinib only or imatinib followed by dasatinib and/or nilotinib and for whom treatment with the remaining TKI was considered unsuitable

As was performed for the Study 200 population as a whole, the post-hoc analysis of clinical efficacy and safety in the unmet clinical need subpopulation was stratified by treatment stage and disease phase i.e second-line CP CML (n=15), third-line CP CML (n=21) and advanced phase CML (n=16). These results are presented in Section 10.16.3

10.16.3 Clinical efficacy results in the post-hoc unmet clinical need subpopulation

UNMET CLINICAL NEED SUBPOPULATION

Summary of efficacy: unmet clinical need subpopulation

- In total, 36 CP CML patients with unmet clinical need were identified. For all of these patients, first-line treatment with imatinib had failed and dasatinib or nilotinib were deemed inappropriate treatment options. For the purpose of evaluating efficacy outcomes these patients were further stratified according to the number of previous TKIs experienced.
    - 15 patients had no additional TKI exposure (received bosutinib second-line)
    - 21 patients had previously also received dasatinib and/or nilotinib (received bosutinib third-line)
- Of the total 36 CP CML patients with unmet clinical need, 18 patients (50%) attained or maintained a response of MCyR or better
    - Of the 15 patients with unmet clinical need who received bosutinib in the second-line setting, 9 patients (60%) attained or maintained a response of MCyR or better
    - Of the 21 patients with unmet clinical need who received bosutinib in the third-line setting, 9 patients (43%) attained or maintained a response of MCyR or better
- In total, 16 advanced phase CML patients with unmet clinical need were identified. For all of these patients, first-line treatment with imatinib had failed and dasatinib or nilotinib were deemed inappropriate treatment options. This 16 patient population consisted of 5 AP CML patients and 11 BP CML patients.
- Of the 16 advanced phase CML patients with unmet clinical need, 7 patients (44%) attained or maintained a response of major haematological response (MHR) or better
    - Of the 5 AP CML patients with unmet clinical need, 4 patients (80%) achieved a response of MHR or better
    - Of the 11 BP CML patients with unmet clinical need, 3 patients (27%) attained or maintained a response of MHR or better

- These data are reflective of the efficacy results for the Study 200 populations from which the subgroups of the post-hoc unmet clinical need subpopulation were derived. This suggests that bosutinib would represent a valuable alternative to the current standard of care (BSC), once the currently available TKI treatment options have been exhausted.

The presentation of efficacy data for the 52 patient post-hoc unmet clinical need subpopulation is stratified the following subgroups:

- Unmet clinical need subpopulation in CP CML (second-line)
- Unmet clinical need subpopulation in CP CML (third-line)
- Unmet clinical need subpopulation in advanced phase CML

Presentation of the data in this manner means that efficacy data for use of bosutinib in each of the clinical scenarios in which an unmet clinical need could arise is clearly presented.

Unmet clinical need subpopulation in chronic phase CML (second-line) (n=15)

Of the 15 patients in this subpopulation, 9 (60%) attained or maintained a response of MCyR or better, with distribution of these 9 patients as follows:

- CMR: 3 patients
- MMR: 1 patient
- CCyR: 4 patients
- PCyR: 1 patient

Among these 9 patients with notable responses, duration of MCyR ranged from 12 to 155+ weeks and treatment duration ranged from 24 to 197+ weeks, as of the data snapshot of 28th March 2011.

The efficacy results for patients in this second-line subgroup of the unmet clinical need subpopulation are largely consistent with data demonstrating the efficacy of bosutinib in the second-line CP CML population of Study 200 from which these patients were derived-cumulative MCyR rate in this population was 53%.

Unmet clinical need subpopulation in CP CML (third-line) (n=21)

Of 21 patients in this subpopulation, 9 patients (42.9%) attained or maintained a response on bosutinib treatment of MCyR or better.

Outcome measures regarded as better than MCyR were CMR, MMR, CCyR or PCyR. Of the 9 patients achieving MCyR or better, the number of patients achieving these respective measures was as follows:

- CMR: 2 patients
- MMR: 1 patient
- CCyR: 4 patients
- PCyR: 2 patients

Among the 9 patients with these notable responses, duration of MCyR ranged from 8 to 204+ weeks and treatment duration ranged from 35 to 315+ weeks, as of the data snapshot of March 28th 2011.

Of the remaining 12 patients who did not reach a level of response of MCyR or better, 9 patients attained or maintained a complete haematological response (CHR) with bosutinib treatment.

The efficacy results for this third-line subgroup of the unmet clinical need subpopulation are largely consistent with data demonstrating the efficacy of bosutinib in the third-line CP CML population from which these patients were derived- 39% of patients in this population with a valid baseline cytogenetic assessment attained or maintained MCyR.

Unmet clinical need subpopulation in advanced phase CML (n=16)

In this study, 16 patients with advanced phase CML with unmet clinical need (5 AP and 11 BP) were treated with bosutinib. Of these 16 patients, 8 had received prior imatinib and at least one other TKI; 8 had received imatinib as the only prior TKI therapy.

In total, 7 of these 16 patients attained or maintained a major haematological response (MHR), or better. These 7 patients were comprised of 4 patients from the accelerated phase group and 3 patients from the blast phase group, as demonstrated below.

Of the 5 AP patients with unmet clinical need who were treated with bosutinib, 4 patients attained or maintained a response of MHR or better. The distribution of responses amongst these 4 patients was as follows:

- CCyR: 2 patients
- CMR: 1 patient
- Major haematological response: 1 patient

Among these 4 AP patients with notable responses, treatment duration ranged from 46 to 114 weeks.

Of the 11 BP patients with unmet clinical need who were treated with bosutinib, 3 patients attained or maintained a response on bosutinib treatment, as follows:

- CCyR: 2 patients
- Major haematological response: 1 patient

Among these BP patients with notable responses, treatment duration ranged from 46 to 118 weeks.

The efficacy results for this advanced phase subgroup of the unmet clinical need subpopulation are largely consistent with data demonstrating the efficacy of bosutinib in the advanced phase CML population from which these patients were derived- 55.1% of AP patients and 28.3% of BP patients attained or maintained a confirmed OHR.

Summary of results for the unmet clinical need subpopulation

These efficacy data represent the results of a post-hoc analysis. Despite the limitations associated with post hoc analyses, it is evident that the clinical efficacy observed through this post-hoc analysis of patients with an unmet clinical need is consistent with the efficacy observed in the larger, Study 200 populations from which these post-hoc patients were derived. Bosutinib therefore represents a valid treatment alternative to the current standard of care (BSC) for patients for whom treatment with any of the currently approved TKIs is not appropriate.

10.16.4 Safety results in the post-hoc unmet clinical need subpopulation

Summary of safety: unmet clinical need subpopulation

- The most common TEAEs in the unmet clinical need subpopulation were consistent

with the most common TEAEs in the corresponding Study 200 populations
- Safety profile of bosutinib acceptable in patients with a history of pleural effusions, cardiovascular disease, diabetes or hyperglycaemia events

Safety outcomes for this patient subpopulation were:

- Treatment-emergent adverse events (TEAEs) of any grade
- Grade 3 or 4 TEAEs
- TEAEs leading to discontinuation (discont.)
- Serious adverse events (SAEs)

Incidence rates for the above safety measures in the subpopulation of unmet clinical need, as of the data snapshot 28th March 2011, are presented in Table **B110**.

Table B110 Incidence rates of adverse events by type for the unmet clinical need subpopulation

Event	CP (second-line) (n=15)	CP (third line) (n=21)	Total CP CML (n=36)	AP CML (n=5)	BP CML (n=11)	Total advanced phase CML (n=16)	Total subpopulation of unmet clinical need (n=52)
Any TEAE (N, %)	15 (100)	21 (100)	36 (100)	5 (100)	11 (100)	16 (100)	52 (100)
Grade 3 or 4 TEAEs (N, %)	11 (73.3)	12 (57.1)	23 (63.9)	5 (100)	8 (72.7)	13 (81.3)	36 (69.2)
TEAEs leading to discont. (N, %)	4 (26.7)	5 (23.8)	9 (25.0)	1 (20)	3 (27.3)	4 (25.0)	13 (25)
SAEs (N, %)	6 (40.0)	10 (47.6)	16 (44.4)	4 (80.0)	8 (72.7)	12 (75.0)	28 (53.8)

There were no cases of unexpected safety signals or intolerance in this subpopulation of unmet clinical need, based on the known safety profile of bosutinib.
The most common TEAEs in the unmet clinical need subpopulation as a whole were
Patients with a history of pleural effusions or of discontinuation of treatment with a previous TKI due to pleural effusion were demonstrated to have minimal cross-intolerance on bosutinib treatment, although the population size is small.

The safety profile of bosutinb also appeared to be acceptable in patients who had a history of cardiovascular, diabetes or hyperglycaemia events.

The incidence rate of TEAEs leading to treatment discontinuation in this post-hoc unmet clinical need subpopulation (25%) is consistent with discontinuation rate due to AEs in the second-line CP CML population (23%) and third-line CP CML population (22%) of Study 200, presented in Section 6.8.5.

Safety results for the unmet clinical need subpopulation as a whole, and each group within this subpopulation (i.e. CP CML (second-line), CP CML (third-line) and advanced phase CML) were consistent with the safety results of the corresponding Study 200 populations from which these post-hoc patients were derived (see Section 6.9).

Post-hoc unmet clinical need subpopulation:

50% of CP patients in this subpopulation attained or maintained a response of MCyR or better, and 44% of advanced phase patients in this subpopulation attained or maintained a response of MCyR or better. Bosutinib therefore demonstrates meaningful clinical benefit for a population of patients with an unmet clinical need.

10.17 Appendix 17: Compassionate Use Data

As part of the European regulatory review, the EMA requested the manufacturer to provide anonymised patient narratives of patients who received “compassionate use” supply, as illustrations of positive treatment experiences of bosutinib within the proposed label. These patients had a diagnosis of Ph+ CML in CP, AP, or BP, and were considered by their treating physicians to have no other available or suitable TKI option.

Of the sixteen patient case reports illustrating the benefit of Bosutinib within the product label, all received prior imatinib therapy, and 15 of the 16 also received both dasatinib and nilotinib.

The following table provides a by-patient line listing of the prior therapy and best response on bosutinib, as reported by the treating physician, for these patients.

Table B 111: CP2L: Imatinib Resistant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
73 / Male	Lack of Efficacy (F359V)	Not administered due to pleural effusion	Not administered due to F359V mutation	PCyR

Table B 112: CP4L: Imatinib, Dasatinib and Nilotinib Resistant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
69 / Female	Progressive Disease - “Various mutations"	Progressive Disease - “Various mutations"	Progressive Disease – Loss of CHR	MMR

Table B 113: CP4L: Imatinib and Nilotinib Resistant, Dasatinib Intolerant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
71 /Male*	Primary Resistance	Intolerance - Recurrent Pleural Effusion and Rising	Primary Resistance	CMR

		Pulmonary Arterial Pressure		
45 / Female	Primary Resistance	Intolerance - Fever. Pain	Progressive Disease- Mutation (G250E)	MMR
69 / Male	Progressive Disease- Loss of Cytogenetic Response	Intolerance - Pleural Effusion	Progressive Disease- Mutation (F359C)	CMR
73 / Female	Progressive Disease- Loss of Cytogenetic Response (Y253H, E459K)	Intolerance - Severe Allergic Reaction	Progressive Disease- Loss of Cytogenetic Response	CMR
64 / Female	Progressive Disease- Loss of CHR	Intolerance - Pleural Effusion	Progressive Disease- Loss of Cytogenetic Response (F359V)	CCyR

*This patient is also ponatinib resistant

Table B 114: CP4L: Imatinib and Dasatinib Resistant, Nilotinib Intolerant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
57 / Female	Progressive Disease- Loss of CHR	Progressive Disease- Loss of CHR	Intolerance - Not specified	CHR

Table B 115: CP4L: Imatinib Resistant, Dasatinib and Nilotinib Intolerant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
62 / Male	Progressive Disease- Mutation (F359V)	Intolerance - Arthralgias	Intolerance - Headache	CCyR
27 / Female	Progressive Disease - Fatigue	Intolerance - Not specified	Intolerance - Not specified	CMR

Table B 116: CP4L: Imatinib and Dasatinib Intolerant, Nilotinib Resistant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
73 / Male	Intolerance - Diarrhoea, cytopenia	Intolerance - Pleural Effusion	No Molecular Response	MHR

Table B 117: CP4L: Imatinib, Dasatanib and Nilotinib Intolerant

Patient Age / Gender	Reason for Imatinib Discontinuation	Reason for Dasatinib Discontinuation	Reason for Nilotinib Discontinuation	Bosutinib Best Response
62 / Male	Intolerance - Stomatitis G3, hepatic/renal toxicity G2, skin rash G2	Intolerance - Neuropathic disorders	Intolerance - Cardiotoxicity	CMR
67 / Female	Intolerance - Dermal Toxicity	Intolerance - Pleural Effusion	Intolerance - Myocardial Infarction	CMR
43 / Female	Intolerance - Severe diarrhea and weight loss	Intolerance - Inflammatory drug eruptions, skin lesions	Intolerance - LFT elevations	PMR
74 / Female	Intolerance - Rash	Intolerance - Throat tightness	Intolerance - Rash	CMR
44 / Male	Intolerance - Rash	Intolerance - Interstitial Pulmonary Oedema	Intolerance - Severe abdominal and back pain	MMR

In conclusion, the patients identified in the compassionate use population discontinued prior TKI therapies for a wide variety of reasons, which have been detailed as much as possible above based on all information available.

Although sample sizes are too small for definitive assessment given the heterogeneity of reasons for drug resistance and intolerance, notably responses were observed in all subsets, demonstrating value in the identified unmet need population. Bosutinib should be considered a useful additional treatment option for these various patient populations.

[redacted]

Table B 118: UK Compassionate Use patients with previous TKI data: initiated 22/10/08 to 06/07/12

[redacted]								

10.18 Appendix 18: Additional data presentation for the cost-effectiveness model

The statistical package R (R Foundation for Statistical Computing, Vienna, www.r-project.org) was used to fit parametric curves to the patient level data from Study 200. The exponential curve was considered to be the most appropriate according to AIC, IBS and visual inspection.

Overall survival – Bosutinib- Chronic Phase 3rd line

Figure B 60: Kaplan-Meir Overall survival – Bosutinib- Chronic Phase 3rd line

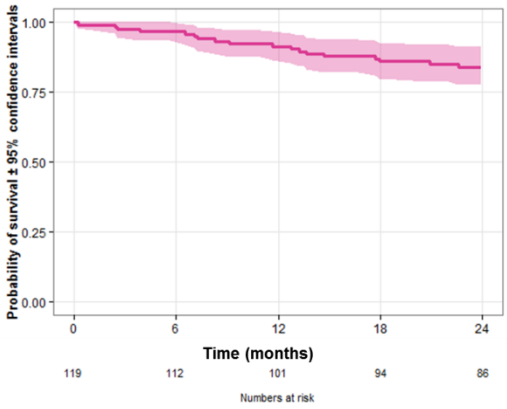


Figure B 61: Parametric curve fits to the Kaplan-Meir Overall survival – Bosutinib- Chronic Phase 3rd line

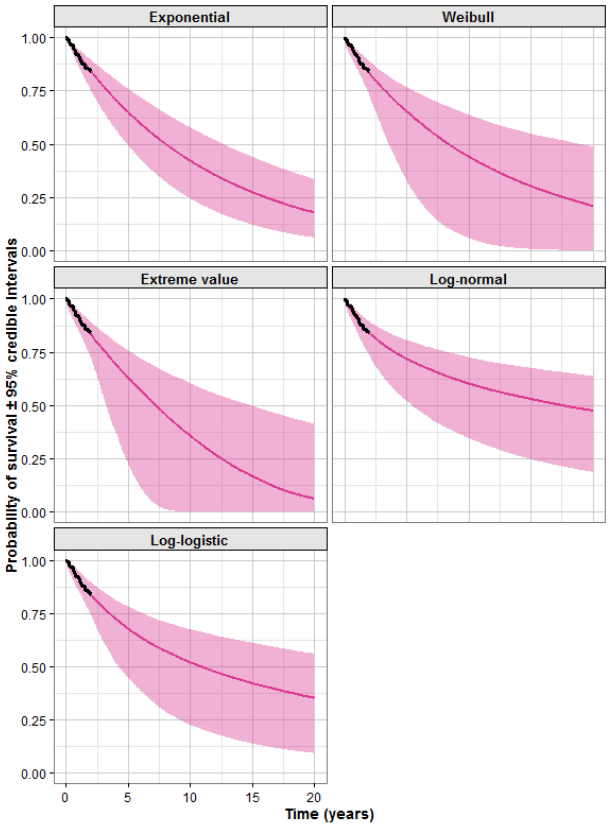


Table B 119: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – Bosutinib- Chronic Phase 3rd line

Model	AIC
Log-normal	128.02
Extreme Value	127.65
Weibull	127.57
Log-logistic	127.52
Exponential	125.63

Model	Brier Score
Log-normal	0.07022
Extreme Value	0.07013
Weibull	0.07014
Log-logistic	0.07015
Exponential	0.06993

Best-fitting model: exponential

Progression-free survival – Bosutinib - Chronic Phase 3rd line

Figure B 62: Kaplan-Meir PFS – Bosutinib - Chronic Phase 3rd line

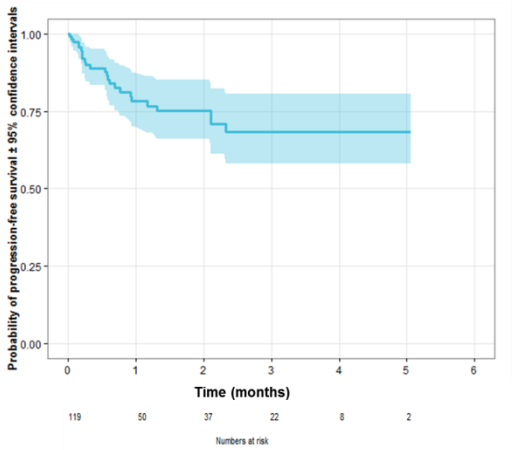


Figure B 63: Parametric curve fits to the Kaplan-Meir PFS – Bosutinib - Chronic Phase 3rd line

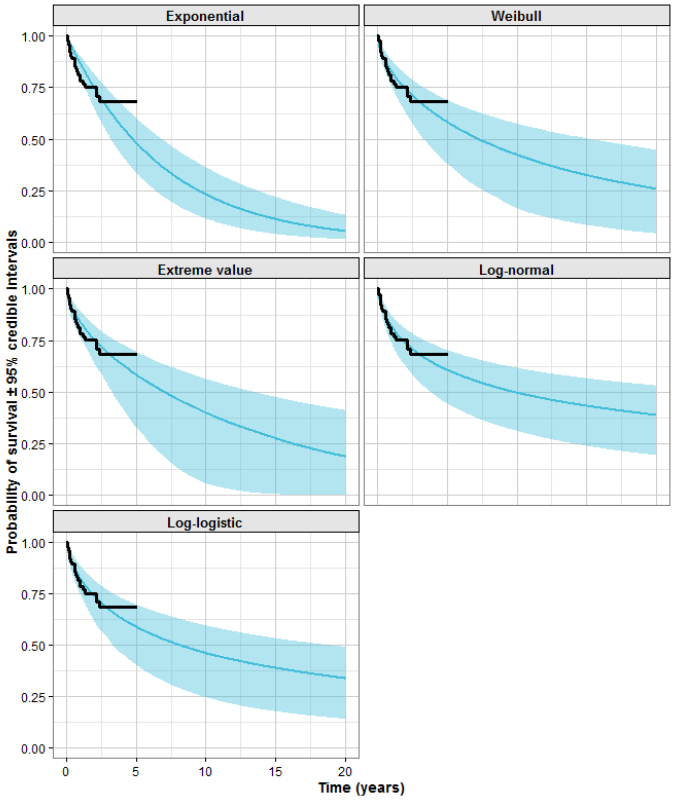


Table B 120: Goodness of fit measures for parametric curve fits to the Kaplan-Meir PFS – Bosutinib - Chronic Phase 3rd line

Model	AIC
Log-normal	139.27
Extreme Value	144.00
Weibull	142.81
Log-logistic	141.49
Exponential	147.95

Model	Brier Score
Log-normal	0.18514
Extreme Value	0.18571
Weibull	0.18570
Log-logistic	0.18572
Exponential	0.18966

Best-fitting model: exponential

Time to Discontinuation – Bosutinib – Chronic Phase 3rd line

Figure B 64: Kaplan-Meir Time to Discontinuation – Bosutinib – Chronic Phase 3rd line

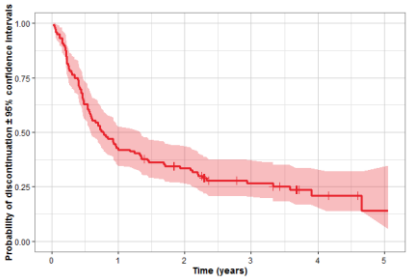


Figure B 65: **Parametric curve fits to the Kaplan-Meir Time to Discontinuation – Bosutinib – Chronic Phase 3rd line**

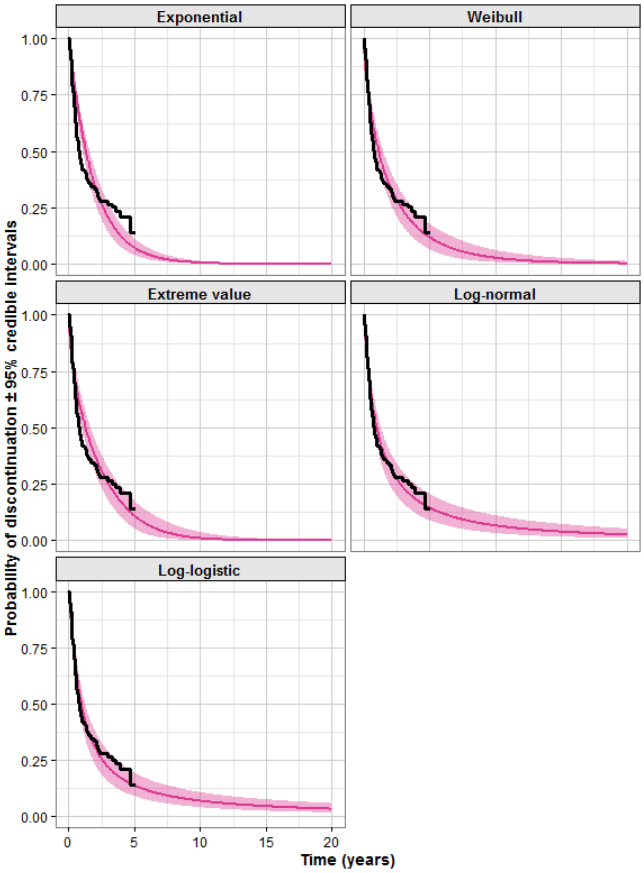


Table B 121: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Time to Discontinuation – Bosutinib – Chronic Phase 3rd line

Model	AIC
Log-normal	272.57
Extreme Value	299.42
Weibull	288.47
Log-logistic	274.95
Exponential	296.73

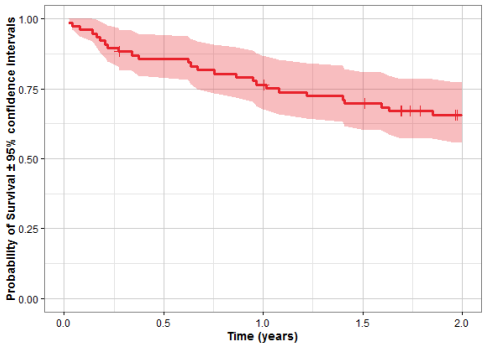
Model	Brier Score
Log-normal	0.2015
Extreme Value	0.2048
Weibull	0.2034
Log-logistic	0.2020
Exponential	0.2086

Best fitting model: log-normal

2nd best-fitting model: log-logistic

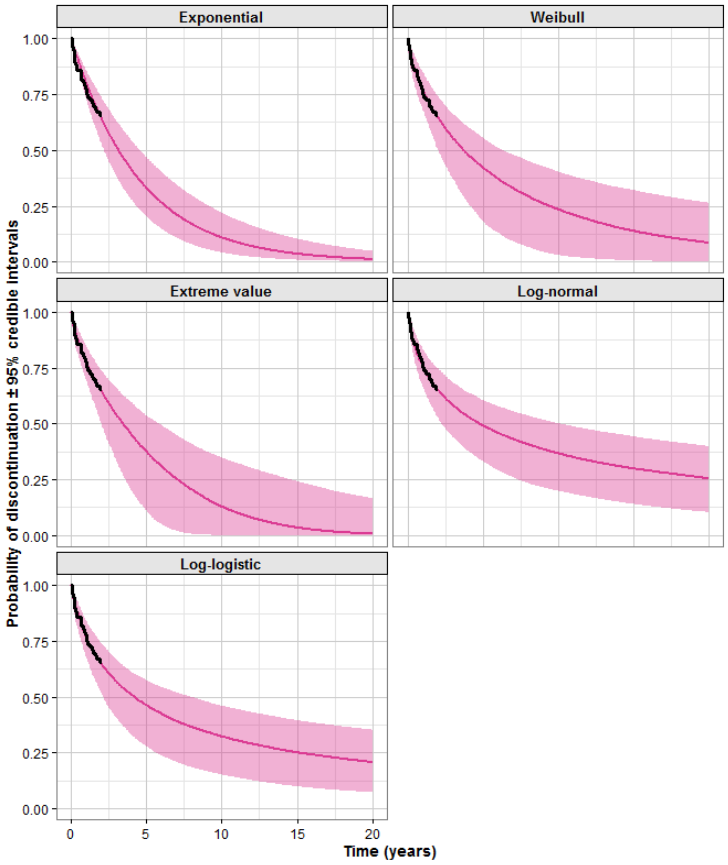
Overall Survival – Bosutinib – Accelerated Phase

Figure B 66: Kaplan-Meir Overall Survival – Bosutinib – Accelerated Phase



X

XFigure B 67: Parametric curve fits to the Overall Survival – Bosutinib – Accelerated Phase



XTable B 122: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall Survival – Bosutinib – Accelerated Phase

Model	AIC
Log-normal	130.39
Extreme Value	131.94
Weibull	131.47
Log-logistic	131.06
Exponential	131.90

Model	Brier Score
Log-normal	0.15857
Extreme Value	0.15853
Weibull	0.15856
Log-logistic	0.15864
Exponential	0.15895

Best fitting curve: exponential
2nd best-fitting curve: extreme value

Progression-free Survival – Bosutinib – Accelerated Phase

Figure B 68: Kaplan-Meir Progression-free Survival – Bosutinib – Accelerated Phase

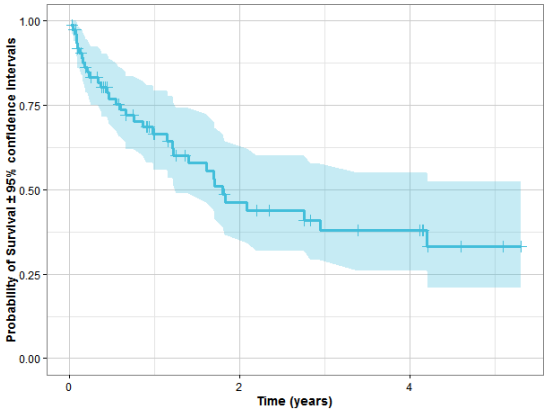


Figure B 69: Parametric curve fits to the Progression-free Survival – Bosutinib – Accelerated Phase

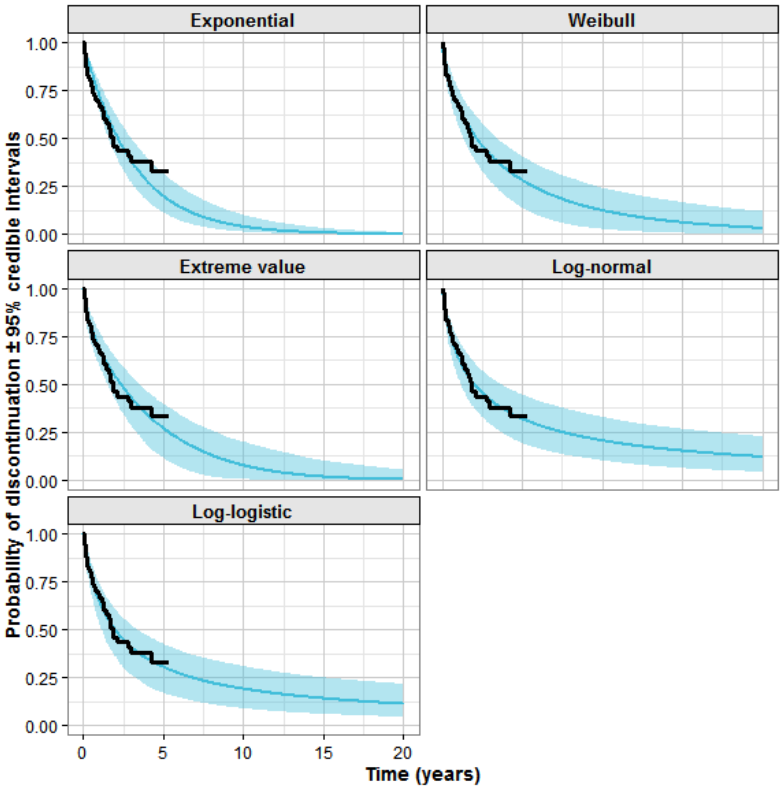


Table B 123: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Progression-free Survival – Bosutinib – Accelerated Phase

Model	AIC
Log-normal	144.22
Extreme Value	145.42
Weibull	147.23
Log-logistic	149.44
Exponential	151.42

Model	Brier Score
Log-normal	0.23089
Extreme Value	0.23236
Weibull	0.23191
Log-logistic	0.23121
Exponential	0.23535

Best fitting curve: weibull

Time to Discontinuation – Bosutinib – Accelerated Phase

Figure B 70: Kaplan-Meir Time to Discontinuation – Bosutinib – Accelerated Phase

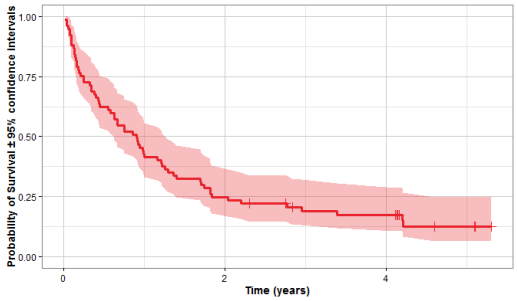


Figure B 71: Parametric curve fits to the Kaplan-Meir Time to Discontinuation – Bosutinib – Accelerated Phase

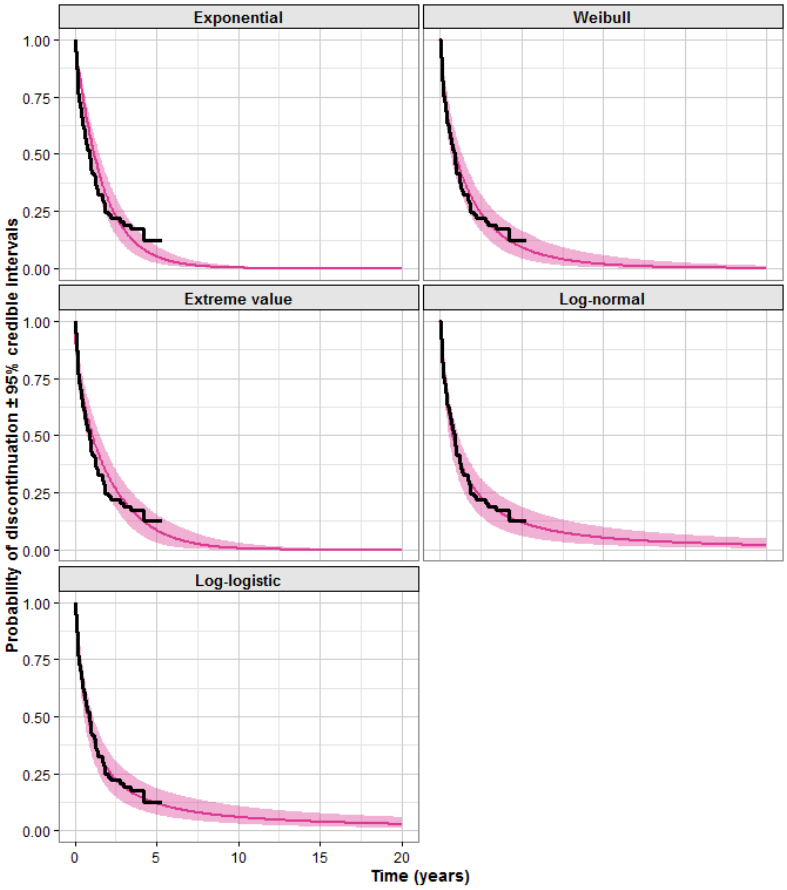


Table B 124: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Time to Discontinuation – Bosutinib – Accelerated Phase

Model	AIC
Log-normal	183.53
Extreme Value	198.97
Weibull	191.62
Log-logistic	185.20
Exponential	199.42

Model	Brier Score
Log-normal	0.17592
Extreme Value	0.17833
Weibull	0.17683
Log-logistic	0.17588
Exponential	0.18045

Best fitting curve: log-normal

2nd best-fitting curve: log-logistic

Overall Survival – Bosutinib – Blast Phase

Figure B 72: Kaplan-Meir Overall Survival – Bosutinib – Blast Phase

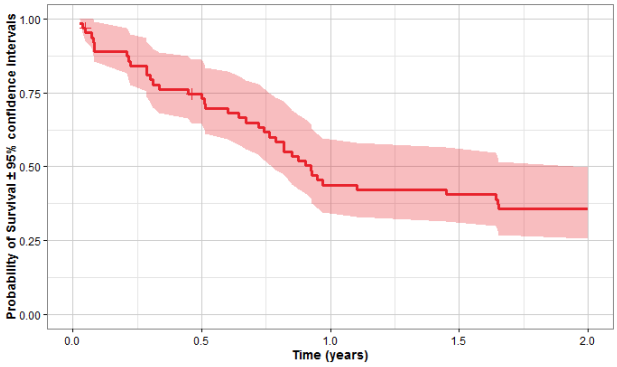


Figure B 73: Parametric curve fits to the Kaplan-Meir Overall Survival – Bosutinib – Blast Phase

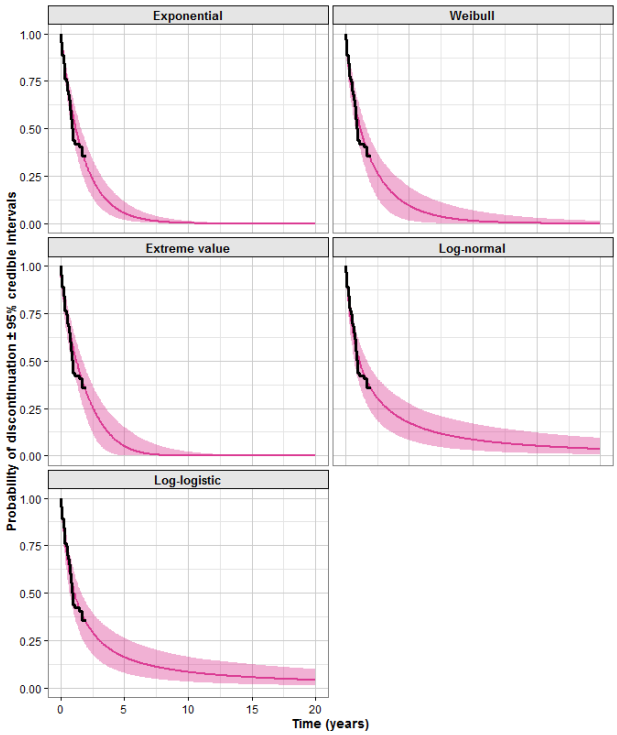


Table B 125: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall Survival – Bosutinib – Blast Phase

Model	AIC
Log-normal	124.23
Extreme Value	129.15
Weibull	126.71
Log-logistic	124.51
Exponential	126.21

Model	Brier Score
Log-normal	0.21226
Extreme Value	0.21351
Weibull	0.21268
Log-logistic	0.21221
Exponential	0.21310

Best fitting curve: exponential

2nd best-fitting curve: weibull

Progression-free Survival – Bosutinib – Blast Phase

Figure B 74: Kaplan-Meir Progression-free Survival – Bosutinib – Blast Phase

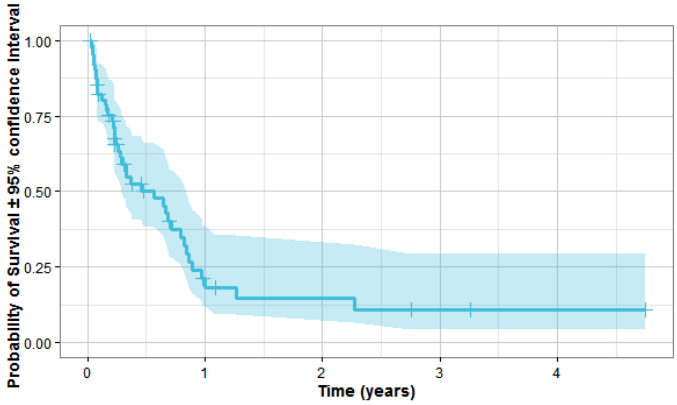


Figure B 75: Parametric curve fits to the Kaplan-Meir Progression-free Survival – Bosutinib – Blast Phase

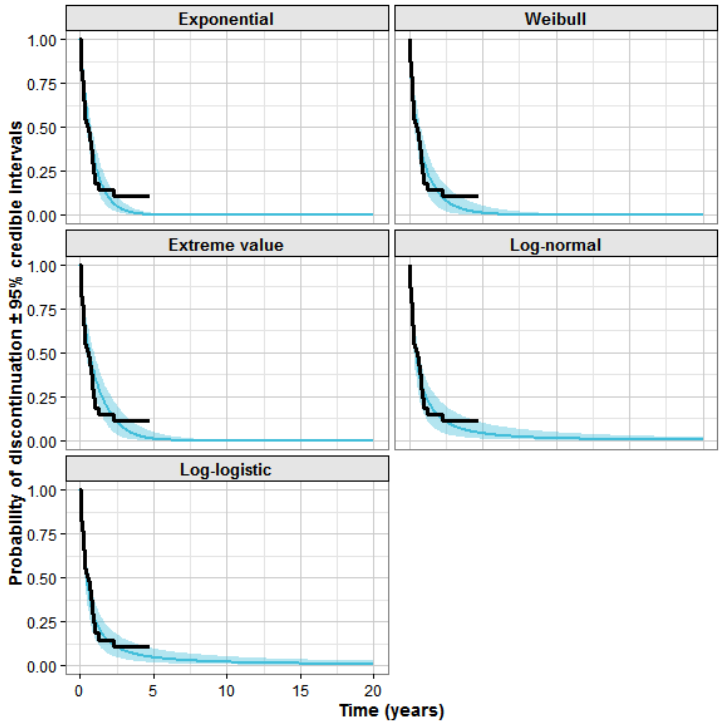


Table B 126: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Progression-free Survival – Bosutinib – Blast Phase

Model	AIC
Log-normal	60.86
Extreme Value	77.27
Weibull	69.02
Log-logistic	61.83
Exponential	70.33

Model	Brier Score
Log-normal	0.17004
Extreme Value	0.17721
Weibull	0.17238
Log-logistic	0.16943
Exponential	0.17280

Best fitting curve: Weibull

Time to Discontinuation – Bosutinib – Blast Phase

Figure B 76: Kaplan-Meir Time to Discontinuation – Bosutinib – Blast Phase

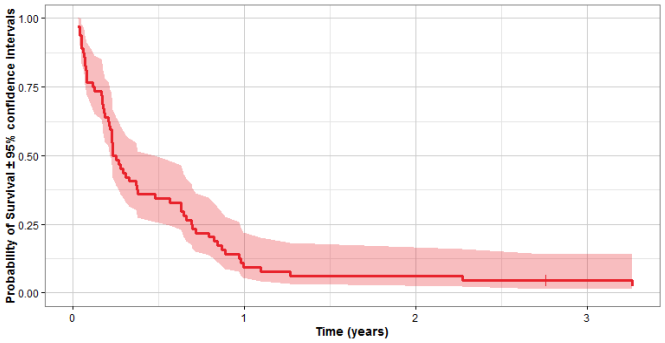


Figure B 77: Parametric curve fits to the Kaplan-Meir Time to Discontinuation – Bosutinib – Blast Phase

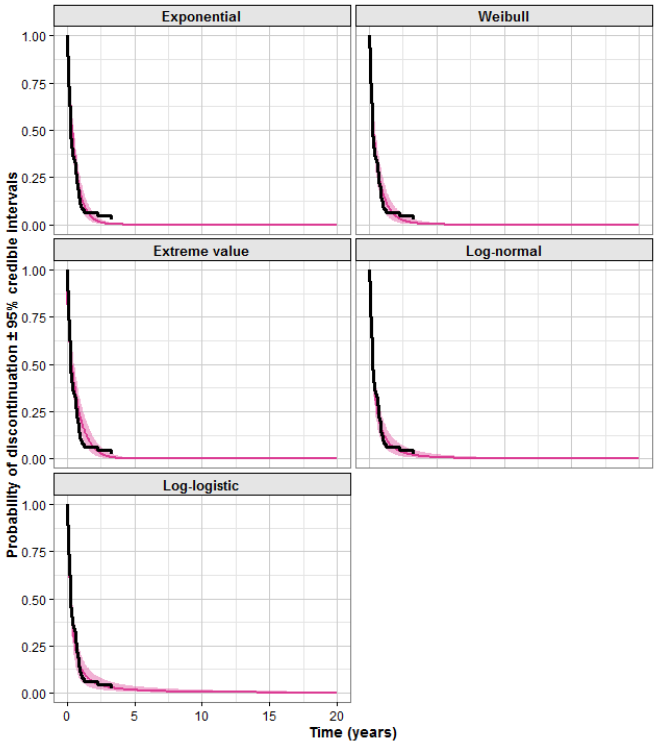


Table B 127: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Time to Discontinuation – Bosutinib – Blast Phase

Model	AIC
Log-normal	41.83
Extreme Value	66.66
Weibull	53.16
Log-logistic	44.03
Exponential	55.03

Model	Brier Score
Log-normal	0.11859
Extreme Value	0.12382
Weibull	0.12016
Log-logistic	0.11861
Exponential	0.12197

Best fitting curve: log-normal

2nd best-fitting curve: log-logistic

Overall survival – SCT – CP – Oehler

Figure B 78: Kaplan-Meir Overall survival – SCT – CP – Oehler

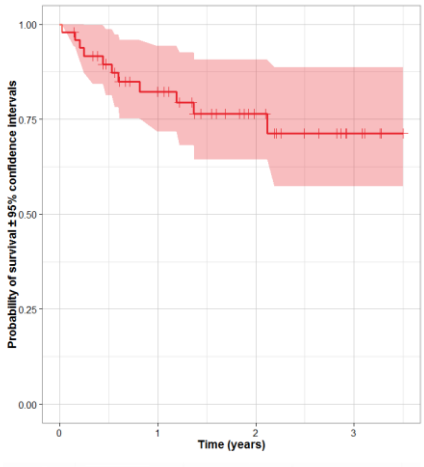


Figure B 79: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – CP – Oehler

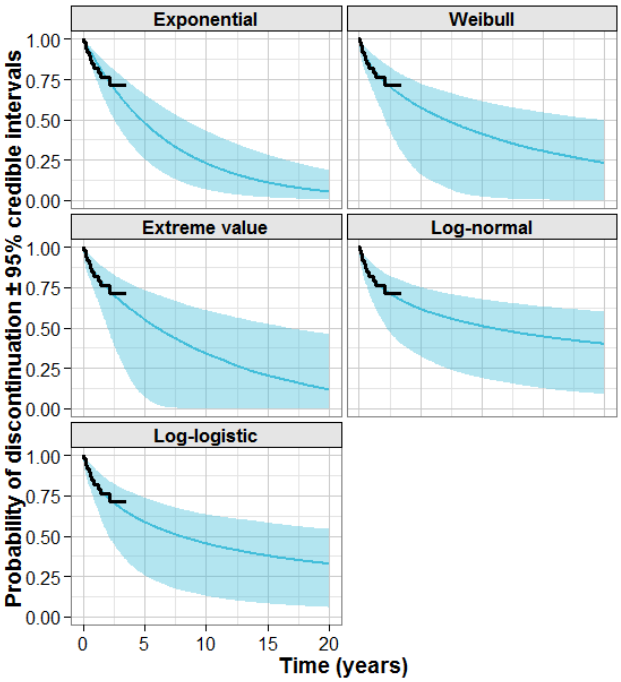


Table B 128: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – CP – Oehler

Model	AIC
Log-normal	65.46470
Extreme Value	66.51378
Weibull	66.22134
Log-logistic	65.92277
Exponential	66.13627

Model	Brier Score
Log-normal	0.165429
Extreme Value	0.165772
Weibull	0.165800
Log-logistic	0.165807
Exponential	0.166646

Best fitting curve: exponential

Overall survival – SCT – AP – Oehler

Figure B 80: Kaplan-Meir Overall survival – SCT – AP – Oehler

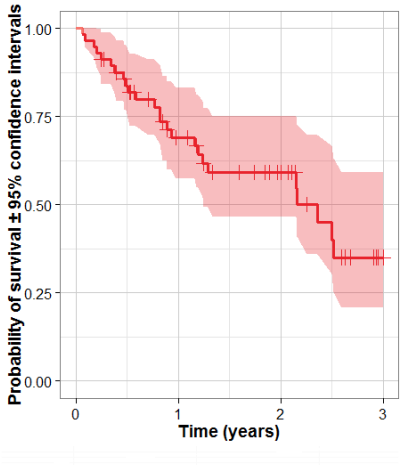


Figure B 81: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – AP – Oehler

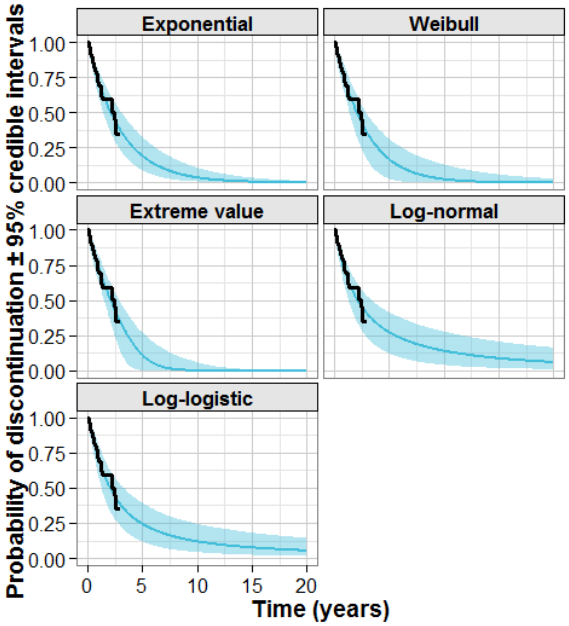


Table B 129: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – AP – Oehler

Model	AIC
Log-normal	108.4120
Extreme Value	109.2822
Weibull	108.8111
Log-logistic	108.7405
Exponential	106.9092

Model	Brier Score
Log-normal	0.201417
Extreme Value	0.201455
Weibull	0.201628
Log-logistic	0.201751
Exponential	0.200627

Best fitting curve: exponential

2nd best fitting curve: weibull

Overall survival – SCT – BP – Oehler

Figure B 82: Kaplan-Meir Overall survival – SCT – BP – Oehler

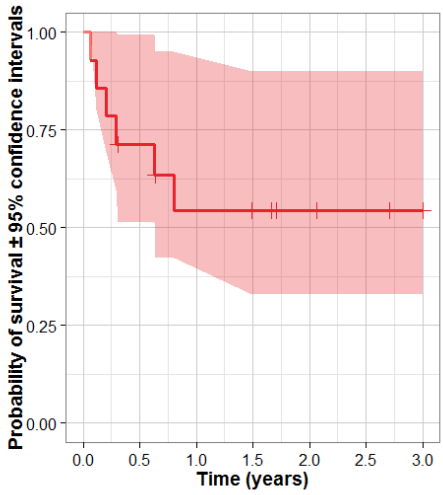


Figure B 83: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – BP – Oehler

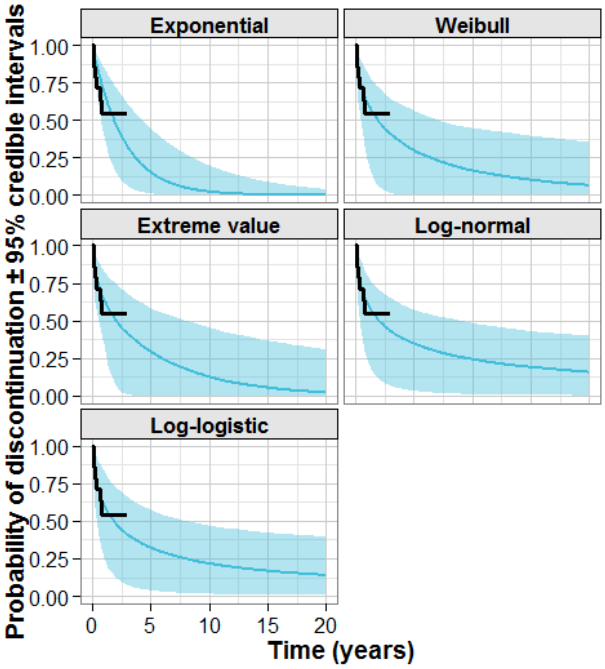


Table B 130: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – BP – Oehler

Model	AIC
Log-normal	23.65976
Extreme Value	25.72193
Weibull	25.11988
Log-logistic	24.33079
Exponential	25.52308

Model	Brier Score
Log-normal	0.260113
Extreme Value	0.258380
Weibull	0.259455
Log-logistic	0.262326
Exponential	0.267484

Best fitting curve: exponential

2nd best fitting curve: weibull

Overall survival – SCT – CP – Jabbour

Figure B 84: Kaplan-Meir Overall survival – SCT – CP – Jabbour

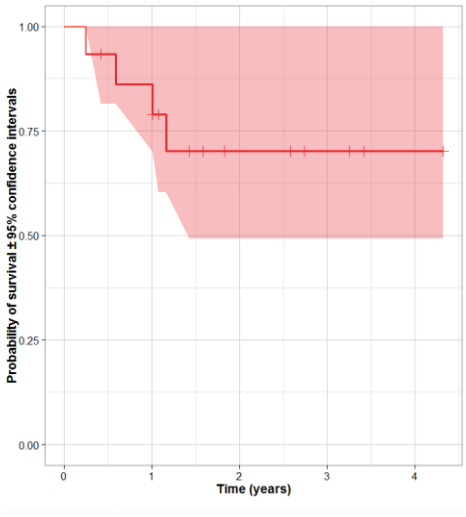


Figure B 85: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – CP – Jabbour

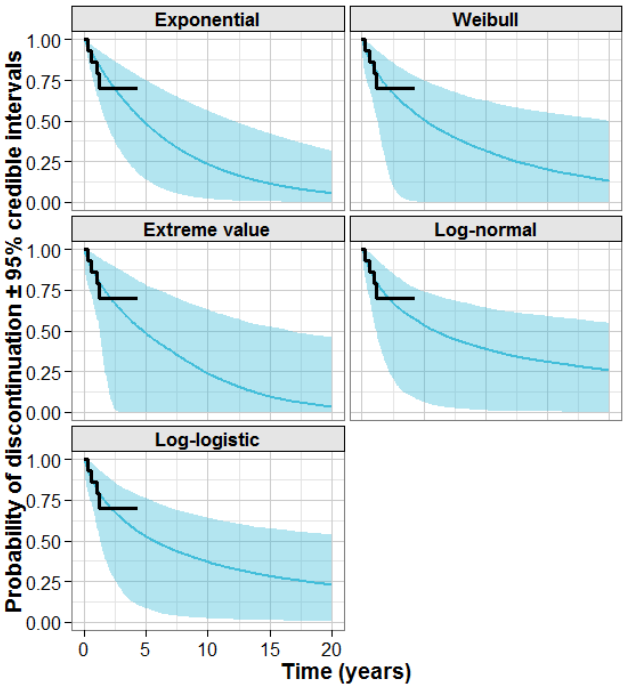


Table B 131: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – CP – Jabbour

Model	AIC
Log-normal	26.14015
Extreme Value	27.32345
Weibull	27.02612
Log-logistic	26.66631
Exponential	25.17696

Model	Brier Score
Log-normal	0.190153
Extreme Value	0.188253
Weibull	0.189425
Log-logistic	0.191417
Exponential	0.189540

Best fitting curve: exponential
2nd best fitting curve: weibull

Overall survival – SCT – Advanced Phases – Jabbour

Figure B 86: Kaplan-Meir Overall survival – SCT – Advanced Phases – Jabbour

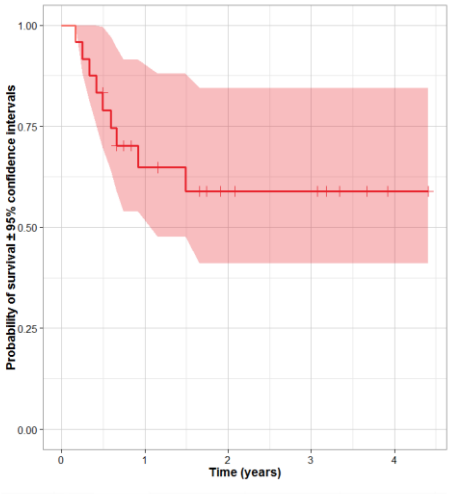


Figure B 87: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – Advanced Phases – Jabbour

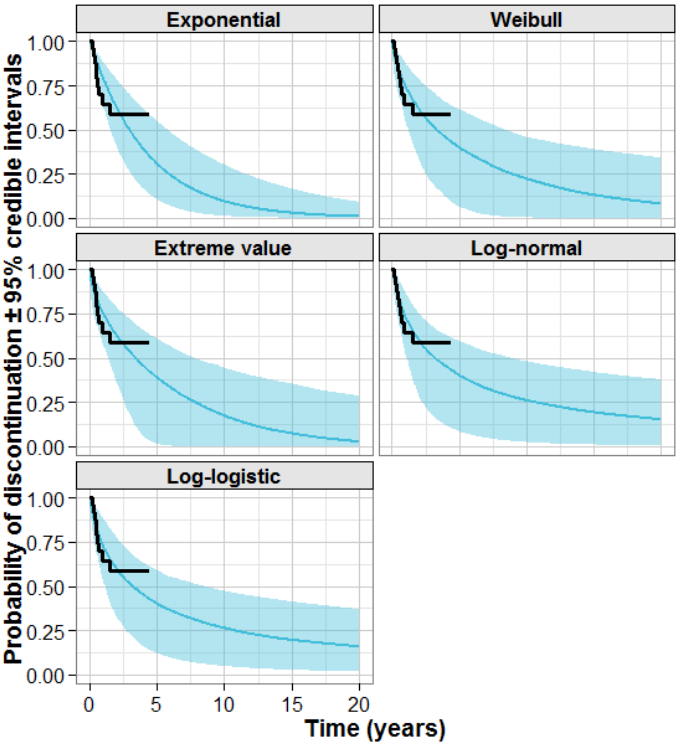


Table B 132: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – Advanced Phases – Jabbour

Model	AIC
Log-normal	44.25348
Extreme Value	47.68981
Weibull	46.72808
Log-logistic	45.45144
Exponential	46.01513

Model	Brier Score
Log-normal	0.236841
Extreme Value	0.235448
Weibull	0.236320
Log-logistic	0.238715
Exponential	0.240880

Best fitting curve: exponential

Overall survival – SCT – CP – Saussele

Figure B 88: Kaplan-Meir Overall survival – SCT – CP – Saussele

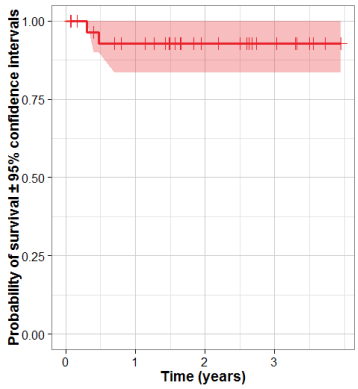


Figure B 89: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – CP – Saussele

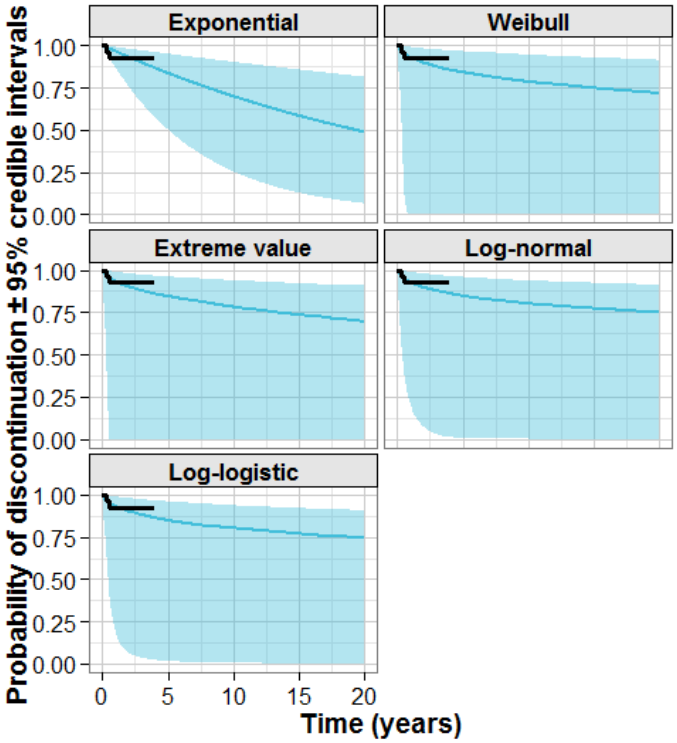


Table B 133: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – CP – Saussele

Model	AIC
Log-normal	20.32534
Extreme Value	20.75618
Weibull	20.71217
Log-logistic	20.66548
Exponential	19.47777

Model	Brier Score
Log-normal	0.236841
Extreme Value	0.235448
Weibull	0.236320
Log-logistic	0.238715
Exponential	0.240880

Best fitting curve: exponential

Overall survival – SCT – Advanced Phases – Saussele

Figure B 90: Kaplan-Meir Overall survival – SCT – Advanced Phases – Saussele

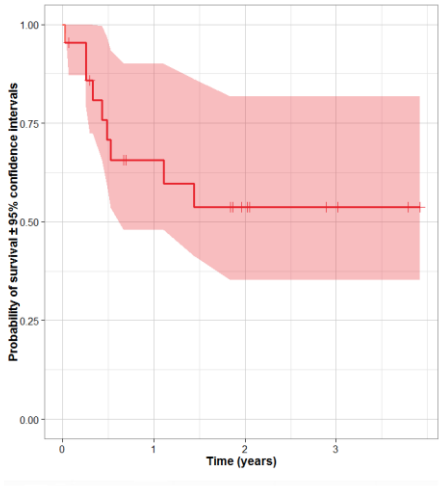


Figure B 91: Parametric curve fits to the Kaplan-Meir Overall survival – SCT – Advanced Phases – Saussele

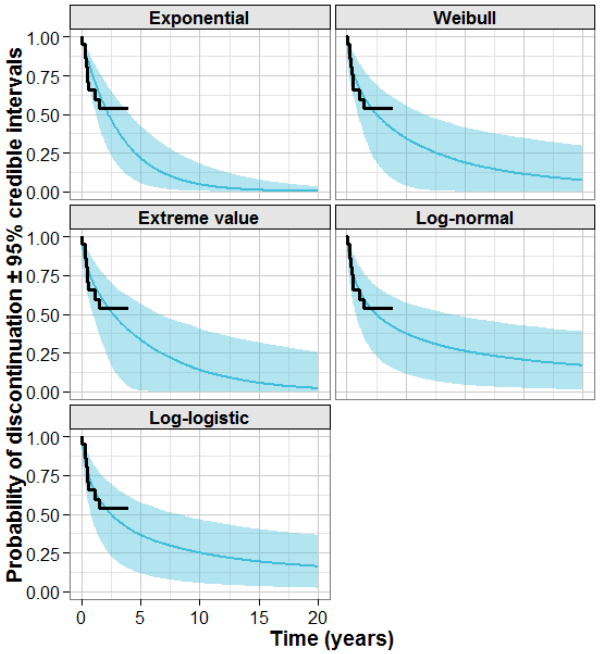


Table B 134: Goodness of fit measures for parametric curve fits to the Kaplan-Meir Overall survival – SCT – Advanced Phases – Saussele

Model	AIC
Log-normal	39.71727
Extreme Value	41.80358
Weibull	41.05335
Log-logistic	40.14057
Exponential	41.62463

Model	Brier Score
Log-normal	0.240700
Extreme Value	0.242002
Weibull	0.242251
Log-logistic	0.242754
Exponential	0.248394

Best fitting curve: exponential

10.19 Appendix 19: Variables included in the cost-effective analysis

A full list of parameters used in the cost-effective analysis is presented in Table B 135:

Table B 135: Parameters used in cost-effectiveness analysis

Parameter	Value	Reference	Distribution (if used in PSA)
Number of days in model cycle	30.4375		
Time horizon	50		
Cost discount rate	3.5%	NICE Methods Guide	
QALY discount rate	3.5%	NICE Methods Guide	
LY discount rate	0		
Patient starting age - CP	54	Study 200	
Patient starting age - CP	50	Study 200	
Patient starting age - CP	47	Study 200	
Daily bosutinib dose (Licensed)	50 0 mg		
Bosutinib - proportion of patients - CP - 600mg dose	0.12	Study 200	Beta(20,99)
Bosutinib - proportion of patients - CP - 500mg dose	0.42		Beta(44,55)
Bosutinib - proportion of patients - CP - 400mg dose	0.28		Beta(38,17)
Bosutinib - proportion of patients - CP - 300mg dose	0.18		
Bosutinib - proportion of patients - AP - 600mg dose	0.17		Beta(12,65)
Bosutinib - proportion of patients - AP - 500mg dose	0.37		Beta(35,30)
Bosutinib - proportion of patients - AP - 400mg dose	0.32		Beta(16,14)
Bosutinib - proportion of patients - AP - 300mg dose	0.14		
Bosutinib - proportion of patients - BP - 600mg dose	0.16		Beta(14,50)
Bosutinib - proportion of patients - BP - 500mg dose	0.45		Beta(32,18)
Bosutinib - proportion of patients - BP - 400mg dose	0.21		Beta(14,4)
Bosutinib - proportion of patients - BP - 300mg dose	0.18		
28 x 500mg bosutinib pack cost	3436.67		
28 x 100mg bosutinib pack cost	859.17		
Daily hydroxycarbamide dose	2g	Loveman et al, 2012[85]	
100 x 500mg Hydroxycarbamide pack cost	£10.47	BNF 64	
Daily interferon dose	8.65mU	Rogers et al, 2012[84]	

Parameter	Value	Reference	Distribution (if used in PSA)
Interferon 4.5mU injection cost	21.29	BNF 64	
Nurse visit cost (for interferon injection)	£39	PSSRU 2012	
Proportion of interferon users require nurse assistance	25%	Rogers et al, 2012	Beta (25,75)
SCT month 0 cost (2010)	71549	NHS Blood & Transplant 2010	Normal(71549, 715.49)
SCT months 1-6 total cost (2010)	29713	NHS Blood & Transplant 2010	Normal(29713, 297.13)
SCT months 7-12 total cost (2010)	18119	NHS Blood & Transplant 2010	Normal(18119, 181.19)
SCT months total 13-24 cost (2010)	13075	NHS Blood & Transplant 2010	Normal(13075, 130.75)
SCT month 25+ daily dose ciclosporin	100mg	Clinician Advice	
30 x 100mg ciclosporin pack cost	69.11	BNF 64	
Nurse-led appointments per month - CP	0.40	Hoyle et al, 2011a[80]	Normal(0.4, 0.04)
Oncologist-led appointments per month - CP	0.90	Hoyle et al, 2011a	Normal(0.9,0.09)
Inpatient ward days per month - CP	0.00	Hoyle et al, 2011a	
Inpatient ICU days per month - CP	0.00	Hoyle et al, 2011a	
Nurse-led appointments per month - AP/BP	0.50	Hoyle et al, 2011a	Normal(0.5, 0.05)
Oncologist-led appointments per month - AP/BP	1.30	Hoyle et al, 2011a	Normal(1.3,0.13)
Inpatient ward days per month - AP/BP	1.72	Hoyle et al, 2011a	Normal(1.72,0.172)
Inpatient ICU days per month - AP/BP	0.10	Hoyle et al, 2011a	Normal(0.1,0.01)
Nurse-led appointment cost	£106	PSSRU 2012	Normal(106,10.6)
Oncologist-led appointment cost	£124	PSSRU 2012	Normal(124,12.4)
Inpatient ward day cost	£322	NHS Reference Costs 2011-12	Normal(322,32.2)
Inpatient ICU day cost	£1,109	NHS Reference Costs 2011-12	Normal(1109,110.9)
Cost of tests - CP (2011)	216.07	Hoyle et al, 2011a	Normal(216.07,21.607)
Cost of tests - AP/BP (2011)	352.45	Hoyle et al,	Normal(352.45,35.245)

Parameter	Value	Reference	Distribution (if used in PSA)
		2011a	
Cost of death (2008)	5401	Dewer & Addicott, 2008	Normal(5401,54.01)
Alternative cost of death	£569	Hoyle et al, 2011a	Normal(569,56.9)
HCHS - Pay & Prices Index - 2008	257.0	PSSRU 2012	
HCHS - Pay & Prices Index - 2009	267.0	PSSRU 2012	
HCHS - Pay & Prices Index - 2010	268.6	PSSRU 2012	
HCHS - Pay & Prices Index - 2011	276.7	PSSRU 2012	
HCHS - Pay & Prices Index - 2012	285.7	PSSRU 2012	
Utility: controlled CP - bosutinib	0.85	IRIS	Beta(85,15)
Utility: controlled CP - hydroxycarbamide	0.85	IRIS	Beta(85,15)
Utility: controlled CP - interferon-alpha	0.71	IRIS	Beta(71,29)
Utility: controlled CP - stem cell transplant	0.71	IRIS	Beta(71,29)
Utility: uncontrolled CP/AP - bosutinib	0.73	IRIS	Beta(73,27)
Utility: uncontrolled CP/AP - hydroxycarbamide	0.73	IRIS	Beta(73,27)
Utility: uncontrolled CP/AP - interferon-alpha	0.73	IRIS	Beta(73,27)
Utility: uncontrolled CP/AP - stem cell transplant	0.71	IRIS	Beta(71,29)
Utility: BC - bosutinib	0.52	IRIS	Beta(52,48)
Utility: BC - hydroxycarbamide	0.52	IRIS	Beta(52,48)
Utility: BC - interferon-alpha	0.52	IRIS	Beta(52,48)
Utility: BC - stem cell transplant	0.52	IRIS	Beta(52,48)
Average utility for 56 year old	0.80	Kind & Dolan, 1999	
Thrombocytopenia - cost	503.99	Oxford Outcomes	Normal(503.99, 50.399)
Neutropenia - cost	506.13	Oxford Outcomes	Normal(506.13,50.613)
Anaemia - cost	346.69	Oxford Outcomes	Normal(346.69,34.469)
Cardiac disorders - cost	169.81	Oxford Outcomes	Normal(169.81,16.981)
Gastrointestinal disorders - cost	281.07	Erlotinib ERG report	Normal(281.07, 28.107)

Parameter	Value	Reference	Distribution (if used in PSA)
Hepatobiliary disorders - cost	215.85	NHS reference costs	Normal(215.85,21.585)
Infections and infestations - cost	933.23	NHS reference costs	Normal(933.23,93.323,)
Investigations - cost	31.02	NHS reference costs	Normal(31.02,3.102)
Metabolism and nutrition disorders - cost	1576.37	NHS reference costs	Normal(1576.37,157.637)
Musculoskeletal and connective tissue disorders - cost	717.03	NHS reference costs	Normal(717.03,71.703)
Neoplasms benign, malignant and unspecified - cost	1570.14	NHS reference costs	Normal(1570.14,157.014)
Nervous system disorders - cost	1091.02	NHS reference costs	Normal(1091.02,109.102)
Respiratory, thoracic and mediastinal disorders - cost	32.10	Oxford Outcomes	Normal(32.10,3.21)
Skin and subcutaneous tissue disorders - cost	138.76	expert panel	Normal(138.76,13.876)
Thrombocytopenia - proportion	0.25	Study 200	Beta(30,88)
Neutropenia - proportion	0.14		Beta(17,101)
Anaemia - proportion	0.05		Beta(6,112)
Cardiac disorders - proportion	0.04		Beta(5,113)
Gastrointestinal disorders - proportion	0.14		Beta(16,102)
Hepatobiliary disorders - proportion	0.04		Beta(5,113)
Infections and infestations - proportion	0.03		Beta(4.5,114.5)
Investigations - proportion	0.09		Beta(11,107)
Metabolism and nutrition disorders - proportion	0.03		Beta(4.5,114.5)
Musculoskeletal and connective tissue disorders - proportion	0.06		Beta(7,111)
Neoplasms bening, malignant and unspecified - proportion	0.03		Beta(4.5,114.5)
Nervous system disorders - proportion	0.04		Beta(5,113)
Respiratory, thoracic and mediastinal disorders - proportion	0.03		Beta(3.5,115.5)
Skin and subcutaneous tissue disorders - proportion	0.02		Beta(2.5,116.5)
Bosutinib - CP - PFS -	[redacted]		Multinormal, using

Parameter	Value	Reference	Distribution (if used in PSA)
exponential - log(scale)			variance-covariance matrices
Bosutinib - CP - OS - exponential - log(scale)	4.92		
Bosutinib - CP - OS - Weibull - log(scale)	5.02		
Bosutinib - CP - OS - Weibull - log(shape)	5.02		
Bosutinib - CP - time to discontinuation - lognormal - log(scale)	[redacted]		
Bosutinib - CP - time to discontinuation - lognormal - log(shape)	[redacted]		
Bosutinib - CP - time to discontinuation - loglogistic - log(scale)	[redacted]		
Bosutinib - CP - time to discontinuation - loglogistic - log(shape)	[redacted]		
Hydroxycarbamide mean OS - CP	42.00	Rogers et al, 2012	Triangular(24,78,42)
Interferon mean OS - CP	43.20	Rogers et al, 2012	Triangular(12,132,43.2)
Interferon mean time on treatment - CP	6.00	Rogers et al, 2012	
Responders - OS - Weibull - alpha	1.70		
Responders - OS - Weibull - beta	190.54		
Non-responders - hazard ratio	0.37	Rogers et al, 2012	Normal(0.37,0.11)
MCyR for bosutinib	0.39	Khoury et al, 2012	Beta(42,66)
PFS - interferon - exponential - parameter	0.02		
Time in blast phase	6.00	Hoyle et al, 2011a	Triangular(3,13,6)
Time in accelerated phase	10.00	Hoyle et al, 2011a	Normal(10,0.69)
Bosutinib - AP - OS - exponential - log(scale)	7.39862		Multinormal, using variance-covariance matrices
Bosutinib - AP - OS - extreme value - log(scale)	8.08043		
Bosutinib - AP - OS - extreme value - log(shape)	-0.36623		
Bosutinib - AP - time to discontinuation - lognormal - log(scale)	[redacted]		
Bosutinib - AP - time to discontinuation - lognormal - log(shape)	[redacted]		
Bosutinib - AP - time to	[redacted]		

Parameter	Value	Reference	Distribution (if used in PSA)
discontinuation - loglogistic - log(scale)			
Bosutinib - AP - time to discontinuation - loglogistic - log(shape)	[redacted]		
Bosutinib - AP - PFS - Weibull - log(scale)	[redacted]		
Bosutinib - AP - PFS - Weibull - log(shape)	[redacted]		
Bosutinib - BP - OS - exponential - log(scale)	6.45323		Multinormal, using variance-covariance matrices
Bosutinib - BP - OS - weibull - log(scale)	6.49249		
Bosutinib - BP - OS - weibull - log(shape)	-0.16525		
Bosutinib - BP - time to discontinuation - lognormal - log(scale)	[redacted]		
Bosutinib - BP - time to discontinuation - lognormal - log(shape)	[redacted]		
Bosutinib - BP - time to discontinuation - loglogistic - log(scale)	[redacted]		
Bosutinib - BP - time to discontinuation - loglogistic - log(shape)	[redacted]		
Bosutinib - BP - PFS - Weibull - log(scale)	-0.19129		
Bosutinib - BP - PFS - Weibull - log(shape)	-0.19583		
SCT - CP - Jabbour - exponential - log(scale)	1.89712		Multinormal, using variance-covariance matrices
SCT - CP - Jabbour - weibull - log(scale)	2.10072		
SCT - CP - Jabbour - weibull - log(shape)	-0.16551		
SCT - CP - Oehler - exponential - log(scale)	1.91529		
SCT - AP - Oehler - exponential - log(scale)	1.09818		
SCT - AP - Oehler - weibull - log(scale)	1.0679		
SCT - AP - Oehler - weibull - log(shape)	0.05412		
SCT - Advanced Phases - Jabbour - exponential - log(scale)	1.44529		
SCT - BP - Oehler - exponential - log(scale)	0.96026		
SCT - BP - Oehler - weibull -	1.34032		

Parameter	Value	Reference	Distribution (if used in PSA)
log(scale)			
SCT - BP - Oehler - weibull - log(shape)	-0.49958		
SCT - Advanced Phases - Saussele - exponential - log(scale)	3.36944		

10.20 Appendix 20: FLAG-IDA costing methodology

The cost of two cycles of treatment with the FLAG-IDA chemotherapy regimen was estimated using drug costs from the British National Formulary (BNF) and NHS reference costs.

The regimen features four drugs; fludarabine, cytarabine, idarubicin and a granulocyte-colony stimulating factor (G-CSF). The dosages received by patients were defined as reported by Pastore et al. (2003)[128], and this is shown in Table B136. For the dosage calculations, the average patient weight was estimated as 80kg, based on Trend Tables from the Health Survey for England (2011)[129], and the average patient body surface area was estimated as 1.79m^2, based on Sacco et al. (2010).[130]

Table B136: Dosing regimen as reported by Pastore et al. (2003).[128]

Drug	Dose concentration	Dosage required per day (mg)	Days of treatment
Fludarabine	30mg/m^2	53.70	Days 1-5
Cytarabine	2g/m^2	3580.00	Days 1-5
Idarubicin	10mg/m^2	17.90	Days 1-3
G-CSF	5µg/kg	0.40	Day 7 until blood count recovery

The time to blood count recovery was estimated as 23 days, as reported by Steinmetz et al. (1999).[131] It is assumed that patients will remain in hospital, receiving G-CSF, until this time.

As there are several G-CSFs available for use in the UK, prescription trends were taken from the Prescription Cost Analysis 2011.[132] The quantity of each G-CSF preparation prescribed in England in 2011 was used to produce a market share for each product with which to weight the average cost, based on the quantity of each product that would be required to meet the dose requirement of the FLAG-IDA regimen. The calculation is laid out in Table B137. The prices of each preparation were taken from the BNF.[133]

Table B137: Weighted average of G-CSF drug costs.

G-CSF Product Description	Number Prescribed (000's)	Market Share	Cost per Item	Dosage per item (mg)	Quantity Required for Dose	Cost per dose
Neupogen - 30mega u/1ml Vial for injection	0.066	21.50%	£ 52.71	0.3	2	£ 105.42
Neupogen - 300mcg/0.5ml Prefilled syringe	0.203	66.12%	£ 52.71	0.3	2	£ 105.42
Neupogen - 480mcg/0.5ml Prefilled syringe	0.005	1.63%	£ 84.06	0.48	1	£ 84.06

Nivestim - 12mu/0.2ml Prefilled syringe	0.001	0.33%	£ 36.00	0.12	4	£ 144.00
Nivestim - 30mu/0.5ml Prefilled syringe	0.002	0.65%	£ 58.00	0.3	2	£ 116.00
Ratiograstim - 30mega u/0.5ml Prefilled syringe	0.013	4.23%	£ 62.26	0.3	2	£ 124.52
Tevagrastim - 30mega u/0.5ml Prefilled syringe	0.013	4.23%	£ 62.25	0.3	2	£ 124.50
Tevagrastim - 48mega u/0.8ml Prefilled syringe	0.004	1.30%	£ 99.29	0.48	1	£ 99.29
Weighted Average						**£ 106.80**

The drug costs for each of the four components are shown together in Table B138, along with the total expected drug costs for a single cycle of FLAG-IDA. As before, the cost incorporated was that of the number of each item required to meet the required dose.

Table B138: Drug costs of one cycle of FLAG-IDA treatment.

Drug	Cost per Item	Dosage per item (mg)	Quantity Required for Dose	Cost per Dose	Number of Treatment Days	Total Treatment Costs
Fludarabine – 50mg Vial for injection	£147.07	50	2	£ 294.14	5	£ 1,470.70
Cytarabine – 10ml Vial for injection	£ 39.00	1000	4	£ 156.00	5	£ 780.00
Idarubicin – 5mg Vial for injection	£ 87.36	5	4	£ 349.44	3	£ 1,048.32
G-CSF – Weighted Average				£ 106.80	18	£ 1,922.46
Total drug costs for one cycle of treatment:						**£ 5,221.48**

Hospital and resource use costs were estimated from the NHS National Schedule of Reference Costs 2011-12.[134] These are shown in

Table **B139**. Patients were assumed to receive one set of blood tests at the beginning of each cycle, and their inpatient stay was assumed to last until their platelet and neutrophil blood counts had recovered after 23 days. The average length of an elective inpatient stay for acute myeloid leukaemia patients was 9 days. This was supplemented with excess bed days, up to the total of 23 days in hospital.

Table B139: Resource use costs of one cycle of FLAG-IDA treatment.

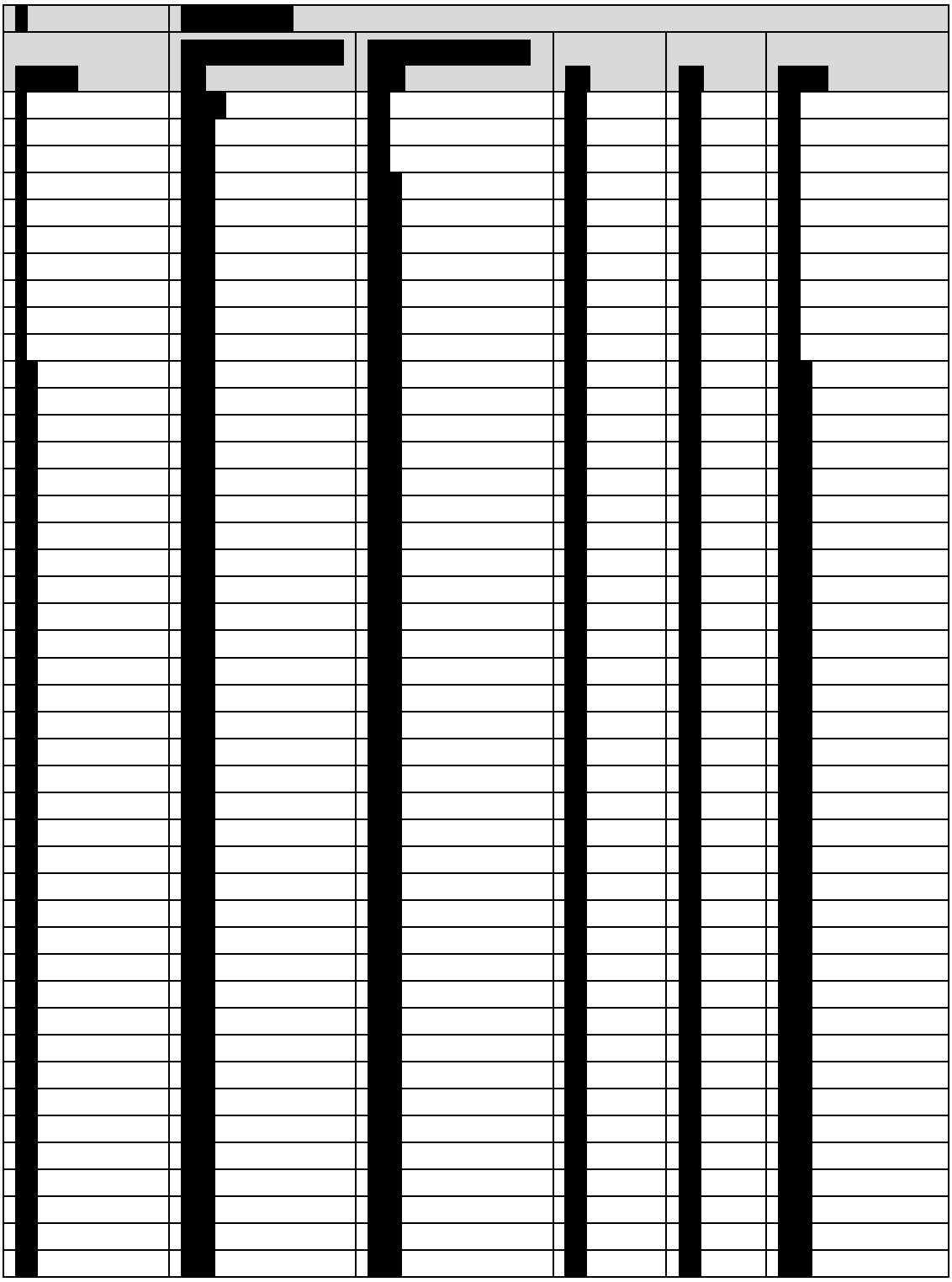
Resource Description	Mean Cost per Unit	Units Required	Total Cost
DAP823 Haematology Tests	£ 3.09	1	£ 3.09
SA25F Acute Myeloid Leukaemia without CC: Elective Inpatient Stay	£ 4,866.13	1	£ 4,866.13
SA25F Acute Myeloid Leukaemia without CC: Elective Excess Bed Day	£ 322.34	14	£ 4,515.22

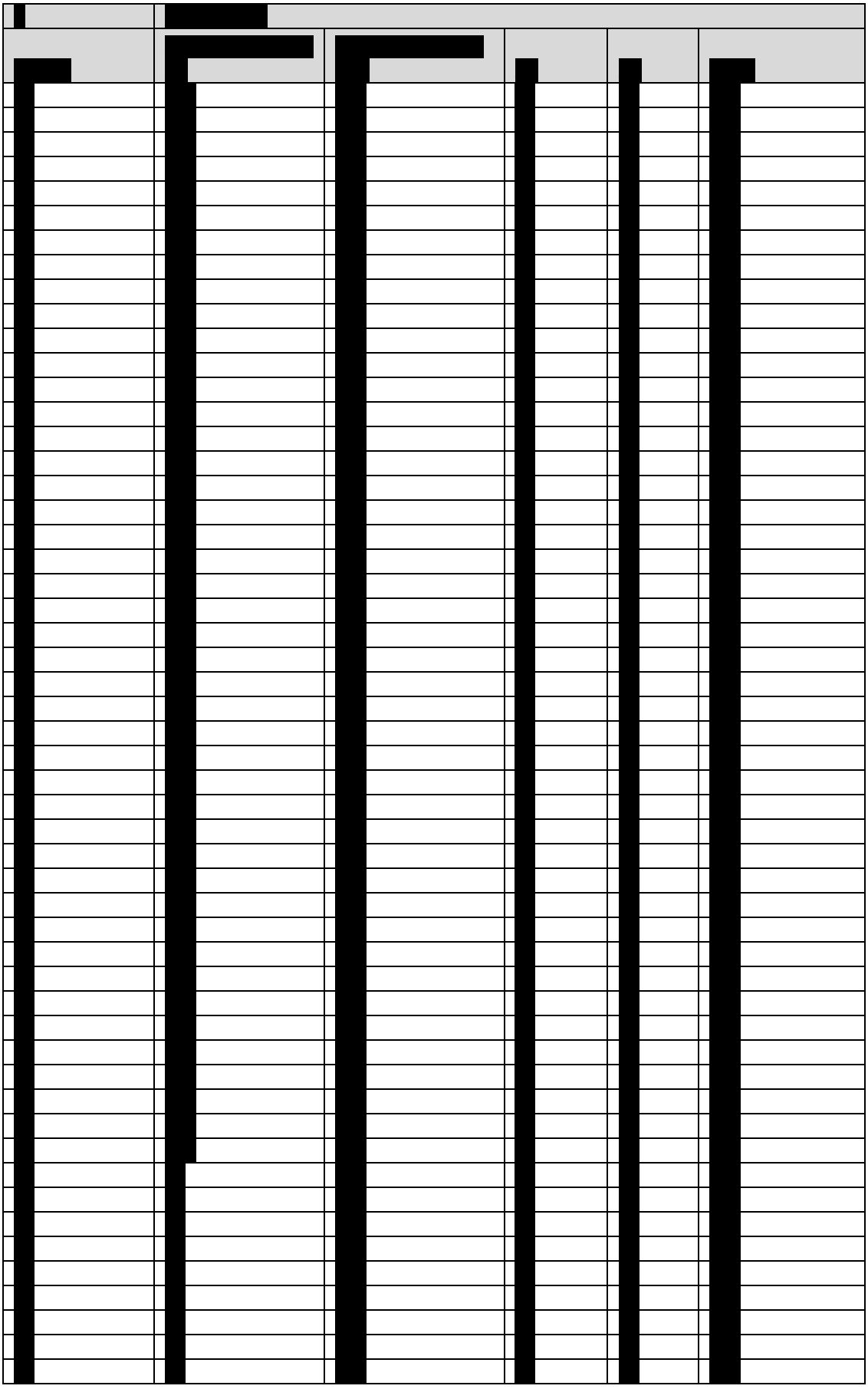
Total resource use costs for one cycle of treatment:	**£ 9,384.44**

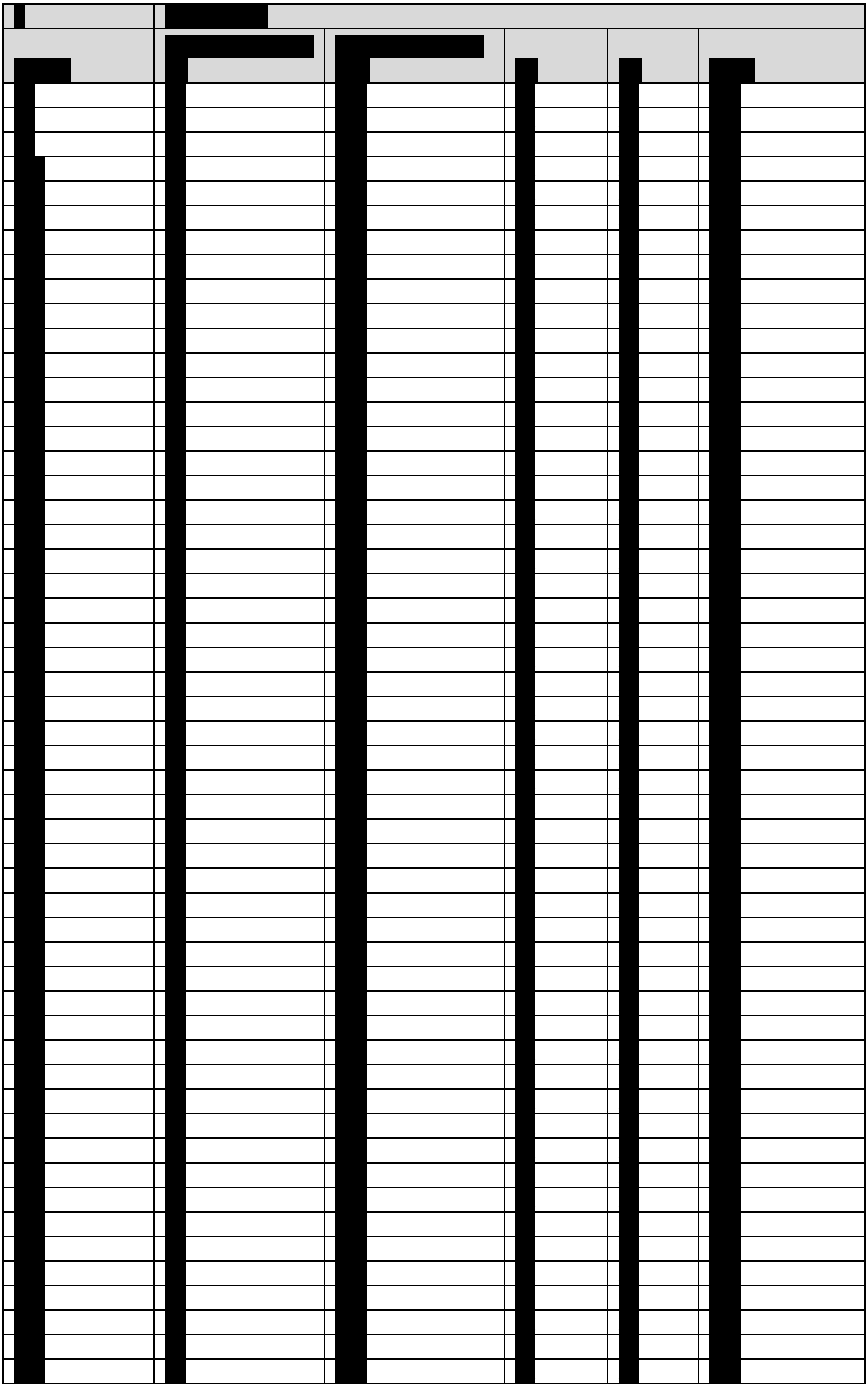
The drug and resource costs per cycle were combined and doubled to provide an estimate of the cost of two cycles of treatment of £29,212.

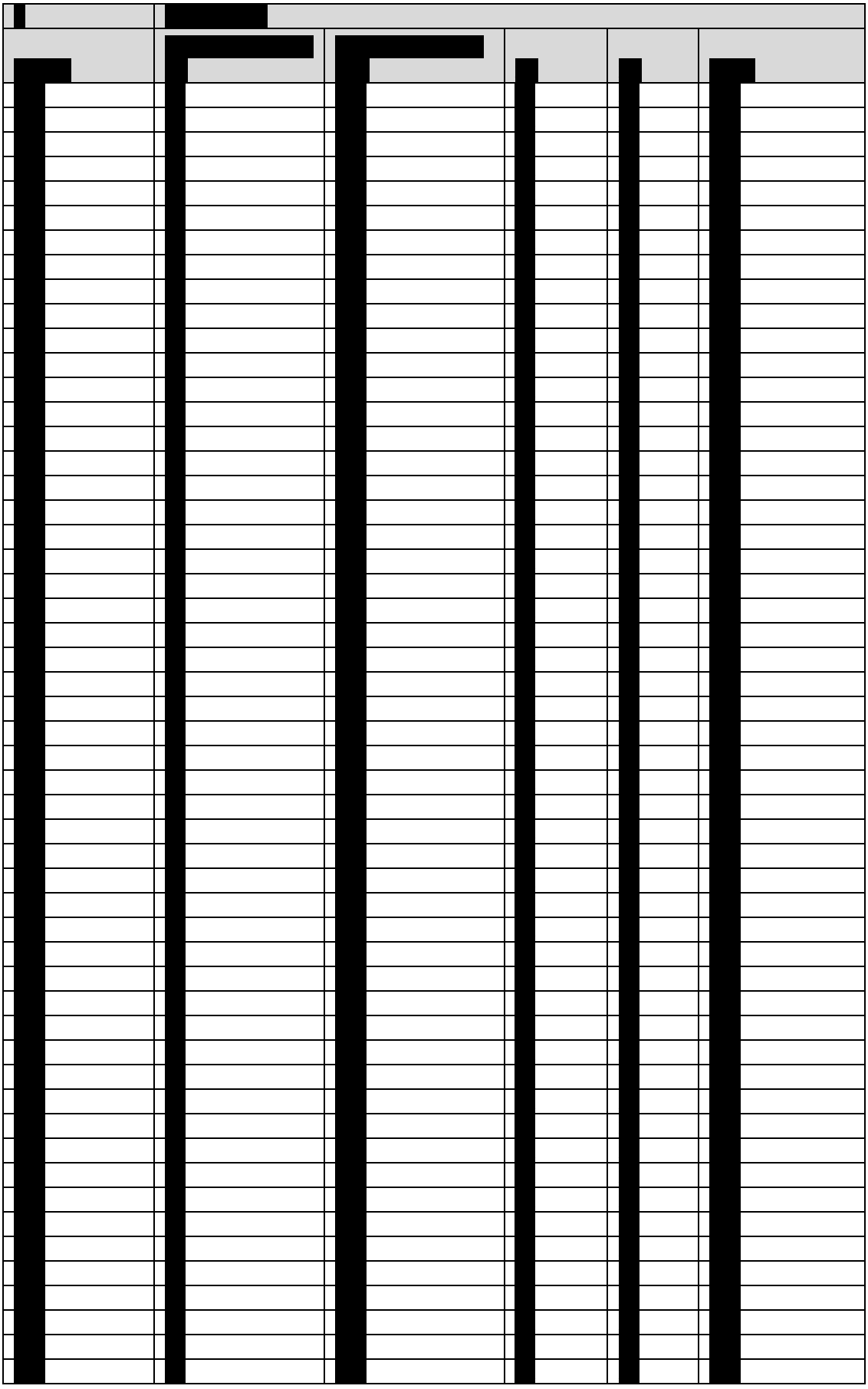
10.21 Appendix 21: Tabulated markov traces for CP, AP and BP

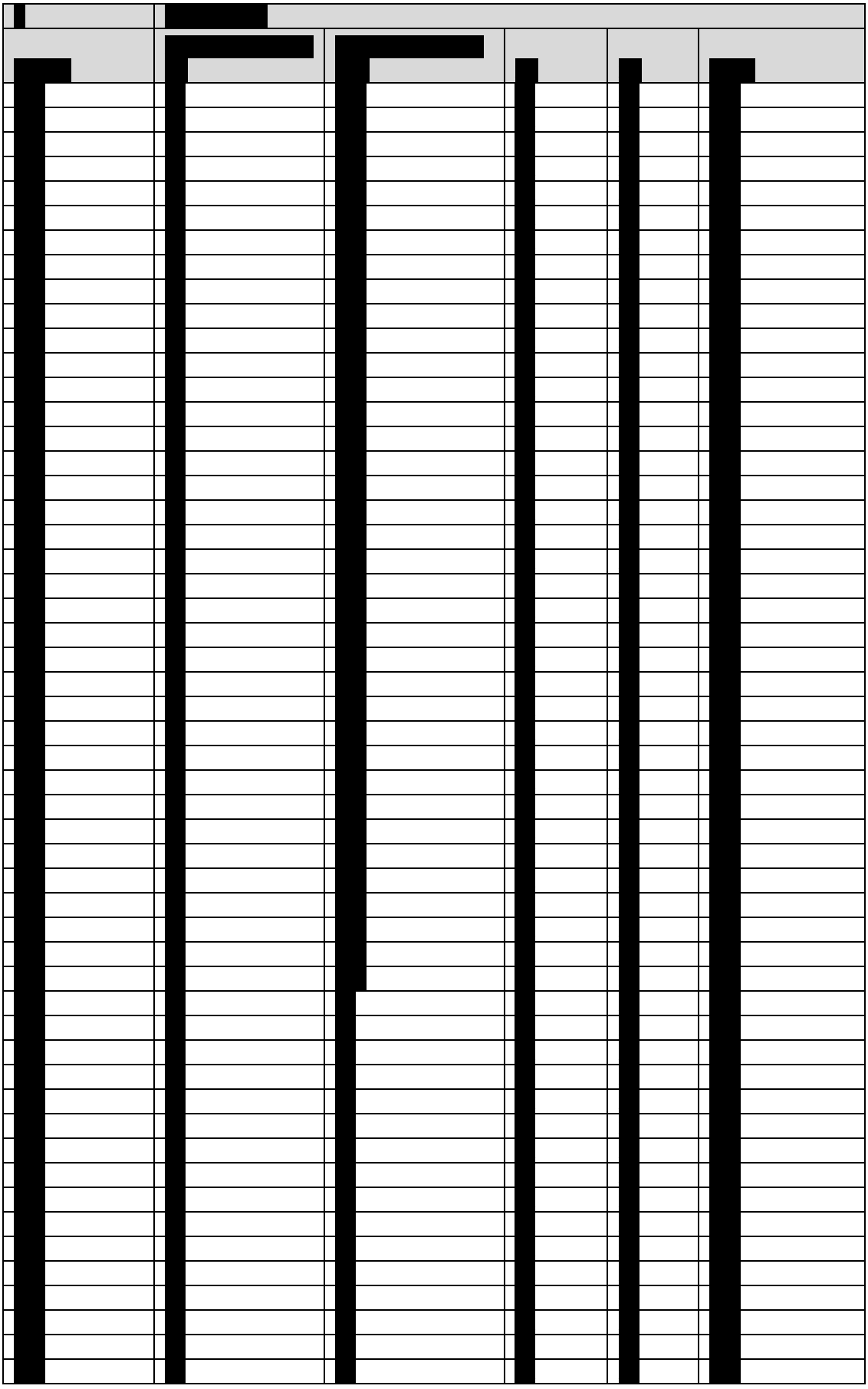
Table B140: Tabulated markov trace for CP model - Bosutinib

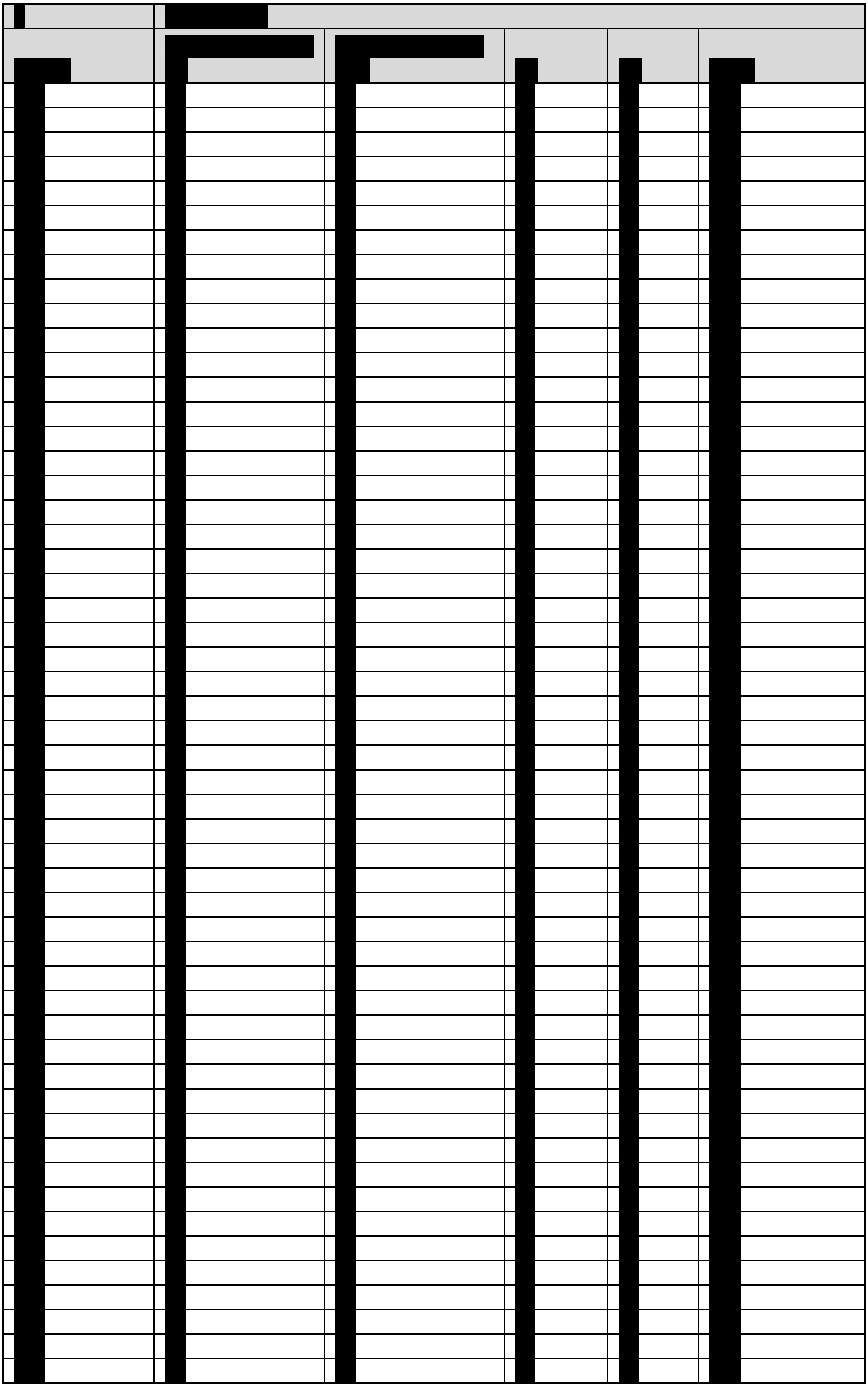


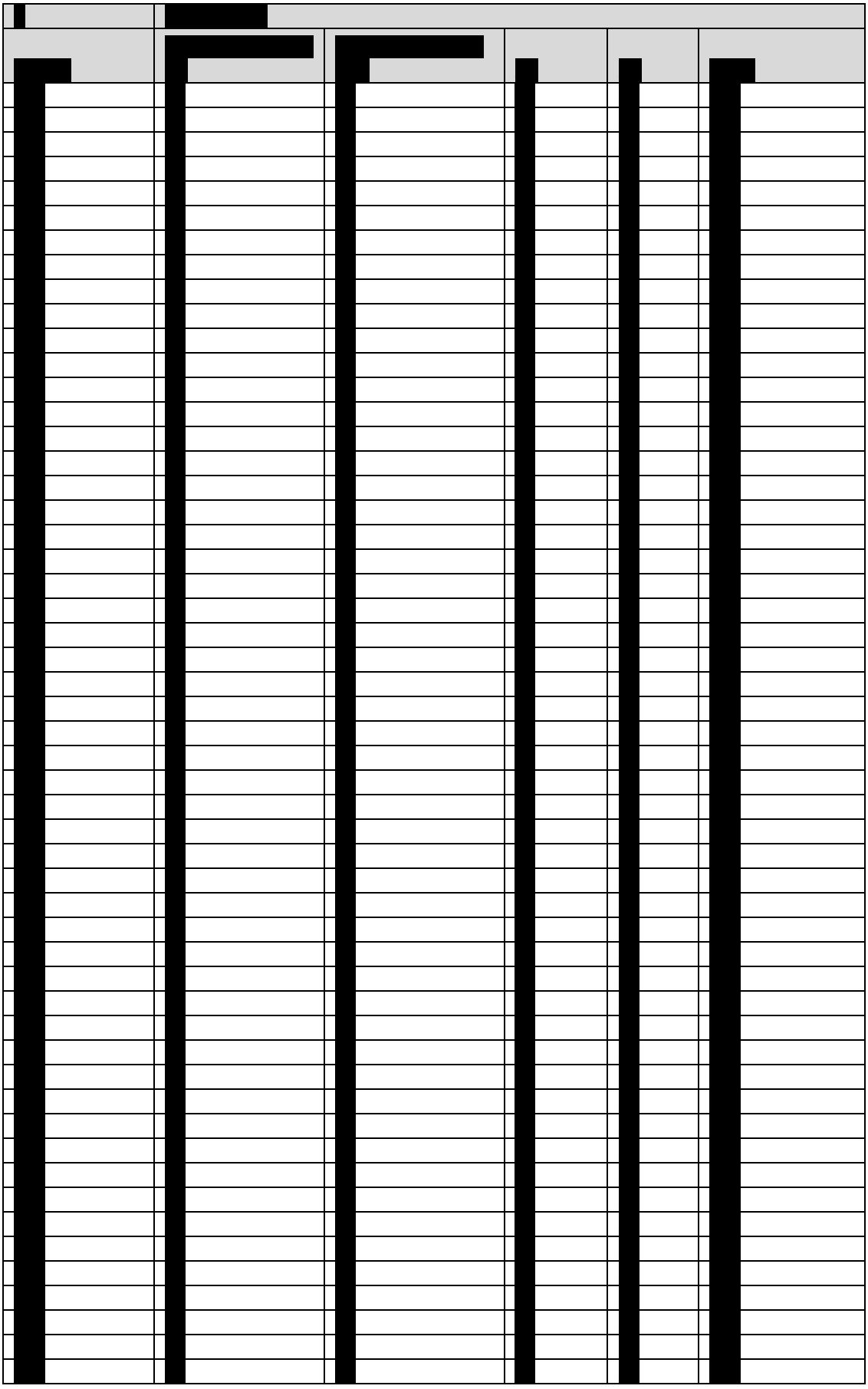


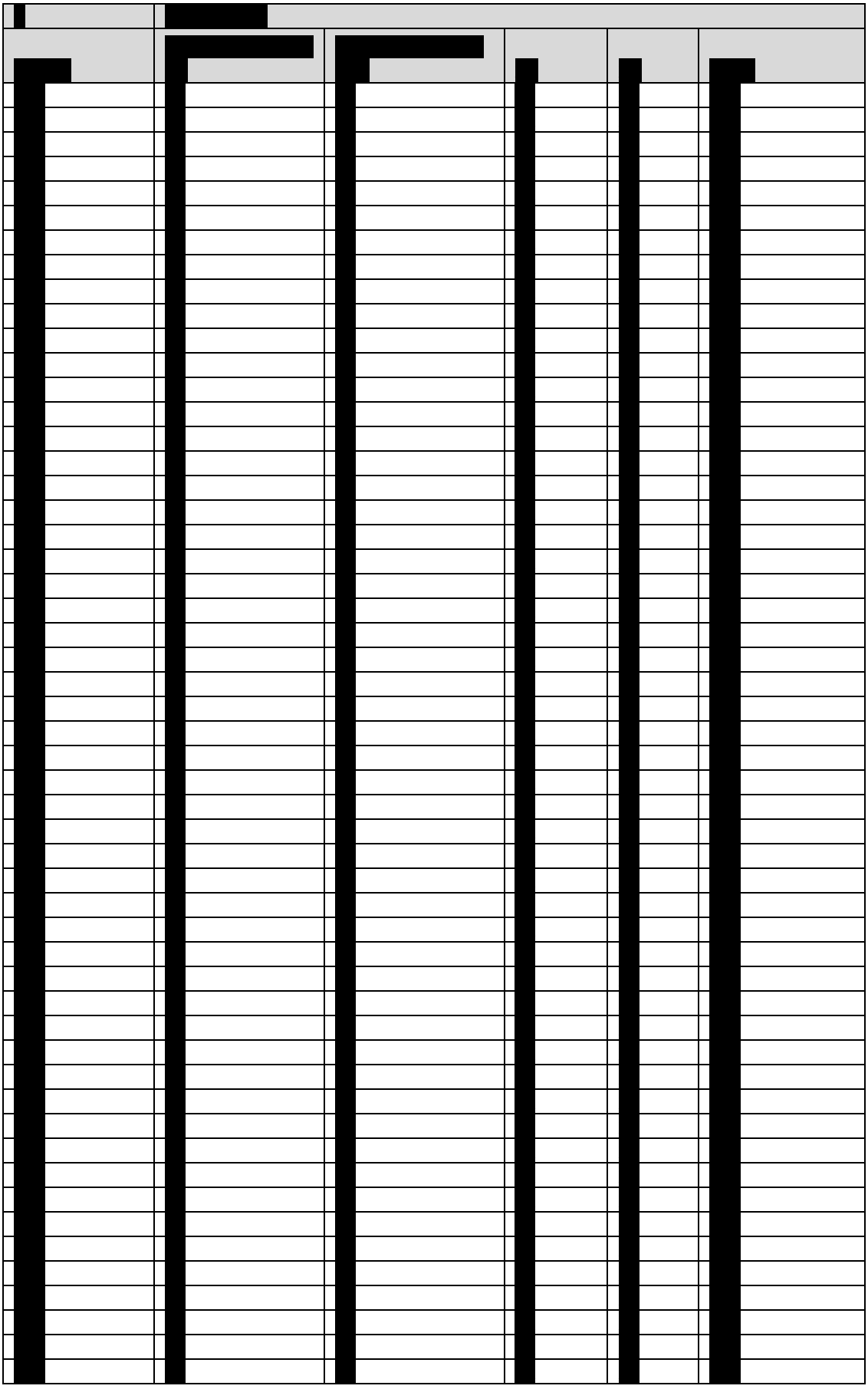












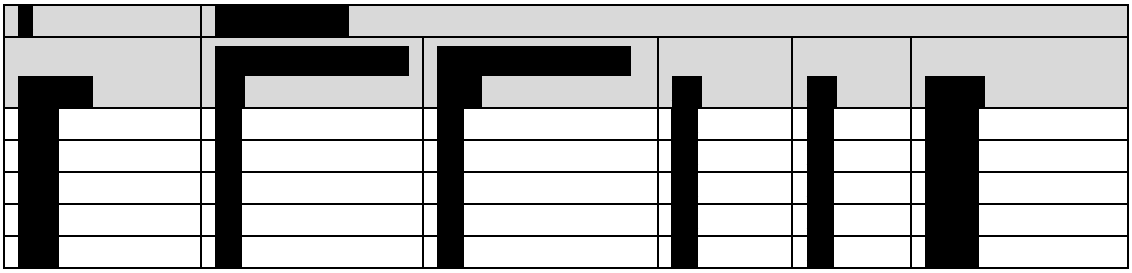


Table B 141: Tabulated markov trace for CP model- Hydroxycarbamide

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
0	100%	0%	0%	0%
1	98%	0%	0%	2%
2	93%	0%	2%	5%
3	88%	0%	5%	7%
4	84%	0%	7%	9%
5	80%	0%	9%	11%
6	75%	0%	11%	13%
7	71%	0%	13%	15%
8	67%	2%	13%	17%
9	63%	5%	13%	19%
10	60%	7%	12%	21%
11	56%	9%	12%	23%
12	52%	11%	12%	25%
13	49%	13%	12%	27%
14	45%	15%	11%	28%
15	42%	17%	11%	30%
16	38%	19%	11%	32%
17	35%	21%	10%	33%
18	34%	21%	10%	35%
19	33%	20%	10%	36%
20	33%	20%	10%	38%
21	32%	19%	10%	39%
22	31%	19%	9%	41%
23	30%	18%	9%	42%
24	30%	18%	9%	44%
25	29%	18%	9%	45%
26	28%	17%	8%	46%
27	28%	17%	8%	47%
28	27%	16%	8%	49%
29	26%	16%	8%	50%
30	26%	16%	8%	51%
31	25%	15%	8%	52%
32	25%	15%	7%	53%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
33	24%	14%	7%	54%
34	23%	14%	7%	55%
35	23%	14%	7%	57%
36	22%	13%	7%	58%
37	22%	13%	7%	59%
38	21%	13%	6%	60%
39	21%	13%	6%	60%
40	20%	12%	6%	61%
41	20%	12%	6%	62%
42	19%	12%	6%	63%
43	19%	11%	6%	64%
44	18%	11%	6%	65%
45	18%	11%	5%	66%
46	18%	11%	5%	67%
47	17%	10%	5%	67%
48	17%	10%	5%	68%
49	16%	10%	5%	69%
50	16%	10%	5%	70%
51	16%	9%	5%	70%
52	15%	9%	5%	71%
53	15%	9%	4%	72%
54	15%	9%	4%	72%
55	14%	9%	4%	73%
56	14%	8%	4%	74%
57	14%	8%	4%	74%
58	13%	8%	4%	75%
59	13%	8%	4%	75%
60	13%	8%	4%	76%
61	12%	7%	4%	77%
62	12%	7%	4%	77%
63	12%	7%	4%	78%
64	11%	7%	3%	78%
65	11%	7%	3%	79%
66	11%	7%	3%	79%
67	11%	6%	3%	80%
68	10%	6%	3%	80%
69	10%	6%	3%	81%
70	10%	6%	3%	81%
71	10%	6%	3%	82%
72	9%	6%	3%	82%
73	9%	6%	3%	82%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
74	9%	5%	3%	83%
75	9%	5%	3%	83%
76	9%	5%	3%	84%
77	8%	5%	3%	84%
78	8%	5%	2%	84%
79	8%	5%	2%	85%
80	8%	5%	2%	85%
81	8%	5%	2%	85%
82	7%	5%	2%	86%
83	7%	4%	2%	86%
84	7%	4%	2%	86%
85	7%	4%	2%	87%
86	7%	4%	2%	87%
87	7%	4%	2%	87%
88	6%	4%	2%	88%
89	6%	4%	2%	88%
90	6%	4%	2%	88%
91	6%	4%	2%	89%
92	6%	4%	2%	89%
93	6%	3%	2%	89%
94	6%	3%	2%	89%
95	5%	3%	2%	90%
96	5%	3%	2%	90%
97	5%	3%	2%	90%
98	5%	3%	2%	90%
99	5%	3%	1%	91%
100	5%	3%	1%	91%
101	5%	3%	1%	91%
102	5%	3%	1%	91%
103	4%	3%	1%	91%
104	4%	3%	1%	92%
105	4%	3%	1%	92%
106	4%	3%	1%	92%
107	4%	2%	1%	92%
108	4%	2%	1%	92%
109	4%	2%	1%	93%
110	4%	2%	1%	93%
111	4%	2%	1%	93%
112	4%	2%	1%	93%
113	4%	2%	1%	93%
114	3%	2%	1%	93%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
115	3%	2%	1%	94%
116	3%	2%	1%	94%
117	3%	2%	1%	94%
118	3%	2%	1%	94%
119	3%	2%	1%	94%
120	3%	2%	1%	94%
121	3%	2%	1%	94%
122	3%	2%	1%	95%
123	3%	2%	1%	95%
124	3%	2%	1%	95%
125	3%	2%	1%	95%
126	3%	2%	1%	95%
127	3%	2%	1%	95%
128	2%	2%	1%	95%
129	2%	1%	1%	95%
130	2%	1%	1%	96%
131	2%	1%	1%	96%
132	2%	1%	1%	96%
133	2%	1%	1%	96%
134	2%	1%	1%	96%
135	2%	1%	1%	96%
136	2%	1%	1%	96%
137	2%	1%	1%	96%
138	2%	1%	1%	96%
139	2%	1%	1%	96%
140	2%	1%	1%	96%
141	2%	1%	1%	97%
142	2%	1%	1%	97%
143	2%	1%	1%	97%
144	2%	1%	1%	97%
145	2%	1%	1%	97%
146	2%	1%	0%	97%
147	2%	1%	0%	97%
148	1%	1%	0%	97%
149	1%	1%	0%	97%
150	1%	1%	0%	97%
151	1%	1%	0%	97%
152	1%	1%	0%	97%
153	1%	1%	0%	97%
154	1%	1%	0%	98%
155	1%	1%	0%	98%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
156	1%	1%	0%	98%
157	1%	1%	0%	98%
158	1%	1%	0%	98%
159	1%	1%	0%	98%
160	1%	1%	0%	98%
161	1%	1%	0%	98%
162	1%	1%	0%	98%
163	1%	1%	0%	98%
164	1%	1%	0%	98%
165	1%	1%	0%	98%
166	1%	1%	0%	98%
167	1%	1%	0%	98%
168	1%	1%	0%	98%
169	1%	1%	0%	98%
170	1%	1%	0%	98%
171	1%	1%	0%	98%
172	1%	1%	0%	98%
173	1%	1%	0%	98%
174	1%	1%	0%	98%
175	1%	1%	0%	99%
176	1%	0%	0%	99%
177	1%	0%	0%	99%
178	1%	0%	0%	99%
179	1%	0%	0%	99%
180	1%	0%	0%	99%
181	1%	0%	0%	99%
182	1%	0%	0%	99%
183	1%	0%	0%	99%
184	1%	0%	0%	99%
185	1%	0%	0%	99%
186	1%	0%	0%	99%
187	1%	0%	0%	99%
188	0%	0%	0%	99%
189	0%	0%	0%	99%
190	0%	0%	0%	99%
191	0%	0%	0%	99%
192	0%	0%	0%	99%
193	0%	0%	0%	99%
194	0%	0%	0%	99%
195	0%	0%	0%	99%
196	0%	0%	0%	99%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
197	0%	0%	0%	99%
198	0%	0%	0%	99%
199	0%	0%	0%	99%
200	0%	0%	0%	99%
201	0%	0%	0%	99%
202	0%	0%	0%	99%
203	0%	0%	0%	99%
204	0%	0%	0%	99%
205	0%	0%	0%	99%
206	0%	0%	0%	99%
207	0%	0%	0%	99%
208	0%	0%	0%	99%
209	0%	0%	0%	99%
210	0%	0%	0%	99%
211	0%	0%	0%	99%
212	0%	0%	0%	99%
213	0%	0%	0%	99%
214	0%	0%	0%	100%
215	0%	0%	0%	100%
216	0%	0%	0%	100%
217	0%	0%	0%	100%
218	0%	0%	0%	100%
219	0%	0%	0%	100%
220	0%	0%	0%	100%
221	0%	0%	0%	100%
222	0%	0%	0%	100%
223	0%	0%	0%	100%
224	0%	0%	0%	100%
225	0%	0%	0%	100%
226	0%	0%	0%	100%
227	0%	0%	0%	100%
228	0%	0%	0%	100%
229	0%	0%	0%	100%
230	0%	0%	0%	100%
231	0%	0%	0%	100%
232	0%	0%	0%	100%
233	0%	0%	0%	100%
234	0%	0%	0%	100%
235	0%	0%	0%	100%
236	0%	0%	0%	100%
237	0%	0%	0%	100%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
238	0%	0%	0%	100%
239	0%	0%	0%	100%
240	0%	0%	0%	100%
241	0%	0%	0%	100%
242	0%	0%	0%	100%
243	0%	0%	0%	100%
244	0%	0%	0%	100%
245	0%	0%	0%	100%
246	0%	0%	0%	100%
247	0%	0%	0%	100%
248	0%	0%	0%	100%
249	0%	0%	0%	100%
250	0%	0%	0%	100%
251	0%	0%	0%	100%
252	0%	0%	0%	100%
253	0%	0%	0%	100%
254	0%	0%	0%	100%
255	0%	0%	0%	100%
256	0%	0%	0%	100%
257	0%	0%	0%	100%
258	0%	0%	0%	100%
259	0%	0%	0%	100%
260	0%	0%	0%	100%
261	0%	0%	0%	100%
262	0%	0%	0%	100%
263	0%	0%	0%	100%
264	0%	0%	0%	100%
265	0%	0%	0%	100%
266	0%	0%	0%	100%
267	0%	0%	0%	100%
268	0%	0%	0%	100%
269	0%	0%	0%	100%
270	0%	0%	0%	100%
271	0%	0%	0%	100%
272	0%	0%	0%	100%
273	0%	0%	0%	100%
274	0%	0%	0%	100%
275	0%	0%	0%	100%
276	0%	0%	0%	100%
277	0%	0%	0%	100%
278	0%	0%	0%	100%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
279	0%	0%	0%	100%
280	0%	0%	0%	100%
281	0%	0%	0%	100%
282	0%	0%	0%	100%
283	0%	0%	0%	100%
284	0%	0%	0%	100%
285	0%	0%	0%	100%
286	0%	0%	0%	100%
287	0%	0%	0%	100%
288	0%	0%	0%	100%
289	0%	0%	0%	100%
290	0%	0%	0%	100%
291	0%	0%	0%	100%
292	0%	0%	0%	100%
293	0%	0%	0%	100%
294	0%	0%	0%	100%
295	0%	0%	0%	100%
296	0%	0%	0%	100%
297	0%	0%	0%	100%
298	0%	0%	0%	100%
299	0%	0%	0%	100%
300	0%	0%	0%	100%
301	0%	0%	0%	100%
302	0%	0%	0%	100%
303	0%	0%	0%	100%
304	0%	0%	0%	100%
305	0%	0%	0%	100%
306	0%	0%	0%	100%
307	0%	0%	0%	100%
308	0%	0%	0%	100%
309	0%	0%	0%	100%
310	0%	0%	0%	100%
311	0%	0%	0%	100%
312	0%	0%	0%	100%
313	0%	0%	0%	100%
314	0%	0%	0%	100%
315	0%	0%	0%	100%
316	0%	0%	0%	100%
317	0%	0%	0%	100%
318	0%	0%	0%	100%
319	0%	0%	0%	100%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
320	0%	0%	0%	100%
321	0%	0%	0%	100%
322	0%	0%	0%	100%
323	0%	0%	0%	100%
324	0%	0%	0%	100%
325	0%	0%	0%	100%
326	0%	0%	0%	100%
327	0%	0%	0%	100%
328	0%	0%	0%	100%
329	0%	0%	0%	100%
330	0%	0%	0%	100%
331	0%	0%	0%	100%
332	0%	0%	0%	100%
333	0%	0%	0%	100%
334	0%	0%	0%	100%
335	0%	0%	0%	100%
336	0%	0%	0%	100%
337	0%	0%	0%	100%
338	0%	0%	0%	100%
339	0%	0%	0%	100%
340	0%	0%	0%	100%
341	0%	0%	0%	100%
342	0%	0%	0%	100%
343	0%	0%	0%	100%
344	0%	0%	0%	100%
345	0%	0%	0%	100%
346	0%	0%	0%	100%
347	0%	0%	0%	100%
348	0%	0%	0%	100%
349	0%	0%	0%	100%
350	0%	0%	0%	100%
351	0%	0%	0%	100%
352	0%	0%	0%	100%
353	0%	0%	0%	100%
354	0%	0%	0%	100%
355	0%	0%	0%	100%
356	0%	0%	0%	100%
357	0%	0%	0%	100%
358	0%	0%	0%	100%
359	0%	0%	0%	100%
360	0%	0%	0%	100%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
361	0%	0%	0%	100%
362	0%	0%	0%	100%
363	0%	0%	0%	100%
364	0%	0%	0%	100%
365	0%	0%	0%	100%
366	0%	0%	0%	100%
367	0%	0%	0%	100%
368	0%	0%	0%	100%
369	0%	0%	0%	100%
370	0%	0%	0%	100%
371	0%	0%	0%	100%
372	0%	0%	0%	100%
373	0%	0%	0%	100%
374	0%	0%	0%	100%
375	0%	0%	0%	100%
376	0%	0%	0%	100%
377	0%	0%	0%	100%
378	0%	0%	0%	100%
379	0%	0%	0%	100%
380	0%	0%	0%	100%
381	0%	0%	0%	100%
382	0%	0%	0%	100%
383	0%	0%	0%	100%
384	0%	0%	0%	100%
385	0%	0%	0%	100%
386	0%	0%	0%	100%
387	0%	0%	0%	100%
388	0%	0%	0%	100%
389	0%	0%	0%	100%
390	0%	0%	0%	100%
391	0%	0%	0%	100%
392	0%	0%	0%	100%
393	0%	0%	0%	100%
394	0%	0%	0%	100%
395	0%	0%	0%	100%
396	0%	0%	0%	100%
397	0%	0%	0%	100%
398	0%	0%	0%	100%
399	0%	0%	0%	100%
400	0%	0%	0%	100%
401	0%	0%	0%	100%

	Hydroxycarbamide			
Month	CP	AP	BP	Dead
402	0%	0%	0%	100%
403	0%	0%	0%	100%
404	0%	0%	0%	100%
405	0%	0%	0%	100%
406	0%	0%	0%	100%
407	0%	0%	0%	100%
408	0%	0%	0%	100%
409	0%	0%	0%	100%
410	0%	0%	0%	100%
411	0%	0%	0%	100%
412	0%	0%	0%	100%
413	0%	0%	0%	100%
414	0%	0%	0%	100%
415	0%	0%	0%	100%
416	0%	0%	0%	100%
417	0%	0%	0%	100%
418	0%	0%	0%	100%
419	0%	0%	0%	100%

Table B 142: Tabulated markov trace for CP model – Stem Cell Transplant

	Stem Cell Transplant			
Month	**CP**	**AP**	**BP**	**Dead**
0	100%	0%	0%	0%
1	99%	0%	0%	1%
2	98%	0%	0%	2%
3	96%	0%	0%	4%
4	95%	0%	0%	5%
5	94%	0%	0%	6%
6	93%	0%	0%	7%
7	92%	0%	0%	8%
8	90%	0%	0%	10%
9	89%	0%	0%	11%
10	88%	0%	0%	12%
11	87%	0%	0%	13%
12	86%	0%	0%	14%
13	85%	0%	0%	15%
14	84%	0%	0%	16%
15	83%	0%	0%	17%
16	82%	0%	0%	18%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
17	81%	0%	0%	19%
18	80%	0%	0%	20%
19	79%	0%	0%	21%
20	78%	0%	0%	22%
21	77%	0%	0%	23%
22	76%	0%	0%	24%
23	75%	0%	0%	25%
24	74%	0%	0%	26%
25	73%	0%	0%	27%
26	72%	0%	0%	28%
27	71%	0%	0%	29%
28	70%	0%	0%	30%
29	70%	0%	0%	30%
30	69%	0%	0%	31%
31	68%	0%	0%	32%
32	67%	0%	0%	33%
33	66%	0%	0%	34%
34	65%	0%	0%	35%
35	65%	0%	0%	35%
36	64%	0%	0%	36%
37	63%	0%	0%	37%
38	62%	0%	0%	38%
39	61%	0%	0%	39%
40	61%	0%	0%	39%
41	60%	0%	0%	40%
42	59%	0%	0%	41%
43	58%	0%	0%	42%
44	58%	0%	0%	42%
45	57%	0%	0%	43%
46	56%	0%	0%	44%
47	56%	0%	0%	44%
48	55%	0%	0%	45%
49	54%	0%	0%	46%
50	54%	0%	0%	46%
51	53%	0%	0%	47%
52	52%	0%	0%	48%
53	52%	0%	0%	48%
54	51%	0%	0%	49%
55	50%	0%	0%	50%
56	50%	0%	0%	50%
57	49%	0%	0%	51%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
58	48%	0%	0%	52%
59	48%	0%	0%	52%
60	47%	0%	0%	53%
61	47%	0%	0%	53%
62	46%	0%	0%	54%
63	45%	0%	0%	55%
64	45%	0%	0%	55%
65	44%	0%	0%	56%
66	44%	0%	0%	56%
67	43%	0%	0%	57%
68	43%	0%	0%	57%
69	42%	0%	0%	58%
70	42%	0%	0%	58%
71	41%	0%	0%	59%
72	41%	0%	0%	59%
73	40%	0%	0%	60%
74	40%	0%	0%	60%
75	39%	0%	0%	61%
76	39%	0%	0%	61%
77	38%	0%	0%	62%
78	38%	0%	0%	62%
79	37%	0%	0%	63%
80	37%	0%	0%	63%
81	36%	0%	0%	64%
82	36%	0%	0%	64%
83	35%	0%	0%	65%
84	35%	0%	0%	65%
85	35%	0%	0%	65%
86	34%	0%	0%	66%
87	34%	0%	0%	66%
88	33%	0%	0%	67%
89	33%	0%	0%	67%
90	32%	0%	0%	68%
91	32%	0%	0%	68%
92	32%	0%	0%	68%
93	31%	0%	0%	69%
94	31%	0%	0%	69%
95	30%	0%	0%	70%
96	30%	0%	0%	70%
97	30%	0%	0%	70%
98	29%	0%	0%	71%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
99	29%	0%	0%	71%
100	29%	0%	0%	71%
101	28%	0%	0%	72%
102	28%	0%	0%	72%
103	28%	0%	0%	72%
104	27%	0%	0%	73%
105	27%	0%	0%	73%
106	27%	0%	0%	73%
107	26%	0%	0%	74%
108	26%	0%	0%	74%
109	26%	0%	0%	74%
110	25%	0%	0%	75%
111	25%	0%	0%	75%
112	25%	0%	0%	75%
113	24%	0%	0%	76%
114	24%	0%	0%	76%
115	24%	0%	0%	76%
116	23%	0%	0%	77%
117	23%	0%	0%	77%
118	23%	0%	0%	77%
119	23%	0%	0%	77%
120	22%	0%	0%	78%
121	22%	0%	0%	78%
122	22%	0%	0%	78%
123	21%	0%	0%	79%
124	21%	0%	0%	79%
125	21%	0%	0%	79%
126	21%	0%	0%	79%
127	20%	0%	0%	80%
128	20%	0%	0%	80%
129	20%	0%	0%	80%
130	20%	0%	0%	80%
131	19%	0%	0%	81%
132	19%	0%	0%	81%
133	19%	0%	0%	81%
134	19%	0%	0%	81%
135	18%	0%	0%	82%
136	18%	0%	0%	82%
137	18%	0%	0%	82%
138	18%	0%	0%	82%
139	18%	0%	0%	82%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
140	17%	0%	0%	83%
141	17%	0%	0%	83%
142	17%	0%	0%	83%
143	17%	0%	0%	83%
144	16%	0%	0%	84%
145	16%	0%	0%	84%
146	16%	0%	0%	84%
147	16%	0%	0%	84%
148	16%	0%	0%	84%
149	15%	0%	0%	85%
150	15%	0%	0%	85%
151	15%	0%	0%	85%
152	15%	0%	0%	85%
153	15%	0%	0%	85%
154	15%	0%	0%	85%
155	14%	0%	0%	86%
156	14%	0%	0%	86%
157	14%	0%	0%	86%
158	14%	0%	0%	86%
159	14%	0%	0%	86%
160	13%	0%	0%	87%
161	13%	0%	0%	87%
162	13%	0%	0%	87%
163	13%	0%	0%	87%
164	13%	0%	0%	87%
165	13%	0%	0%	87%
166	12%	0%	0%	88%
167	12%	0%	0%	88%
168	12%	0%	0%	88%
169	12%	0%	0%	88%
170	12%	0%	0%	88%
171	12%	0%	0%	88%
172	12%	0%	0%	88%
173	11%	0%	0%	89%
174	11%	0%	0%	89%
175	11%	0%	0%	89%
176	11%	0%	0%	89%
177	11%	0%	0%	89%
178	11%	0%	0%	89%
179	11%	0%	0%	89%
180	10%	0%	0%	90%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
181	10%	0%	0%	90%
182	10%	0%	0%	90%
183	10%	0%	0%	90%
184	10%	0%	0%	90%
185	10%	0%	0%	90%
186	10%	0%	0%	90%
187	10%	0%	0%	90%
188	9%	0%	0%	91%
189	9%	0%	0%	91%
190	9%	0%	0%	91%
191	9%	0%	0%	91%
192	9%	0%	0%	91%
193	9%	0%	0%	91%
194	9%	0%	0%	91%
195	9%	0%	0%	91%
196	9%	0%	0%	91%
197	8%	0%	0%	92%
198	8%	0%	0%	92%
199	8%	0%	0%	92%
200	8%	0%	0%	92%
201	8%	0%	0%	92%
202	8%	0%	0%	92%
203	8%	0%	0%	92%
204	8%	0%	0%	92%
205	8%	0%	0%	92%
206	7%	0%	0%	93%
207	7%	0%	0%	93%
208	7%	0%	0%	93%
209	7%	0%	0%	93%
210	7%	0%	0%	93%
211	7%	0%	0%	93%
212	7%	0%	0%	93%
213	7%	0%	0%	93%
214	7%	0%	0%	93%
215	7%	0%	0%	93%
216	7%	0%	0%	93%
217	6%	0%	0%	94%
218	6%	0%	0%	94%
219	6%	0%	0%	94%
220	6%	0%	0%	94%
221	6%	0%	0%	94%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
222	6%	0%	0%	94%
223	6%	0%	0%	94%
224	6%	0%	0%	94%
225	6%	0%	0%	94%
226	6%	0%	0%	94%
227	6%	0%	0%	94%
228	6%	0%	0%	94%
229	6%	0%	0%	94%
230	5%	0%	0%	95%
231	5%	0%	0%	95%
232	5%	0%	0%	95%
233	5%	0%	0%	95%
234	5%	0%	0%	95%
235	5%	0%	0%	95%
236	5%	0%	0%	95%
237	5%	0%	0%	95%
238	5%	0%	0%	95%
239	5%	0%	0%	95%
240	5%	0%	0%	95%
241	5%	0%	0%	95%
242	5%	0%	0%	95%
243	5%	0%	0%	95%
244	5%	0%	0%	95%
245	4%	0%	0%	96%
246	4%	0%	0%	96%
247	4%	0%	0%	96%
248	4%	0%	0%	96%
249	4%	0%	0%	96%
250	4%	0%	0%	96%
251	4%	0%	0%	96%
252	4%	0%	0%	96%
253	4%	0%	0%	96%
254	4%	0%	0%	96%
255	4%	0%	0%	96%
256	4%	0%	0%	96%
257	4%	0%	0%	96%
258	4%	0%	0%	96%
259	4%	0%	0%	96%
260	4%	0%	0%	96%
261	4%	0%	0%	96%
262	4%	0%	0%	96%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
263	4%	0%	0%	96%
264	3%	0%	0%	97%
265	3%	0%	0%	97%
266	3%	0%	0%	97%
267	3%	0%	0%	97%
268	3%	0%	0%	97%
269	3%	0%	0%	97%
270	3%	0%	0%	97%
271	3%	0%	0%	97%
272	3%	0%	0%	97%
273	3%	0%	0%	97%
274	3%	0%	0%	97%
275	3%	0%	0%	97%
276	3%	0%	0%	97%
277	3%	0%	0%	97%
278	3%	0%	0%	97%
279	3%	0%	0%	97%
280	3%	0%	0%	97%
281	3%	0%	0%	97%
282	3%	0%	0%	97%
283	3%	0%	0%	97%
284	3%	0%	0%	97%
285	3%	0%	0%	97%
286	3%	0%	0%	97%
287	3%	0%	0%	97%
288	2%	0%	0%	98%
289	2%	0%	0%	98%
290	2%	0%	0%	98%
291	2%	0%	0%	98%
292	2%	0%	0%	98%
293	2%	0%	0%	98%
294	2%	0%	0%	98%
295	2%	0%	0%	98%
296	2%	0%	0%	98%
297	2%	0%	0%	98%
298	2%	0%	0%	98%
299	2%	0%	0%	98%
300	2%	0%	0%	98%
301	2%	0%	0%	98%
302	2%	0%	0%	98%
303	2%	0%	0%	98%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
304	2%	0%	0%	98%
305	2%	0%	0%	98%
306	2%	0%	0%	98%
307	2%	0%	0%	98%
308	2%	0%	0%	98%
309	2%	0%	0%	98%
310	2%	0%	0%	98%
311	2%	0%	0%	98%
312	2%	0%	0%	98%
313	2%	0%	0%	98%
314	2%	0%	0%	98%
315	2%	0%	0%	98%
316	2%	0%	0%	98%
317	2%	0%	0%	98%
318	1%	0%	0%	99%
319	1%	0%	0%	99%
320	1%	0%	0%	99%
321	1%	0%	0%	99%
322	1%	0%	0%	99%
323	1%	0%	0%	99%
324	1%	0%	0%	99%
325	1%	0%	0%	99%
326	1%	0%	0%	99%
327	1%	0%	0%	99%
328	1%	0%	0%	99%
329	1%	0%	0%	99%
330	1%	0%	0%	99%
331	1%	0%	0%	99%
332	1%	0%	0%	99%
333	1%	0%	0%	99%
334	1%	0%	0%	99%
335	1%	0%	0%	99%
336	1%	0%	0%	99%
337	1%	0%	0%	99%
338	1%	0%	0%	99%
339	1%	0%	0%	99%
340	1%	0%	0%	99%
341	1%	0%	0%	99%
342	1%	0%	0%	99%
343	1%	0%	0%	99%
344	1%	0%	0%	99%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
345	1%	0%	0%	99%
346	1%	0%	0%	99%
347	1%	0%	0%	99%
348	1%	0%	0%	99%
349	1%	0%	0%	99%
350	1%	0%	0%	99%
351	1%	0%	0%	99%
352	1%	0%	0%	99%
353	1%	0%	0%	99%
354	1%	0%	0%	99%
355	1%	0%	0%	99%
356	1%	0%	0%	99%
357	1%	0%	0%	99%
358	1%	0%	0%	99%
359	1%	0%	0%	99%
360	0%	0%	0%	100%
361	0%	0%	0%	100%
362	0%	0%	0%	100%
363	0%	0%	0%	100%
364	0%	0%	0%	100%
365	0%	0%	0%	100%
366	0%	0%	0%	100%
367	0%	0%	0%	100%
368	0%	0%	0%	100%
369	0%	0%	0%	100%
370	0%	0%	0%	100%
371	0%	0%	0%	100%
372	0%	0%	0%	100%
373	0%	0%	0%	100%
374	0%	0%	0%	100%
375	0%	0%	0%	100%
376	0%	0%	0%	100%
377	0%	0%	0%	100%
378	0%	0%	0%	100%
379	0%	0%	0%	100%
380	0%	0%	0%	100%
381	0%	0%	0%	100%
382	0%	0%	0%	100%
383	0%	0%	0%	100%
384	0%	0%	0%	100%
385	0%	0%	0%	100%

	Stem Cell Transplant			
Month	CP	AP	BP	Dead
386	0%	0%	0%	100%
387	0%	0%	0%	100%
388	0%	0%	0%	100%
389	0%	0%	0%	100%
390	0%	0%	0%	100%
391	0%	0%	0%	100%
392	0%	0%	0%	100%
393	0%	0%	0%	100%
394	0%	0%	0%	100%
395	0%	0%	0%	100%
396	0%	0%	0%	100%
397	0%	0%	0%	100%
398	0%	0%	0%	100%
399	0%	0%	0%	100%
400	0%	0%	0%	100%
401	0%	0%	0%	100%
402	0%	0%	0%	100%
403	0%	0%	0%	100%
404	0%	0%	0%	100%
405	0%	0%	0%	100%
406	0%	0%	0%	100%
407	0%	0%	0%	100%
408	0%	0%	0%	100%
409	0%	0%	0%	100%
410	0%	0%	0%	100%
411	0%	0%	0%	100%
412	0%	0%	0%	100%
413	0%	0%	0%	100%
414	0%	0%	0%	100%
415	0%	0%	0%	100%
416	0%	0%	0%	100%
417	0%	0%	0%	100%
418	0%	0%	0%	100%
419	0%	0%	0%	100%

Table B 143: Tabulated markov trace for CP model – Interferon

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
0	100%	0%	0%	0%	0%
1	85%	13%	0%	0%	2%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
2	72%	22%	0%	2%	5%
3	61%	28%	0%	4%	7%
4	51%	34%	0%	6%	9%
5	43%	38%	0%	8%	11%
6	37%	41%	0%	10%	13%
7	31%	43%	0%	11%	15%
8	26%	44%	2%	11%	17%
9	22%	45%	3%	11%	19%
10	19%	45%	5%	11%	21%
11	16%	45%	6%	10%	22%
12	14%	45%	8%	10%	24%
13	11%	44%	9%	10%	26%
14	10%	43%	10%	10%	28%
15	8%	42%	11%	9%	29%
16	7%	41%	12%	9%	31%
17	6%	40%	13%	9%	33%
18	5%	40%	12%	9%	34%
19	4%	40%	12%	9%	36%
20	4%	39%	12%	8%	37%
21	3%	39%	12%	8%	38%
22	3%	38%	11%	8%	40%
23	2%	38%	11%	8%	41%
24	2%	37%	11%	8%	43%
25	2%	37%	11%	7%	44%
26	1%	36%	10%	7%	45%
27	1%	35%	10%	7%	46%
28	1%	35%	10%	7%	48%
29	1%	34%	10%	7%	49%
30	1%	33%	9%	7%	50%
31	1%	33%	9%	6%	51%
32	0%	32%	9%	6%	52%
33	0%	31%	9%	6%	53%
34	0%	31%	9%	6%	54%
35	0%	30%	8%	6%	56%
36	0%	29%	8%	6%	57%
37	0%	29%	8%	6%	58%
38	0%	28%	8%	6%	59%
39	0%	27%	8%	5%	59%
40	0%	27%	7%	5%	60%
41	0%	26%	7%	5%	61%
42	0%	26%	7%	5%	62%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
43	0%	25%	7%	5%	63%
44	0%	24%	7%	5%	64%
45	0%	24%	7%	5%	65%
46	0%	23%	6%	5%	66%
47	0%	23%	6%	4%	66%
48	0%	22%	6%	4%	67%
49	0%	22%	6%	4%	68%
50	0%	21%	6%	4%	69%
51	0%	21%	6%	4%	69%
52	0%	20%	6%	4%	70%
53	0%	20%	6%	4%	71%
54	0%	19%	5%	4%	71%
55	0%	19%	5%	4%	72%
56	0%	19%	5%	4%	73%
57	0%	18%	5%	4%	73%
58	0%	18%	5%	3%	74%
59	0%	17%	5%	3%	74%
60	0%	17%	5%	3%	75%
61	0%	17%	5%	3%	76%
62	0%	16%	4%	3%	76%
63	0%	16%	4%	3%	77%
64	0%	15%	4%	3%	77%
65	0%	15%	4%	3%	78%
66	0%	15%	4%	3%	78%
67	0%	14%	4%	3%	79%
68	0%	14%	4%	3%	79%
69	0%	14%	4%	3%	80%
70	0%	13%	4%	3%	80%
71	0%	13%	4%	3%	81%
72	0%	13%	4%	3%	81%
73	0%	13%	3%	2%	82%
74	0%	12%	3%	2%	82%
75	0%	12%	3%	2%	82%
76	0%	12%	3%	2%	83%
77	0%	11%	3%	2%	83%
78	0%	11%	3%	2%	84%
79	0%	11%	3%	2%	84%
80	0%	11%	3%	2%	84%
81	0%	10%	3%	2%	85%
82	0%	10%	3%	2%	85%
83	0%	10%	3%	2%	85%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
84	0%	10%	3%	2%	86%
85	0%	9%	3%	2%	86%
86	0%	9%	3%	2%	86%
87	0%	9%	3%	2%	87%
88	0%	9%	2%	2%	87%
89	0%	9%	2%	2%	87%
90	0%	8%	2%	2%	88%
91	0%	8%	2%	2%	88%
92	0%	8%	2%	2%	88%
93	0%	8%	2%	2%	88%
94	0%	8%	2%	2%	89%
95	0%	7%	2%	1%	89%
96	0%	7%	2%	1%	89%
97	0%	7%	2%	1%	89%
98	0%	7%	2%	1%	90%
99	0%	7%	2%	1%	90%
100	0%	7%	2%	1%	90%
101	0%	7%	2%	1%	90%
102	0%	6%	2%	1%	91%
103	0%	6%	2%	1%	91%
104	0%	6%	2%	1%	91%
105	0%	6%	2%	1%	91%
106	0%	6%	2%	1%	91%
107	0%	6%	2%	1%	92%
108	0%	6%	2%	1%	92%
109	0%	5%	2%	1%	92%
110	0%	5%	1%	1%	92%
111	0%	5%	1%	1%	92%
112	0%	5%	1%	1%	93%
113	0%	5%	1%	1%	93%
114	0%	5%	1%	1%	93%
115	0%	5%	1%	1%	93%
116	0%	5%	1%	1%	93%
117	0%	4%	1%	1%	93%
118	0%	4%	1%	1%	94%
119	0%	4%	1%	1%	94%
120	0%	4%	1%	1%	94%
121	0%	4%	1%	1%	94%
122	0%	4%	1%	1%	94%
123	0%	4%	1%	1%	94%
124	0%	4%	1%	1%	94%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
125	0%	4%	1%	1%	95%
126	0%	4%	1%	1%	95%
127	0%	4%	1%	1%	95%
128	0%	3%	1%	1%	95%
129	0%	3%	1%	1%	95%
130	0%	3%	1%	1%	95%
131	0%	3%	1%	1%	95%
132	0%	3%	1%	1%	95%
133	0%	3%	1%	1%	95%
134	0%	3%	1%	1%	96%
135	0%	3%	1%	1%	96%
136	0%	3%	1%	1%	96%
137	0%	3%	1%	1%	96%
138	0%	3%	1%	1%	96%
139	0%	3%	1%	1%	96%
140	0%	3%	1%	1%	96%
141	0%	3%	1%	1%	96%
142	0%	2%	1%	1%	96%
143	0%	2%	1%	0%	96%
144	0%	2%	1%	0%	96%
145	0%	2%	1%	0%	97%
146	0%	2%	1%	0%	97%
147	0%	2%	1%	0%	97%
148	0%	2%	1%	0%	97%
149	0%	2%	1%	0%	97%
150	0%	2%	1%	0%	97%
151	0%	2%	1%	0%	97%
152	0%	2%	1%	0%	97%
153	0%	2%	1%	0%	97%
154	0%	2%	1%	0%	97%
155	0%	2%	1%	0%	97%
156	0%	2%	1%	0%	97%
157	0%	2%	1%	0%	97%
158	0%	2%	0%	0%	97%
159	0%	2%	0%	0%	98%
160	0%	2%	0%	0%	98%
161	0%	2%	0%	0%	98%
162	0%	2%	0%	0%	98%
163	0%	1%	0%	0%	98%
164	0%	1%	0%	0%	98%
165	0%	1%	0%	0%	98%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
166	0%	1%	0%	0%	98%
167	0%	1%	0%	0%	98%
168	0%	1%	0%	0%	98%
169	0%	1%	0%	0%	98%
170	0%	1%	0%	0%	98%
171	0%	1%	0%	0%	98%
172	0%	1%	0%	0%	98%
173	0%	1%	0%	0%	98%
174	0%	1%	0%	0%	98%
175	0%	1%	0%	0%	98%
176	0%	1%	0%	0%	98%
177	0%	1%	0%	0%	98%
178	0%	1%	0%	0%	98%
179	0%	1%	0%	0%	98%
180	0%	1%	0%	0%	99%
181	0%	1%	0%	0%	99%
182	0%	1%	0%	0%	99%
183	0%	1%	0%	0%	99%
184	0%	1%	0%	0%	99%
185	0%	1%	0%	0%	99%
186	0%	1%	0%	0%	99%
187	0%	1%	0%	0%	99%
188	0%	1%	0%	0%	99%
189	0%	1%	0%	0%	99%
190	0%	1%	0%	0%	99%
191	0%	1%	0%	0%	99%
192	0%	1%	0%	0%	99%
193	0%	1%	0%	0%	99%
194	0%	1%	0%	0%	99%
195	0%	1%	0%	0%	99%
196	0%	1%	0%	0%	99%
197	0%	1%	0%	0%	99%
198	0%	1%	0%	0%	99%
199	0%	1%	0%	0%	99%
200	0%	1%	0%	0%	99%
201	0%	1%	0%	0%	99%
202	0%	0%	0%	0%	99%
203	0%	0%	0%	0%	99%
204	0%	0%	0%	0%	99%
205	0%	0%	0%	0%	99%
206	0%	0%	0%	0%	99%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
207	0%	0%	0%	0%	99%
208	0%	0%	0%	0%	99%
209	0%	0%	0%	0%	99%
210	0%	0%	0%	0%	99%
211	0%	0%	0%	0%	99%
212	0%	0%	0%	0%	99%
213	0%	0%	0%	0%	99%
214	0%	0%	0%	0%	99%
215	0%	0%	0%	0%	99%
216	0%	0%	0%	0%	99%
217	0%	0%	0%	0%	99%
218	0%	0%	0%	0%	99%
219	0%	0%	0%	0%	100%
220	0%	0%	0%	0%	100%
221	0%	0%	0%	0%	100%
222	0%	0%	0%	0%	100%
223	0%	0%	0%	0%	100%
224	0%	0%	0%	0%	100%
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228	0%	0%	0%	0%	100%
229	0%	0%	0%	0%	100%
230	0%	0%	0%	0%	100%
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244	0%	0%	0%	0%	100%
245	0%	0%	0%	0%	100%
246	0%	0%	0%	0%	100%
247	0%	0%	0%	0%	100%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
248	0%	0%	0%	0%	100%
249	0%	0%	0%	0%	100%
250	0%	0%	0%	0%	100%
251	0%	0%	0%	0%	100%
252	0%	0%	0%	0%	100%
253	0%	0%	0%	0%	100%
254	0%	0%	0%	0%	100%
255	0%	0%	0%	0%	100%
256	0%	0%	0%	0%	100%
257	0%	0%	0%	0%	100%
258	0%	0%	0%	0%	100%
259	0%	0%	0%	0%	100%
260	0%	0%	0%	0%	100%
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270	0%	0%	0%	0%	100%
271	0%	0%	0%	0%	100%
272	0%	0%	0%	0%	100%
273	0%	0%	0%	0%	100%
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275	0%	0%	0%	0%	100%
276	0%	0%	0%	0%	100%
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278	0%	0%	0%	0%	100%
279	0%	0%	0%	0%	100%
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281	0%	0%	0%	0%	100%
282	0%	0%	0%	0%	100%
283	0%	0%	0%	0%	100%
284	0%	0%	0%	0%	100%
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286	0%	0%	0%	0%	100%
287	0%	0%	0%	0%	100%
288	0%	0%	0%	0%	100%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
289	0%	0%	0%	0%	100%
290	0%	0%	0%	0%	100%
291	0%	0%	0%	0%	100%
292	0%	0%	0%	0%	100%
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329	0%	0%	0%	0%	100%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
330	0%	0%	0%	0%	100%
331	0%	0%	0%	0%	100%
332	0%	0%	0%	0%	100%
333	0%	0%	0%	0%	100%
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369	0%	0%	0%	0%	100%
370	0%	0%	0%	0%	100%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
371	0%	0%	0%	0%	100%
372	0%	0%	0%	0%	100%
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374	0%	0%	0%	0%	100%
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410	0%	0%	0%	0%	100%
411	0%	0%	0%	0%	100%

	Interferon				
Month	CP on treatment	CP off treatment	AP	BP	Dead
412	0%	0%	0%	0%	100%
413	0%	0%	0%	0%	100%
414	0%	0%	0%	0%	100%
415	0%	0%	0%	0%	100%
416	0%	0%	0%	0%	100%
417	0%	0%	0%	0%	100%
418	0%	0%	0%	0%	100%
419	0%	0%	0%	0%	100%

Accelerated phase

Table B144: Tabulated markov trace for AP model - Bosutinib

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Table B145: Tabulated markov trace for AP model- Hydroxycarbamide

	Hydroxycarbamide		
Month	AP	BP	Dead
0	100%	0%	0%

	Hydroxycarbamide		
Month	AP	BP	Dead
1	94%	0%	6%
2	83%	6%	12%
3	73%	10%	17%
4	64%	14%	22%
5	56%	17%	27%
6	49%	20%	31%
7	43%	21%	35%
8	40%	20%	39%
9	38%	19%	43%
10	36%	18%	46%
11	34%	17%	50%
12	31%	16%	53%
13	30%	15%	56%
14	28%	14%	58%
15	26%	13%	61%
16	25%	12%	63%
17	23%	12%	65%
18	22%	11%	68%
19	20%	10%	70%
20	19%	10%	71%
21	18%	9%	73%
22	17%	8%	75%
23	16%	8%	76%
24	15%	7%	78%
25	14%	7%	79%
26	13%	7%	80%
27	12%	6%	82%
28	12%	6%	83%
29	11%	5%	84%
30	10%	5%	85%
31	10%	5%	86%
32	9%	5%	86%
33	8%	4%	87%
34	8%	4%	88%
35	7%	4%	89%
36	7%	4%	89%
37	7%	3%	90%
38	6%	3%	91%
39	6%	3%	91%
40	5%	3%	92%
41	5%	3%	92%

	Hydroxycarbamide		
Month	AP	BP	Dead
42	5%	2%	93%
43	5%	2%	93%
44	4%	2%	94%
45	4%	2%	94%
46	4%	2%	94%
47	4%	2%	95%
48	3%	2%	95%
49	3%	2%	95%
50	3%	1%	96%
51	3%	1%	96%
52	3%	1%	96%
53	2%	1%	96%
54	2%	1%	97%
55	2%	1%	97%
56	2%	1%	97%
57	2%	1%	97%
58	2%	1%	97%
59	2%	1%	98%
60	2%	1%	98%
61	1%	1%	98%
62	1%	1%	98%
63	1%	1%	98%
64	1%	1%	98%
65	1%	1%	98%
66	1%	1%	98%
67	1%	1%	99%
68	1%	0%	99%
69	1%	0%	99%
70	1%	0%	99%
71	1%	0%	99%
72	1%	0%	99%
73	1%	0%	99%
74	1%	0%	99%
75	1%	0%	99%
76	1%	0%	99%
77	0%	0%	99%
78	0%	0%	99%
79	0%	0%	99%
80	0%	0%	99%
81	0%	0%	99%
82	0%	0%	99%

	Hydroxycarbamide		
Month	AP	BP	Dead
83	0%	0%	99%
84	0%	0%	100%
85	0%	0%	100%
86	0%	0%	100%
87	0%	0%	100%
88	0%	0%	100%
89	0%	0%	100%
90	0%	0%	100%
91	0%	0%	100%
92	0%	0%	100%
93	0%	0%	100%
94	0%	0%	100%
95	0%	0%	100%
96	0%	0%	100%
97	0%	0%	100%
98	0%	0%	100%
99	0%	0%	100%
100	0%	0%	100%
101	0%	0%	100%
102	0%	0%	100%
103	0%	0%	100%
104	0%	0%	100%
105	0%	0%	100%
106	0%	0%	100%
107	0%	0%	100%
108	0%	0%	100%
109	0%	0%	100%
110	0%	0%	100%
111	0%	0%	100%
112	0%	0%	100%
113	0%	0%	100%
114	0%	0%	100%
115	0%	0%	100%
116	0%	0%	100%
117	0%	0%	100%
118	0%	0%	100%
119	0%	0%	100%
120	0%	0%	100%
121	0%	0%	100%
122	0%	0%	100%
123	0%	0%	100%

	Hydroxycarbamide		
Month	AP	BP	Dead
124	0%	0%	100%
125	0%	0%	100%
126	0%	0%	100%
127	0%	0%	100%
128	0%	0%	100%
129	0%	0%	100%
130	0%	0%	100%
131	0%	0%	100%
132	0%	0%	100%
133	0%	0%	100%
134	0%	0%	100%
135	0%	0%	100%
136	0%	0%	100%
137	0%	0%	100%
138	0%	0%	100%
139	0%	0%	100%
140	0%	0%	100%
141	0%	0%	100%
142	0%	0%	100%
143	0%	0%	100%
144	0%	0%	100%
145	0%	0%	100%
146	0%	0%	100%
147	0%	0%	100%
148	0%	0%	100%
149	0%	0%	100%
150	0%	0%	100%
151	0%	0%	100%
152	0%	0%	100%
153	0%	0%	100%
154	0%	0%	100%
155	0%	0%	100%
156	0%	0%	100%
157	0%	0%	100%
158	0%	0%	100%
159	0%	0%	100%
160	0%	0%	100%
161	0%	0%	100%
162	0%	0%	100%
163	0%	0%	100%
164	0%	0%	100%

	Hydroxycarbamide		
Month	AP	BP	Dead
165	0%	0%	100%
166	0%	0%	100%
167	0%	0%	100%
168	0%	0%	100%
169	0%	0%	100%
170	0%	0%	100%
171	0%	0%	100%
172	0%	0%	100%
173	0%	0%	100%
174	0%	0%	100%
175	0%	0%	100%
176	0%	0%	100%
177	0%	0%	100%
178	0%	0%	100%
179	0%	0%	100%
180	0%	0%	100%
181	0%	0%	100%
182	0%	0%	100%
183	0%	0%	100%
184	0%	0%	100%
185	0%	0%	100%
186	0%	0%	100%
187	0%	0%	100%
188	0%	0%	100%
189	0%	0%	100%
190	0%	0%	100%
191	0%	0%	100%
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194	0%	0%	100%
195	0%	0%	100%
196	0%	0%	100%
197	0%	0%	100%
198	0%	0%	100%
199	0%	0%	100%
200	0%	0%	100%
201	0%	0%	100%
202	0%	0%	100%
203	0%	0%	100%
204	0%	0%	100%
205	0%	0%	100%

	Hydroxycarbamide		
Month	AP	BP	Dead
206	0%	0%	100%
207	0%	0%	100%
208	0%	0%	100%
209	0%	0%	100%
210	0%	0%	100%
211	0%	0%	100%
212	0%	0%	100%
213	0%	0%	100%
214	0%	0%	100%
215	0%	0%	100%
216	0%	0%	100%
217	0%	0%	100%
218	0%	0%	100%
219	0%	0%	100%
220	0%	0%	100%
221	0%	0%	100%
222	0%	0%	100%
223	0%	0%	100%
224	0%	0%	100%
225	0%	0%	100%
226	0%	0%	100%
227	0%	0%	100%
228	0%	0%	100%
229	0%	0%	100%
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238	0%	0%	100%
239	0%	0%	100%
240	0%	0%	100%
241	0%	0%	100%
242	0%	0%	100%
243	0%	0%	100%
244	0%	0%	100%
245	0%	0%	100%
246	0%	0%	100%

	Hydroxycarbamide		
Month	AP	BP	Dead
247	0%	0%	100%
248	0%	0%	100%
249	0%	0%	100%
250	0%	0%	100%
251	0%	0%	100%
252	0%	0%	100%
253	0%	0%	100%
254	0%	0%	100%
255	0%	0%	100%
256	0%	0%	100%
257	0%	0%	100%
258	0%	0%	100%
259	0%	0%	100%
260	0%	0%	100%
261	0%	0%	100%
262	0%	0%	100%
263	0%	0%	100%
264	0%	0%	100%
265	0%	0%	100%
266	0%	0%	100%
267	0%	0%	100%
268	0%	0%	100%
269	0%	0%	100%
270	0%	0%	100%
271	0%	0%	100%
272	0%	0%	100%
273	0%	0%	100%

Table B146: Tabulated markov trace for AP model – Stem Cell Transplantation

	SCT		
Month	AP	BP	Dead
0	100%	0%	0%
1	98%	0%	2%
2	95%	0%	5%
3	92%	0%	8%
4	90%	0%	10%
5	87%	0%	13%
6	85%	0%	15%
7	82%	0%	18%
8	80%	0%	20%
9	78%	0%	22%
10	75%	0%	25%

	SCT		
Month	AP	BP	Dead
11	73%	0%	27%
12	71%	0%	29%
13	69%	0%	31%
14	67%	0%	33%
15	65%	0%	35%
16	63%	0%	37%
17	61%	0%	39%
18	59%	0%	41%
19	57%	0%	43%
20	55%	0%	45%
21	54%	0%	46%
22	52%	0%	48%
23	50%	0%	50%
24	49%	0%	51%
25	47%	0%	53%
26	46%	0%	54%
27	44%	0%	56%
28	43%	0%	57%
29	42%	0%	58%
30	40%	0%	60%
31	39%	0%	61%
32	38%	0%	62%
33	37%	0%	63%
34	36%	0%	64%
35	34%	0%	66%
36	33%	0%	67%
37	32%	0%	68%
38	31%	0%	69%
39	30%	0%	70%
40	29%	0%	71%
41	28%	0%	72%
42	27%	0%	73%
43	27%	0%	73%
44	26%	0%	74%
45	25%	0%	75%
46	24%	0%	76%
47	23%	0%	77%
48	23%	0%	77%
49	22%	0%	78%
50	21%	0%	79%
51	20%	0%	80%
52	20%	0%	80%

	SCT		
Month	AP	BP	Dead
53	19%	0%	81%
54	19%	0%	81%
55	18%	0%	82%
56	17%	0%	83%
57	17%	0%	83%
58	16%	0%	84%
59	16%	0%	84%
60	15%	0%	85%
61	15%	0%	85%
62	14%	0%	86%
63	14%	0%	86%
64	13%	0%	87%
65	13%	0%	87%
66	12%	0%	88%
67	12%	0%	88%
68	12%	0%	88%
69	11%	0%	89%
70	11%	0%	89%
71	11%	0%	89%
72	10%	0%	90%
73	10%	0%	90%
74	10%	0%	90%
75	9%	0%	91%
76	9%	0%	91%
77	9%	0%	91%
78	8%	0%	92%
79	8%	0%	92%
80	8%	0%	92%
81	8%	0%	92%
82	7%	0%	93%
83	7%	0%	93%
84	7%	0%	93%
85	7%	0%	93%
86	6%	0%	94%
87	6%	0%	94%
88	6%	0%	94%
89	6%	0%	94%
90	6%	0%	94%
91	5%	0%	95%
92	5%	0%	95%
93	5%	0%	95%
94	5%	0%	95%

	SCT		
Month	AP	BP	Dead
95	5%	0%	95%
96	5%	0%	95%
97	4%	0%	96%
98	4%	0%	96%
99	4%	0%	96%
100	4%	0%	96%
101	4%	0%	96%
102	4%	0%	96%
103	4%	0%	96%
104	3%	0%	97%
105	3%	0%	97%
106	3%	0%	97%
107	3%	0%	97%
108	3%	0%	97%
109	3%	0%	97%
110	3%	0%	97%
111	3%	0%	97%
112	3%	0%	97%
113	3%	0%	97%
114	2%	0%	98%
115	2%	0%	98%
116	2%	0%	98%
117	2%	0%	98%
118	2%	0%	98%
119	2%	0%	98%
120	2%	0%	98%
121	2%	0%	98%
122	2%	0%	98%
123	2%	0%	98%
124	2%	0%	98%
125	2%	0%	98%
126	2%	0%	98%
127	2%	0%	98%
128	1%	0%	99%
129	1%	0%	99%
130	1%	0%	99%
131	1%	0%	99%
132	1%	0%	99%
133	1%	0%	99%
134	1%	0%	99%
135	1%	0%	99%
136	1%	0%	99%

	SCT		
Month	AP	BP	Dead
137	1%	0%	99%
138	1%	0%	99%
139	1%	0%	99%
140	1%	0%	99%
141	1%	0%	99%
142	1%	0%	99%
143	1%	0%	99%
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145	1%	0%	99%
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153	1%	0%	99%
154	1%	0%	99%
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157	0%	0%	100%
158	0%	0%	100%
159	0%	0%	100%
160	0%	0%	100%
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162	0%	0%	100%
163	0%	0%	100%
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171	0%	0%	100%
172	0%	0%	100%
173	0%	0%	100%
174	0%	0%	100%
175	0%	0%	100%
176	0%	0%	100%
177	0%	0%	100%
178	0%	0%	100%

	SCT		
Month	AP	BP	Dead
179	0%	0%	100%
180	0%	0%	100%
181	0%	0%	100%
182	0%	0%	100%
183	0%	0%	100%
184	0%	0%	100%
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213	0%	0%	100%
214	0%	0%	100%
215	0%	0%	100%
216	0%	0%	100%
217	0%	0%	100%
218	0%	0%	100%
219	0%	0%	100%
220	0%	0%	100%

	SCT		
Month	AP	BP	Dead
221	0%	0%	100%
222	0%	0%	100%
223	0%	0%	100%
224	0%	0%	100%
225	0%	0%	100%
226	0%	0%	100%
227	0%	0%	100%
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253	0%	0%	100%
254	0%	0%	100%
255	0%	0%	100%
256	0%	0%	100%
257	0%	0%	100%
258	0%	0%	100%
259	0%	0%	100%
260	0%	0%	100%
261	0%	0%	100%
262	0%	0%	100%

	SCT		
Month	AP	BP	Dead
263	0%	0%	100%
264	0%	0%	100%
265	0%	0%	100%
266	0%	0%	100%
267	0%	0%	100%
268	0%	0%	100%
269	0%	0%	100%
270	0%	0%	100%
271	0%	0%	100%
272	0%	0%	100%
273	0%	0%	100%

Blast phase

Table B147: Tabulated markov trace for BP model - Bosutinib

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Table B148: Tabulated markov trace BP model - Hydroxycarbamide

	Hydroxycarbamide	
Month	**BP**	**Dead**
0	100%	0%
1	85%	15%
2	72%	28%
3	61%	39%
4	51%	49%
5	43%	57%
6	37%	63%
7	31%	69%
8	26%	74%

	Hydroxycarbamide	
Month	BP	Dead
9	22%	78%
10	19%	81%
11	16%	84%
12	14%	86%
13	11%	89%
14	10%	90%
15	8%	92%
16	7%	93%
17	6%	94%
18	5%	95%
19	4%	96%
20	4%	96%
21	3%	97%
22	3%	97%
23	2%	98%
24	2%	98%
25	2%	98%
26	1%	99%
27	1%	99%
28	1%	99%
29	1%	99%
30	1%	99%
31	1%	99%
32	0%	100%
33	0%	100%
34	0%	100%
35	0%	100%
36	0%	100%
37	0%	100%
38	0%	100%
39	0%	100%
40	0%	100%
41	0%	100%
42	0%	100%
43	0%	100%
44	0%	100%
45	0%	100%
46	0%	100%
47	0%	100%
48	0%	100%
49	0%	100%

	Hydroxycarbamide	
Month	BP	Dead
50	0%	100%
51	0%	100%
52	0%	100%
53	0%	100%
54	0%	100%
55	0%	100%
56	0%	100%
57	0%	100%
58	0%	100%
59	0%	100%
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80	0%	100%
81	0%	100%
82	0%	100%
83	0%	100%
84	0%	100%
85	0%	100%
86	0%	100%
87	0%	100%
88	0%	100%
89	0%	100%
90	0%	100%

	Hydroxycarbamide	
Month	BP	Dead
91	0%	100%
92	0%	100%
93	0%	100%
94	0%	100%
95	0%	100%
96	0%	100%
97	0%	100%
98	0%	100%
99	0%	100%
100	0%	100%
101	0%	100%
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124	0%	100%
125	0%	100%
126	0%	100%
127	0%	100%
128	0%	100%
129	0%	100%
130	0%	100%
131	0%	100%

	Hydroxycarbamide	
Month	BP	Dead
132	0%	100%
133	0%	100%
134	0%	100%
135	0%	100%
136	0%	100%
137	0%	100%
138	0%	100%
139	0%	100%
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141	0%	100%
142	0%	100%
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144	0%	100%
145	0%	100%
146	0%	100%
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165	0%	100%
166	0%	100%
167	0%	100%
168	0%	100%
169	0%	100%
170	0%	100%
171	0%	100%
172	0%	100%

	Hydroxycarbamide	
Month	BP	Dead
173	0%	100%
174	0%	100%
175	0%	100%
176	0%	100%
177	0%	100%
178	0%	100%
179	0%	100%
180	0%	100%

Table B149: Tabulated markov trace – Stem Cell Transplantation

	SCT	
Month	BP	Dead
0	100%	0%
1	97%	3%
2	94%	6%
3	91%	9%
4	88%	12%
5	85%	15%
6	83%	17%
7	80%	20%
8	77%	23%
9	75%	25%
10	73%	27%
11	70%	30%
12	68%	32%
13	66%	34%
14	64%	36%
15	62%	38%
16	60%	40%
17	58%	42%
18	56%	44%
19	55%	45%
20	53%	47%
21	51%	49%
22	50%	50%
23	48%	52%
24	46%	54%
25	45%	55%
26	44%	56%
27	42%	58%
28	41%	59%
29	40%	60%

	SCT	
Month	BP	Dead
30	38%	62%
31	37%	63%
32	36%	64%
33	35%	65%
34	34%	66%
35	33%	67%
36	32%	68%
37	31%	69%
38	30%	70%
39	29%	71%
40	28%	72%
41	27%	73%
42	26%	74%
43	25%	75%
44	25%	75%
45	24%	76%
46	23%	77%
47	22%	78%
48	22%	78%
49	21%	79%
50	20%	80%
51	20%	80%
52	19%	81%
53	18%	82%
54	18%	82%
55	17%	83%
56	17%	83%
57	16%	84%
58	16%	84%
59	15%	85%
60	15%	85%
61	14%	86%
62	14%	86%
63	13%	87%
64	13%	87%
65	13%	87%
66	12%	88%
67	12%	88%
68	11%	89%
69	11%	89%
70	11%	89%
71	10%	90%

	SCT	
Month	BP	Dead
72	10%	90%
73	10%	90%
74	9%	91%
75	9%	91%
76	9%	91%
77	9%	91%
78	8%	92%
79	8%	92%
80	8%	92%
81	8%	92%
82	7%	93%
83	7%	93%
84	7%	93%
85	7%	93%
86	6%	94%
87	6%	94%
88	6%	94%
89	6%	94%
90	6%	94%
91	5%	95%
92	5%	95%
93	5%	95%
94	5%	95%
95	5%	95%
96	5%	95%
97	4%	96%
98	4%	96%
99	4%	96%
100	4%	96%
101	4%	96%
102	4%	96%
103	4%	96%
104	4%	96%
105	3%	97%
106	3%	97%
107	3%	97%
108	3%	97%
109	3%	97%
110	3%	97%
111	3%	97%
112	3%	97%
113	3%	97%

	SCT	
Month	BP	Dead
114	3%	97%
115	3%	97%
116	2%	98%
117	2%	98%
118	2%	98%
119	2%	98%
120	2%	98%
121	2%	98%
122	2%	98%
123	2%	98%
124	2%	98%
125	2%	98%
126	2%	98%
127	2%	98%
128	2%	98%
129	2%	98%
130	2%	98%
131	1%	99%
132	1%	99%
133	1%	99%
134	1%	99%
135	1%	99%
136	1%	99%
137	1%	99%
138	1%	99%
139	1%	99%
140	1%	99%
141	1%	99%
142	1%	99%
143	1%	99%
144	1%	99%
145	1%	99%
146	1%	99%
147	1%	99%
148	1%	99%
149	1%	99%
150	1%	99%
151	1%	99%
152	1%	99%
153	1%	99%
154	1%	99%
155	1%	99%

	SCT	
Month	**BP**	**Dead**
156	1%	99%
157	1%	99%
158	1%	99%
159	1%	99%
160	1%	99%
161	1%	99%
162	1%	99%
163	0%	100%
164	0%	100%
165	0%	100%
166	0%	100%
167	0%	100%
168	0%	100%
169	0%	100%
170	0%	100%
171	0%	100%
172	0%	100%
173	0%	100%
174	0%	100%
175	0%	100%
176	0%	100%
177	0%	100%
178	0%	100%
179	0%	100%
180	0%	100%

10.22 Appendix 22: Scenario analysis - CP

1) Patient population

In the base case the patient population is comprised of the 3rd line CP patient population from Study 200 as previously described. In the sensitivity analysis, the effectiveness associated with other subgroups from Study 200 is explored. The efficacy parameters used in this analysis relate to MCyR (data snapshot 28 Mar 2011) and discontinuation data (patient level data at data snapshot 15 Feb 2012).

- The post-hoc analysis of the third-line CP cohort to identify the 'unmet need' subpopulation for whom treatment with imatinib, nilotinib and dasatinib would be unsuitable, as requested by the EMA (n=21) (28 Mar 2011)
    - 9/21 (43%) attained or maintained a MCyR or better on bosutinib
- The chronic phase, second line patient population (n=288) (15 Feb 2012)
    - 168/286 (59%) attained or maintained a MCyR or better on bosutinib
- The post-hoc 'unmet need' subpopulation analysis of the third-line and second-line chronic phase cohorts are combined (2nd line post-hoc and 3rd line post-hoc patients) (n=36) (28 Mar 2011)
    - 18/36 (50%) attained or maintained a MCyR or better on bosutinib (9/15 in second-line post-hoc patients population)

Table B150: Sensitivity analysis: CP – patient population

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Patient population set to 3rd line post-hoc (n=21)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.38	10.54	[redacted]	3.95	7.02	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.68	-3.94	Dominated	£111,511
Patient population set to chronic phase 2nd line, full Study 200 population (n=288)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.92	11.51	[redacted]	4.49	7.99	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-3.22	-4.91	Dominated	£111,511
Patient population set to 2nd line post-hoc and 3rd line post-hoc (n=36)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.63	10.97	[redacted]	4.20	7.45	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.92	-4.38	Dominated	£111,511

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

2) Overall survival - Bosutinib

In the base case overall survival for bosutinib is estimated based on the relationship between MCyR and OS, detailed in Section 7.2.2. In sensitivity analysis the hazard ratio for survival is changed from 0.37 to:

- 0.156 (lower 95% of pooled estimate, Rogers (2012)[84])
- 0.876 (upper 95% of pooled estimate, Rogers (2012)[84])

An alternative approach to modelling survival for bosutinib is conisderd, in which

- Overall survival is estimated by fitting a parametric curve. As described in Section 7.2.8, the best fitting curve was an exponential curve.
- Overall survival is equal to progression-free survival, plus 10 months in AP and 6 months in BP (similar to the cumulative survival approach in TA251)

Table B151: Sensitivity analysis: CP - Overall survival modelling - Bosutinib

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hazard ratio set to 0.156								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	4.85	7.98	[redacted]	2.42	4.46	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-1.15	-1.38	Dominated	£111,511
Hazard ratio set to 0.876								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	8.04	13.50	[redacted]	5.61	9.97	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-4.33	-6.90	Dominated	£111,511

Bosutinib overall survival estimated by parametric curve fits to clinical trials (exponential curve)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.40	10.95	[redacted]	3.97	7.43	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.70	-4.35	Dominated	£111,511
Cumulative survival approach								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	5.16	8.06	[redacted]	2.73	4.53	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-1.45	-1.46	Dominated	£111,511
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

3) Overall survival – SCT

In the base case, Stem Cell Transplant efficacy is taken from Jabbour (2011)[58], with a parametric curve fitted to survival results (exponential). In sensitivity analysis this is changed to:

- OS predicted by the second-best fitting curve (according to AIC and visual inspection) for the Jabbour 2011 CP patients (Weibull)
- Survival curves for stem cell transplant estimated based on Oheler (2007) – a study of stem cell transplant following imatinib treatment (i.e. second-line)

Table B152: Sensitivity analysis: CP - Overall survival modelling – SCT

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Stem Cell Transplant OS modelled as Weibull curve (2nd best AIC)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£191,063	5.69	12.05	[redacted]	-0.56	1.76	Dominated	£49,625
Stem Cell Transplant OS from Oehler (2007)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£172,126	3.76	6.71	[redacted]	-2.49	-3.58	Dominated	£107,503
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

4) Overall survival – Hydroxycarbamide

In the base case, hydroxycarbamide patients are estimated to survive for 3.5 years (42 months) however this figure is estimated from a study in which hydroxycarbamide is used in a second-line setting (Kantarjian 2007[36]). In this sensitivity analysis, overall survival for hydroxycarbamide is:

- Reduced to 38 months, in line with the ratio of estimated OS between bosutinib 2nd line and bosutinib 3rd line patients in Study 200
    - When the 2nd line bosutinib population is modelled, the life years are 11.51, compared to 10.30 in the base case. (10.30/11.51)*42 = 38.

- Reduced to 2 years, the lower end of the plausible range considered by Rogers (2012)
- Increased to 6.5 years, the upper end of the plausible range considered by Rogers (2012)[84]

Table B153: Sensitivity analysis: CP - Overall survival modelling - Hydroxycarbamide

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide mean survival reduced to 38 months								
Hydroxycarbamide	£28,036	2.22	3.19					
Interferon	£38,268	2.42	3.62	£10,232	0.20	0.43	£50,547	£50,547
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.83	6.68	[redacted]	[redacted]
SCT	£172,126	3.76	6.71	[redacted]	-2.49	-3.58	Dominated	£93,503
Hydroxycarbamide mean survival reduced to 2 years								
Hydroxycarbamide	£22,243	1.44	2.04					
Interferon	£38,268	2.42	3.62	£16,025	0.98	1.58	£16,291	£16,291
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.83	6.68	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£65,790
Hydroxycarbamide mean survival increased to 6.5 years								
Interferon	£38,268	2.42	3.62					
Hydroxycarbamide	£40,092	4.17	6.44	£1,824	1.75	2.82	£1,041	
Bosutinib	[redacted]	6.25	10.30	[redacted]	2.08	3.86	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	Dominated
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

5) Time spent in Blast Phase

In the base case, estimates from TA241 have been used for time spent in blast phase, which is set to 6 months for all patients. In sensitivity analysis this is changed to

- 13 months, based on Rogers (2012)[84]
- 3 months (assumption), in order to explore the sensitivity of the model to a reduction in this value

Table B154: Sensitivity analysis: CP – Alternative assumption of time spent in BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
BP Patients assumed to survive 13 months (Rogers, 2012)[84]								
Hydroxycarbamide	£31,512	2.34	3.52					
Interferon	£40,356	2.33	3.62	£8,844	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.15	10.30	[redacted]	3.80	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.44	-3.70	Dominated	£102,886
BP Patients assumed to survive 3 months (assumption)								
Hydroxycarbamide	£28,353	2.48	3.52					
Interferon	£37,129	2.47	3.62	£8,776	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.30	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]

SCT	£171,539	3.70	6.60	[redacted]	-2.59	-3.70	Dominated	£116,795
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

6) Patients who receive SCT can transform

In the base case, patients who receive SCT remain in CP until death, as SCT is assumed to be a curative treatment.

- In sensitivity analysis, SCT patients spend the same fixed periods in AP and BP as patients on other comparators

Table B155: Sensitivity analysis: CP – SCT patients can transform to AP and BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
SCT patients transform to AP and BP								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£180,887	3.64	6.60	[redacted]	-2.61	-3.70	Dominated	£125,553

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

7) Estimated Time on Treatment

In the base case, time on treatment is estimated by fitting a parametric curve to the discontinuation data from Study 200. In sensitivity analysis this approach is varied to consider:

- Bosutinib time on treatment set to be equal to PFS minus discontinuation due to adverse events, as described by Rogers (2012)[84] This approach was taken by Rogers (2012)[84] in the absence of trial data, and the assumptions used in estimating time on treatment have not been validated with actual data (as far as we are aware). As such, using the discontinuation data from study 200 is a much more accurate and appropriate method of modelling time on treatment.
- Bosutinib time on treatment modelled as log-logistic curve (2nd best fitting curve)

Table B156: Sensitivity analysis: CP – Bosutinib time on treatment

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Bosutinib time on treatment set to PFS minus discontinuation due to AE [as per Rogers et al, 2012][84]								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
SCT	£171,539	3.70	6.60	£142,066	1.27	3.07	£111,511	£111,511
Bosutinib	[redacted]	6.25	10.30	[redacted]	2.55	3.70	[redacted]	[redacted]
Bosutinib time on treatment modelled as log-logistic curve (2nd best AIC)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£111,511

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

8) Bosutinib dosing as from Study 200

In the base case, all patients are assumed to receive the licensed dose of 500mg once daily, with no potential for dose adjustment.

- As described in Table B5, patients on bosutinib may escalate dose up to 600mg once daily or reduce dose to 400mg or 300mg daily. In the CP third line patients of Study 200, the mean dose intensity was found to be approximately [redacted] in the third line cohort (relative dose intensity was [redacted]). The number of Study 200 patients who received increased or reduced doses of bosutinib was reported and summarised in Table B157. As the duration of time at the new dose and time to new dose is not reported, it is assumed that all patients receive the adjusted dose for the entire duration of their treatment with bosutinib. The mean daily cost for the chronic phase third-line population in study 200 was [redacted].

Table B157: % of third-line CP patients at different doses in Study 200

mg/day	% patients
600	[redacted]
400	[redacted]
300	[redacted]
500	[redacted]

Table B158: Sensitivity analysis: CP – Dose of bosutinib including expected dose escalation and reduction

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cost of bosutinib set to dosing seen in Study 200								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£111,511

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

9) Resource use

In the base case, resource use is taken from TA251.

- In sensitivity analysis, the medical management costs for the health states from TA241 are considered. Medical management costs from TA241 are less appropriate as a base-case than costs from TA251, since the sources of the TA241 data are not known, whereas the TA251 resource use data are referenced. Furthermore, TA251 represents a more recent source of data. Therefore, the use of TA241 resource use data is confined to a sensitivity analysis.

Table B159: Sensitivity analysis: CP – Resource use from TA241

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Resource use from TA241								
Hydroxycarbamide	£16,397	2.43	3.52					
Interferon	£22,574	2.42	3.62	£6,178	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]

SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£121,775

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

10) Cost of 'CP Off Treatment' health state

In the base case, patients are assumed to switch to hydroxycarbamide treatment. In sensitivity analysis, this assumption is varied to include scenarios where:

- Patients receiving hydroxycarbamide (both in the hydroxycarbamide arm, and by extension going off treatment with bosutinib and interferon) incur an off treatment cost (prior to AP) of £1039.53 per month (Rogers et al, 2012)[84]

Table B160: Sensitivity analysis: CP – Cost of off-treatment health state

	Total			Incremental			ICER	ICER v interferon
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Additional cost of £1039 per month in hydroxycarbamide and bosutinib arms in the CP-off treatment states								
Hydroxycarbamide	£58,965	2.43	3.52					
Interferon	£61,961	2.42	3.62	£2,997	-0.01	0.10	Dominated	Dominated
SCT	£171,539	3.70	6.60	£112,574	1.27	3.07	£88,362	£88,362
Bosutinib	[redacted]	6.25	10.30	[redacted]	2.55	3.70	[redacted]	[redacted]

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

11) Cost of AP and BP health states

In the base case, the cost of AP and BP are taken from resource use estimated by Hoyle et al 2011a[80] (Section 7.4.16). The sensitivity of the model to these estimates is explored in two scenarios where

- The cost of AP is doubled from £1,268 per month to £2,536 per month
- The cost of BP is doubled from £1,268 per month to £2,536 per month

Table B161: Sensitivity analysis: CP – Cost of AP and BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cost of AP set to £2,278 per month								
Hydroxycarbamide	£36,288	2.43	3.52					
Interferon	£45,154	2.42	3.62	£8,866	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£106,162
Cost of BP set to £2,278 per month								
Hydroxycarbamide	£35,413	2.43	3.52					
Interferon	£44,213	2.42	3.62	£8,800	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£106,848

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

12) Cost of death

In the base case, the cost of death is taken from a report by Addicott & Dewer[99] published by the King's Fund, detailing the costs of end of life care. In sensitivity analysis, to explore the sensitivity of the model to this variable, this is changed to:

- The cost of death being costed as per Hoyle et al (2011a)[80] – 2 palliative care non-medical specialist visits, and 1 inpatient palliative hospital stay

Table B162: Sensitivity analysis: CP – Cost of death set to 2 palliative care non-medical specialist visits + 1 inpatient palliative hospital stay [as per Hoyle et al, 2011a][80]

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide	£24,552	2.43	3.52					
Interferon	£33,363	2.42	3.62	£8,810	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£167,048	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£111,848

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

13) Cost of best supportive care

In the base case, treatment with hydroxycarbamide is associated with monthly costs of £13 per month, in addition to the medical management costs associated with the health states. As previously described, in practice best-supportive care may consist of hydroxycarbamide in combination with other interventions such as blood transfusions or antibiotics. In sensitivity analyses, additional costs are considered for treatment with hydroxycarbamide as a more realistic proxy for best-supportive care, in two ways:

- There is an additional cost of £100 per month applied to all states in the hydroxycarbamide arm only
- There is an additional cost of £100 per month applied to all states in the hydroxycarbamide arm, and the bosutinib and interferon arms where patients are not receiving active treatment

Table B163: Sensitivity analysis: CP – Cost of best supportive care

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Additional £100 per month cost, only in hydroxycarbamide arm								
Hydroxycarbamide	£33,316	2.43	3.52					
Interferon	£38,268	2.42	3.62	£4,953	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£108,495
Additional £100 per month cost for treatment with hydroxycarbamide								
Hydroxycarbamide	£33,316	2.43	3.52					
Interferon	£41,559	2.42	3.62	£8,243	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£108,495

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

14) Cohort starting age

In the base case, the patient cohort starts aged 54. In sensitivity, analysis, the starting age is varied by ±10% (as in Rogers (2012)[84]), such that two scenarios are performed:

- The cohort has a starting age of 49
- The cohort has a starting age of 59

Table B164: Sensitivity analysis: CP – Cohort starting age

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cohort starting age 49								
Hydroxycarbamide	£29,498	2.52	3.53					
Interferon	£38,295	2.51	3.63	£8,796	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.46	10.34	[redacted]	3.94	6.81	[redacted]	[redacted]
SCT	£171,639	3.84	6.63	[redacted]	-2.62	-3.71	Dominated	£107,849
Cohort starting age 59								
Interferon	£29,436	2.37	3.51					
Hydroxycarbamide	£38,230	2.37	3.61	£8,794	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.12	10.23	[redacted]	3.75	6.73	[redacted]	[redacted]
SCT	£171,397	3.63	6.55	[redacted]	-2.50	-3.68	Dominated	£113,343

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

15) Utility

In the base case, utilities used are taken from TA241 and TA251 for consistency with previous technology appraisals (based on the IRIS RCT). Utility decrements are applied to interferon treatment (due to adverse event profile), and the utility of patients is assumed to decline as patients age.

The following sensitivity analyses were performed:

- Utilities from Study 200 are used. Study 200 utility values are slightly lower in chronic phase compared to those taken from TA241/TA251 (0.80 for Study 200 and 0.85 for TA251/TA241), and have a lower sample size (Section 7.4.3). In this analysis interferon and SCT are not considered as information about the appliciability of the Study 200 utility to these comparators is not available.
- No decrement is applied to interferon treatment
- Utilities are not adjusted for patients aging in the model time horizon
- The utility value for CP from Study 200 is used for CP on treatment for bosutinib, all other utilities are as per the base-case
- The utility value for SCT is equal to that of the general population minus 0.0505 (Hoyle et al, 2011a)[80]

Table B165: Sensitivity analysis: CP – Utility values

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Utilities taken from Study 200								
Hydroxycarbamide	£29,473	2.47	3.52					
Bosutinib	[redacted]	6.10	10.30	[redacted]	3.63	6.78	[redacted]	[redacted]
No decrement to quality of life from interferon treatment								
Hydroxycarbamide	£29,473	2.43	3.52	-	-	-	-	-
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.55	-3.70	Dominated	£111,511
Utilities not adjusted to account for patient aging								
Hydroxycarbamide	£29,473	2.54	3.52					
Interferon	£38,268	2.53	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.64	10.30	[redacted]	4.10	6.78	[redacted]	[redacted]

SCT	£171,539	3.91	6.60	[redacted]	-2.73	-3.70	Dominated	£103,577
Utility decrement for Bosutinib (from study 200)								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.16	10.30	[redacted]	3.73	6.78	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-2.46	-3.70	Dominated	£111,511
SCT utility from Hoyle et al (2011a)[80]								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.25	10.30	[redacted]	3.82	6.78	[redacted]	[redacted]
SCT	£171,539	4.16	6.60	[redacted]	-2.09	-3.70	Dominated	£82,290
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

16) Time horizon

In the base case, the time horizon is set to 50 years, where all patients have died (the last patient from a cohort of 65, the number expected to be treated in 5 years in the UK, would be expected to die at year 34). The sensitivity of the model to the time horizon is therefore explored in three scenarios, setting the time horizon to:

- 2 years (trial period on which extrapolation of overall survival is based)
- 5 years
- 10 years
- 25 years

Table B166: Sensitivity analysis: CP – Time horizon

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
2 year time horizon								
Hydroxycarbamide	£12,672	1.19	1.54					
Interferon	£20,859	1.13	1.55	£8,187	-0.06	0.01	Dominated	Dominated
Bosutinib	[redacted]	1.44	1.80	[redacted]	0.24	0.25	[redacted]	[redacted]
SCT	£143,415	1.18	1.74	[redacted]	-0.25	-0.06	Dominated	Dominated
5 year time horizon								
Hydroxycarbamide	£23,072	1.96	2.69					
Interferon	£31,531	1.92	2.73	£8,459	-0.04	0.04	Dominated	Dominated
Bosutinib	[redacted]	3.01	4.02	[redacted]	1.05	1.33	[redacted]	[redacted]
SCT	£155,878	2.27	3.54	[redacted]	-0.74	-0.48	Dominated	£431,170
10 year time horizon								
Hydroxycarbamide	£28,219	2.34	3.34					
Interferon	£36,893	2.32	3.41	£8,674	-0.02	0.08	Dominated	Dominated
Bosutinib	[redacted]	4.70	6.76	[redacted]	2.35	3.42	[redacted]	[redacted]
SCT	£165,455	3.16	5.21	[redacted]	-1.54	-1.55	Dominated	£168,277
25 year time horizon								
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	6.17	10.00	[redacted]	3.74	6.48	[redacted]	[redacted]
SCT	£171,323	3.69	6.53	[redacted]	-2.48	-3.47	Dominated	£112,781

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations

10.23 Appendix 23: Scenario analysis - AP

1) Overall survival - bosutinib

In the base case overall survival for bosutinib is modelled based on the best fitting curve (according to the AIC), the exponential curve

- As a sensitivity analysis, the second best fitting curve is used, the extreme value

Table B167: Sensitivity analysis: AP - Overall survival modelling - Bosutinib

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Alternative curve fit (extreme value)								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.99	4.87	[redacted]	2.09	3.50	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-1.02	-1.85	Dominated	£142,982
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

2) Overall survival – SCT

In the base case overall survival for stem cell transplant is modelled based on the best-fitting curve (according to the AIC) – the exponential curve – fitted to the accelerated phase overall survival from a study by Oehler (2007)

- As a sensitivity analysis, the second best fitting curve is used, the Weibull curve
- As a sensitivity analysis, overall survival is modelled based on a curve fitted to the 'advanced phases' overall survival from Jabbour et al (2011)

Table B168: Sensitivity analysis: AP - Overall survival modelling – Stem Cell Transplant

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Stem Cell Transplant OS modelled as Weibull curve (2nd best AIC)								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£173,848	1.79	2.72	[redacted]	-0.97	-1.75	Dominated	£165,173
Stem Cell Transplant OS from Jabbour (2011)								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£197,588	2.65	4.25	[redacted]	-0.12	-0.23	Dominated	£98,279
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

3) Time spent in Blast Phase

In the base case, estimates from TA241 have been used for time spent in blast phase, which is set to 6 months for all patients. In sensitivity analysis this is changed to:

- 13 months, based on Rogers (2012)[84]

- 3 months (assumption), in order to explore the sensitivity of the model to a reduction in this value

Table B169: Sensitivity analysis: AP – Alternative assumption of time spent in BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
BP Patients assumed to survive 13 months (Rogers, 2012)[84]								
Hydroxycarbamide	£34,028	1.23	1.95					
Bosutinib	[redacted]	2.69	4.48	[redacted]	1.46	2.53	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.73	-1.45	Dominated	£195,626
BP Patients assumed to survive 3 months (assumption)								
Hydroxycarbamide	£22,575	0.76	1.12					
Bosutinib	£156,264	2.80	4.48	£133,689	2.04	3.35	£65,554	£65,554
SCT	£178,093	1.96	3.02	£21,829	-0.84	-1.45	Dominated	£129,309

4) Patients who receive SCT can transform

In the base case, patients who receive SCT remain in CP until death, as SCT is assumed to be a curative treatment.

- In sensitivity analysis, SCT patients spend the same fixed periods in BP as patients on other comparators

Table B170: Sensitivity analysis: AP – SCT patients can transform to BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
SCT patients can transform								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	1.89	3.02	[redacted]	-0.87	-1.45	Dominated	£153,493

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

5) Estimated time on treatment

In the base case, patients are assumed to follow the time on treatment seen in Study 200. This study provides 5 years of data, to which a parametric curve is fitted. In sensitivity analysis this approach is varied to include

- Bosutinib time on treatment set to be equal to Progression Free Survival
- Bosutinib time on treatment set to be equal to PFS minus discontinuation due to adverse events, as used in Rogers (2012)[84]
- Patients receive bosutinib until they progress to blast phase (ie they receive treatment for the whole of AP)

Table B171: Sensitivity analysis: AP – Bosutinib time on treatment

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Bosutinib time on treatment equal to progression free survival								

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide	£26,078	0.90	1.37					
SCT	£178,093	1.96	3.02	£152,015	1.06	1.65	£142,982	£142,982
Bosutinib	[redacted]	2.76	4.48	[redacted]	0.80	1.45	[redacted]	[redacted]
Bosutinib time on treatment modelled as log-logistic curve (2nd best AIC)								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.80	1.45	Dominated	£142,982

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

6) Bosutinib dosing as from Study 200

In the base case, patients are assumed to receive the licensed dosing with no potential for dose adjustment.

- In sensitivity analysis, the assumption is altered such that patients receive the dosing from the trial. In the accelerated phase patients, the average dose across the trial was higher than for chronic phase at [redacted] (relative dose intensity of [redacted]). The mean daily cost for the AP population in study 200 was [redacted].

Table B172: % of AP patients at different doses in Study 200

mg/day	% patients
600	[redacted]
400	[redacted]
300	[redacted]
500	[redacted]

Table B173: Sensitivity analysis: AP – Dose of bosutinib including expected dose escalation and reduction

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cost of bosutinib set to dosing seen in Study 200								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£142,982

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

7) Resource use

In the base case, resource use is taken from TA251.

- In sensitivity analysis, the medical management costs for the health states from TA241 are considered.

Table B174: Sensitivity analysis: AP – Resource use from TA241

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Resource use from TA241								
Hydroxycarbamide	£12,458	0.90	1.37					

Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£140,117	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£120,074
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.								

8) Cost of AP and BP health states

In the base case, the cost of AP and BP are taken from resource use estimated by Hoyle et al 2011a[80] (Section 7.4.16). The sensitivity of the model to these estimates is explored in two scenarios where

- The cost of AP is doubled from £1,181 per month to £2,278 per month
- The cost of BP is doubled from £1,181 per month to £2,278 per month

Table B175: Sensitivity analysis: AP – Cost of AP and BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cost of AP set to £2,278 per month								
Hydroxycarbamide	£41,195	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted] Dominated	[redacted]
SCT	£220,137	1.96	3.02	[redacted]	-0.80	-1.45		£168,310
Cost of BP set to £2,278 per month								
Hydroxycarbamide	£31,222	0.90	1.37					
Bosutinib	£162,029	2.76	4.48	£130,807	1.86	3.11	£70,248	£70,248
SCT	£178,093	1.96	3.02	£16,063	-0.80	-1.45	Dominated	£138,144

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

9) Cost of death

In the base case, the cost of death is taken from a report by Addicott & Dewer[99] published by the King's Fund, detailing the costs of end of life care. In sensitivity analysis, to explore the sensitivity of the model to this variable, this is changed to:

- The cost of death being costed as per Hoyle et al (2011a)[80] – 2 palliative care non-medical specialist visits, and 1 inpatient palliative hospital stay

Table B176: Sensitivity analysis: AP – Cost of death set to 2 palliative care non-medical specialist visits + 1 inpatient palliative hospital stay [as per Hoyle et al, 2011][80]

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide	£20,812	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£173,096	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£143,235

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

10) Cost of best supportive care

In the base case, treatment with hydroxycarbamide is assumed to represent best supportive care, and incur only the drug costs of hydroxycarbamide (£13 per month), in addition to the medical management costs associated with the health states. In sensitivity analysis, additional costs are considered for treatment with hydroxycarbamide, in two ways

- There is an additional cost of £100 per month applied to all states in the hydroxycarbamide arm only
- There is an additional cost of £100 per month applied to all states in the hydroxycarbamide arm, and the bosutinib and infterferon arms where patients are not receiving active treatment

Table B177: Sensitivity analysis: AP – Cost of best supportive care

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Additional £100 per month cost, only in hydroxycarbamide arm								
Hydroxycarbamide	£27,676	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£141,480
Additional £100 per month cost for treatment with hydroxycarbamide								
Hydroxycarbamide	£27,676	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£141,480

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

11) Cohort starting age

In the base case, the patient cohort starts aged 50, as per the accelerated phase cohort in Study 200. In sensitivity, analysis, the starting age is varied by ±10% (as in Rogers, 2012)[84], such that two scenarios are performed:

- The cohort has a starting age of 45
- The cohort has a starting age of 55

Table B178: Sensitivity analysis: AP – Cohort starting age

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cohort starting age 45								
Hydroxycarbamide	£26,096	0.90	1.37					
Bosutinib	[redacted]	2.80	4.49	[redacted]	1.90	3.11	[redacted]	[redacted]
SCT	£178,152	1.98	3.03	[redacted]	-0.82	-1.46	Dominated	£140,888
Cohort starting age 55								
Hydroxycarbamide	£26,053	0.85	1.37					
Bosutinib	[redacted]	2.63	4.46	[redacted]	1.79	3.09	[redacted]	[redacted]
SCT	£178,005	1.86	3.02	[redacted]	-0.77	-1.44	Dominated	£149,861

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

12) Utility

In the base case, utilities used are taken from TA21 and TA251 for consistency with previous appraisals. The utility of patients is assumed to decline as patients' age. In sensitivity analysis four scenarios are performed

- Utilities from Study 200 are used. These are higher than those seen in TA241 and TA251, however have a lower sample size (Section 7.4.3)
- Utilities are not adjusted for patients aging in the model time horizon
- The utility value for AP from Study 200 is used for CP on treatment for bosutinib
- The utility value for SCT is equal to that of the general population minus 0.0505 (Hoyle et al, 2011a)[80]

Table B179: Sensitivity analysis: AP – Utility values

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Utility values taken from Study 200								
Hydroxycarbamide	£26,078	1.06	1.37					
Bosutinib	[redacted]	3.13	4.48	[redacted]	2.07	3.11	[redacted]	[redacted]
Utilities not adjusted for patient aging								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.81	4.48	[redacted]	1.91	3.11	[redacted]	[redacted]
SCT	£178,093	1.98	3.02	[redacted]	-0.83	-1.45	Dominated	£140,682
AP on bosutinib from study 200								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.92	4.48	[redacted]	2.02	3.11	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.96	-1.45	Dominated	£142,982
SCT utility from Hoyle et al (2011a)[80]								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.11	[redacted]	[redacted]
SCT	£178,093	2.21	3.02	[redacted]	-0.55	-1.45	Dominated	£116,101

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

13) Time horizon

In the base case, the time horizon is set to 50 years, where all patients have died (the last patient from a cohort of 65, the number expected to be treated in 5 years in the UK, would be expected to die at year 21). The sensitivity of the model to the time horizon is therefore explored in three scenarios, setting the time horizon to:

- Study 200 time horizon (2 years)
- 5 years
- 10 years
- 25 years

Table B180: Sensitivity analysis: AP – Time horizon

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Study 200 time horizon (2 years)								
Hydroxycarbamide	£20,603	0.72	1.07					

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Bosutinib	[redacted]	1.14	1.63	[redacted]	0.42	0.56	[redacted]	[redacted]
SCT	£152,564	1.04	1.48	[redacted]	-0.11	-0.15	Dominated	£417,691
5 year time horizon								
Hydroxycarbamide	£25,590	0.89	1.34					
Bosutinib	[redacted]	2.05	3.04	[redacted]	1.16	1.70	[redacted]	[redacted]
SCT	£169,886	1.67	2.47	[redacted]	-0.37	-0.57	Dominated	£183,409
10 year time horizon								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.57	4.03	[redacted]	1.67	2.66	[redacted]	[redacted]
SCT	£176,887	1.92	2.93	[redacted]	-0.65	-1.10	Dominated	£147,725
25 year time horizon								
Hydroxycarbamide	£26,078	0.90	1.37					
Bosutinib	[redacted]	2.76	4.48	[redacted]	1.86	3.10	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	-0.80	-1.45	Dominated	£142,982
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

10.24 Appendix 24: Sensitivity analysis – BP

1) Overall survival - Bosutinib

In the base case overall survival for bosutinib is modelled based on the best fitting curve (according to the AIC), the exponential curve

- As a sensitivity analysis, the second best fitting curve is used, the Weibull

Table B181: Sensitivity analysis: BP - Overall survival modelling - Bosutinib

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Alternative curve fit (Weibull)								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	1.07	2.17	[redacted]	0.79	1.62	[redacted]	[redacted]
SCT	£200,526	1.28	2.64	[redacted]	0.21	0.48	[redacted]	£186,265
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

2) Overall survival – SCT

In the base case overall survival for stem cell transplant is modelled based on the best-fitting curve (according to the AIC) – the exponential curve – fitted to the blast phase overall survival from a study by Oehler (2007)

- As a sensitivity analysis, the second best fitting curve is used, the Weibull curve
- As a sensitivity analysis, overall survival is modelled based on a curve fitted to the 'advanced phases' overall survival from Saussele (2010)

Table B182: Sensitivity analysis: BP - Overall survival modelling – Stem Cell Transplant

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Stem Cell Transplant OS modelled as Weibull curve (2nd best AIC)								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£286,954	3.78	11.19	[redacted]	2.90	9.42	[redacted]	£77,867
Stem Cell Transplant OS from Saussele (2010)								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£212,771	1.59	3.35	[redacted]	0.70	1.58	[redacted]	£152,166
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

3) Time spent in Blast Phase

In the base case, estimates from TA241 have been used for time spent in blast phase, which is set to 6 months for all patients. In sensitivity analysis this is changed to

- 13 months, based on Rogers (2012)[84]
- 3 months (assumption), in order to explore the sensitivity of the model to a reduction in this value

Table B183: Sensitivity analysis: BP – Alternative assumption of time spent in BP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
BP Patients assumed to survive 13 months (Rogers, 2012)[84]								
Hydroxycarbamide	£22,584	0.57	1.12					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.31	0.65	[redacted]	[redacted]
SCT	£200,526	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£250,817
BP Patients assumed to survive 3 months (assumption)								
Hydroxycarbamide	£10,463	0.15	0.29					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.73	1.48	[redacted]	[redacted]
SCT	£200,526	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£168,460

4) Cost of stem cell transplant

In the base case from expert opinion, patients in BP who are to receive a SCT first must receive chemotherapy (FLAG-IDA) at a cost of £29,212

- In sensitivity analysis this cost is removed, such that patients only incur the cost of SCT

Table B184: Sensitivity analysis: BP – Cost of SCT

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
No cost for chemotherapy								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£157,068
Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations								

5) Estimated Time on Treatment

In the base case, patients are assumed to follow the time on treatment seen in Study 200. This study provides 5 years of data, to which a parametric curve is fitted. In sensitivity analysis this approach is varied to include

- Bosutinib time on treatment set to be equal to Progression Free Survival
- Bosutinib time on treatment modelled as log-logistic curve (2nd best AIC)
- Patients remain on treatment until death

Table B185: Sensitivity analysis: BP – Bosutinib time on treatment

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Bosutinib time on treatment equal to progression free survival								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£157,068
Bosutinib time on treatment modelled as log-logistic curve (2nd best AIC)								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£157,068

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

6) Bosutinib dosing as from Study 200

In the base case, patients are assumed to receive the licensed dosing with no potential for dose adjustment.

- In sensitivity analysis, the assumption is altered such that patients receive the dosing from the trial. In the blast phase patients, the average dose across the trial was higher than for chronic phase at [redacted] (relative dose intensity of [redacted]). The mean daily cost for the BP population in study 200 was [redacted].

Table B186: % of AP patients at different doses in Study 200

mg/day	% patients
600	[redacted]
400	[redacted]
300	[redacted]
500	[redacted]

Table B187: Sensitivity analysis: BP – Dose of bosutinib including expected dose escalation and reduction

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		

Cost of bosutinib set to dosing seen in Study 200								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£157,068

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

7) Resource use

In the base case, resource use is taken from TA251.

- In sensitivity analysis, the medical management costs for the health states from TA241 are considered.

Table B188: Sensitivity analysis: BP – Resource use from TA241

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Resource use from TA241								
Hydroxycarbamide	£14,005	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£210,941	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£196,840

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

8) Cost of BP health states

In the base case, the cost of BP is taken from resource use estimated by Hoyle et al (2011a)[80] (Section 7.4.16). The sensitivity of the model to this estimate is

- The cost of BP is doubled from £1,268per month to £2,536 per month

Table B189: Sensitivity analysis: BP – Cost of BP

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Cost of BP set to £2,278 per month								
Hydroxycarbamide	£22,373	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£237,706	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£215,228

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

9) Cost of death

In the base case, the cost of death is taken from a report by Addicott & Dewer[99] published by the King's Fund, detailing the costs of end of life care. In sensitivity analysis, to explore the sensitivity of the model to this variable, this is changed to:

- The cost of death being costed as per Hoyle et al (2011)[80] – 2 palliative care non-medical specialist visits, and 1 inpatient palliative hospital stay

Table B190: Sensitivity analysis: BP – Cost of death set to 2 palliative care non-medical specialist visits + 1 inpatient palliative hospital stay [as per Hoyle et al, 2011a][80]

	Total			Incremental			ICER	ICER v
	Cost	QALYs	LYs	Cost	QALYs	LYs		hydroxycarbamide
Hydroxycarbamide	£8,769	0.28	0.54					

Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£166,257	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£157,412

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

10) Cost of best supportive care

In the base case, treatment with hydroxycarbamide is assumed to represent best supportive care, and incur only the drug costs of hydroxycarbamide (£13 per month), in addition to the medical management costs associated with the health states. In sensitivity analysis, additional costs are considered for treatment with hydroxycarbamide, in two ways:

- There is an additional cost of £100 per month applied to all states in the hydroxycarbamide arm only
- There is an additional cost of £100 per month applied to all states in the hydroxycarbamide arm, and the bosutinib and infterferon arms where patients are not receiving active treatment

Table B191: Sensitivity analysis: BP – Cost of best supportive care

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Additional £100 per month cost, only in hydroxycarbamide arm								
Hydroxycarbamide	£14,817	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£156,421
Additional £100 per month cost for treatment with hydroxycarbamide								
Hydroxycarbamide	£14,817	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£156,421

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

11) Cohort starting age

In the base case, the patient cohort starts aged 47, as per the mean age of the blast phase cohort in Study 200. In sensitivity, analysis, the starting age is varied by ±10% (as in Rogers (2012)[84]), such that two scenarios are performed:

- The cohort has a starting age of 42
- The cohort has a starting age of 52

Table B192: Sensitivity analysis: BP – Cohort starting age

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Cohort starting age 42								
Hydroxycarbamide	£14,174	0.30	0.54					
Bosutinib	[redacted]	0.94	1.78	[redacted]	0.64	1.23	[redacted]	[redacted]
SCT	£171,353	1.35	2.65	[redacted]	0.41	0.87	[redacted]	£149,866
Cohort starting age 52								
Hydroxycarbamide	£14,163	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,255	1.26	2.64	[redacted]	0.38	0.87	[redacted]	£160,264

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

12) Utility

In the base case, utilities used are taken from TA21 and TA251 for consistency. The utility of patients is assumed to decline as patients age. In sensitivity analysis 3 scenarios are performed

- Utilities from Study 200 are used. These are higher than those seen in TA241 and TA251, however have a lower sample size (Section 7.4.3)
- Utilities are not adjusted for patients aging in the model time horizon
- The utility for BP from study 200 is used as the utility for BP on treatment for bosutinib
- The utility value for SCT is equal to that of the general population minus 0.0505 (Hoyle et al, 2011a)[80]

Table B193: Sensitivity analysis: BP – Utility values taken from bosutinib clinical trial

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Utility values taken from Study 200								
Hydroxycarbamide	£14,170	0.41	0.54					
Bosutinib	[redacted]	1.30	1.77	[redacted]	0.89	1.23	[redacted]	[redacted]
Utilities not adjusted for patient aging								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£156,671
BP utility on Bosutinib from study 200								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	1.03	1.77	[redacted]	0.75	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.25	0.87	[redacted]	£157,068
SCT utility from Hoyle et al (2011a)[80]								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£200,526	1.97	2.64	[redacted]	1.08	0.87	[redacted]	£110,357

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

13) Time horizon

In the base case, the time horizon is set to 50 years, where all patients have died (the last patient from a cohort of 65- the number expected to be treated in 5 years in the UK, would be expected to die at year 5). The sensitivity of the model to the time horizon is therefore explored in three scenarios, setting the time horizon to:

- The length of Study 200 (2 years)
- 5 years
- 10 years
- 25 years

Table B194: Sensitivity analysis: BP – Time horizon

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Study 200 time horizon (2 years)								
Hydroxycarbamide	£13,919	0.28	0.53					
Bosutinib	[redacted]	0.62	1.22	[redacted]	0.35	0.68	[redacted]	[redacted]
SCT	£150,475	0.73	1.42	[redacted]	0.10	0.20	[redacted]	£301,964
5 year time horizon								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.84	1.68	[redacted]	0.56	1.14	[redacted]	[redacted]
SCT	£165,548	1.13	2.26	[redacted]	0.28	0.58	[redacted]	£178,878
10 year time horizon								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£170,662	1.26	2.59	[redacted]	0.38	0.82	[redacted]	£159,036
25 year time horizon								
Hydroxycarbamide	£14,170	0.28	0.54					
Bosutinib	[redacted]	0.88	1.77	[redacted]	0.60	1.23	[redacted]	[redacted]
SCT	£171,314	1.28	2.64	[redacted]	0.40	0.87	[redacted]	£157,068

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

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Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia ID495

Dear [redacted]

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 8 March 2013 by Pfizer. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm**, **Thursday 18 April 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Lead ([redacted]). Any procedural questions should be addressed to [redacted], Project Manager ([redacted]) in the first instance.

Yours sincerely

[redacted] – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A1. A separate search for adverse event literature was not conducted (p217). Are there additional trials known to the manufacturer which were not identified by the systematic review of clinical evidence in the submission which would provide alternative estimates of the profile of adverse events due to bosutinib, including trials of bosutinib as a first-line TKI?

A2. The eligibility criteria for Study 200 were changed on the 10th June 2008 so that patients with a T315I mutation were excluded from the study (p53). Please clarify:

- How many patients with the T315I mutation were included in Study 200?
- How is the addition of this exclusion criterion anticipated to have influenced the clinical effectiveness data and estimates?
- How prevalent is this mutation in the CML population?

A3. Please update table B8 on page 55 to provide the median duration of CML disease and range for each of the accelerated and blast phase patient groups (equivalent to the CML disease duration and range provided in table B7 (p54) for the chronic phase population).

A4. Please clarify why the numbers of participants recruited for the advanced phases and chronic phases do not match the sample size calculations on pages 58 and 59 of the submission. In addition, the sample size calculation is based on "clinical estimates" for the third line CP CML population and "published data" for the AP and BP CML populations (p58-59, p351). Please clarify the data used for these calculations and the references for the published data.

A5. Section 6.9 adverse events (p80), reports data based on a minimum follow-up of 12 months for the third line CP CML population. Please provide an update with 24 month follow up data (15th February 2012 snapshot) for the following populations (as described in table B20):

- Imatinib and dasatinib resistant
- Imatinib and dasatinib intolerant
- Imatinib and nilotinib resistant
- Prior treatment with imatinib and dasatinib, with or without nilotinib.
- All people with CP CML

A6. Table B29 on page 84 provides adverse event rates for the accelerated phase and blast phase CML populations. Please update this table to provide data for the following populations:

- Accelerated phase patients receiving bosutinib 2nd line
- Accelerated phase patients following multi-TKI failure
- Blast phase patients receiving bosutinib 2nd line
- Blast phase patients following multi-TKI failure

A7. In order to allow comparison of data from the second line CP CML population with data from the third line CP CML population, please provide separate data for the imatinib-resistant and the imatinib intolerant populations for all results presented in appendix 15.

A8. Figure B35 on page 164 appears to be a duplicate of Figure B46 on page 175 please provide the correct figure B35.

Section B: Clarification on cost-effectiveness data

B1. **Priority request:** The calculation of overall survival for patients not having/achieving MCyR is incorrect. In PF_Bosutinib column N the part of the formula **(1-WEIBULL(B11, p_os_w_a,p_os_w_b, TRUE)^p_mcyr_hr)** should be replaced with **POWER(1-WEIBULL(B11, p_os_w_a,p_os_w_b, TRUE, 1/p_mcyr_hr)** for correct incorporation of the hazard ratio. Please amend the model.

B2. **Priority request:** The error identified in question B1 has a substantial effect on the shape of the overall survival of bosutinib patients and means that unless the Weibull parameters **p_os_w_a** and **p_os_w_b** are recalibrated to the overall survival data from Jabbour et al 2009, the estimates of cost-effectiveness will not be valid. Please:

- Recalibrate these parameters
- Provide the extracted Kaplan Meier data from Jabbour et al 2009 which is used to calibrate
- Provide a full description of the method used to calibrate to ensure reproducibility
- Provide updated results, in particular the updated base case, one way sensitivity analyses and probabilistic sensitivity analyses.

B3. Bosutinib could be considered as a second-line TKI for CP CML. In order for exploratory analysis of the cost-effectiveness of bosutinib in such patients, please provide the following information for patients in the CP second line CML cohort in Study 200:

- Kaplan-Meier curves for treatment discontinuation and overall survival calculated from the most recently available data (ideally separately for imatinib resistant and imatinib intolerant patients).
- MCyR rate (best cumulative response in patients who both maintained and attained a MCyR) at a minimum follow-up duration of 12 months (i.e., data snapshot around 28 March 2010; ideally estimated separately for imatinib resistant, imatinib intolerant and for all CP second line CML patients), or alternatively:
- MCyR rate (best cumulative response in patients who both maintained and attained a MCyR by or within 12 months with any patients progressing or dying within 12 months counting as non-responders; ideally estimated separately for imatinib resistant, imatinib intolerant and for all CP second line CML patients).

B4. In order to allow exploration of the differences in cost-effectiveness of bosutinib following imatinib discontinuation and bosutinib following multiple TKI failure in patients with AP/BP CML, please provide the following information separately for the AP and BP cohorts from Study 200:

- Kaplan-Meier curve for treatment discontinuation for people receiving bosutinib second line
- Kaplan- Meier curve for treatment discontinuation for people receiving bosutinib following multiple TKI failure

- Kaplan-Meier curve for overall survival for people receiving bosutinib second line
- Kaplan-Meier curve for overall survival for people receiving bosutinib following multiple TKI failure

B5. The calculation of the mean daily cost for bosutinib (p472) ignores treatment interruptions, although treatment interruptions are indicated for non-haematological adverse reactions (Table A1, p21), and some patients did have treatment with bosutinib interrupted due to adverse events (p359). Please provide an indication of the mean time that patients were not receiving bosutinib due to dose interruptions for the chronic, accelerated and blast phase populations separately if possible otherwise averaged over all patients.

Section C: Literature searching

C1. **Priority request**: Page 18 of the submission says that a draft EPAR is available. Please provide the draft EPAR.

C2. Appendix 2 (p201). Please clarify the date on which the search of conference proceedings was carried out?

C3. Appendix 2 (p201). Please clarify how the search for conference proceedings was carried out (i.e. through web-sites, hand-searching of journal supplements or through the web of science database)?

C4. Appendix 2 (p201). Please clarify the rationale behind the date limit applied to the search of conference proceedings (2010-2012)?

C5. Appendix 8 (p217). Please clarify why a separate searches for adverse event literature was not undertaken?

C6. Appendix 10 (p218). The searches for the clinical effectiveness section of the submission were carried out in January 2013 whereas the cost effectiveness literature searches were carried out in October 2012. Please clarify why the cost-effectiveness searches were not updated in January 2013 for the submission?

C7. Appendix 10 (p221). Please clarify what the 'horizon scans' entailed, when they were run and how, giving enough information for these searches to be repeated.

Section A: Clarification on effectiveness data

A1. A separate search for adverse event literature was not conducted (p217). Are there additional trials known to the manufacturer which were not identified by the systematic review of clinical evidence in the submission which would provide alternative estimates of the profile of adverse events due to bosutinib, including trials of bosutinib as a first-line TKI?

In the submission, safety data in previously treated subjects with Ph+ leukaemia was presented from Study 200 (bosutinib n=570) as this was felt to be the most relevant to the licensed indication. Clinical safety data, including long-term safety, are also available from the Phase III Study 3000 in subjects with newly diagnosed CP CML (bosutinib n=248/ imatinib N=251) and this is presented in Table 1 below.

As noted in the bosutinib EPAR, other safety data is also available from phase I/II studies conducted in patients with solid tumours (mainly breast cancer). In total, 1572 subjects were exposed with bosutinib in clinical studies from phase I to III and 1209 patients received at least 1 dose of oral bosutinib alone or in combination with another anticancer agent. However, this data is not presented below as it is not felt to be relevant to the licensed indication.

Table 1: Number (%) of Subjects Experiencing Drug Related Treatment-Emergent Adverse Events (TEAEs) with an Incidence of ≥5%: Safety Population of study 3000

	Treatment		
System Organ Class Preferred Term	**Bosutinib N=248**	**Imatinib N=251**	**Total N=499**
ANY ADVERSE EVENT	227 (91.5)	218 (86.9)	445 (89.2)
Blood and lymphatic system disorders	94 (37.9)	118 (47.0)	212 (42.5)
Thrombocytopenia	65 (26.2)	67 (26.7)	132 (26.5)
Neutropenia	29 (11.7)	65 (25.9)	94 (18.8)
Anaemia	37 (14.9)	45 (17.9)	82 (16.4)
Leukopenia	21 (8.5)	50 (19.9)	71 (14.2)
Eye disorders	8 (3.2)	34 (13.5)	42 (8.4)
Eyelid oedema	2 (0.8)	18 (7.2)	20 (4.0)
Gastrointestinal disorders	181 (73.0)	106 (42.2)	287 (57.5)
Diarrhoea	163 (65.7)	45 (17.9)	208 (41.7)
Nausea	66 (26.6)	81 (32.3)	147 (29.5)
Vomiting	61 (24.6)	22 (8.8)	83 (16.6)
Abdominal pain upper	24 (9.7)	10 (4.0)	34 (6.8)
Abdominal pain	21 (8.5)	7 (2.8)	28 (5.6)
General disorders and administration site conditions	54 (21.8)	68 (27.1)	122 (24.4)
Fatigue	22 (8.9)	22 (8.8)	44 (8.8)
Oedema peripheral	4 (1.6)	21 (8.4)	25 (5.0)
Investigations	123 (49.6)	75 (29.9)	198 (39.7)
Alanine aminotransferase increased	73 (29.4)	14 (5.6)	87 (17.4)
Aspartate aminotransferase increased	59 (23.8)	12 (4.8)	71 (14.2)
Lipase increased	25 (10.1)	20 (8.0)	45 (9.0)
Blood creatine phosphokinase increased	10 (4.0)	22 (8.8)	32 (6.4)
Blood alkaline phosphatase increased	14 (5.6)	9 (3.6)	23 (4.6)
Gamma-glutamyltransferase increased	14(5.6)	1 (0.4)	15 (3.0)
Metabolism and nutrition disorders	39 (15.7)	43 (17.1)	82 (16.4)
Hypophosphataemia	12 (4.8)	25 (10.0)	37 (7.4)
Decreased appetite	19 (7.7)	3 (1.2)	22 (4.4)
Musculoskeletal and connective tissue disorders	19 (7.7)	80 (31.9)	99 (19.8)

	Treatment		
System Organ Class Preferred Term	**Bosutinib N=248**	**Imatinib N=251**	**Total N=499**
Muscle spasms	1 (0.4)	44 (17.5)	45 (9.0)
Myalgia	6 (2.4)	21 (8.4)	27 (5.4)
Bone pain	2 (0.8)	16 (6.4)	18 (3.6)
Nervous system disorders	34 (13.7)	18 (7.2)	52 (10.4)
Headache	13 (5.2)	6 (2.4)	19 (3.8)
Skin and subcutaneous tissue disorders	80 (32.3)	69 (27.5)	149 (29.9)
Rash	45 (18.1)	28 (11.2)	73 (14.6)
Periorbital oedema	0	34 (13.5)	34 (6.8)
System organ class totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same system organ class. Date of snapshot: 31AUG2010			

In addition, the SPC and EPAR for bosutinib contains an evaluation of the adverse reaction data from 870 patients with newly diagnosed Ph+ chronic phase CML, or with Ph+ chronic, accelerated, or blast phase CML or Ph+ acute lymphoblastic leukaemia (ALL) resistant or intolerant to prior therapy and who have received at least 1 dose of single agent bosutinib.

Table 2: Adverse reactions for bosutinib from SPC

System Organ Class	***Frequency***	***Adverse reactions***	***All Grades n (%)***	***Grade 3 n (%)***	***Grade 4 n (%)***
Infections and infestations	Very common	Respiratory tract infection[a]	99 (11.4)	4 (0.5)	0
	Common	Pneumonia[b]	45 (5.2)	21 (2.4)	5 (0.6)
		Influenza	47 (5.4)	2 (0.2)	0
		Bronchitis	27 (3.1)	1 (0.1)	0
		Nasopharyngitis	81 (9.3)	0	0
Blood and lymphatic system disorders	Very common	Thrombocytopenia	335 (38.5)	127 (14.6)	94 (10.8)
		Neutropenia	141 (16.2)	67 (7.7)	33 (3.8)
		Anaemia	238 (27.4)	82 (9.4)	25 (2.9)
		Leukopenia	94 (10.8)	31 (3.6)	8 (0.9)
	Common	Febrile Neutropenia	13 (1.5)	8 (0.9)	3 (0.3)
	Uncommon	Granulocytopenia	2 (0.2)	0	2 (0.2)
Immune system disorders	Common	Drug hypersensitivity	12 (1.4)	7 (0.8)	0
	Uncommon	Anaphylactic shock	2 (0.2)	0	2 (0.2)
Metabolism and nutrition disorders	Very Common	Decreased appetite	109 (12.5)	4 (0.5)	0
	Common	Dehydration	20 (2.3)	2 (0.2)	0
		Hyperkalaemia	23 (2.6)	2 (0.2)	1 (0.1)
		Hypophosphataemia	54 (6.2)	18 (2.1)	0
Nervous system disorders	Very common	Headache	148 (17.0)	9 (1.0)	3 (0.3)
	Common	Dizziness	74 (8.5)	2 (0.2)	0
		Dysgeusia	18 (2.1)	0	0
Ear and labyrinth disorders	Uncommon	Tinnitus	8 (0.9)	0	0
Cardiac disorders	Common	Pericardial effusion	16 (1.8)	2 (0.2)	1 (0.1)
		Electrocardiogram QT prolonged[c]	10 (1.1)	1 (0.1)	0

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
	Uncommon	Pericarditis	1 (0.1)	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	125 (14.4)	0	0
	Common	Dyspnoea	82 (9.4)	15 (1.7)	3 (0.3)
		Pleural effusion	52 (6.0)	14 (1.6)	1 (0.1)
	Uncommon	Respiratory failure	5 (0.6)	1 (0.1)	1 (0.1)
		Acute pulmonary oedema	3 (0.3)	1 (0.1)	1 (0.1)
		Pulmonary hypertension	4 (0.5)	1 (0.1)	0
Gastrointestinal disorders	Very common	Diarrhoea	683 (78.5)	78 (9.0)	1 (0.1)
		Vomiting	323 (37.1)	25 (2.9)	0
		Nausea	366 (42.1)	10 (1.1)	0
		Abdominal pain[d]	291 (33.4)	15 (1.7)	0
	Common	Gastritis	25 (2.9)	3 (0.3)	1 (0.1)
	Uncommon	Acute pancreatitis	3 (0.3)	2 (0.2)	1 (0.1)
		Gastrointestinal haemorrhage[e]	6 (0.7)	5 (0.6)	0
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	194 (22.3)	79 (9.1)	10 (1.1)
		Aspartate aminotransferase increased	160 (18.4)	41 (4.7)	3 (0.3)
	Common	Hepatotoxicity[f]	15 (1.7)	5 (0.6)	1 (0.1)
		Hepatic function abnormal	27 (3.1)	8 (0.9)	3 (0.3)
		Blood bilirubin increased	33 (3.8)	8 (0.9)	0
		Gamma-glutamyltransferase increased	29 (3.3)	7 (0.8)	0
	Uncommon	Liver Injury	2 (0.2)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	Very common	Rash[g]	282 (32.4)	51 (5.9)	2 (0.2)
	Common	Urticaria	26 (3.0)	2 (0.2)	1 (0.1)
		Acne	25 (2.9)	0	0
		Pruritus	71 (8.2)	3 (0.3)	0
	Uncommon	Erythema multiforme	1 (0.1)	0	1 (0.1)
		Exfoliative rash	6 (0.7)	1 (0.1)	0
		Drug eruption	5 (0.6)	1 (0.1)	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	96 (11.0)	3 (0.3)	0
	Common	Myalgia	49 (5.6)	3 (0.3)	0
		Back pain	72 (8.3)	7 (0.8)	1 (0.1)
Renal and urinary disorders	Common	Renal failure	13 (1.5)	2 (0.2)	1 (0.1)
	Uncommon	Renal failure acute	7 (0.8)	3 (0.3)	1 (0.1)
		Renal impairment	8 (0.9)	1 (0.1)	0

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
General disorders and administration site conditions	Very common	Pyrexia	204 (23.4)	6 (0.7)	1 (0.1)
		Oedema[h]	100 (11.5)	1 (0.1)	0
		Fatigue[i]	169 (19.4)	14 (1.6)	1 (0.1)
	Common	Chest pain[j]	61 (7.0)	4 (0.5)	1 (0.1)
		Pain	41 (4.7)	5 (0.6)	0
		Asthenia	86 (9.9)	7 (0.8)	2.(0.2)
Investigations	Common	Lipase increased	76 (8.7)	41 (4.7)	4 (0.5)
		Blood creatinine increased	42 (4.8)	2 (0.2)	0
		Blood amylase increased	31 (3.6)	7 (0.8)	0
		Blood creatine phosphokinase increased	28 (3.2)	3 (0.3)	2 (0.2)

The following terms have been combined:
[a] Respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral.
[b] Pneumonia, bronchopneumonia, primary atypical pneumonia, lobar pneumonia.
[c] Electrocardiogram QT prolonged, long QT syndrome.
[d] Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain.
[e] Gastrointestinal haemorrhage, gastric haemorrhage, upper gastrointestinal haemorrhage.
[f] Hepatotoxicity, toxic hepatitis, cytolytic hepatitis.
[g] Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash.
[h] Oedema, face oedema, localized oedema, peripheral oedema.
[i] Fatigue, malaise.
[j] Chest pain, chest discomfort.

As noted in the bosutinib EPAR, the incidence and types of SAEs in Study 200 appears to be consistent and comparable with the data previously reported from study 3000, where the number of subjects with SAEs was significantly higher in the bosutinib arm (68 subjects; 27.4 %), compared with the imatinib arm (37 subjects; 14.1%) [updated analysis from 15 November 2011]. SAEs considered to be related to treatment were also more frequent in the bosutinib arm (32 subjects; 12.9%) compared with the imatinib arm (13 subjects; 5.1%). Also, SAEs in the bosutinib arm led more frequently to treatment discontinuation (13 subjects, 19.1 %) compared with the imatinib arm (3 subjects, 8.1%). However, SAEs leading to death occurred more often in the imatinib arm (7 subjects, 18.9%) compared with the bosutinib arm (3 subjects, 4.4%). The updated analysis at 24 months in general has confirmed these results.

A2. The eligibility criteria for Study 200 were changed on the 10th June 2008 so that patients with a T315I mutation were excluded from the study (p53). Please clarify:

- How many patients with the T315I mutation were included in Study 200?

Patients with a documented history of prior T315I Bcr-Abl mutation were excluded from Study 200 as of 10 June 2008 due to lack of efficacy in this group.

A mutation assessment at baseline was not carried out for all patients in Study 200. The table below summarises the proportion of patients in each cohort of Study 200 who received a mutation assessment and of these the proportion of T315I mutations.

Table 3: Proportion of patients with a T315I mutation at baseline

	N of patients assessed for mutations at baseline	**N of patients assessed with a T315I mutation at baseline**

CP2L	212/288 (74.6%)	9/212 (4.2%)
CP3L	83/118 (70.3%)	7/83 (8.4%)
Advanced phase	117/140 (83.6%)	15/117 (12.8%)

- How is the addition of this exclusion criterion anticipated to have influenced the clinical effectiveness data and estimates?

The efficacy of those patients with a baseline T315I mutation appears to be significantly worse when compared with the efficacy of the whole cohort in Study 200, however the numbers are small and therefore caution is required in drawing any conclusions from this data.

Table 4: Efficacy in full Study 200 evaluable populations versus those with a baseline T315I mutation

	Evaluable population		T315I subpopulation	
	CHR	**MCyR**	**CHR**	**MCyR**
CP2L	85.0%	53.4%	22.2%	22.2%
CP3L	73.3%	38.9%	28.6%	0%
Advanced phase	25.6%	32.5%	0%	7.7%

Based on this, it can be expected that the addition of this exclusion criteria may have improved the overall clinical effectiveness data and estimates. However, bosutinib is not proposed to be used in patients with T315I mutations. In the UK, it is standard practice to undertake mutation testing in all patients at second line or later and therefore it is not recommended that bosutinib be used in patients with a T315I mutation. The lack of clinical effectiveness on the T315I patient is specifically mentioned in both the bosutinib EPAR and our SPC.

Indeed, if these patients are excluded from our analyses, it would likely improve our overall clinical effectiveness data. For example in the CP3L cohort, if T315I patients are excluded, the MCyR rate improves from 38.9% (42/108) to 41.2% (42/102). As such, the results presented in our submission and used in our model are likely be an under-estimate of the efficacy that may be achieved in practice.

- How prevalent is this mutation in the CML population?

The reported T315I mutation frequency in imatinib resistant CML patients ranges between 2% and 20%[1-5]. This variability is likely related to patient cohort characteristics and treatment.

1. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphiapositive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin Cancer Res. 2006;12(24):7374-7379.
2. Branford S, Rudzki Z, Walsh S, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood. 2003;102(1):276- 283
3. Jabbour E, Kantarjian H, Jones D, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. Leukemia. 2006; 20(10):1767-1773.

4. Willis SG, Lange T, Demehri S, et al. Highsensitivity detection of BCR-ABL kinase domain mutations in imatinib-naive patients: correlation with clonal cytogenetic evolution but not response to therapy. Blood. 2005;106(6):2128-2137
5. Nicolini FE, Corm S, Le QH, et al. Mutation status and clinical outcome of 89 imatinib mesylateresistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi-LMC GROUP). Leukemia. 2006;20(6):1061-1066

A3. Please update table B8 on page 55 to provide the median duration of CML disease and range for each of the accelerated and blast phase patient groups (equivalent to the CML disease duration and range provided in table B7 (p54) for the chronic phase population).

Table 5 (B8): Baseline characteristics for the advanced phase CML population

Characteristic	AP IM only (n=45)	AP Multi TKI (n=31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Duration of CML						
N	41	29	70	34	29	63
Median	3.85	8.25	5.06	1.75	5.75	3.08
Range	1.11-22.06	1.5 - 19.22	1.11-22.06	0.35 - 5.56	1.05 - 14.46	0.35-14.46

IM only= only prior TKI exposure is to imatinib; Multi TKI = Multiple TKI exposure
*Race Other: Afghan (1), Hispanic (7), Turkish (1)
†If a patient received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the patient is only counted once for the respective treatment
‡Other reason for discontinuing imatinib: Unknown

A4. Please clarify why the numbers of participants recruited for the advanced phases and chronic phases do not match the sample size calculations on pages 58 and 59 of the submission.

The planned, expected evaluable and enrolled patient numbers for all cohorts in Study 200 are summarised in Table 6 below. To compensate for the expected dropout or not evaluable rate of 10%, approximately 186 subjects with chronic phase imatinib-resistant CML and with no other prior TKI therapy were to be enrolled in the study so that there was a minimum of 167 evaluable subjects in the primary cohort. The same dropout rate or not evaluable rate of 10% was applied for all cohorts.

It is worth noting, that when the original protocol was written, the intent was to analyse subjects with advanced leukaemia (AP CML, BP CML, and Ph+ ALL) as either having received prior imatinib or prior imatinib and at least 1 other TKI. Based on the first interim analysis, 1 of 11 subjects with advanced leukaemia (3 AP, 5 BP, 3 Ph+ ALL) receiving second-line bosutinib had confirmed CHR by 24 Weeks; thus, the study failed to meet the criteria for futility at the interim analysis. One (1) additional subject had confirmed CHR at Week 13, but was not counted, since this cohort was predefined to consist of only the first 11 subjects. Among 6 subjects with AP CML, BP CML, and Ph+ ALL who received third or fourth line bosutinib treatment, 0 out of 6 subjects had CHR. These results led to the decision not to enrol any additional subjects with advanced leukaemia to receive third or fourth line bosutinib treatment and no additional Ph+ ALL subjects to receive second-line bosutinib. Enrolment continued for subjects with AP and BP CML who had only received prior imatinib. These results, when taken with emerging data from studies of other agents, suggested that efficacy in subjects with AP CML and BP CML who were imatinib-

resistant and unexposed to other TKIs should be assessed using the endpoint of 48-Week OHR. The revised analysis strategy was described on page 59 of our submission and is summarised in Table 6 below.

Table 6: Number of Planned and Enrolled Subjects

Subject Group Study Cohort	Planned	Expected Evaluable	Enrolled
Chronic Phase Second-line (Prior Imatinib)			
Imatinib Resistant	186	167	200
Imatinib Intolerant	61	55	88
Chronic Phase Third line (Prior Imatinib + ≥1 Additional TKI)			
IM + NI-Intolerant or IM + D and NI	Descriptively analysed – no testing planned		4
IM + D-Resistant	32	29	37
IM + D-Intolerant	39	35	50
IM + NI-Resistant	32	29	27
Advanced Leukaemia (≥1 Prior TKI)[a]			
AP CML – 2nd Line	55	49	45
BP CML – 2nd Line	50	45	35
AP/BP – Multi-TKI	Descriptively analysed – no testing planned		60

Abbreviations: AP=accelerated phase, BP=blast phase, CML=chronic myelogenous leukaemia, D=dasatinib, IM=imatinib, NA=not applicable, NI=nilotinib, Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukaemia, TKI=tyrosine kinase inhibitor
All subjects in the advanced leukaemia group received imatinib; some subjects also received at least 1 additional TKI. Date of Snapshot: 28MAR11

The reason there were more second and third line chronic phase patients enrolled than planned is because the definition of evaluable population changed after enrolment was finished. Previously, evaluable was defined as all treated patients with a valid baseline and post-baseline measurement or early death or progression. However, this was found to produce a biased analysis, as those subjects who discontinued early due to adverse events are 'unevaluable'. Therefore, the evaluable population definition was changed to all treated subjects with a valid baseline assessment, which increased the numbers from the Protocol.

It was decided the study should be closed after accrual of 571 subjects without reaching planned sample sizes in the CP3L nilotinib cohorts, AP cohort and BP cohort, due to slow accrual. Testing was still done at the one-sided 0.05 level, although power was reduced. No adjustments for multiple comparisons were made for the remaining secondary or exploratory analyses.

- In addition, the sample size calculation is based on "clinical estimates" for the third line CP CML population and "published data" for the AP and BP CML populations (p58-59, p351). Please clarify the data used for these calculations and the references for the published data.

Due to the paucity of data available in the third line CP CML population when the study was designed, we were unable to provide sample size estimates based on specific clinical trial data. Although the original expectations for the treatment effect for this heavily pre-treated population were based on 2L clinical experience, the response rates observed were considered clinically meaningful within this heavily pre-treated cohort.

The published dasatinib data upon which the accelerated phase sample size calculation was based was taken from the three references below, whilst the blast phase sub-group estimates were based on the first two publications.

1. Talpaz M, Apperley JF, Kim DW, et al. Dasatinib (D) in patients with accelerated phase chronic myeloid leukemia (AP-CML) who are resistant or intolerant to imatinib: Results of the CA180005 'START-A' study. J Clin Oncol. 2006;24: 6526
2. Cortes JE, Kim DW, Rosti G, et al. Dasatinib (D) in patients (pts) with chronic myelogenous leukemia (CML) in myeloid blast crisis (MBC) who are imatinib-resistant (IM-R) or IMintolerant (IM-I): Results of the CA180006 'START-B' study. J Clin Oncol. 2006;24:6529
3. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or –intolerant accelerated-phase chronic myelogenous leukemia. Blood. 2008;111:1834 -1839

A5. Section 6.9 adverse events (p80), reports data based on a minimum follow-up of 12 months for the third line CP CML population. Please provide an update with 24 month follow up data (15th February 2012 snapshot) for the following populations (as described in table B20):

- Imatinib and dasatinib resistant
- Imatinib and dasatinib intolerant
- Imatinib and nilotinib resistant
- Prior treatment with imatinib and dasatinib, with or without nilotinib.
- All people with CP CML

As of the 15 February 2012 database snapshot, there was 1 new TEAE with a ≥20.0% incidence: abdominal pain was reported in 24 (20.2%) patients compared with 23 (19.5%) patients reported in the Study 200 CSR (28 Mar 2011 snapshot). There were no new Grade 3 or 4 TEAEs with a 10.0% incidence. Overall, the incidence and types of TEAEs and Grade 3 or 4 TEAEs appeared to be consistent with the 28 Mar 2011 snapshot.

Similarly, as of the 15 February 2012 database snapshot, there were no new SAEs with a ≥2% incidence. Overall, the incidence and types of SAEs appeared to be consistent with the 28 Mar 2011 snapshot.

Finally, as of 15 February 2012, 6 additional patients had AEs that led to discontinuation of bosutinib treatment since the data snapshot for the Study 200 CSR (28 Mar 2011), including 2 patients who discontinued treatment because of thrombocytopenia and 1 patient each because of diarrhoea, anaemia, myocardial infarction (MI), and disease progression. Overall, the incidence and types of AEs that led to discontinuation of treatment appeared to be consistent with the 28 Mar 2011 snapshot.

Table 7: Number (%) of Subjects Reporting ≥10% TEAEs (CP3L Safety Population) (15 Feb 2012 snapshot)

System Organ Class a Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	4 (100)	38 (100)	50 (100)	27 (100)	119 (100)
Blood and lymphatic	2 (50.0)	20 (52.6)	23 (46.0)	14 (51.9)	59

system disorders					(49.6)
Thrombocytopenia	2 (50.0)	9 (23.7)	18 (36.0)	12 (44.4)	41 (34.5)
Neutropenia	1 (25.0)	8 (21.1)	7 (14.0)	7 (25.9)	23 (19.3)
Anaemia	1 (25.0)	7 (18.4)	7 (14.0)	6 (22.2)	21 (17.6)
Leukopenia	0	4 (10.5)	0	0	4 (3.4)
Cardiac disorders	0	4 (10.5)	10 (20.0)	2 (7.4)	16 (13.4)
Ear and labyrinth disorders	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Eye disorders	2 (50.0)	5 (13.2)	8 (16.0)	3 (11.1)	18 (15.1)
Eye oedema	1 (25.0)	0	0	0	1 (0.8)
Scleral haemorrhage	1 (25.0)	0	0	0	1 (0.8)
Gastrointestinal disorders	4 (100)	37 (97.4)	47 (94.0)	24 (88.9)	112 (94.1)
Diarrhoea	4 (100)	30 (78.9)	41 (82.0)	23 (85.2)	98 (82.4)
Nausea	2 (50.0)	21 (55.3)	22 (44.0)	13 (48.1)	58 (48.7)
Vomiting	0	15 (39.5)	24 (48.0)	8 (29.6)	47 (39.5)
Abdominal pain	0	6 (15.8)	12 (24.0)	6 (22.2)	24 (20.2)
Abdominal pain upper	0	8 (21.1)	8 (16.0)	4 (14.8)	20 (16.8)
Constipation	2 (50.0)	4 (10.5)	6 (12.0)	3 (11.1)	15 (12.6)
Dyspepsia	0	7 (18.4)	4 (8.0)	1 (3.7)	12 (10.1)
Flatulence	0	4 (10.5)	2 (4.0)	2 (7.4)	8 (6.7)
Toothache	1 (25.0)	2 (5.3)	2 (4.0)	0	5 (4.2)
Haemorrhoids	0	1 (2.6)	0	3 (11.1)	4 (3.4)
Gingival pain	1 (25.0)	2 (5.3)	0	0	3 (2.5)
Gastrointestinal sounds abnormal	1 (25.0)	0	1 (2.0)	0	2 (1.7)
General disorders and administration site conditions	3 (75.0)	19 (50.0)	28 (56.0)	10 (37.0)	60 (50.4)
Fatigue	3 (75.0)	8 (21.1)	14 (28.0)	3 (11.1)	28 (23.5)
Pyrexia	1 (25.0)	6 (15.8)	7 (14.0)	4 (14.8)	18 (15.1)
Oedema peripheral	1 (25.0)	1 (2.6)	5 (10.0)	4 (14.8)	11 (9.2)
Asthenia	1 (25.0)	1 (2.6)	2 (4.0)	4 (14.8)	8 (6.7)
Pain	2 (50.0)	1 (2.6)	2 (4.0)	1 (3.7)	6 (5.0)
Chest pain	1 (25.0)	0	3 (6.0)	0	4 (3.4)
Temperature intolerance	1 (25.0)	0	0	0	1 (0.8)
Hepatobiliary disorders	1 (25.0)	0	3 (6.0)	2 (7.4)	6 (5.0)
Hyperbilirubinaemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Immune system disorders	0	5 (13.2)	2 (4.0)	3 (11.1)	10 (8.4)
Infections and infestations	3 (75.0)	15 (39.5)	20 (40.0)	11 (40.7)	49 (41.2)
Nasopharyngitis	1 (25.0)	2 (5.3)	5 (10.0)	4 (14.8)	12 (10.1)
Influenza	0	4 (10.5)	3 (6.0)	3 (11.1)	10 (8.4)
Upper respiratory tract infection	2 (50.0)	2 (5.3)	5 (10.0)	0	9 (7.6)
Lower respiratory tract infection	1 (25.0)	0	2 (4.0)	0	3 (2.5)

Respiratory tract infection viral	0	0	0	3 (11.1)	3 (2.5)
Pharyngitis	1 (25.0)	1 (2.6)	0	0	2 (1.7)
Wound infection	1 (25.0)	0	0	0	1 (0.8)
Injury, poisoning and procedural complications	1 (25.0)	6 (15.8)	8 (16.0)	0	15 (12.6)
Procedural pain	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Investigations	2 (50.0)	15 (39.5)	18 (36.0)	12 (44.4)	47 (39.5)
Alanine aminotransferase increased	1 (25.0)	7 (18.4)	5 (10.0)	6 (22.2)	19 (16.0)
Blood creatinine increased	0	4 (10.5)	4 (8.0)	3 (11.1)	11 (9.2)
Aspartate aminotransferase increased	0	2 (5.3)	3 (6.0)	5 (18.5)	10 (8.4)
Blood alkaline phosphatase increased	0	2 (5.3)	0	3 (11.1)	5 (4.2)
White blood cells urine positive	1 (25.0)	0	0	0	1 (0.8)
Metabolism and nutrition disorders	2 (50.0)	9 (23.7)	18 (36.0)	9 (33.3)	38 (31.9)
Decreased appetite	0	3 (7.9)	6 (12.0)	4 (14.8)	13 (10.9)
Hyperuricaemia	1 (25.0)	1 (2.6)	4 (8.0)	0	6 (5.0)
Hyperkalaemia	0	0	1 (2.0)	3 (11.1)	4 (3.4)
Hypophosphataemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal and connective tissue disorders	3 (75.0)	17 (44.7)	21 (42.0)	9 (33.3)	50 (42.0)
Arthralgia	0	5 (13.2)	9 (18.0)	4 (14.8)	18 (15.1)
Back pain	1 (25.0)	5 (13.2)	4 (8.0)	3 (11.1)	13 (10.9)
Bone pain	0	5 (13.2)	3 (6.0)	1 (3.7)	9 (7.6)
Pain in extremity	0	1 (2.6)	5 (10.0)	3 (11.1)	9 (7.6)
Musculoskeletal pain	0	4 (10.5)	1 (2.0)	1 (3.7)	6 (5.0)
Joint swelling	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal stiffness	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Nervous system disorders	1 (25.0)	12 (31.6)	21 (42.0)	14 (51.9)	48 (40.3)
Headache	1 (25.0)	9 (23.7)	13 (26.0)	8 (29.6)	31 (26.1)
Dizziness	1 (25.0)	5 (13.2)	8 (16.0)	3 (11.1)	17 (14.3)
Dysgeusia	1 (25.0)	0	1 (2.0)	1 (3.7)	3 (2.5)
Paraesthesia	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Neuropathy peripheral	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Sensory disturbance	1 (25.0)	0	0	0	1 (0.8)
Psychiatric disorders	1 (25.0)	2 (5.3)	9 (18.0)	1 (3.7)	13 (10.9)
Insomnia	1 (25.0)	2 (5.3)	4 (8.0)	1 (3.7)	8 (6.7)
Renal and urinary disorders	0	5 (13.2)	4 (8.0)	5 (18.5)	14 (11.8)
Reproductive system and breast disorders	0	2 (5.3)	2 (4.0)	4 (14.8)	8 (6.7)
Respiratory, thoracic and mediastinal disorders	2 (50.0)	13 (34.2)	26 (52.0)	8 (29.6)	49 (41.2)
Cough	1 (25.0)	5 (13.2)	11 (22.0)	4 (14.8)	21 (17.6)
Pleural effusion	0	2 (5.3)	11 (22.0)	1 (3.7)	14 (11.8)
Dyspnoea	0	1 (2.6)	10 (20.0)	1 (3.7)	12 (10.1)
Oropharyngeal pain	1 (25.0)	3 (7.9)	3 (6.0)	2 (7.4)	9 (7.6)
Dyspnoea exertional	1 (25.0)	1 (2.6)	3 (6.0)	0	5 (4.2)
Productive cough	0	0	5 (10.0)	0	5 (4.2)

Skin and subcutaneous tissue disorders	1 (25.0)	22 (57.9)	28 (56.0)	12 (44.4)	63 (52.9)
Rash	1 (25.0)	9 (23.7)	19 (38.0)	3 (11.1)	32 (26.9)
Pruritus	0	10 (26.3)	7 (14.0)	2 (7.4)	19 (16.0)
Dry skin	0	1 (2.6)	2 (4.0)	3 (11.1)	6 (5.0)
Alopecia	1 (25.0)	1 (2.6)	2 (4.0)	0	4 (3.4)
Skin depigmentation	1 (25.0)	0	0	0	1 (0.8)
Vascular disorders	1 (25.0)	1 (2.6)	9 (18.0)	2 (7.4)	13 (10.9)
Hypertension	0	1 (2.6)	6 (12.0)	0	7 (5.9)
Flushing	1 (25.0)	0	0	0	1 (0.8)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

Table 8: Number (%) of Subjects Reporting ≥5% TEAEs Grades 3 or 4 AEs Only (CP3L Safety Population) (Data snapshot 15 Feb 2012)

System Organ Class [a] Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	1 (25.0)	22 (57.9)	38 (76.0)	15 (55.6)	76 (63.9)
Blood and lymphatic system disorders	1 (25.0)	11 (28.9)	16 (32.0)	8 (29.6)	36 (30.3)
Thrombocytopenia	0	7 (18.4)	15 (30.0)	8 (29.6)	30 (25.2)
Neutropenia	1 (25.0)	5 (13.2)	7 (14.0)	4 (14.8)	17 (14.3)
Anaemia	0	2 (5.3)	4 (8.0)	1 (3.7)	7 (5.9)
Cardiac disorders	0	1 (2.6)	7 (14.0)	0	8 (6.7)
Gastrointestinal disorders	0	7 (18.4)	7 (14.0)	2 (7.4)	16 (13.4)
Diarrhoea	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Hepatobiliary disorders	0	0	3 (6.0)	2 (7.4)	5 (4.2)
Infections and infestations	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Investigations	0	2 (5.3)	5 (10.0)	4 (14.8)	11 (9.2)
Alanine aminotransferase increased	0	1 (2.6)	3 (6.0)	4 (14.8)	8 (6.7)
Lipase increased	0	1 (2.6)	1 (2.0)	2 (7.4)	4 (3.4)
Aspartate aminotransferase increased	0	0	1 (2.0)	2 (7.4)	3 (2.5)
Metabolism and nutrition disorders	0	2 (5.3)	1 (2.0)	1 (3.7)	4 (3.4)
Musculoskeletal and connective tissue disorders	0	1 (2.6)	4 (8.0)	2 (7.4)	7 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (6.0)	1 (3.7)	4 (3.4)
Nervous system disorders	0	1 (2.6)	4 (8.0)	0	5 (4.2)
Headache	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6)	5 (10.0)	0	6 (5.0)
Pleural effusion	0	0	3 (6.0)	0	3 (2.5)
Skin and subcutaneous tissue disorders	0	2 (5.3)	6 (12.0)	0	8 (6.7)
Rash	0	0	3 (6.0)	0	3 (2.5)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the
incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject
may report two or more different adverse events within the higher level category.

A6. Table B29 on page 84 provides adverse event rates for the accelerated phase and blast phase CML populations. Please update this table to provide data for the following populations:

- Accelerated phase patients receiving bosutinib 2nd line
- Accelerated phase patients following multi-TKI failure
- Blast phase patients receiving bosutinib 2nd line
- Blast phase patients following multi-TKI failure

The adverse event data for the advanced phase patients separated by 2nd line and multi-TKI patients is summarised below, however it is worth noting that the numbers are small and therefore results should be interpreted with caution.

Table 9: Summary of adverse events for the advanced phase CML population

Event	AP IM only (n=45)	AP Multi TKI (n-31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Any TEAE	45 (100)	31 (100)	76 (100)	34 (97.1)	29 (100)	63 (98.4)
TEAEs related to study drug	45 (100)	30 (96.8)	75 (98.7)	34 (97.1)	26 (89.7)	60 (93.8)
Grade 3 or 4 TEAEs	36 (80)	30 (96.8)	66 (86.8)	26 (74.3)	23 (79.3)	49 (76.6)
Grade 3 or 4 TEAEs related to study drug	25 (55.6)	22 (71)	47 (61.8)	19 (54.3)	15 (51.7)	34 (53.1)
SAEs	23 (51.1)	18 (58.1)	41 (53.9)	18 (51.4)	17 (58.6)	35 (54.7)
TEAEs leading to discontinuation	10 (22.2)	8 (25.8)	18 (23.7)	1 (2.9)	5 (17.2)	6 (9.4)
TEAEs leading to dose reduction	17 (37.8)	14 (45.2)	31 (40.8)	11 (31.4)	6 (20.7)	17 (26.6)
TEAEs leading to dose delay	23 (51.1)	21 (67.7)	44 (57.9)	17 (48.6)	11 (37.9)	28 (43.8)

Table 10: Rates of most common (≥10%) treatment-emergent adverse events in the advanced phase CML population

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	76 (100)	45(100)	31(100)	63 (98.4)	34 (97.1)	29 (100)
Blood and lymphatic system disorders	56 (73.7)	32 (71.1)	24 (77.4)	35 (54.7)	19 (54.3)	16 (55.2)
Anaemia	32 (42.1)	15 (33.3)	17 (54.8)	18 (28.1)	10 (28.6)	8 (27.6)
Thrombocytopaenia	32 (42.1)	16 (35.6)	16 (51.6)	18 (28.1)	9 (25.7)	9 (31.0)
Neutropaenia	12 (15.8)	4 (8.9)	8 (25.8)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	3 (4.7)	3 (8.6) 0	0
Leukopenia	6 (7.9)	3 (6.7)	3 (9.7)	7 (10.9)	3 (8.6)	4 (13.8)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Leukocytosis	6 (7.9)	4 (8.9)	2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Cardiac disorders	14 (18.4)	7 (15.6)	7 (22.6)	8 (12.5)	5 (14.3)	3 (10.3)
Eye disorders	15 (19.7)	7 (15.6)	8 (25.8)	8 (12.5)	6 (17.1)	2 (6.9)
Gastrointestinal disorders	72 (94.7)	42 (93.3)	30 (96.8)	53 (82.8)	28 (80.0)	25 (86.2)
Diarrhoea	65 (85.5)	38 (84.4)	27 (87.1)	42 (65.6)	23 (65.7)	19 (65.5)
Nausea	34 (44.7)	17 (37.8)	17 (54.8)	32 (50.0)	18 (51.4)	14 (48.3)
Vomiting	34 (44.7)	23 (51.1)	11 (35.5)	25 (39.1)	11 (31.4)	14 (48.3)
Abdominal pain	20 (26.3)	16 (35.6)	4 (12.9)	11 (17.2)	9 (25.7)	2 (6.9)
Abdominal pain upper	10 (13.2)	7 (15.6)	3 (9.7)	5 (7.8)	2 (5.7)	3 (10.3)
Constipation	13 (17.1)	8 (17.8)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
General disorders and administration site conditions	47 (61.8)	24 (53.3)	23 (74.2)	41 (64.1)	23 (65.7)	18 (62.1)
Pyrexia	28 (36.8)	16 (35.6)	12 (38.7)	22 (34.4)	16 (45.7)	6 (20.7)
Fatigue	15 (19.7)	3 (6.7)	12 (38.7)	12 (18.8)	5 (14.3)	7 (24.1)
Asthenia	10 (13.2)	6 (13.3)	4 (12.9)	4 (6.3)	4 (11.4)	0
General physical health deterioration	1 (1.3)	0	1 (3.2)	3 (4.7)	0	3 (10.3)
Oedema peripheral	3 (6.7)	4 (12.9)	7 (9.2)	0	4 (13.8)	4 (6.3)
Hepatobiliary disorders	5 (6.6)	3 (6.7)	2 (6.5)	4 (6.3)	4 (11.4)	0
Hyperbilirubinaemia	-	-	-	-	-	-
Infections and infestations	42 (55.3)	23 (51.1)	19 (61.3)	34 (53.1)	19 (54.3)	15 (51.7)
Pneumonia	8 (10.5)	4 (8.9)	4 (12.9)	10 (15.6)	4 (11.4)	6 (20.7)
Sepsis	-	-	-	-	-	-
Upper respiratory tract infection	8 (10.5)	6 (13.3)	2 (6.5)	2 (3.1)	1 (2.9)	1 (3.4)
Investigations	38 (50.0)	20 (44.4)	18 (58.1)	31 (48.4)	18 (51.4)	13 (44.8)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	10 (13.2)	5 (11.1)	5 (16.1)	4 (6.3)	4 (11.4)	0
Neutrophil count decreased	-	-	-	-	-	-
Aspartate aminotransferase increased	11 (14.5)	7 (15.6)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)
Lipase increased	-	-	-	-	-	-
Metabolism and nutrition disorders	27 (35.5)	17 (37.8)	10 (32.3)	22 (34.4)	11 (31.4)	11 (37.9)
Decreased appetite	6 (7.9)	4 (8.9)	2 (6.5)	12 (18.8)	5 (14.3)	7 (24.1)
Hypokalaemia	2 (2.6)	0	0 2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Hypophosphataemia	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	26 (34.2)	18 (40.0)	8 (25.8)	24 (37.5)	13 (37.1)	11 (37.9)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Arthralgia	10 (13.2)	8 (17.8)	2 (6.5)	7 (10.9)	6 (17.1)	1 (3.4)
Pain in extremity	10 (13.2)	7 (15.6)	3 (9.7)	6 (9.4)	4 (11.4)	2 (6.9)
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	11 (14.5)	6 (13.3)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
Blast crisis in myelogenous leukaemia	-	-	-	-	-	-
Nervous system disorders	24 (31.6)	14 (31.1)	10 (32.3)	26 (40.6)	16 (45.7)	10 (34.5)
Headache	12 (15.8)	9 (20.0)	3 (9.7)	13 (20.3)	9 (25.7)	4 (13.8)
Dizziness	8 (10.5)	4 (8.9)	4 (12.9)	9 (14.1)	6 (17.1)	3 (10.3)
Psychiatric disorders	16 (21.1)	6 (13.3)	10 (32.3)	11 (17.2)	6 (17.1)	5 (17.2)
Renal and urinary disorders	11 (14.5)	5 (11.1)	6 (19.4)	8 (12.5)	5 (14.3)	3 (10.3)
Renal failure acute	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	35 (46.1)	19 (42.2)	16 (51.6)	23 (35.9)	14 (40.0)	9 (31.0)
Dyspnoea	14 (18.4)	8 (17.8)	6 (19.4)	12 (18.8)	7 (20.0)	5 (17.2)
Cough	13 (28.9)	8 (25.8)	21 (27.6)	6 (17.1)	3 (10.3)	9 (14.1)
Oropharyngeal pain	8 (10.5)	4 (8.9)	4 (12.9)	2 (3.1)	1 (2.9)	1 (3.4)
Pleural effusion	9 (11.8)	5 (11.1)	4 (12.9)	4 (6.3)	2 (5.7)	2 (6.9)
Skin and subcutaneous tissue disorders	42 (55.3)	25 (55.6)	17 (54.8)	30 (46.9)	17 (48.6)	13 (44.8)
Rash	25 (32.9)	16 (35.6)	9 (29.0)	20 (31.3)	10 (28.6)	10 (34.5)
Vascular disorders	11 (14.5)	4 (8.9)	7 (22.6)	7 (10.9)	7 (20.0)	0
Hypertension	7 (9.2)	3 (6.7)	4 (12.9)	2 (3.1)	2 (5.7)	0

Table 11: Rates of TEAEs (grade 3/4) occurring in ≥5% of the advanced phase populations

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	66 (86.8)	36 (80.0)	30 (96.8)	49 (76.7)	26 (74.3)	23 (79.3)
Blood and lymphatic system disorders	42 (55.3)	20 (44.4)	22 (71.0)	29 (45.3)	18 (51.4)	11 (37.9)
Anaemia	23 (30.3)	11 (24.4)	12 (38.7)	12 (18.8)	7 (20.0)	5 (17.2)
Thrombocytopaenia	25 (32.9)	11 (24.4)	14 (45.2)	17 (26.6)	9 (25.7)	8 (27.6)
Neutropaenia	11 (14.5)	4 (8.9)	7 (22.6)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Leukopenia	3 (3.9)	1 (2.2)	2 (6.5)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	3 (3.9)	2 (4.4)	1 (3.2)	2 (3.1)	0	2 (6.9)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Cardiac disorders	5 (6.6)	3 (6.7)	2 (6.5)	3 (4.7)	1 (2.9)	2 (6.9)
Eye disorders	0	0	0	3 (4.7)	1 (2.9)	2 (6.9)
Gastrointestinal disorders	14 (18.4)	7 (15.6)	7 (22.6)	14 (21.9)	5 (14.3)	9 (31.0)
Diarrhoea	3 (3.9)	1 (2.2)	2 (6.5)	4 (6.3)	2 (5.7)	2 (6.9)
Nausea	-	-	-	-	-	-
Vomiting	3 (3.9)	1 (2.2)	2 (6.5)	2 (3.1)	0	2 (6.9)
Abdominal pain	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Abdominal pain upper	-	-	-	-	-	-
Constipation	-	-	-	-	-	-
General disorders and administration site conditions	7 (9.2)	1 (2.2)	6 (19.4)	10 (15.6)	4 (11.4)	6 (20.7)
Pyrexia	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Fatigue	3 (3.9)	0	3 (9.7)	2 (3.1)	0	2 (6.9)
Asthenia	-	-	-	-	-	-
General physical health deterioration	0	0	0	2 (3.1)	0	2 (6.9)
Hepatobiliary disorders	2 (2.6)	1 (2.2)	1 (3.2)	3 (4.7)	3 (8.6)	0
Hyperbilirubinaemia	0	0	0	3 (4.7)	3 (8.6)	0
Infections and infestations	12 (15.8)	5 (11.1)	7 (22.6)	14 (21.9)	4 (11.4)	10 (34.5)
Pneumonia	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	1 (2.9)	3 (10.3)
Sepsis	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9) 0	1 (2.9) 0
Upper respiratory tract infection	-	-	-	-	-	-
Investigations	14 (18.4)	8 (17.8)	6 (19.4)	11 (17.2)	5 (14.3)	6 (20.7)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	6 (7.9)	3 (6.7)	3 (9.7)	1 (1.6)	1 (2.9)	0
Neutrophil count decreased	1 (1.3)	1 (2.2)	0	0	0	0
Aspartate aminotransferase increased	4 (5.3)	3 (6.7)	1 (3.2)	0	0	0
Lipase increased	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Metabolism and nutrition disorders	9 (11.8)	4 (8.9)	5 (16.1)	7 (10.9)	3 (8.6)	4 (13.8)
Decreased appetite	-	-	-	-	-	-
Hypokalaemia	1 (1.3)	0	1 (3.2)	3 (4.7)	1 (2.9)	2 (6.9)
Hypophosphataemia	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9)	0
Musculoskeletal and connective tissue disorders	4 (5.3)	3 (6.7)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Arthralgia	-	-	-	-	-	-
Pain in extremity	-	-	-	-	-	-
Neoplasms, benign	7 (9.2)	3 (6.7)	4	4 (6.3)	3 (8.6)	1 (3.4)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
malignant and unspecified (incl. cysts and polyps)			(12.9)			
Blast crisis in myelogenous leukaemia	2 (2.6)	0	0 2 (6.5)	1 (1.6)	1 (2.9)	0
Nervous system disorders	4 (5.3)	1 (2.2)	3 (9.7)	6 (9.4)	2 (5.7)	4 (13.8)
Headache	2 (2.6)	1 (2.2)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Dizziness	-	-	-	-	-	-
Psychiatric disorders	1 (1.3)	0	1 (3.2)	2 (3.1)	0	2 (6.9)
Renal and urinary disorders	1 (1.3)	0	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Renal failure acute	0	0	0	2 (3.1)	2 (5.7)	0
Respiratory, thoracic and mediastinal disorders	8 (10.5)	3 (6.7)	5 (16.1)	6 (9.4)	4 (11.4)	2 (6.9)
Dyspnoea	6 (7.9)	2 (4.4)	4 (12.9)	2 (3.1)	2 (5.7)	0
Cough	-	-	-	-	-	-
Pleural effusion	4 (5.3)	1 (2.2)	3 (9.7)	2 (3.1)	1 (2.9)	1 (3.4)
Skin and subcutaneous tissue disorders	3 (3.9)	3 (6.7)	0	5 (7.8)	2 (5.7)	3 (10.3)
Rash	3 (3.9)	3 (6.7)	0	2 (3.1)	1 (2.9)	1 (3.4)
Vascular disorders	5 (6.6)	1 (2.2)	4 (12.9)	1 (1.6)	1 (2.9)	0
Hypertension	4 (5.3)	1 (2.2)	3 (9.7)	1 (1.6)	1 (2.9)	0

A7. In order to allow comparison of data from the second line CP CML population with data from the third line CP CML population, please provide separate data for the imatinib-resistant and the imatinib intolerant populations for all results presented in appendix 15.

Table 12: Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]

Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.

Table 13: Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.

Table 14: Duration of response, second CP CML evaluable population, 28 March 2011 snapshot

Response, % (95% CI)	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
K-M estimate of maintaining MCyR at:			
Evaluable	266	186	80
Year 1	73.7(65.0,80.5)	68.4(57.8,76.9)	88.0(71.1,95.3)
Year 2	73.7(65.0,80.5)	68.4(57.8,76.9)	88.0(71.1,95.3)
K-M estimate of maintaining CHR at:			
Evaluable	287	199	88
Year 1	84.6(79.0,88.8)	83.2(76.2,88.2)	88.3(77.0,94.3)
Year 2	72.1(65.2,77.8)	68.2(59.9,75.2)	82.4(69.6,90.2)

Table 15: Duration of response, second CP CML evaluable population, 15 May 2012 snapshot

Response, % (95% CI)	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
K-M estimate of maintaining MCyR at:			
Evaluable	155	106	49

Year 3	76 (68,83)	71 (61,79)	88 (74,95)
K-M estimate of maintaining CHR at:			
Evaluable	244	167	77
Year 3	70 (63,76)	65 (57,72)	83 (70,90)

Table 16: Kaplan-Meier Estimate of Progression-free Survival Chronic Phase Second-line All-treated Population, 28 March 2011 snapshot

PFS, K-M estimates, % (95%CI)	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Year 1	91.3 (86.8,94.3)	89.9 (84.2,93.6)	95.1 (85.5,98.4)
Year 2	80.6 (74.3,85.4)	76.2 (68.4,82.3)	92.8 (81.6,97.3)

Table 17: Cumulative incidence of on-treatment progression or death in the second-line CP CML population, 15 May 2012 snapshot

Progression/death, % (95%CI)	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Year 3	17 (13,22)	21 (16,28)	7 (3,15)

Table 18: AP/BP transformation in second-line CP CML population

Transformation	Total population	IM-R population	IM-I population
28 March 2011 snapshot, n (%) [95%CI]			
Subjects in analysis	288	200	88
Transformation	11 (3.8) [1.9,6.7]	10 (5.0) [2.4,9.0]	1 (1.1) [0.0,6.2]
15 May 2012 snapshot, % (95%CI)			
Subjects in analysis	286	195	91
Transformation	N/A	5 (3, 9)	2 (1, 9)

Table 19: Kaplan-Meier Estimate of Overall Survival Chronic Phase Second-line All-treated Population, 28 March 2011 snapshot

OS, K-M estimates, % (95%CI)	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Year 1	96.8 (94.0,98.3)	95.9 (92.0,97.9)	98.8 (92.0,99.8)
Year 2	90.6 (86.5,93.5)	87.6 (82.1,91.5)	97.6 (90.9,99.4)

At the 15 May 2012 snapshot, OS data at 3 years were not provided as they may be unreliable since the study protocol specified following patients for only 2 years after bosutinib discontinuation. A total of 34 (12% of patients) deaths occurred during the study, including 5 deaths that occurred within 30 days after the last study dose. However, this snapshot did not provide a stratification of deaths by imatinib-resistant and imatinib-intolerant sub-groups.

A response by baseline mutation status was not reported for imatinib-resistant and imatinib-intolerant sub-groups in either the 28 March 2011 or 15 May 2012 snapshots.

Table 20: Treatment discontinuation in the second-line CP CML population, 28 March 2011 snapshot

Reason for discontinued treatment[a]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Discontinued treatment, n (%)	159 (55.2)	108 (54.0)	51 (58.0)
AE	64 (22.2)	33 (16.5)	31 (35.2)
Disease progression	41 (14.2)	35 (17.5)	6 (6.8)
Lack of efficacy	21 (7.3)	17 (8.5)	4 (4.5)
Patient request	18 (6.3)	11 (5.5)	7 (8.0)
Death	5 (1.7)	5 (2.5)	0
Investigator Request	1 (0.3)	1 (0.5)	0
Lost to follow-up	2 (0.7)	2 (1.0)	0
Other[b]	7 (2.4)	4 (2.0)	3 (3.4)

(a) Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
(b) Other: For imatinib resistant: no CCyR at Week 48 (1 subject), non-compliance (1 subject), T315I mutation (1 subject), no CCyR, investigator/subject request, loss of CCyR, and increasing transcript levels (1 subject); For imatinib intolerant: transplant (2 subjects), non-compliance (1 subject).

Table 21: Treatment discontinuation in the second-line CP CML population, 15 May 2012 snapshot

Reason for discontinued treatment	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Discontinued treatment, n (%)	166 (58)	109 (56)	57 (63)
AE	66 (23)	30 (15)	36 (40)
Disease progression	41 (14)	35 (18)	6 (7)
Lack of efficacy	24 (8)	19 (10)	5 (6)
Patient request	17 (6)	11 (6)	6 (7)
Death	6 (2)	6 (3)	0
Investigator Request	2 (1)	2 (1)	0
Lost to follow-up	2 (1)	2 (1)	0
Other	8 (3)	4 (2)	4 (4)

Table 22: Grade 3/4 On-treatment Laboratory Abnormalities Reported in ≥5% of Patients, 28 March 2011 snapshot

Event, n (%)	IM-R population (N=200)	IM-I population (N=88)
Hematologic abnormalities		
Thrombocytopenia	36 (18.0)	24 (27.3)
Neutropenia	12 (6.0)	9 (10.2)
Lymphopenia	-	-
Anemia	17 (8.5)	6 (6.8)
Leukopenia	-	-
Non-hematologic abnormalities		
Hypophosphatemia	-	-
Elevated ALT	13 (6.5)	8 (9.1)
Elevated lipase	-	-
Hypermagnesemia	-	-
Elevated AST	6 (3.0)	5 (5.7)
Hypocalcemia	-	-

Table 23: Grade 3/4 On-treatment Laboratory Abnormalities Reported in ≥5% of Patients, 15 May 2012 snapshot

Event, n (%)	IM-R population (N=195)	IM-I population (N=91)
Hematologic abnormalities		
Thrombocytopenia	41 (21)	29 (32)
Neutropenia	29 (15)	23 (25)
Lymphopenia	29 (15)	16 (18)
Anemia	21 (11)	18 (20)
Leukopenia	12 (6)	10 (11)
Non-hematologic abnormalities		
Hypophosphatemia	22 (11)	7 (8)
Elevated ALT	19 (10)	12 (13)
Elevated lipase	17 (9)	8 (9)
Hypermagnesemia	14 (7)	18 (20)
Elevated AST	7 (4)	6 (7)
Hypocalcemia	6 (3)	5 (6)

A8. Figure B35 on page 164 appears to be a duplicate of Figure B46 on page 175 please provide the correct figure B35.

The amended figure B35 can be found below.

Figure 1 (B35): Markov Trace – Bosutinib - AP

Section B: Clarification on cost-effectiveness data

B1. **Priority request:** The calculation of overall survival for patients not having/achieving MCyR is incorrect. In PF_Bosutinib column N the part of the formula **(1-WEIBULL(B11, p_os_w_a,p_os_w_b, TRUE)^p_mcyr_hr)** should be replaced with **POWER(1-WEIBULL(B11, p_os_w_a,p_os_w_b, TRUE, 1/p_mcyr_hr)** for correct incorporation of the hazard ratio. Please amend the model.

In our original model, we had based the calculation of overall survival for non-responders versus responders on the following equation presented in Appendix 6 of Rogers et al (2012) (equation 1):

$$S_{\text{NON-RESP}}{}^{\text{CML}}(t) = [S_{\text{RESP}}{}^{\text{CML}}(t)]^{\lambda} \text{ (where } \lambda < 1)$$

We had therefore used the following equation in our model:

$$S^{CML}_{NON-RESP}(t) = 1 - \left[1 - S^{CML}_{RESP}(t)\right]^{\lambda}$$

However, the clarification question above would suggest we should have used the following equation instead:

$$S^{CML}_{NON-RESP}(t) = \left[S^{CML}_{RESP}(t)\right]^{\frac{1}{\lambda}}$$

In our original approach, we followed the method described by Rogers et al (2012) in Appendix 6. We modelled the survival of responders using a Weibull curve with dummy parameters, and then the survival of non-responders using the equation above. We used Solver in Excel to calibrate these variables to the overall survival reported by Jabbour et al (2009): to do this, we digitized some points on the Kaplan-Meier graph for overall survival, and minimized R^2 between our equation for combined survival and the values from Jabbour et al (2009) at these points. This gave us Weibull parameters alpha = 1.7015 and beta = 190.54.

We have now amended the model to use the correct equation as described above, and in doing so have reconsidered our methodology. It is unclear whether Rogers et al (2012) calibrated overall survival using some digitized points from the Kaplan-Meier graph from Jabbour et al (2009), or whether a parametric curve was fitted to the data from Jabbour et al (2009). We consider now that it may be more appropriate to fit a parametric curve to the data, as this allows us to calibrate our combined survival curve to an existing smooth curve. The Kaplan-Meier graph itself contains steps which are smoothed out when a curve is fitted to this data. By trying to fit our combined survival curve to these steps, our combined survival curve will not necessarily match a parametric curve fitted to the steps. Furthermore, we could risk over-fitting our combined survival curve to the tail of the Kaplan-Meier graph.

As such, in our revised approach, we firstly fit a survival curve to the overall survival data from Jabbour et al (2009). We then use the methodology from Rogers et al (2012) to calibrate the overall survival parameters and this is described in detail below.

B2. **Priority request:** The error identified in question B1 has a substantial effect on the shape of the overall survival of bosutinib patients and means that unless the Weibull parameters **p_os_w_a** and **p_os_w_b** are recalibrated to the overall survival data from Jabbour et al 2009, the estimates of cost-effectiveness will not be valid. Please:
    - Recalibrate these parameters
    - Provide the extracted Kaplan Meier data from Jabbour et al 2009 which is used to calibrate
    - Provide a full description of the method used to calibrate to ensure reproducibility
    - Provide updated results, in particular the updated base case, one way sensitivity analyses and probabilistic sensitivity analyses.

We calculate the overall survival for patients not having/achieving MCyR based on the relationship between MCyR and survival as described in Appendix 6 of Rogers et al (2012). We followed the method described as closely as we could, but accept that there may be some differences due to the inherent difficulties in following someone else's approach, and that Rogers et al (2012) may have had access to additional data.

To address this question, we have taken the following steps:

1. Estimating OS from Jabbour et al (2009)
    a. Extracting the overall survival data from Jabbour et al (2009)
    b. Fitting parametric curves to the overall survival from Jabbour et al (2009)
2. Calculating OS for responders and non-responders
    a. Calculating survival curves for responders and non-responders from Jabbour et al (2009) using the hazard ratio from Rogers et al (2012)
    b. Calculating overall survival by combining the survival for responders and non-responders using the response rate from Jabbour et al (2009) and relationship from Rogers (2012)
    c. Calibrating the parameters for these survival curves using Solver in Excel
3. Calculating OS for bosutinib
    a. Using the survival curves for responders and non-responders with the MCyR rate for bosutinib to calculate overall survival
4. Producing updated results for the base case, PSA, and scenario analyses.

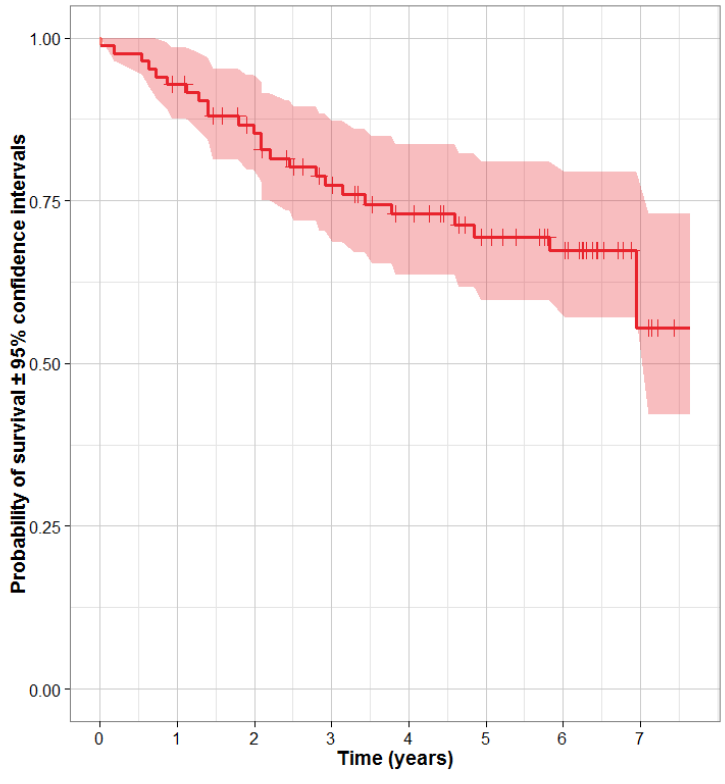
1. Estimating OS from Jabbour et al (2009)

Please see the workbook "Jabbour Data"

Firstly, we extracted the Kaplan-Meier survival data from Jabbour et al (2009) - please see the attached workbook "Jabbour Data". We used GetData GraphDigitizer to digitize the overall survival curve of Figure 2 (overall, event-free and transformation-free survival for all patients receiving imatinib dose escalation after imatinib failure). We then reconstructed the patient level data, using the following steps:

1. We set the x-axis and y-axis limits according to the published figure.
2. We clicked on the censored points, in order to find out the times at which patients were censored.
3. We clicked on the steps in the graph, in order to calculate the Kaplan-Meier probabilities of survival at each time point.
4. We converted times from years into days.
5. Since we had the time points at which patients were censored, the Kaplan-Meier survival probabilities and the number of patients (84), we were able to calculate how many patients died each day.
6. We then reconstructed the patient level data, assuming that all remaining patients were censored at day 2795. The Kaplan-Meier graph is shown in **Figure 2**.

Figure 2: Kaplan-Meier from Jabbour et al 2009



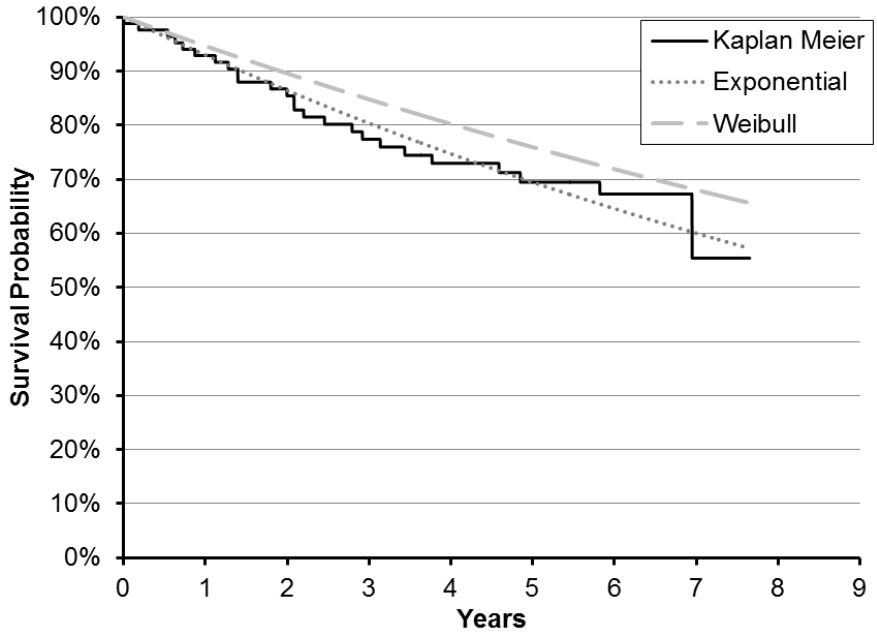
Secondly, we used R to fit parametric curves to the OS data. Rogers et al (2012) used Weibull curves for the survival of responders, but it is unclear whether a Weibull (or other) curve was fitted to the OS data itself. According to the AIC, the exponential model was the best-fitting curve (**Table 24**).

Table 24: AIC for parametric curves fitted to digitised Jabbour et al (2009) data

Model	AIC
Exponential	197.3865
Weibull	198.7486
Log-logistic	69578.1471
Log-normal	70109.7934
Extreme value	71355.9105

The exponential curve also allows for easier parameter manipulation to fit a new dataset, as there is only one parameter to consider. The Kaplan-Meier graph is shown along with the Weibull and exponential curves in Figure 3. The Weibull curve gives a mean overall survival of 11.03 years (95% CI 7.54- 13.3), and the exponential gives a mean overall survival of 10.55 years (95% CI 8.17-12.67). We considered that since the mean is slightly lower for the exponential than the Weibull, this would also provide a more accurate estimate of overall survival for bosutinib. The curves are shown over 50 years in Figure 4.

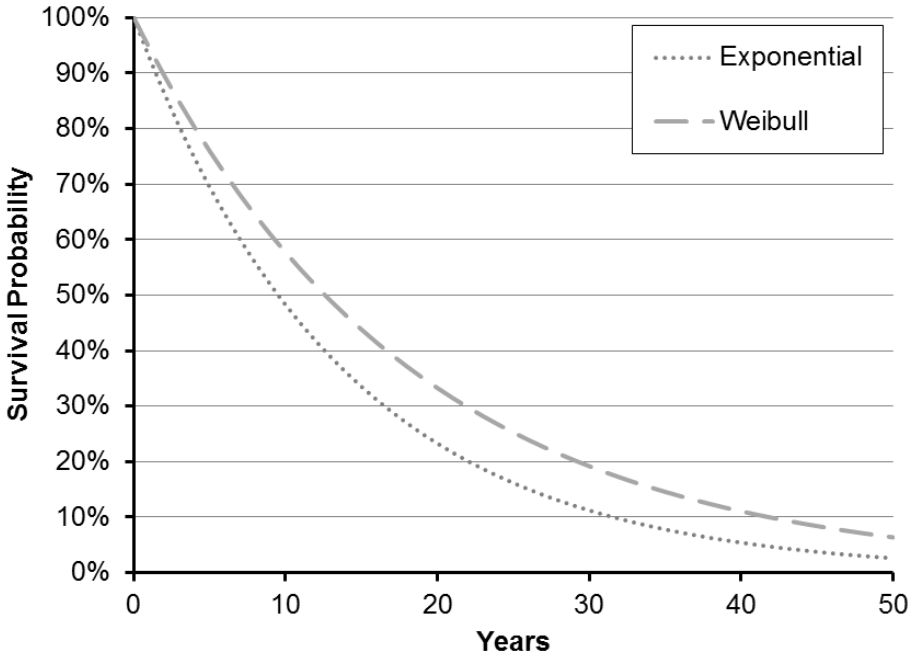
Figure 3: Kaplan-Meier and parametric curves



Using this approach, an exponential parameter of 2.62 was derived, using the following parameterisation, where t is time in years:

$$S^{Overall}_{ALL\ PATIENTS}(t) = e^{-t \times e^{-2.62}}$$

Figure 4: Exponential and Weibull curves extrapolated over 50 years



2. Calculating OS for responders and non-responders

For this section, please see the workbook "OS Surrogate".

a) Stage 1 of Appendix 6 (Rogers et al, 2012) describes the relationship between CML-survival for responders and non-responders (equation 1, page 385) and provides the hazard ratio of 0.37.

$$S_{\text{NON-RESP}}^{\text{CML}}(t) = [S_{\text{RESP}}^{\text{CML}}(t)]^{\lambda} \text{ (where } \lambda < 1)$$

We set up two columns for CML-survival: one for responders, and one for non-responders, using this equation with a dummy exponential parameter α, where:

$$S_{RESP}^{CML}(t) = e^{-t \times e^{-\alpha}}$$

And

$$S_{NON-RESP}^{CML}(t) = S_{RESP}^{CML}(t)^{\frac{1}{\lambda}} = \left[e^{-t \times e^{-\alpha}}\right]^{\frac{1}{\lambda}}$$

We then followed stage 2 of Appendix 6 (Rogers et al, 2012) to allow for CML- and non-CML-related mortality using UK life tables with a 50:50 male:female ratio, and a starting age of 56 years.

b) We then used equation 5 from stage 3 of Appendix 6 (Rogers et al, 2012) to estimate overall survival for the population in Jabbour et al (2009) by combining the survival for responders and non-responders:

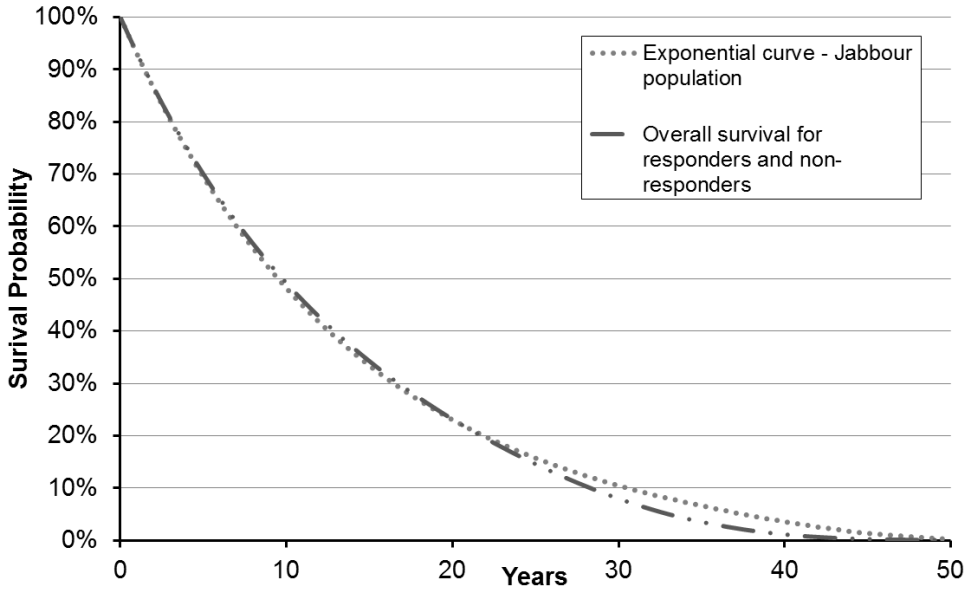
$$OS(t) = (MCyR\%)\ S_{RESP}{}^{overall}(t) + (100\% - MCyR\%)\ S_{NON\text{-}RESP}{}^{overall}(t)$$

We used a MCyR rate of 41.7% to give the proportion of responders and non-responders (35/84; "Thirty-five of the 44 patients (80%) who achieved PCyR or CCyR…did so within 12 months from the start of dose escalation." – p 2156).

c) We then plotted overall survival for the population as calculated using equation 5 from stage 3 on a graph (derived from responders and non-responders) and the overall survival as calculated in step 1 from the digitised Jabbour et al (2009) data[1] (Figure 5).

We then adjusted the exponential parameter for the survival curves for responders and non-responders, using Solver to minimise the R^2 between the two curves. The fitted curve under-predicted survival in the tail, but we considered this to be clinically plausible, and noted that this would provide a more conservative estimate of survival for bosutinib.

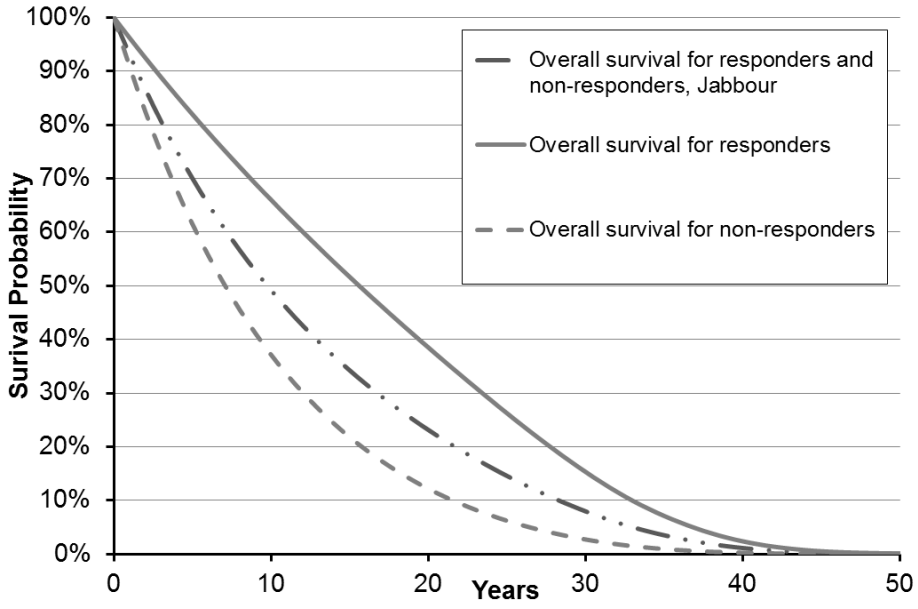
Figure 5: Curve for population and responders/non-responders – Jabbour et al (2009)



We then had two overall survival curves: one for responders and one for non-responders. These used the exponential distribution as parameterised earlier, with α = 3.39 and λ = 0.37. These are shown with the overall survival curve for responders and non-responders in Figure 6.

[1] We adjusted the OS curve derived from Jabbour et al (2009) for background mortality, because although it already incorporated the background mortality for the trial population (aged 56), background mortality increases as patients age. To do this, we added the general population mortality rate for a 56-year old population to the exponential curve at all time points, and subtracted the general population mortality rate specific to the population age at each time point (for example, at 10 years, the population is aged 66).

Figure 6: Survival curves for responders, non-responders, and combined



3. Calculating OS for bosutinib

We then used the overall survival curves for responders and non-responders (exponential, with α = 3.39 and λ = 0.37) with the MCyR rate for bosutinib (38.9%).

We used the following stages:

1. Estimation of survival owing to CML-related deaths for responders and non-responders.
   We used the following equations:

$$S_{RESP}^{CML}(t) = e^{-t \times e^{-3.39}} \text{ and } S_{NON-RESP}^{CML}(t) = \left[e^{-t \times e^{-3.39}}\right]^{\frac{1}{0.37}}$$

2. Estimation of overall (CML- and non-CML-related deaths) for responders and non-responders.
   The bosutinib patient population had a mean age of 54, so we used this as the starting age for calculating background mortality. We calculated the rate of CML-related mortality separately for responders and non-responders. The rate of CML-related mortality at time t is:

$$r^{CML}(t) = \frac{S^{CML}(t-1) - S^{CML}(t)}{S^{CML}(t-1)}$$

   The general background mortality rate at time t was taken from UK life tables. We then calculate the overall survival separately for responders and non-responders – CML-related mortality differs between the two populations, but background mortality is the same. Overall survival is calculated as:

$$S^{overall}(t) = S^{overall}(t-1) \times [1 - r^{CML}(t) - r^{general}(t)]$$

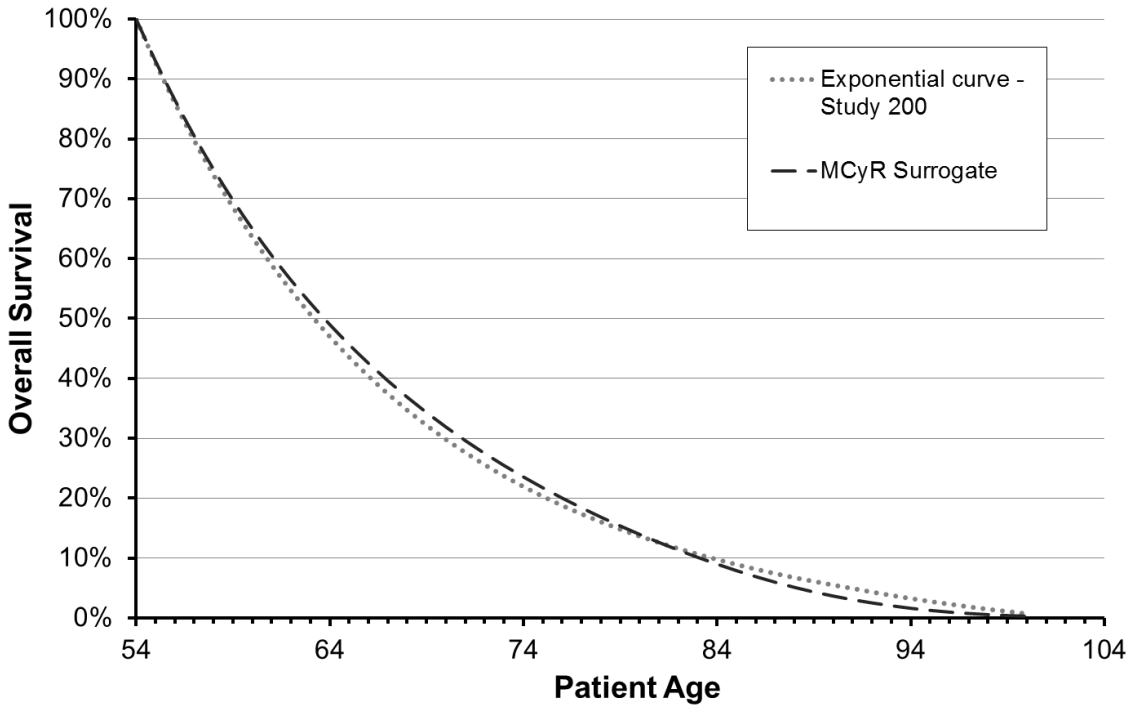
3. Estimation of overall survival for bosutinib
   Overall survival for bosutinib at time t, OS(t) is:

$$\mathrm{OS}(t) = 38.9\% \times S_{RESP}^{overall}(\mathrm{t}) + (100\% - 38.9\%) \times S_{NON-RESP}^{overall}(\mathrm{t})$$

The overall survival curve from the MCyR relationship is compared to the fitted parametric curve from the study200 data in Figure 7. It can be seen that the curves are similar, which we consider validates the approach we have taken.

The MCyR approach is used in the base case only for the third-line chronic phase population.

Figure 7: Overall survival from study 200 and using surrogate outcomes



4. Update results for bosutinib

The results using the revised MCyR relationship are provided in Table 25, and the impact of this revision is to reduce the overall ICER for bosutinib versus hydroxycarbamide from [redacted] to [redacted]/QALY. The ICER for SCT versus hydroxycarbamide is unchanged.

Table 25: Base-case results: CP

	Total			Incremental			ICER	ICER v hydroxycarbamide
	Cost	QALYs	LYs	Cost	QALYs	LYs		
Hydroxycarbamide	£29,473	2.43	3.52					
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated	Dominated
Bosutinib	[redacted]	7.26	12.75	[redacted]	4.83	9.23	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	-3.56	-6.16	Dominated	£111,511

Costs and QALYs discounted at 3.5%, LYs undiscounted. Dominated strategies not included in incremental calculations.

Figure 8: Cost-effectiveness plane: CP

Table 26: Deterministic vs Probabilistic point estimates (1,000 simulations)

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		
Deterministic results						
Hydroxycarbamide	£29,473	2.43				
Interferon	£38,268	2.42	£8,795	-0.01	Dominated	Dominated
Bosutinib	[redacted]	7.26	[redacted]	4.83	[redacted]	[redacted]
SCT	£171,539	3.70	[redacted]	-3.56	Dominated	£111,511
Probabilistic results						
Hydroxycarbamide	£29,389	2.43				
Interferon	£36,091	2.39	£6,702	-0.04	Dominated	Dominated
Bosutinib	[redacted]	7.15	[redacted]	4.72	[redacted]	[redacted]
SCT	£173,948	3.84	[redacted]	-3.31	Dominated	£102,873

Costs and QALYs discounted at 3.5%. Dominated strategies not included in incremental calculations.

Figure 9: Scatterplot of probabilistic sensitivity analysis, all strategies

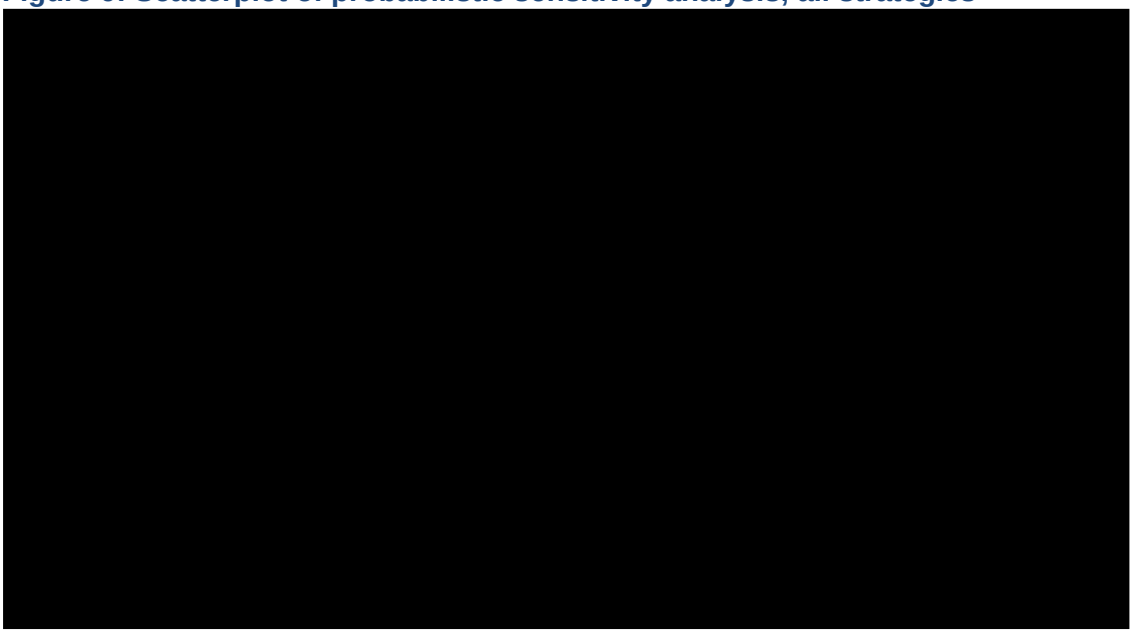


Figure 10: Cost-effectiveness acceptability curve, all strategies

Figure 11: Pairwise comparison of hydroxycarbamide and bosutinib intervention

Scenario Analysis - CP

Scenario analysis for the CP model is summarised in **Table 27**. As in the base-case, in most scenarios interferon is dominated by hydroxycarbamide and so these ICERs are not presented. The incremental ICER for bosutinib versus hydroxycarbamide is therefore presented in the first column below. SCT is in turn dominated by bosutinib in virtually all scenarios, and this ICER is not presented, instead the ICER for SCT versus hydroxycarbamide is presented for the sake of completeness.

In the few scenarios where interferon is not dominated by hydroxycarbamide and SCT is not dominated by bosutinib, the missing incremental ICERs are presented in brackets after the ICER versus hydroxycarbamide.

Table 27: Scenario analysis – CP model

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
Base case	N/A	N/A	[redacted]	£111,511
Patient population				
Bosutinib patient population	3rd line CP patient population from Study 200	Post-hoc analysis of 3rd line CP cohort to identify 'unmet need' subpopulation, as requested by the EMA	[redacted]	£111,511
		Full 2rd line CP patient population from Study 200	[redacted]	£111,511
		Combined analysis of patients identified in the post-hoc analysis of 2nd line cohort and 3rd line cohort from Study 200, as requested by the EMA	[redacted]	£111,511
Cohort	54 years (Study	49 years (-10%)	[redacted]	£107,849

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
starting age	200)	59 years (+10%)	[redacted]	£113,343
Overall survival				
Bosutinib overall survival	MCyR using hazard ratio for survival of 0.37 (Rogers (2012)[84])	MCyR using hazard ratio for survival of 0.156 (lower 95% of pooled estimate, Rogers (2012))	[redacted]	£111,511
		MCyR using hazard ratio for survival of 0.876 (upper 95% of pooled estimate, Rogers (2012))	[redacted]	£111,511
		OS estimated by fitting a parametric curve (exponential) to third-line CP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	£111,511
		Cumulative survival approach (OS = PFS [estimated by fitting a parametric curve to third-line CP cohort in Study 200] + 10 months AP + 6 months BP)	[redacted]	£111,511
Stem Cell Transplant overall survival	Exponential curve fitted to Jabbour (2011)	Weibull curve fitted to Jabbour (2011)	[redacted]	£49,625
		Exponential curve fitted to Oehler (2007)	[redacted]	£107,503
Hydroxycarbamide overall survival	Mean overall survival = 3.5 years (42 months) in **second-line** patients	Mean OS for hydroxycarbamide is adjusted by the ratio of 2nd and 3rd line OS from Study 200 to consider a more 'third-line' OS estimate for hydroxycarbamide. Mean OS for hydroxycarbamide = 2nd line LYs (11.51) divided by 3rd line LYs (10.30) multiplied by 42 = **38 months**	[redacted] IFN vs hydroxy-carbamide: £50,547 Bos vs IFN: [redacted]	£96,437
		Mean OS = 2 years (lower end of plausible range, Rogers (2012))	[redacted] IFN vs hydroxy-carbamide: £16,291 Bos vs IFN: [redacted]	£65,790
		Mean OS = 6.5 years (upper end of plausible range, Rogers (2012))	[redacted] Hydroxy-carbamide vs IFN: £1,041	Dominated
Transformation to AP and BP				
Time in blast phase	6 months	13 months (Rogers (2012))	[redacted]	£102,886
		3 months (assumption)	[redacted]	£116,795
Transformation following SCT	Patients cannot transform to AP or BP, but	Patients transform to AP and BP for 10 months and 6 months respectively before death.	[redacted]	£125,553

Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
	remain in CP			
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200	Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	£111,511
		Time on treatment equal to PFS minus discontinuation due to AEs (Rogers (2012))	[redacted] Bos vs SCT: [redacted]	£111,511
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial), the average cost per day for bosutinib is [redacted]	[redacted]	£111,511
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011a)[80]	Medical management resource use from TA241	[redacted]	£121,775
Cost of CP off treatment health state	Patients receive hydroxycarbamide, costing £12.75 per month	Patients receive further treatment post-discontinuation in CP (e.g. other TKIs or SCT) costing £1040 per month (similar approach to TA241).	[redacted] Bos vs SCT: [redacted]	£88,362
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP £2,536/month (doubled)	[redacted]	£106,162
		BP £1,268/month(doubled)		£106,848
Cost of death	£6,004 - Dewer & Addicot	£569 – Hoyle (2011a)[80]	[redacted]	£111,848
Cost of best supportive care	Best supportive care = hydroxycarbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	£108,495
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	£108,495
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility at screening for CP third-line cohort from Study 200 used for all patients in CP on bosutinib and hydroxycarbamide	[redacted]	N/A
		Utility at screening for CP third-line cohort from Study 200 used for patients in CP on bosutinib only	[redacted]	£111,511

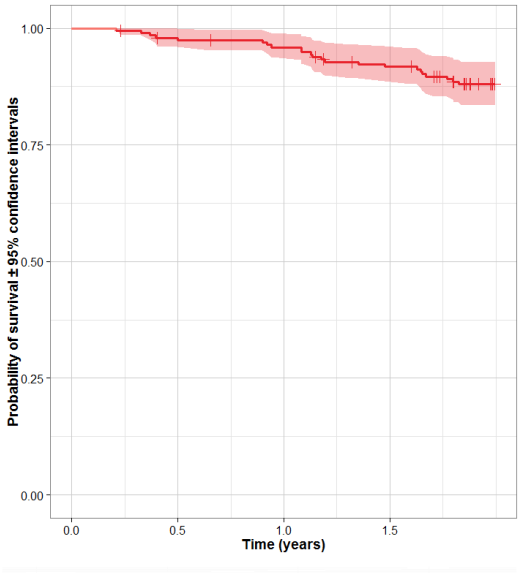
Parameter	Base Case	Sensitivity Analysis	ICERs	
			Bosutinib v hydroxy-carbamide	SCT v hydroxy-carbamide
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011a)[80]	[redacted]	£82,290
Interferon on-treatment utility value	Decrement to HRQL from interferon treatment	No decrement to HRQL from interferon treatment	[redacted] IFN vs hydroxy-carbamide: £138,728 Bos vs IFN: [redacted]	£111,511
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	£103,577
Model Settings				
Time horizon	50 years	2 years	[redacted]	Dominated
		5 years	[redacted]	£431,170
		10 years	[redacted]	£168,277
		25 years	[redacted]	£112,781

B3. Bosutinib could be considered as a second-line TKI for CP CML. In order for exploratory analysis of the cost-effectiveness of bosutinib in such patients, please provide the following information for patients in the CP second line CML cohort in Study 200:

- Kaplan-Meier curves for treatment discontinuation and overall survival calculated from the most recently available data (ideally separately for imatinib resistant and imatinib intolerant patients).

Figure 12: CP2L - OS

Imatinib resistant



Imatinib intolerant

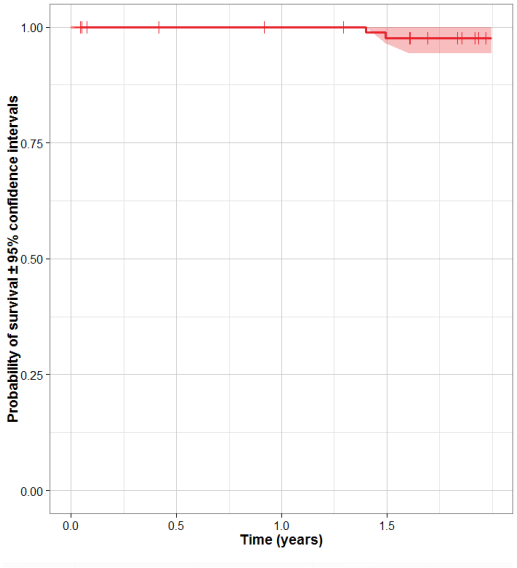


Figure 13: CP2L - Discontinuation

Imatinib resistant

Imatinib intolerant

- MCyR rate (best cumulative response in patients who both maintained and attained a MCyR) at a minimum follow-up duration of 12 months (i.e., data snapshot around 28 March 2010; ideally estimated separately for imatinib resistant, imatinib intolerant and for all CP second line CML patients), or alternatively:

- MCyR rate (best cumulative response in patients who both maintained and attained a MCyR by or within 12 months with any patients progressing or dying within 12 months counting as non-responders; ideally estimated separately for imatinib resistant, imatinib intolerant and for all CP second line CML patients).

The MCyR rate (best cumulative response in patients who both maintained and attained a MCyR) in second-line CP patients at a minimum follow-up duration of 12 months is provided in: *Cortes et al. 2011. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome–positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 118 (17) 4567-4576.*

As of the data cutoff for this analysis on June 3, 2010, the median duration of follow-up was 24.2 months. The MCyR for second-line CP is shown in Table 28 below; 33% of imatinib resistant and 27% of imatinib intolerant patients maintained or attained a MCyR over the duration of this study.

Table 28: Cytogenetic response at minimum follow-up of 12 months (data snapshot 3 June 2010) for second-line chronic phase patients

	Imatinib resistant		Imatinib intolerant		Total	
	N	%	N	%	N	%
Response at 24 weeks						
All treated patients*	200		88		288	
Major†	66	33	24	27	90	31
Complete	45	23	20	23	65	23
Cumulative response						
Evaluable patients	186		80		266	
Major†	101	54	39	49	140	53
Complete	77	41	33	41	110	41
Reason for exclusion from analysis						
No baseline assessment	14		8		22	

*Patients without a baseline or week 24 assessment were counted as non-responders.
†Major cytogenetic response complete partial cytogenetic response.

B4. In order to allow exploration of the differences in cost-effectiveness of bosutinib following imatinib discontinuation and bosutinib following multiple TKI failure in patients with AP/BP CML, please provide the following information separately for the AP and BP cohorts from Study 200:

- Kaplan-Meier curve for treatment discontinuation for people receiving bosutinib second line

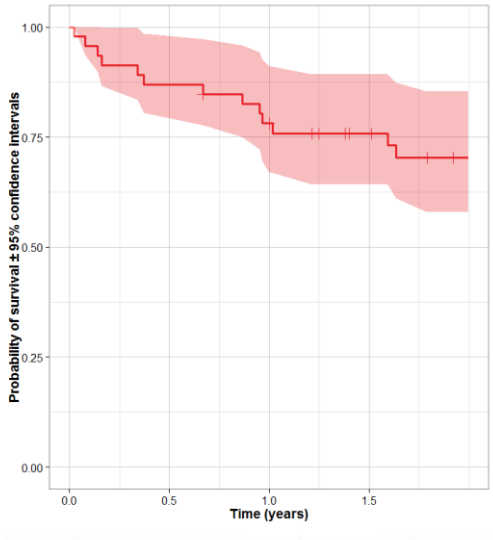
Discontinuation: AP-2L **Discontinuation: BP-2L**

- Kaplan- Meier curve for treatment discontinuation for people receiving bosutinib following multiple TKI failure

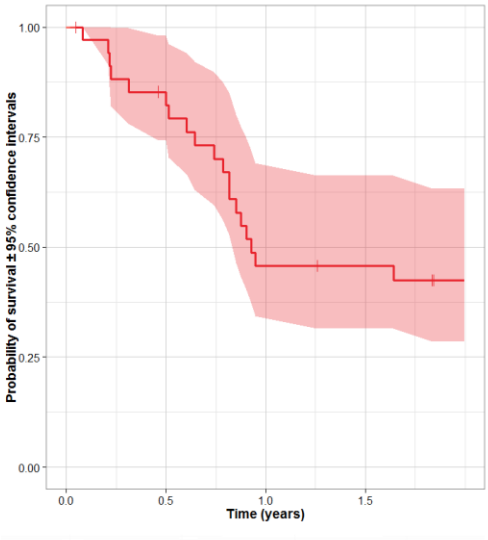
Discontinuation: AP-Multi TKI **Discontinuation: BP-Multi TKI**

- Kaplan-Meier curve for overall survival for people receiving bosutinib second line

OS: AP-2L

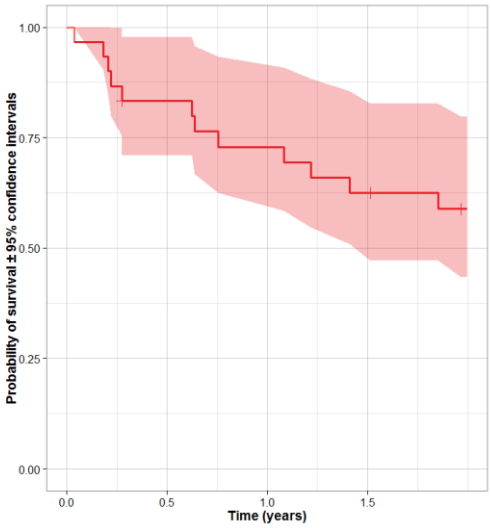


OS: BP-2L

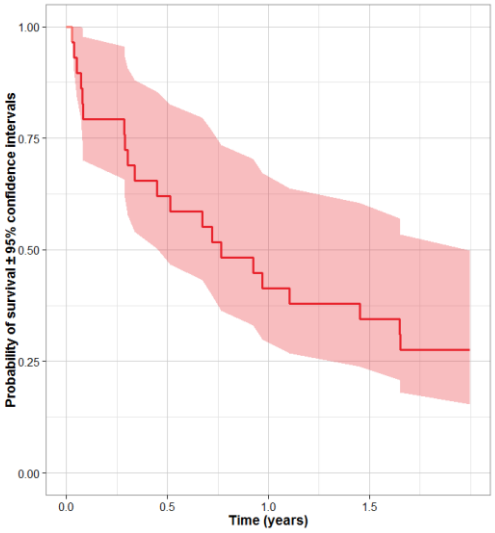


- Kaplan-Meier curve for overall survival for people receiving bosutinib following multiple TKI failure

OS: AP-Multi TKI



OS: BP-Multi TKI



B5. The calculation of the mean daily cost for bosutinib (p472) ignores treatment interruptions, although treatment interruptions are indicated for non-haematological adverse reactions (Table A1, p21), and some patients did have treatment with bosutinib interrupted due to adverse events (p359). Please provide an indication of the mean time that patients were not receiving bosutinib due to dose interruptions for the chronic, accelerated and blast phase populations separately if possible otherwise averaged over all patients.

In Study 200, the reasons for dose Interruptions were as follows: 'Disease progression', 'Disease progression or intolerance' 'Subject Noncompliance', 'temporarily stopped due to Adverse Event', 'subject request'. The mean number of days interrupted is available and is calculated by summing all interrupted days together except gaps (days unaccounted for with no dose recorded) (Table 29). The impact of treatment interruptions may be to reduce the average per patient cost of bosutinib, and hence improve cost-effectiveness. The number of days interrupted appears to be around 30 days, which is equivalent to 1 pack of bosutinib per patient over the total course of treatment.

Table 29: Mean days of treatment interruption in Study 200

	CP2L (N=288)	CP3L (N=118)	AP (N=76)	BP (N=64)
N of patients with an interruption (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean of days of Interrupted (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Section C: Literature searching

C1. **Priority request**: Page 18 of the submission says that a draft EPAR is available. Please provide the draft EPAR.

The finalised EPAR is now available and can be downloaded from the EMA website. We have also attached a version for your convenience.

C2. Appendix 2 (p201). Please clarify the date on which the search of conference proceedings was carried out?

The conference proceedings searches were performed w/c 4th February 2013 and completed by 7th February 2013.

C3. Appendix 2 (p201). Please clarify how the search for conference proceedings was carried out (i.e. through web-sites, hand-searching of journal supplements or through the web of science database)?

For all three congresses (EHA, ASCO, ASH), abstracts were accessed via the congress websites using key words (eg 'chronic myeloid leukemia', 'CML', 'transplant*', 'bosutinib'):

- EHA: http://www.ehaweb.org/congress-and-events/18th-congress/previous-congresses-2/
- ASCO: http://meetinglibrary.asco.org/abstracts
- ASH (e.g. 2012 abstracts): https://ash.confex.com/ash/2012/webprogram/start.html

C4. Appendix 2 (p201). Please clarify the rationale behind the date limit applied to the search of conference proceedings (2010-2012)?

Selected conference proceedings were searched for the last 3 years (2010-2012), since it is anticipated that most conference posters or presentations published before 2010 should have by now been published in a peer-reviewed journal and would therefore be identified in the MEDLINE, EMBASE and Cochrane Library literature searches in the submission. In the event that any relevant conference abstract that pre-dates 2010 has remained unpublished, this should have been identified in NICE STA 241. Since STA 241 was scanned for relevant evidence, it is anticipated that no relevant conference abstracts published prior to 2010 have been omitted from the current submission.

C5. Appendix 8 (p217). Please clarify why a separate searches for adverse event literature was not undertaken?

It is normal practise when conducting literature searches not to include specific search terms for efficacy or safety outcomes and events, since not all relevant research evidence is keyword-coded according to the outcomes being investigated. To overcome this shortcoming in the keyword coding process, standard practise is to

conduct broad literature searches focused on the relevant population, intervention and comparison treatments, and study designs. This ensures that a broad search is conducted that captures the highest number of articles reporting relevant efficacy and safety outcomes. This was the approach taken in the current submission, and for this reason separate searches specifically targeting adverse event literature were not conducted.

C6. Appendix 10 (p218). The searches for the clinical effectiveness section of the submission were carried out in January 2013 whereas the cost effectiveness literature searches were carried out in October 2012. Please clarify why the cost-effectiveness searches were not updated in January 2013 for the submission?

The cost-effectiveness systematic reviews have now been updated to April 2013, to ensure that no relevant articles have been published since October 2012.
The same search terms were employed in the databases as outlined in the original submission for the cost-effectiveness, utility and cost/resource use reviews. The searches were limited by:

- Database articles that had the field 'Date Created' were filtered from 01/10/12 to 09/04/13
- Database articles that did not have the field 'Date Created' were filtered from the beginning of 2012 to 09/04/13

The abstract and titles of each article were reviewed by a single reviewer. The full texts of potentially relevant articles were obtained and reviewed independently by two reviewers, who then came to a consensus on those to be included.

Cost-effectiveness systematic review
150 articles were identified by the searches. Eleven articles were classed as potentially relevant based on abstract and title. Five of these had been captured by the previous systematic review. The other six were all economic evaluations in first-line CML and were therefore excluded.1-6

Utility systematic review
21 articles were identified by the searches. One full text was assessed as potentially relevant. No articles were included in the second-line or later review, but the one full text was included as providing utility data for first-line CML patients (Pavey et al. 20121). However, this seems to be an update of the 1st line HTA report originally referenced as Hoyle et al 2011a7, and includes no additional utility sources to those that were referenced in the original submission.

Cost/Resource use systematic review
150 articles were identified by the searches. Three articles were classed as potentially relevant based on abstract and title. Two of these had been captured by the previous systematic review, and the other was excluded when the full text was assessed as it did not report any cost or resource use data.

1. Pavey T, Hoyle M, Ciani O, Crathorne L, Jones-Hughes T, Cooper C, Osipenko L, Venkatachalam M, Rudin C, Ukoumunne O, Garside R, Anderson R. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: Systematic reviews and economic analyses. Health Technology Assessment. 16 (42) (pp 1-278), 2012. Date of Publication: 2012. 2012.
2. Wu B, Zhong H, Saglio G, Chen F. Different strategies for first-line treatment of chronic myeloid leukaemia: An economic analysis. Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH 2012 Atlanta, GA United States. Conference Start: 20121208 Conference End: 20121211. Conference Publication: (var.pagings). 120 (21) , 2012. Date of Publication: 16 Nov 2012. 2012.
3. Yagudina R, Kulikov A, Komarov I. Cost-effectiveness of nilotinib versus imatinib as first-line treatment for newly diagnosed patients with philadelphia chromosome-positive (PH<) chronic myeloid leukemia in the chronic phase (CML-CP) in russian federation. Value in Health. Conference: ISPOR 15th Annual European Congress Berlin Germany. Conference Start: 20121103 Conference End: 20121107. Conference Publication: (var.pagings). 15 (7) (pp A426), 2012. Date of Publication: November 2012. 2012.
4. Hoyle M, Pavey T, Ciani O, Crathorne L, Jones-Hughes T, Cooper C, Osipenko L, Venkatachalam M, Rudin C, Ukoumunne O, Garside R, Anderson R. General methodological issues in cost-effectiveness analysis inspired by the assessment of dasatinib, nilotinib and imatinib for 1st-line chronic myeloid Leukaemia. Value in Health. Conference: ISPOR 15th Annual European Congress Berlin Germany. Conference Start: 20121103 Conference End: 20121107. Conference Publication: (var.pagings). 15 (7) (pp A471), 2012. Date of Publication: November 2012. 2012.
5. Inocencio TJ, Seetasith A, Newland A, Bose P, Holdford D. Cost-utility analysis of nilotinib compared to imatinib for newly diagnosed chronic myeloid leukemia (CML) in chronic phase. Value in Health. Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States. Conference Start: 20120602 Conference End: 20120606. Conference Publication: (var.pagings). 15 (4) (pp A223), 2012. Date of Publication: June 2012. 2012.
6. Mealing S, Taylor M, Scott D, Clark J, Mckenna M, Lebmeier M, Gilloteau I, Davis C. A UK based cost-effectiveness analysis of dasatinib (sprycel) 100mg daily compared to imatinib (glivec) 400mg daily in newly diagnosed patients with chronic myeloid leukemia (CML). Value in Health. Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States. Conference Start: 20120602 Conference End: 20120606. Conference Publication: (var.pagings). 15 (4) (pp A105), 2012. Date of Publication: June 2012. 2012.
7. Hoyle M, Pavey T, Ciana O, Crathorne L, Jones-Hughes T, Cooper C, Osipenko L, Venkatachalam M, Rudin C, Okoumunne O, Garside R, Anderson R. Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. 2011.

C7. Appendix 10 (p221). Please clarify what the 'horizon scans' entailed, when they were run and how, giving enough information for these searches to be repeated.

Horizon scanning involved searching the Google advanced search engine for relevant articles not captured by the previous searches. On the 'advanced search' page, the following terms were put into the 'any of these words' field:

> *Chronic myeloid leukaemia cost-effectiveness OR CML cost-effectiveness OR chronic myeloid leukaemia cost-utility OR CML cost-utility OR chronic myeloid leukaemia model OR CML model*

The date range for this search was 'before 02 October 2012'.

These results were then checked manually by one reviewer for any articles that met the eligibility criteria as described in Table B12. No articles were found in addition to those already identified within the EMBASE, MEDLINE, MEDLINE In-Process, Cochrane Library, EconLit, and NHS Economic Evaluations Database searches.

Appendix G – Patient/carer organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: David Ryner

Name of your organisation: Chronic Myeloid Leukaemia Support Group (CMLSG)

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology? ✔
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) ✔Trustee
- other? (please specify)
- **NB I assume the 8 page submission limit referred to above excludes this facing page.**

Appendix G – Patient/carer organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

1. Advantages (a) & (b) of bosutinib

1.1. The best evidence currently available for tyrosine kinase inhibitor (TKI) use in chronic myeloid leukaemia (CML) treatment, in any disease phase, following failure of more than a single TKI is set out in one of the two published studies that arose from the clinical trial (CT) referred to in the technology description entry in the final scope document.

(The CT is US Federal Drug Agency NCT:00261846 and the study is; *Khoury et al 'Bosutinib is active in chronic phase chronic myeloid leukaemia after imatinib and dasatinib and/or nilotinib therapy failure' Blood April 12, 2012; 119 (15):3403-12)*

Bosutinib is a 3rd generation member of the CML TKI class and the study analysis indicates that it demonstrates efficacy against chronic phase (CP) CML after previous treatment with more than one TKI.The patients, many of whom had also been treated with therapies from the pre-TKI era, would have welcomed any intervention that halts or slows disease progression as would any CML patient unable to obtain a durable response from available therapies.

1.2. The treatment of CML has been transformed since the introduction of imatinib into standard use in the NHS following NICE guidance being issued in 2002. Analysis reported in a recent government publication *(National Cancer Intelligence Network 'Haematological malignancies in England' December 2012)* which covers diagnoses from 2001 to 2008 concludes that there has been over a 50% increase in 5 year survival rates for CML patients compared to the (pre-TKI era) 1990s.

All the comparators listed in the final scope were standard NHS treatments in the period preceding that covered by the report and have never been the subject of a NICE technology appraisal.

1.3. The report also notes (on p. 5) that '*It is likely that the outcomes reported here underestimate contemporary survival patterns*' and that '*effective treatment options for patients with some haematological cancers have increased considerably for patients diagnosed since 2008'* with CML included in the cancers mentioned.

Nilotinib and dasatinib, as 2nd generation TKIs, have both been extensively available in the NHS since 2008 as expert clinicians have observed in their evidence at recent appraisals.

Both have offered therapeutical efficacy for a group of CP CML patients that developed toxicity based on imatinib resistance (Im-R) or imatinib intolerance (Im-I) with the same being applicable for those patients whose resistance was due to the development of a BCR-ABL oncogene mutation(s).

There is evidence that over 50% of this group achieve a major cytogenetic response (MCyR) following treatment with one of these 2nd generation TKIs in 2nd line.

1.4. The other study, based on a different patient population, arising from the clinical trial referred to above concluded that bosutinib, as a 2nd line treatment, is also capable of achieving significant rates of MCyR for CP CML patients *(Cortes et al 'Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia*

chromosome–positive chronic myeloid leukaemia patients with resistance or intolerance to imatinib' Blood Oct 27, 2011; 118 (17): 4567-4576).
Included amongst the Cortes group of patients were a sub set who had not achieved MCyR when treated previously with imatinib, 41% of this group achieved MCyR and 25% a complete cytogenetic response (CCyR) following bosutinib treatment.

1.5. However some patients go on to develop resistance or intolerance to both dasatinib and/or nilotinib following 1st line imatinib treatment.The Khoury study analysis concludes that, even in situations of multiple TKI treatment line failure, bosutinib, as a 3rd or even 4th line treatment, is capable of achieving MCyR.

He also concluded, after comparing subpopulation data in his study with that from a number of other researchers' smaller studies, that bosutinib treatment achieves a longer duration of MCyR response compared to nilotinib or dasatinib in 3rd line.

1.6. In summary there are a small group of CP CML patients whose disease is refractory to the both single and multiple TKI treatment for whom bosutinib treatment has proved effective in obtaining an optimal response. The evidence submitted by both the manufacturer and other professional consultees will join that set out in the studies and will no doubt provide exhaustive technical detail.

1.7. Patients, and those that care for them, welcomed news that the primary end point in the Cortes study had been met with 31% of patients achieving MCyR at 24 weeks rising, in a median 24.2 month follow up, to 53% who achieved a MCyR, with 41% also achieving a complete cytogenetic response (CCyR).

More relevant for this STA is that, in the Khoury study, 32% of patients achieved MCyR and 24% achieved a CCyR at a median 28.5 month follow up. CCyR was also achieved by 1 of 3 patients previously treated with 3TKIs. Rates for MCyR and CCyR also saw rises to 39% and 31% respectively when patients who simply retained, but did not improve their responses, were included.

1.8. For patients with narrowing therapeutic options following more than one TKI failure the arrival of bosutinib, a TKI of proven effectiveness in patients with multiple TKI failure, represents a possible solution to their unmet need.

Apart from their expectation, rationally based on the best available evidence, of bosutinib's impact on the haemaotological aspects of their disease, patients also have an understandable concern with the management of the distinct side effects associated with each TKI. They will have noted that bosutinib treatment side effects over the longer term appear manageable for the majority of patients.

1.9. This seems to apply to 2nd line and subsequent treatment lines with over 75% of patients in the 2 studies being able to continue their bosutinib treatment following the appearance of side effects. Side effects tended to be experienced immediately after bosutinib treatment began and were manageable following the introduction of control interventions.

1.10. Under these circumstances patients could expect to enjoy a quality of life benefit gained by use of a home based, oral, once a day therapy with routine outpatient visits to a local clinic or specialist centre at regular intervals whose frequency would depend on their disease load and stage. Over a longer term

patients can also expect to benefit, if of working age, from returning to work and more generally returning to family & social life with participation in community life commensurate to that enjoyed prior to the their being burdened by disease.

Overall those with favourable clinical outcomes would have the possibility of enjoying the psychological benefit accrual granted by a chronic rather than acute/fatal disease outlook.

1.11. They will also have been reassured that, in the Khoury multiple TKI use study, only 4% (n 5) of patients progressed from CP to accelerated phase (AP) and none from AP to blast phase (BP).

2. Disadvantages of bosutinib.

2.1. There will however be a very small group of patients for whom bosutinib use would not represent a rational treatment strategy. Both studies report that patients with the BCR-ABL kinase domain T 315i mutation were unable to obtain any haematological response with bosutinib treatment.

2.2. By far the most common non haematologic side effect associated with bosutinib use is diarrhoea (reported to be 81% & 84%, Khoury & Cortes respectively) with an occurrence rate of around twice that of any other side effect. Its onset is early in treatment ,with a short median duration, with severity limited to a small minority (8% & 9% of patients in Khoury & Cortes respectively) and with no patient at maximum Grade 4 severity level in either study.

In the Cortes 2nd line bosutinib use study only 3% patients discontinued treatment with a further 14% interrupting their treatment for this reason. In the Khoury study none out of the 3% that discontinued were thought to have done so citing diarrhoea as a primary reason. However 20% of patients interrupted their treatment due to adverse events which included gastrointestinal effects (diarrhoea being in that category).

Other gastrointestinal side effects in that study were nausea and vomiting both occurring with approximately half the frequency of diarrhoea, early in treatment, and mostly of a short duration with the same pattern for rash, the only other significant side effect.

3. Are there differences in opinion between patients about the usefulness or otherwise of bosutinib?

3.1. All CML patients welcome the availability of any TKI that demonstrates clinical efficacy. Bosutinib's arrival to join the CML TKI class is no exception.

3.2. Setting aside bosutinib's haematologic effects, differences of opinion about the usefulness of bosutinib would pivot around an individual patient's willingness to tolerate its non haematologic side effects compared to their willingness to tolerate those side effects distinct to other TKI treatments. The latter are well documented and very familiar to CML patients in the UK.

3.3. In this context the usefullness of the technology lies in the extension of choice it grants to patients given the distinct difference in the type and severity of side effects

between bosutinib and other TKIs.Consequently there would be some patients who will, and do, find bosutinib useful and others who will/do find it less so, or not at all.

4. Are there any groups of patients who might benefit more from bosutinib or are there any groups who might benefit less?

4.1. The evidence mentioned in section (1) above, and detailed much more extensively in the two studies referred to throughout, demonstrates that a significant number of patients intolerant or resistant to the TKIs available for the treatment of CML might be able, at least for those in CP, to derive sustained clinical benefit from treatment with bosutinib. For these patients bosutinib answers a demonstrable unmet clinical need and in that sense they would benefit more.

4.2. Other groups of patients who are able to achieve significant clinical benefit from other TKI use including being able to tolerate treatment and enjoy a good quality of life, might or might not derive less benefit from bosutinib treatment. However this remains, excepting for those with the T315i mutation and with all other factors being equal, a hypothetical proposition until undergoing treatment with bosutinib.

5. Comparing bosutinib with alternative available treatments or technologies

(i) Please list any current standard practice (alternatives if any) used in the UK.

5.1. NICE Guidance (TA 241) for TKI use for patients previously treated with imatinib in first line which recommends the use of nilotinib (in 2nd line) as part of a Patient Access Scheme (PAS).

5.2. Nilotinib (under a PAS scheme) is currently also recommended by NICE for 1st line use in CML (TA 251). Included in TA251, the most recently published guidance for CML treatment, is the statement that the committee considers it '*reasonable'* that standard dose imatinib '*should be available first and second line'* (4.3.21. TA 251)

5.3. Dasatinib, currently the subject of a NICE Rapid Review for the (1st line) TA251 PAS, has been and continues to be routinely reimbursed (in England) under the Cancer Drugs Fund (CDF). Extensive, regionally based, data is available to support this statement. It is worth noting that the clinical efficacy of dasatinib was accepted by the committee prior to the publication of TA251.

5.4. Of the comparators listed in the final scope, only allogeneic stem cell transplantation (SCT) and interferon alpha (IFN) possess the capability to effect a complete or partial cytogenetic response (CCyR or PCyR) as treatments for CML. As such they would qualify as 4th line treatment candidates although in practice IFN use in the NHS qualifies for ultra rare status as a treatment strategy. SCT is, as NICE has recognized in previous HTAs, an option available to only a small minority of patients who meet the relevant clinical criteria and for whom suitable donors can be located for what is acknowledged to be a high risk intervention.

5.5. Hydroxycarbamide (HU) and the opaque 'best supportive care' (BSC) are best not described as treatments since they are incapable of halting the natural history of CML.They should rather be considered as agents used prior to, between treatments

and/or in final stage care. The Cortes & Khoury studies assign HU 'between treatment' status and the NICE committee havers between that status and that of a 'treatment' in previous appraisals. As such, and conforming to the NICE response to consultee comments on the draft scope of this appraisal, HU & BSC would only be candidates in a final treatment line when all other treatment options capable of effecting a cytogenetic response have either been exhausted and/or lack feasibility.

(ii) If you think that the bosutinib has any advantages for patients over other current standard practice, please describe them.

5.6. Comparisons of the haematologic efficacy of bosutinib compared to other TKI is set out in section (1) and discussed in detail in both studies. We would emphasise one additional point. Bosutinib shows activity against all mutations except T315i but Khoury notes this includes those '*associated with clinical resistance to dasatinib and nilotinib'.*

Haematologic adverse events:

5.7.In common with treatment with all TKIs, patients treated with bosutinib exhibit low blood cell counts. However Khoury, as does Cortes, reports the incidence and levels arising from bosutinib use compares favourably with the rates for similar occurrences arising from nilotinib and dasatinib treatment.

5.8. Cortes also reports bosutinib does not seem to inhibit c-KIT, a protein found on the surface of cells, and this might be preventative of low blood counts falling to problematic levels.

5.9. Cortes also notes bosutinib has little effect on platelet function whereas for patients treated with other TKIs, particularly dasatinib, problems with bleeding are more common.

5.10. There seems little evidence that bosutinib use, following treatment with more than one TKI, is accompanied by pervasive cross intolerance. Khoury notes that haematologic toxicity is the most common reported cause of the limited cross intolerance observed and Cortes suggests that a 31% discontinuation rate of patients with previous Im-I provides some indirect, but by no means conclusive, evidence of cross intolerance to bosutinib.

Non-haemtologic adverse events:

5.11. Musculoskeletal pain, a side effect reported by patients being treated with imatinib, is little reported by patients treated with bosutinib in either study.

5.12. Both Khoury and Cortes record that fluid retention issues, be they pleural effusion arising from dasatinib treatment or peripheral oedema arising from imatinib treatment, seem not to be reported with any frequency as a troublesome problem by patients treated with bosutinib. It is now orthodox practice for specialist clinicians to prescribe a TKI other than dasatinib to treat patients with COPD or other related co-morbidities.

5.13. On rare occasions Nilotinib prolongs QT intervals. As a result it carries a FDA 'black box' warning for patients with cardiovascular disease. Consequently specialist

clinicians would be cautious in prescribing nilotinib for patients with this kind of co-morbidity. Both Cortes and Khoury report bosutinib treatment to be associated with a low or minimal effect on QT intervals.

5.14. Although all three generations of TKIs are oral medicines whose use is home based there are differences in the administration regimes that accompany their use. The most stark being that for nilotinib requiring patients to follow a strict fasting regime for twice daily dosing whereas bosutinib is a once per day dose without any fasting requirement. The same is applicable for dasatinib. Patients with diabetes, which has its own strict therapeutic regime, might find it difficult to adhere to a strict fasting requirement.

(iii) If you think that bosutinib has any disadvantages for patients compared with current standard practice, please describe them.

5.15 In the Khoury study of the patient sub group treated with more than one TKI, who were also heavily pre-treated with non TKI treatments, a high (71%) discontinuation rate was reported. The bulk of this rate consisted of patients discontinuing because of a lack of efficacy (21%), adverse events (20%) or disease progression (17%). However just under one third of patients (29%) continued with bosutinib treatment at the data cut off date.

5.16. The discontinuation results for less clinically compromised patients in the Cortes study were lower (50%) with nearly the same result for discontinuation because of adverse events (21%), somewhat lower for disease progression (12%) but considerably lower due to lack of efficacy (6%).

5.17. Analysis from both the Khoury and Cortes studies indicates that diarrhoea is by far the most common side effect of bosutinib use (as discussed in 2. above). Consequently it would not be expected that clinicians would, from the suite of TKIs available, recommend bosutinib treatment for patients with gastrointestinal co-morbidities like Crohn's disease.

6. Research evidence on patient or carer views of bosutinib

6.1. Only 2 of the 82 study centres for the CT are located in the UK (London & Newcastle upon Tyne). From conversations with CML patients, leading clinicians working in the UK and traffic on our website discussion forum, we estimate the number of CML patients in England currently being treated with bosutinib in the NHS to be very small. We estimate the total to be somewhere between 30 and 50 patients with the number not enrolled on clinical trials who are receiving bosutinib on compassionate use grounds being much smaller than that total.

6.2. We have not received any reports from this group of patients of their experiences being worse than that reported in the studies

6.3. Although extreme caution should prevail given the number of patients involved, it is worth noting the considerable difference between some of the patients currently being treated in England (and future patient populations likely to be treated) and many of the patients in subpopulations of the two studies.

6.4. Over 60% of the patients in the Khoury study had had IFN treatment with just under 10% having had an SCT with the 32% and 3% being the respective figures for the Cortes study. Since IFN treatment for CML is ultra rare in England (and the UK) there are clear and significant differences between the English bosutinib patient population and the two (non - English) study patient populations. In short the outcomes for the (heavily pre-treated) latter group might not be reflected in those for the former.

7. Relevant research carried out on patient or carer views.

7.1. The transformation of CML from a disease with an acute status with a poor prognosis to one of chronic status, with an anticipated overall survival approaching that of national life expectancy, has shifted patient focus from securing survival to enhancing their quality of life. A patient's estimate of their wellbeing prior to their being aware of their symptoms is an often used as a benchmark to match against any estimate of their current wellbeing. HRQoL measures represent mundane patient estimates when translated into a technical health(care) context.

7.2. There are two published research studies that focus on CML patients HRQoL status during bosutinib treatment. Both used Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) methodology to establish HRQoL values prior to, and over the course of, bosutinib treatment.

7.3.The first focused on Im-R & Im-I CP CML patients and was of a 96 week duration. From the little HRQoL diminution reported at the initial (baseline) stage of the study patients noted *'statistically significant and/or clinically meaningful improvements on several FACT-Leu scales.*' *(Trask et al 'Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia.' Leukemia Research April 2012; 36 (4): 438-442)*

7.4. The second was of broader cohort size and scope covering 3 treatment lines and, in addition to CP patients, those in AP and BP. Unsurprisingly patients at lines distant from 1st reported poorer HRQoL as did patients in later disease phases than CP. In short the later the disease stage, the higher the disease load, the poorer the HRQoL of patients.*(Trask et al 'Health-related quality of life in chronic myeloid leukemia.' Leukemia Research January 2013; 37 (1): 9-13)*

8. Availability of bosutinib to patients in the NHS

8.1. There would be an **ABSOLUTE** difference for that group of patients resistant to or intolerant of all available TKIs and for whom bosutinib treatment has proven to be clinically effective were bosutinib to be available as a standard NHS treatment. For them a clearly defined unmet need would be answered.

8.2. More generally, a key difference would be the addition of another TKI of proven efficacy against CP CML as a standard treatment for CML in the NHS. Current research and debate amongst leading CML clinicians indicates that a key strategic objective in the treatment of CP CML is the achievement of a quick, durable, deep molecular response with TKI treatment. *(Marin et al 'Assessment of BCR-ABL1 Transcript Levels at 3 Months Is the Only Requirement for Predicting Outcome for Patients With Chronic Myeloid Leukemia Treated With Tyrosine Kinase Inhibitors' JCO Jan 2012, Vol 30 No 3 (232-238) and Marin et al 'Predictive value of early*

molecular response in patients with chronic myeloid leukemia treated with first-line dasatinib' Blood May, 2012: (120): 291-294)

From this perspective, movement between lines of TKI treatment is envisaged to be at quarterly intervals for poor responders until optimal efficacy is achieved. It follows that the introduction of another TKI of proven clinical efficacy enhances the treatment options available to clinicians.

8.3. Assuming clinical efficacy could be achieved equally across all TKIs including bosutinib, its addition to the number of TKIs available would also increase patient choice of the TKI best suited to improve their QoL by permitting them to select the TKI whose side effects might prove to be the most personably tolerable.

9. Equality:

9.1. For the first time in an appraisal for a technology for the treatment of CML, the public service provisions of the Equality Act of 2010 would be applicable. Given the technology description in the final scope and the selection of stem cell transplantation (SCT) as one of the comparators this new legal requirement has considerable pertinence for this HTA.The two protected characteristics enshrined in the Act that are relevant for this HTA are 'age' and 'ethnicity'.

9.2. There is evidence that a patient's age can either exclude them from being considered for a treatment, result in less optimal health benefit due to treatment being organized differentially using chronologically age based criteria or that their age can affect the quality of care they might receive *(DH commissioned 2009 studies: Carruthers & Ormondroyd 'Achieving Age Equality in Health & Social Care' and Centre for Policy on Ageing 'Ageism and age discrimination in secondary health care in the UK').*

9.3. The STA ERG's assessment should take into account this changed legislative environment when considering the suitability of SCT as an option for patients in different age bands in contrast to the potentially universal availability of other treatments.

9.4. In addition the committee should be made aware of the necessity of taking positive steps to purge themselves of any tendency to discriminate in their decision making in recommending one treatment over another because the likely beneficiaries may occupy a particular chronological age band.

9.5.There is also evidence that Black and minority ethnic CML patients are considerably disadvantaged relative to the majority population in being able to locate suitable donors for SCTs. The 2010 study *'The Future of Unrelated Donor Stem Cell Transplantation in the UK'* NHS Blood & Transplant service & UK Stem Cell Strategy Forum noted (p. 5):

'Thus while around 90% of north European Caucasian patients might typically find a match, the matching rates for Black and minority ethnic donors may be 40%, or lower, especially for patients of mixed genetic heritage.'

10. Other issues:

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10.1. Sir Michael Rawlins, delivering the annual Office of Health Economics lecture in June last year, argued that there was 'a need to replace rigid evidence hierarchies with a more pragmatic approach'. In appraisals for indications with very small patient populations, where clinical trials are likely to be infrequent and difficult to conduct, we believe both assessment groups and committees should give some attention to this sentiment in their consideration of the evidence.

10.2. There is a proven relationship between the entry of competitors and price signals in markets. In the 'real world' an increase in competitor numbers tends to exert a downward pressure on prices especially where demand lacks elasticity. Standard setting agencies and their appraisal committees play a parallel indirect, price influencing role when they consider the outputs of health economics modelling inevitably preloaded with uncertainty and assumptions. Welcoming entrants into markets should be a consideration that informs committee decision making since it is ultimately they, and not the models and their outputs, that make decisions.

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr JL Byrne

Name of your organisation: Representing the Royal College of Pathologists and the BSH

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Chronic myeloid leukaemia is currently treated with tyrosine kinase inhibitors in the NHS. Until April 2012 Imatinib was the only 1st line NICE approved drug available, but Nilotinib (with a PAS) was also approved by NICE for 1st line use in April 2012.

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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Approximately 75- 80% of patients respond satisfactorily to Imatinib / Nilotinib and achieve complete cytogenetic responses, but the remaining 25% of patients either cannot tolerate the drugs due to side effects and toxicity, or are refractory to these drugs and fail to achieve adequate responses. One cause of a failure to respond is the acquisition of bcr-abl mutations which prevent the binding of, or block the action of the tyrosine kinase inhibitor. There are over 40 bcr-abl mutations reported in the literature, and there are known sensitivities of the different drugs to these mutations eg patients with a specific mutation may be much more likely to respond to one drug than another.

Patients who are refractory or intolerant of their 1st line treatment are eligible to receive Nilotinib, which was also NICE approved as a 2nd line treatment for CML in April 2012. The other licensed 2nd line tyrosine kinase inhibitor, dasatinib, was, however, not approved by NICE for either 1st line or 2nd line use.

Since an increasing number of patients are now receiving Nilotinib as a 1st line treatment, this limits its usefulness as a 2nd line agent in these patients. Furthermore as Nilotinib is generally accepted as a more potent bcr-abl inhibitor than Imatinib, with activity in many but not all the known mutations, there is little point in switching patients who have failed Nilotinib to Imatinib. However, Imatinib may be useful as a 2nd line agent for patients experiencing toxicity on Nilotinib.

Currently the only treatment options apart from Imatinib and Nilotinib are Interferon or allogeneic haemopoietic stem cell transplantation. Interferon has a low response rate of 10-15% and a significant side effect profile, limiting its usefulness as a realistic alternative treatment for CML. Allogeneic bone marrow transplantation depends on a suitable fully matched donor being identified, and on the performance status of the patient being adequate: effectively ruling out patients over the age of 70 years and many patients from ethnic minority backgrounds. Furthermore allogeneic bone marrow transplantation is a complex treatment with a 10-15% transplant-related mortality and a significant number of patients may develop graft versus host disease resulting in significant comorbidities and the need for ongoing immunosuppressive treatments.

The FDA recently approved Omacetaxane for CML patients failing 2 previous CML treatments, but is not yet approved by the EMEA or available in the NHS.

The proposed technology, bosutinib would offer an alternative drug treatment for patients who could not tolerate Imatinib or Nilotinib, or for patients who are refractory to these drugs.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with a high Sokal score may be at higher risk of being refractory to Imatinib treatment.

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Patients aged over 70 years old or from ethnic minority backgrounds are less likely to be able to benefit from the alternative treatment of allogeneic bone marrow transplantation/

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The use of bosutinib would be restricted to secondary care specialist clinics. There would be no requirement for additional professional input.

The technology
If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Bosutinib is not yet widely available in the NHS. So far its use has been restricted to clinical trials and via a compassionate use programme. It has always been used for its licensed indication i.e as a 2nd or 3rd line treatment for CML

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no current guidelines which include bosutinib. The European LeukaemiaNet Guidelines 2009 are due to be updated in 2013. Currently these recommend Imatinib for first line use and dasatinib / nilotinib as second line use.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology will be straightforward to use once it becomes available since it is a simple once daily tablet taken as an out-patient. There are no required concomitant medications or other clinical requirements. It would certainly be much simpler for patients than the alternative treatments of BMT or interferon. Monitoring of treatment response is the same as for the other well established tyrosine kinase inhibitors

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Bosutinib treatment would be monitored by bone marrow cytogenetics and regular q-PCR testing for bcr-abl which is standard for the other TKIs. Patients failing to respond after 6 months of treatment would be recommended to stop and other treatment options considered. Responding patients are currently recommended to continue the tyrosine kinase inhibitors indefinitely. However, there is currently interest in discontinuation of TKIs for patients who achieve complete molecular remissions as a proportion of these appear to remain disease free. Currently this should only be done in the context of a clinical trial, and only about 10% of CML patients are thought likely to have good enough responses to consider this approach.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials that have been done with bosutinib in the 2nd and 3rd line settings are comparable to those observed in routine clinical practice in the UK. The drug was shown to be effective in inducing complete cytogenetic remissions in 41% of patients who were resistant or intolerant of imatinib and in 21% of patients who had failed both imatinib and either nilotinib and dasatinib. Achievement of complete cytogenetic remission is associated with survival in CML patients so is a valid predictor of long term outcome.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The studies report a low level incidence of adverse reactions to the drug which are rarely above Grade 2 and can usually be managed with supportive measures. Some of these side effects appear to be self limiting eg those related to GI toxicity. I am not aware of any new side effects that have subsequently become apparent.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There would be no significant issues in terms of the delivery of care for these patients if the technology was approved. There are no specific educational or training requirements for NHS staff and no additional resources would be required.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

The approval of this technology would allow additional treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the existing alternative treatment which is allogeneic haemopoietic stem cell transplantation.

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Comments submitted by [redacted], [redacted] on behalf of:

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by Dr JL Byrne and Dr D Milojkovic

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Chronic myeloid leukaemia is currently treated with tyrosine kinase inhibitors (TKIs) in the NHS. Until April 2012 Imatinib was the only 1st line NICE approved drug available, but Nilotinib (with a PAS) was also approved by NICE for 1st line use in April 2012. Eligible patients are also offered National Studies, that

compare one TKI against a second or third line TKI (for eg the SPIRIT2 NCRI study, which compares imatinib against dasatinib first line therapy).

Approximately 75- 80% of patients respond satisfactorily to Imatinib / Nilotinib and achieve complete cytogenetic responses, but the remaining 25% of patients either cannot tolerate the drugs due to side effects and toxicity, or are refractory to these drugs and fail to achieve adequate responses. One cause of a failure to respond is the acquisition of bcr-abl mutations which prevent the binding of, or block the action of the tyrosine kinase inhibitor. There are over 40 bcr-abl mutations reported in the literature, and there are known sensitivities of the different drugs to these mutations e.g. patients with a specific mutation may be much more likely to respond to one drug than another. The true efficacy of an individual TKI can be judged by the number of patients that continue to receive the drug after a number of years. After 7 years of first line imatinib therapy, only 60% of patients remain on imatinib for the reasons mentioned.

Patients who are refractory or intolerant of their 1st line treatment are eligible to receive Nilotinib, which was also NICE approved as a 2nd line treatment for CML in April 2012. The other licensed 2nd line tyrosine kinase inhibitor, dasatinib, was, however, not approved by NICE for either 1st line or 2nd line use, although in clinical practice, there is no discernible difference between the efficacy of dasatinib and nilotinib.

Since an increasing number of patients are now receiving Nilotinib as a 1st line treatment, alternative TKIs are required 2nd line agent in these patients. Furthermore as Nilotinib is generally accepted as a more potent bcr-abl inhibitor than Imatinib, with activity in many but not all the known mutations, it would be futile to switch patients who have failed Nilotinib to Imatinib. However, Imatinib may be useful as a 2nd line agent for patients experiencing toxicity on Nilotinib, that have had a good cytogenetic and molecular response.

Currently the only treatment options apart from Imatinib and Nilotinib are Interferon or allogeneic haemopoietic stem cell transplantation. Interferon has a low response rate of 10-15% and a significant side effect profile, limiting its usefulness as a realistic alternative treatment for CML. Allogeneic bone marrow transplantation depends on a suitable fully matched donor being identified, and on the performance status of the patient being adequate: effectively ruling out patients over the age of 70 years and many patients from ethnic minority backgrounds. Furthermore allogeneic bone marrow transplantation is a complex treatment with a 10-15% transplant-related mortality and a significant number of patients may develop graft versus host disease resulting in significant comorbidities and the need for ongoing immunosuppressive treatments.

Dasatinib is available for a limited number of patients through the Cancer drugs fund or separate application to the PCT, with no guarantee of funding. Certainly, the availability of dasatinib to patients varies throughout the country. The FDA recently approved Omacetaxine for CML patients failing 2 previous CML treatments, but is not yet approved by the EMEA or available in the NHS.

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Most professionals would aim to enrol patients in a national trial. There is a difference of opinion as to whether imatinib or nilotinib should be started up-front. If physicians start with nilotinib, most would agree that a 3 month RT-q PCR of bcr-abl < 10% (IS) would be desirable, as these patients have a worse outcome.

The proposed technology, bosutinib would offer an alternative drug treatment for patients who could not tolerate Imatinib or Nilotinib, or for patients who are refractory to these drugs, and have a resistant Abl kinase domain mutation in some cases. Further advantages of bosutinib include once daily dosing (improvement of compliance) and the greatest selectivity forbcr-abl (lack of c-kit and PDGFR inhibition, unlike the other TKIs. Off-target signalling is felt to be responsible for a number of the side-effects on other TKIs).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with a high Sokal score and in advanced phase may be at higher risk of being refractory to Imatinib treatment.
Patients aged over 70 years old or from ethnic minority backgrounds are less likely to be able to benefit from the alternative treatment of allogeneic bone marrow transplantation.
Patients at higher risk of a significant side-effect of nilotinib (and alternative TKIs) due to their co-morbidities would benefit from the technology.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The use of bosutinib would be restricted to secondary care and specialist clinics. There would be no requirement for additional professional input.

The technology
If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Bosutinib is not yet widely available in the NHS. So far its use has been restricted to clinical trials and via a compassionate use programme. It has always been used for its licensed indication ie as a 2nd or 3rd line treatment for CML.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

There are no current guidelines which include bosutinib. The European LeukaemiaNet Guidelines 2009 are due to be updated in 2013. Currently these recommend imatinib for first line use and dasatinib / nilotinib as second line use.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology will be straightforward to use once it becomes available since it is a simple once daily tablet taken as an out-patient. There are no required concomitant medications or other clinical requirements. It would certainly be much simpler for patients than the alternative treatments of BMT or interferon. Monitoring of treatment response is the same as for the other well established tyrosine kinase inhibitors.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Bosutinib treatment would be similarly monitored by bone marrow cytogenetics and regular q-PCR testing for bcr-abl as is standard for the other TKIs. No additional testing is necessary. Patients who are intolerant, or failing to respond (by ELN criteria definition) after 6 months of treatment, would be recommended to stop and other treatment options considered. Responding patients are currently recommended to continue the tyrosine kinase inhibitors indefinitely. However, there is currently interest in discontinuation of TKIs for patients who achieve complete molecular remissions as a proportion of these appear to remain disease free. Currently this should only be done in the context of a clinical trial, and only about 10% of CML patients are thought likely to have good enough responses to consider this approach.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials that have been done with bosutinib in the 2nd and 3rd line settings are comparable to those observed in routine clinical practice in the UK. The bosutinib trials were conducted in a similar way to the other TKI studies. The drug was shown to be effective in inducing complete cytogenetic

remissions in 41% of patients who were resistant or intolerant of imatinib and in 21% of patients who had failed both imatinib and either nilotinib and dasatinib. Achievement of complete cytogenetic remission is associated with survival in CML patients so is a valid predictor of long term outcome.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The studies report a low level incidence of adverse reactions to the drug which are rarely above Grade 2 and can usually be managed with supportive measures. Some of these side effects appear to be self limiting e.g. those related to GI toxicity. Importantly, all the side-effects are reversible, which is sometimes not the case with alternative TKIs. No new side effects have subsequently become apparent.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There would be no significant issues in terms of the delivery of care for these patients if the technology was approved. There are no specific educational or training requirements for NHS staff and no additional resources would be

required. A positive NICE guidance would allow equity of access to all patients requiring the technology.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

The approval of this technology would allow additional treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an alternative TKI that would not manifest itself on bosutinib would benefit considerably with regards to future morbidity and medical intervention.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Please sign and return to:

Jenna Byers, Technology Appraisal Administrator
Email: TACommC@nice.org.uk
Fax: +44 (0)20 7061 9760
Post: NICE, Level 1A, City Tower, Piccadilly Plaza, Manchester, M1 4BT

I confirm that:

- I agree with the content of the statement submitted by The Royal College of Physicians and consequently I will not be submitting a personal statement.

Name: .....Dr Dragana Milojkovic.....

Signed:
.....[redacted].....

Date: .....14/4/2013.....

Appendix K – Clinical Specialist declaration form

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Please sign and return to:

Jenna Byers, Technology Appraisal Administrator
Email: TACommC@nice.org.uk
Fax: +44 (0)20 7061 9760
Post: NICE, Level 1A, City Tower, Piccadilly Plaza, Manchester, M1 4BT

I confirm that:

- I agree with the content of the statement submitted by The Royal College of Pathologists and The British Society for Haematology and consequently I will not be submitting a personal statement.

Name: DR. JENNIFER BYRNE

Signed: [redacted]

Date: 22/3/13

Appendix K – Clinical Specialist declaration form

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Please sign and return to:

Jenna Byers, Technology Appraisal Administrator
Email: TACommC@nice.org.uk
Fax: +44 (0)20 7061 9760
Post: NICE, Level 1A, City Tower, Piccadilly Plaza, Manchester, M1 4BT

I confirm that:

- I agree with the content of the statement submitted by The Royal College of Physicians and consequently I will not be submitting a personal statement.

Name: DR. JENNIFER KING

Signed: [redacted]

Date: 22/3/13

Bosuntinib for previously treated chronic myeloid leukaemia STA

Personal Statement: David Ryner (CML patient carer)

I was the author of the nominating organization consultee, the Chronic Myeloid Leukaemia Support Group (CMLSG), submission for this STA. Unsurprisingly I agree with its contents.

I do not wish to add anything more except to say I am a carer of a Chronic Myeloid Leukaemia (CML) patient, diagnosed with an atypical presentation in accelerated phase, although not of one who has been treated with this particular tyrosine kinase inhibitor (TKI).

She has however received treatment with another TKI, imatinib, both as a stand alone treatment for some years and as a post transplantation part of a low intensity conditioning stem cell transplantation (SCT) clinical trial protocol.

I should add that since her diagnosis in 1999 I have met with very many carers and patients at specialist clinics, seminars, workshops, conferences etc.

I am aware of, and I think I am capable of summarizing more generally, both patient and carer perspectives in consensus form if ask to do so.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: Russell Cooper

Name of your organisation:

CML Support Group

Are you (tick all that apply):

a patient with the condition for which NICE is considering this technology?

- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

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Single technology appraisal (STA)

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. **Advantages**

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

To prevent or delay the onset of CML; to reduce the debilitating symptoms of the illness.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

To extend life expectancy; reduce the debilitating side-effects of CML.

The chance of a more focussed and effective treatment for CML than previous generations of drugs with fewer and less severe side-effects. (eg: muscle and bone ache, chronic fatigue.)

The offer of a chance of an improved life-style; a reduction in the amount of care required, the ability to work longer.

The opportunity to reduce stress not only for the patient but, more particularly, for close relations and carers.

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)

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Single technology appraisal (STA)

2. **Disadvantages**
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

What follows is necessarily subjective and, being on a cocktail of drugs, it is not easy to itemise which drug, if any, is responsible for which side-effects.

My experience of the disadvantages of Bosutinib are relatively minor. Like most I suffered from diarrhoea initially.

My experience since adjusting to Bosutinib is that since starting the treatment I have suffered from chronic haemorrhoids and intermittent, short-term visual disturbance, such as one might experience in a migraine. The associated headache is mild and not severe as might be expected with a migraine. The visual disturbance lasts from as little as 10 minutes to an hour.

It seems to me these debilitating side-effects are tolerable when compared with earlier drug experiences of chronic fatigue and the muscle and bone ache of earlier generational drugs.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

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Single technology appraisal (STA)

See the CML Support Group submission.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

See the CML Support Group submission.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

see CML Support Group submission

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)

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Single technology appraisal (STA)

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

See CML Support Group submission

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

See CML Support Group submission

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Single technology appraisal (STA)

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

It would extend and improve the quality of life for the patient and reduce the stress on close relatives and carers.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

An increase in stress for the patient and the patient's family. It would increase the stress and worry about whether an expensive drug was affordable for them.

Are there groups of patients that have difficulties using the technology?

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Other issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

N/A

Bosutinib for previously treated chronic myeloid leukaemia: a single technology appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School
Authors	Martin Hoyle, Senior Research Fellow, PenTAG
	Tristan Snowsill, Associate Research Fellow, PenTAG
	Marcela Haasova, Associate Research Fellow, PenTAG
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	Claudius Rudin, Consultant Haematologist, Royal Devon & Exeter Hospital, Exeter
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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Martin Hoyle	Project manager, led the critique of Pfizer's economic analysis, and contributed to the writing of the clinical and cost-effectiveness chapters.
Tristan Snowsill	Critiqued Pfizer's economic model and contributed to the writing of the cost-effectiveness chapters. Collated the final report.
Marcela Haasova	Critiqued clinical effectiveness evidence and wrote most of the clinical effectiveness chapter.
Chris Cooper	Critiqued Pfizer's searches for clinical and cost-effectiveness evidence.
Claudius Rudin	Advised on possible use of bosutinib in England and Wales and on CML in general.

About the Peninsula Technology Assessment Group (PenTAG)

PenTAG is part of the Institute of Health Service Research at the University of Exeter Medical School. PenTAG was established in 2000 and currently has two major work streams: independent health technology assessments (HTAs) for NICE and the NIHR HTA programme, and evidence synthesis work in relation to the needs of the SW Peninsula Collaboration for Applied Health Research and Care (PenCLAHRC), as well as for other local and national decision-makers.

The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics.

Website: http://sites.pcmd.ac.uk/pentag/

Disclosure of information

This report contains information designated by the manufacturer as 'commercial in confidence' and 'academic in confidence' (data awaiting publication). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

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Certain figures in this report are designated as commercial in confidence and this is indicated both by underlining and highlighting the caption and underlining and highlighting the figure (although the latter is not always obvious).

Where commercial in confidence and academic in confidence information can both be obtained from text or a figure, commercial in confidence takes precedence, i.e., marking as commercial in confidence does not preclude the information also being academic in confidence.

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LIST OF ABBREVIATIONS

AE/SAE/TEAE	Adverse event/ Serious adverse event/ Treatment-emergent adverse event
ALL	Acute lymphoblastic leukaemia
SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BC	Blast crisis
Bcr-Abl	Breakpoint cluster region-Abelson (an oncogene fusion protein consisting of BCR and ABL)
BMS	Bristol-Myers Squibb
BMT	Bone marrow transplant
BNF	British National Formulary
BP	Blast phase
BSC	Best supportive care
C(A)T	Computerised (axial) tomography
CC	Complication/comorbidity (HRG code)
CCyR	Complete cytogenetic response
CENTRAL	The Cochrane Central Register of Controlled Trials
cGvHD	Chronic graft versus host disease
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
DARE	The Database of Abstracts of Reviews of Effects
DET	Data extraction table
ECOG	Eastern Cooperative Oncology Group
EHA	European Haematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-	European Organisation for Research and Treatment of Cancer Quality of Life

C30	Questionnaire-Core 36
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life- 5 Dimensions questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EWB	Emotional well-being
FACT-Leu	Functional Assessment of Cancer Therapy- Leukemia
FDA	US Food and Drug Administration
FISH	Fluorescence *in situ* hybridisation
FLAG-IDA	Fludarabine, cytarabine, idarubicin and G-CSF chemotherapy regimen
FWB	Functional well-being
GBP	Great British Pounds (currency)
G-CSF	Granulocyte-colony stimulating factor
GP	General Practitioner
GVHD	Graft versus host disease
HCHS	Hospital and community health services
HDI	High-dose imatinib
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HTA	Health Technology Assessment
HTN	Hypertension
HU	Hydroxyurea/hydroxycarbamide
ICER	Incremental cost-effectiveness ratio
ICLLM	International Congress on Leukemia Lymphoma Myeloma
ICU	Intensive-care unit
IFN	Interferon alpha
IFR	Individual funding requests
IM-I	Imatinib-intolerant
IM-R	Imatinib-resistant
INHB	Incremental net health benefit
INR	International Normalised Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LEUS	Leukaemia subscale
MCyR	Major cytogenetic response
mg	Milligrams
MHR	Major haematological response
MiCyR	Minor cytogenetic response
MMR	Major molecular response

MUD	Matched unrelated donor
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	No evidence of leukaemia
NHB	Net health benefit
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation Database
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Clinical Excellence / National Institute for Health and Care Excellence
NR	Not reported
OHR	Overall haematological response
ONS	Office for National Statistics
OS	Overall survival
PAOD	Peripheral arterial occlusive disease
PAS	Patient Access Scheme
PB	Peripheral Blood
PBSCT	Peripheral blood stem cell transplant
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
Ph^+	Philadelphia chromosome-positive
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PWB	Physical well-being
QALY	Quality-adjusted life year
QTc	Corrected QT interval
RCP	Return to chronic phase
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
SmPC/SPC	Summary of Product Characteristics
STC	Stem cell transplant
SWB	Social well-being
TA[number]	Technology appraisal [number]
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor

UK	United Kingdom
ULN	Upper limit of normal
USA/US	United States of America
WBC	White blood cell
WHO	World Health Organisation
WTP	Willingness to pay

(Adapted from Pfizer submission, pp8–12)

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency.

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML)
- Hydroxycarbamide
- Interferon alpha
- Best supportive care

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 1.5.2, p30).

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence of bosutinib (Bosulif®) in treatment of adult patients with Ph+ CML was reviewed. The entire clinical evidence for bosutinib comes from a single arm, phase I/II multi-centre trial, Study 200. Because no RCT evidence was identified, separate clinical effectiveness evidence was submitted for the Scope defined comparators. Thirteen non-randomised comparator studies were included.

1.2.1 Bosutinib

Study 200 (Phase II) examined the efficacy and safety of bosutinib 500mg daily in 546 Ph+ CML patients with previous imatinib failure. Patients in all three phases of Ph+ CML were recruited; second line CP (N=288), third line CP (N=118), AP (N=76) and BP (N=64). In addition, based on

EMA recommendation, a subgroup of patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (population of unmet clinical need) was identified and analysed post hoc. Baseline characteristics across all phases of the disease and lines of treatment are summarised in Table 1.

Table 1. Study 200 baseline patient characteristics

Population	**Age (years) [Median (range)]**	**Male [N (%)]**	**CML duration (years) [Median (range)]**	**IM duration (years) [Median (range)]**	**ECOG performance status N (%)**		
					0	*1*	*2*
CP2L (n=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.11–22.06)	NR	41 (54%)	33 (43%)	2 (3%)
BP (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.35–14.46)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need (N=52)[b]	58 (19-81)	31 (605)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NR = not reported

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

In the complete population of Study 200, bosutinib was associated with good cytogenetic and haematological response rates and overall survival (Table 2). However, the OS data from Study 200 for CP patients is very immature. Cytogenetic and haematological responses were also observed among participants with mutations that would confer the use of nilotinib or dasatinib inappropriate (Table 3). Apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical need population. For example, MCyR was 60%, 42.9%, 60% and 18.2 % for second and third line CP and AP and BP unmet clinical need population respectively. However these response rates are based on very small sample sizes (N=3–21) and are therefore uncertain.

Table 2. Study 200 cytogenetic and haematological response rates for full Study 200 population

	Evaluable population			
	MCyR March 2011	*CCyR March 2011*	*CHR March 2011*	*K-M estimates of OS at 2 years*
CP2L	53.4%	41.4%	84.7%	90.6%[a]
CP3L	38.9%	30.6%	73.3%	84.0%[a]
AP	34.8%	24.6%	34.8%	65.6%[b]
BP	29.6%	20.4%	15%	35.4%[c]

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a 24 month minimum follow-up, median OS had not yet been reached

b 12 month minimum follow-up, median OS had not yet been reached

c 18 month minimum follow-up, median OS for BP patients was 11.1 months

Table 3. Study 200 response rates by baseline mutation

Mutation	**CP2L CHR [n/N %]**	**CP2L MCyR [n/N %]**	**CP3L CHR [n/N %]**	**CP3L MCyR [n/N %]**	**AP & BP CHR [n/N %]**	**AP & BP MCyR [n/N %]**
Y253	2/2 100%	2/2 100%	5/6 83%	4/6 67%	1/7 14.3%	2/7 28.6%
E255	0/2 0%	2/3 67%	NA	NA	0/4 0%	1/3 33.3%
F317	4/4 100%	3/4 75%	4/8 50%	1/7 14%	0/9 0%	0/6 0%
F359	8/9 89%	4/9 44%	0/2 0%	1/2 50%	0/2 0%	1/2 50%

Notes: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, n = numbers of participants with response, N = number of participants with mutation, NA = not applicable

Bosutinib was found to have an acceptable safety profile across all phases of the disease and lines of treatment. Low rates of transformation to the next phase of CML were observed on bosutinib treatment for both chronic and advanced phase populations (Table 4). Adverse events were mainly restricted to gastrointestinal toxicities (Table 4) and in the majority of cases these toxicities were mild in severity. The most common haematological events across all phases of the disease and lines of treatments in both the chronic and advanced phases of the disease were thrombocytopaenia, neutropaenia and anaemia. Severe cases of anaemia seemed to be more pronounced at the more advanced stages of the disease (Table 4). The profile of AE associated with bosutinib appears to be more similar to those associated with nilotinib than with dasatinib. In comparison, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections,

haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI.

Table 4. Study 200 safety

	CP2L	CP3L	AP	BP
Rates of disease transformation to the next phase of CML	3.8%	4%	6.4%	NA
Treatment discontinuation	58% (36 months minimum follow-up)	76% (24 months minimum follow-up)	NR	NR
Treatment discontinuation due to AE	23%	22%	23.7%	9.4%
Diarrhoea	85.3%	82.4%	85.5%	65.6%
Nausea	45.5%	48.7%	44.7%	50%
Vomiting	36.7%	39.5%	44.7%	39.1%
Rash	36%	26.9%	32.9%	31.3%
Thrombocytopenia Grade 3/4	24%	25.4%	32.9%	26.6%
Neutropenia Grade 3/4	18%	14.4%	14.5%	20.3%
Anaemia Grade 3/4	13%	5.1%	30.3%	18.8%

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable, NR = not reported

EQ-5D data were collected in Study 200. The mean EQ-5D utilities, averaged mostly over the first two years of treatment, were [redacted] in the CP 2nd-line, 3rd-line, AP and BP populations respectively.

1.2.2 Comparator treatments

No studies reporting on interferon alpha in a refractory setting were identified. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] However only 7 studies[3, 4, 6, 7, 10, 12, 13] were considered in Pfizer's submission as five SCT studies did not stratify results by disease phase.

In summary, the clinical effectiveness evidence for the comparator treatments is very poor. Hydroxycarbamide was considered to be a proxy for best supportive care. Participants in the comparator studies appear to be younger, and most of the comparator studies are small and the outcomes reported vary. Pfizer describe the HU comparator studies as "not strictly eligible" (p89 Pfizer Submission) for inclusion and only three included SCT studies[7, 10, 13] are considered to be a good quality evidence according to the Chambers (2009)[16] criteria (Pfizer submission, p216). This

further highlights the difficulty inherent to such naïve comparisons and impedes any comparisons of Study 200 with comparator studies.

The CP cost-effectiveness model used data from Kantarjian (2007)[3] for the clinical effectiveness of HU and Jabbour (2011)[10] for the clinical effectiveness of SCT. Of particular importance for the model are:

- OS after SCT in CP of 72% at year 2 in Jabbour (2011)[10]
- OS for HU in CP of 77% at year 2 and 70% at year 3 in Kantarjian (2007)[3]

No safety data were reported for HU, and the grade 3–4 graft versus host disease reported in SCT studies varied across the lines of treatment as well as the studies from 6.25% to 40%.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

First, the main weakness of the clinical effectiveness evidence is the fact that no RCT evidence was identified. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML. Similarly, the evidence for comparator treatments comes from 13 non-randomised comparator studies.

Second, the bosutinib licence is intended for treatment of adult patients with CP, AP and BP Ph+ CML patients previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. However only 52 of the 546 patients in Study 200 fulfilled the criteria for this unmet need population.

Third, Pfizer do not state the nature of treatments given after bosutinib failure. This means that the relevance of the OS data from Study 200 is uncertain, because many patients may have proceeded to take a different TKI on bosutinib failure. Also, the OS data in CP is very immature, which means that it is difficult to estimate mean OS, a key driver of the cost-effectiveness of bosutinib.

Fourth, we cannot stress enough, that the naïve comparison of the single arm Study 200 with non-randomised comparator studies is predisposed to bias. The evidence for the two comparator treatments, HU and SCT, is taken from small studies with populations that mostly did not meet the unmet need criteria.

Fifth, Pfizer present no evidence for the clinical effectiveness of IFN, which is one of the comparator treatments in the CP economic model.

1.4 Summary of cost-effectiveness evidence submitted by the manufacturer

Pfizer conducted a systematic review for cost-effectiveness evidence relating to the decision problem. This did not identify any relevant studies for bosutinib.

Pfizer therefore developed a *de novo* economic model to answer the decision problem. The model developed was an "area-under-the-curve" cohort model where patients could be on or off the principal treatment in the treatment arm and patients could undergo transformation to later disease phases (accelerated and blast crisis phase). Patients could start in either the chronic phase, accelerated phase or blast crisis phase and these are denoted the CP, AP and BP models.

Pfizer consider the following four treatment sequences in the CP model:

- Bosutinib followed by hydroxycarbamide, denoted (Bosutinib, HU),
- Hydroxycarbamide, denoted HU,
- Stem cell transplant, denoted SCT,
- Interferon followed by hydroxycarbamide, denoted (IFN, HU).

For the AP and BP models, they consider the same treatment sequences but without (IFN, HU).

Overall survival was estimated for (Bosutinib, HU) in the CP model using a MCyR surrogate method, which has been used previously by PenTAG in TA241. They did not however use this method to estimate overall survival for comparator treatments, instead extrapolating from trials and using clinical expert opinion. Overall survival for (Bosutinib, HU) in the AP and BP models was estimated by extrapolating from Study 200.

Time on bosutinib treatment was estimated by extrapolating from Study 200. Time on interferon treatment was extrapolated from clinical expert opinion. Patients did not discontinue hydroxycarbamide treatment and patients who received a stem cell transplant were assumed to receive no further drug treatment.

Resource uses and costs were generally based on previous assessments by PenTAG, TA241 and TA251.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 and TA241. Their only departure from our previous assumptions is their estimate of the utility after stem cell transplant in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Importantly, for the estimated utility under bosutinib treatment, they prefer the utilities that we have used previously for utilities for TKIs to those from their Study 200.

1.4.1 CP model results

Pfizer's analysis showed that (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY), and more effective and less costly than SCT, i.e., (Bosutinib, HU) dominates. Pfizer found that (IFN, HU) was less effective and more costly than HU (HU dominates). The ICER of (Bosutinib, HU) versus (IFN, HU) was [redacted] per QALY.

Table 5. Pfizer CP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	(IFN, HU)	SCT
Life years	12.75	3.52	3.62	6.60
QALYs	7.26	2.43	2.42	3.70
Costs	[redacted]	£29,473	£38,268	£171,539

QALYs and costs discounted at 3.5% per annum

1.4.2 AP model results

Pfizer's AP base case results showed that similar to the CP model (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY), and that (Bosutinib, HU) dominates SCT.

Table 6. Pfizer AP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	4.48	1.37	3.02
QALYs	2.76	0.90	1.96
Costs	[redacted]	£26,078	£178,093

QALYs and costs discounted at 3.5% per annum

1.4.3 BP model results

Pfizer's BP base case results showed that (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY). The results also showed that (Bosutinib, HU) was less effective and less costly than SCT (ICER [redacted] per QALY).

Table 7. Pfizer BP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	1.77	0.54	2.64
QALYs	0.88	0.28	1.28
Costs	[redacted]	£14,170	£200,526

QALYs and costs discounted at 3.5% per annum

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

In this section, we highlight our key areas of disagreement with Pfizer's analysis. As a result of our critique of their model, we have developed PenTAG base case ICERs (Section 1.7, p35) for each of the CP, AP and BP models. In order to develop our base case, we have adjusted the following items in Pfizer's CP model:

- The method of estimation of OS for all comparators using our "cumulative survival method",
- Mean overall survival on HU,
- Mean overall survival after SCT,
- Resource use in CP CML.

We have changed just the first item in Pfizer's AP and BP models.

1.5.1 Model wiring errors

We discovered an important wiring error in the version of the model that Pfizer originally sent us on 14th March 2013. Pfizer sent as a corrected version of their model on 19th April 2013. Their base case ICER for bosutinib versus HU in CP then decreased from [redacted] per QALY.

In order to check the wiring of Pfizer's cost-effectiveness model, we built a model that is completely independent of their model. We feel confident that there are no major wiring errors in Pfizer's corrected model because the results from our independent model are very similar to those of Pfizer's model.

1.5.2 Comparator treatment sequences

Pfizer model the four treatment sequences in CP in Section 1.4, p28. In addition, we believe it is important to model the sequence (Bosutinib, SCT) for patients eligible for SCT. In summary, we assume the following comparator treatment sequences for CP:

- (Bosutinib, HU),
- (Bosutinib, SCT) (only for those eligible for SCT),
- HU,
- SCT (only for those eligible for SCT),
- (IFN, HU).

For the AP and BP models, we assume the same comparators, but without (IFN, HU).

We believe that the most important comparison in all model phases is (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Furthermore, we understand that a minority of patients (<30%) will be eligible for SCT and hence (Bosutinib, HU) versus HU is the most important treatment comparison in all disease phases.

1.5.3 Method of overall survival (OS) estimation

As stated in Section 1.4, p28, in the CP model, Pfizer use very different methods to estimate OS across treatments in the CP model. We believe that this lack of consistency, the lack of randomised evidence, and problems specific to the estimation of OS for bosutinib using the MCyR surrogate relationship leads to the following important prediction that lacks face validity. The mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) (shown in Figure 1 below). We believe, and clinical expert advice confirms, that this is unreasonable. Furthermore, this assumption dramatically biases the cost-effectiveness in favour of (Bosutinib, HU) versus HU because the price of HU is negligible.

Figure 1.

[redacted]

Although OS for all treatments is consistently estimated by extrapolating trial data in the AP and BP model, we believe there are still serious problems with Pfizer's method of estimating OS for all treatments in AP and BP. This similarly leads to the implausible prediction that, in both the AP and BP models, the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm.

Instead, we suggest that a far more parsimonious method is required to estimate OS across comparators. Indeed, we suggest such a method, which we describe as the Cumulative Survival method. We believe that it is far preferable for estimating OS for all comparator treatments for all

model phases. We believe that it should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The key assumption of the Cumulative Survival method is that in the (Bosutinib, HU) and (IFN, HU) arms, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. In Figure 1, the heights of the HU sections then become approximately equal. Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

The revised cost-effectiveness results are then:

- In the CP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases substantially, from [redacted] to [redacted] per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY.
- In the AP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY.
- In the BP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY. In their base case, Pfizer estimate an ICER of [redacted] for (Bosutinib, HU) versus SCT, with (Bosutinib, HU) cheaper and less effective than SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY, i.e. (Bosutinib, SCT) gives poor value versus SCT.

Of all the changes we make to Pfizer's model, this has the largest impact on the estimated cost-effectiveness of bosutinib.

1.5.4 OS for HU in CP

Relevant data for OS on HU for patients in CP is sparse. Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] We used this study for this purpose in TA251. Pfizer claim that the agreed estimate of mean OS for HU in CP was 3.5 years in TA251, and they therefore use this value in their base case. However, we disagree. Instead,

we calculated a mean OS of 7.0 years in TA251.[17(p164)] Furthermore, the 3.5 years estimated by Pfizer is clearly incompatible with the Kaplan-Meier OS curve from this study.

The quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is clearly poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available for this purpose.

Pfizer's base case ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY, and the cost-effectiveness of (Bosutinib, HU) versus SCT is unchanged.

1.5.5 OS after SCT in CP

Relevant data for OS after SCT for patients in CP is also sparse. Pfizer's base case estimate of OS after SCT for patients in CP was based on data from the study Jabbour and colleagues (2011).[10] Whilst we agree that this study is relevant, the sample size is extremely small, with only 16 CP patients contributing to the estimates of OS. Instead, we use data from the study by Oehler and colleagues (2007),[12] in our base case, as it is relevant, has a much larger sample of 72 patients and reports OS that is more consistent with the OS from two other relevant studies. Our estimated OS of 11.6 years is far greater than Pfizer's estimate of 6.6 years.

Pfizer's base ICER for (Bosutinib, HU) versus HU then remains unchanged, and (Bosutinib, HU) still dominates SCT, but the cost-effectiveness of (Bosutinib, HU) deteriorates versus SCT.

1.5.6 Medical management costs in CP

Pfizer's assumptions for medical management, monitoring and testing are based on those that we originally used in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey. However, Pfizer seem unaware that after the first NICE committee meeting for TA251, our assumptions were challenged by Novartis, the manufacturer of nilotinib. In response, we amended some of our assumptions for resource use in CP CML in TA251, and these were accepted by the NICE committee.

These changes plus changes to resource use assumptions for patients after SCT are reflected in our base case assumptions. When we amend Pfizer's model, their ICER for (Bosutinib, HU) versus HU decreases from [redacted] to [redacted] per QALY and (Bosutinib, HU) continues to dominate SCT.

1.5.7 Line of treatment

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used 2nd-line. However, we believe that bosutinib will be

used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis also assumes 3rd-line use of bosutinib, and we consider use of bosutinib in 2nd-line in an important scenario analysis.

Pfizer estimate the mean time on 3rd-line bosutinib in CP from Study 200 as [redacted]. Based on the Kaplan-Meier data from Study 200 we requested from Pfizer, we estimate the mean time on 2nd-line bosutinib as being far longer, at [redacted].

Changing Pfizer's model for this estimate and for the 2nd-line MCyR from Study 200, Pfizer's base case ICER for (Bosutinib, HU) versus HU for CP increases substantially, from [redacted] to [redacted] per QALY and (Bosutinib, HU) changes from dominating SCT to being more costly and more effective than SCT (ICER [redacted] per QALY).

1.5.8 Utilities

In short, we accept Pfizer's utilities. However, we believe that there are strong arguments that we should instead use the utilities from Study 200 for bosutinib treatment, and our estimate of 0.80 after SCT in CP in preference to their estimate of 0.71.

In the first case, Pfizer's ICER for (Bosutinib, HU) versus HU in CP increases marginally, from [redacted] to [redacted] per QALY.

In the second case, based on Pfizer's analysis, (Bosutinib, HU) still dominates SCT in CP, but to a lesser extent.

1.5.9 End of Life criteria

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML. By contrast, we believe bosutinib does not meet the criteria in any phase of CML. We believe that bosutinib does not quality in AP and BP due to lack of robustness of the estimates of extension to life.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- Pfizer's analysis was clearly described in their report.
- We found only one important wiring error in Pfizer's model.
- The structure of Pfizer's model is mostly consistent with the natural history of CML.
- With the exception of the Cumulative Survival method, Pfizer clearly studied TA241 and TA251 in detail and adapted their model accordingly.
- The time on bosutinib treatment from Study 200 is mature.

- Extrapolations for time on bosutinib treatment appear reasonable.
- The modelled unit costs seem appropriate.
- The modelled utilities are plausible.

1.6.2 Weaknesses

- The clinical effectiveness evidence is taken from a single non-randomised trial (Study 200).
- Only a small subset of the patient population in Study 200 reflects the population indicated for bosutinib.
- Although some effectiveness results are presented for the patients indicated for bosutinib, some key effectiveness results, such as time on bosutinib treatment, are not.
- OS for patients on bosutinib in CP is very immature.
- In Pfizer's model, all patients were assumed to receive hydroxycarbamide following bosutinib failure. Instead, we believe that some patients would receive SCT after bosutinib.
- Pfizer's important prediction that the mean time in the CP model on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) lacks face validity.
- We believe that Pfizer's estimate of mean OS on HU in CP is logically flawed, as described in Section 1.5.4, p32.
- We believe that Pfizer's estimate of mean OS after SCT in CP is biased, as described in Section 1.5.5, p33.

1.6.3 Areas of uncertainty

There is substantial uncertainty in almost all the key parameters of Pfizer's model. Much of this has already been discussed above, but some of the key parameters which are uncertain include:

- The line of treatment that clinicians would use bosutinib if it were recommended by NICE,
- Mean OS on bosutinib in all phases, specifically for patients unsuited to TKIs,
- Mean time on bosutinib treatment in all phases, specifically for patients unsuited to TKIs,
- Mean OS on HU in all phases of CML,
- Mean OS after SCT in all phases of CML,
- Utilities for patients after SCT.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Summaries of the derivation of our base case ICERs and sensitivity analyses are given in the following tables below:

- Table 8 and Table 9 (CP)

- Table 10 (AP)
- Table 11 (BP)

The key treatment comparisons are highlighted in bold: (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Our base case ICERs for these key comparisons are as follows:

- CP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY
- AP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY
- BP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY

Table 8. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) versus**			**(Bosutinib, SCT) versus**		
	Comparator	*HU*	*SCT*	*IFN*	*HU*	*SCT*	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	n/c	n/c	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	n/c	n/a		
1+2[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+3[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+4[b]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+3+4		[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from Pfizer base case

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT

b Interferon is more costly and more effective than hydroxycarbamide
c Interferon is less costly and less effective than hydroxycarbamide

Table 9. Important scenario analyses applied to PenTAG base case for CP model

Intervention	**(Bosutinib, HU) versus**			**(Bosutinib, SCT) versus**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	[redacted]	[redacted]	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	[redacted]	Dominant	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	[redacted]	[redacted]	[redacted]
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
SCT utility set to TA251 utility	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]

n/c – Not changed from PenTAG base case
Shading as in Table 8
a (Bosutinib, HU) is less costly and less effective than SCT

Table 10. Derivation of PenTAG base case AP CML

	Intervention	**(Bosutinib, HU) versus**		**(Bosutinib, SCT) versus**	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

Shading as in Table 8

Table 11. Derivation of PenTAG base case BP CML

	Intervention	**(Bosutinib, HU) versus**		**(Bosutinib, SCT) versus**	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

Shading as in Table 8
a Bosutinib is less costly and less effective than SCT

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

Leukaemia is a form of cancer affecting blood. Chronic myeloid leukaemia (CML) is characterised by excessive proliferation of white blood cells (mainly granulocytes) in the bone marrow, and an initial slow disease progression.[2] The Haematological Malignancy Research Network (HMRN) estimates that 560 cases of CML are newly diagnosed in the UK each year; an annual age-standardised rate of 1.2 per 100,000 for men and 0.7 per 100,000 for women (based on HMRN 2004-11 and 2001 UK census data). Natural history and epidemiology of CML, technologies and clinical pathways available, as well as the patients' life expectancy were described in Sections 2.1–2.6 of the manufacturer's submission.

2.1.1 Natural history of CML

The introduction of TKIs in the treatment of CML has changed the management and outcome of this disease dramatically. Although a true cure for CML is not generally achieved, CML was transformed from an immediately life-threatening cancer, with a 10–20% mortality rate per year, to a disease, managed with oral medications, and with 1–2% mortality per year.[18]

CML is characterised by the presence of the BCR-ABL fusion gene as the result of a reciprocal chromosome translocation between chromosomes 9 and 22; t(9q34;22q11). This acquired (non-inherited) translocation results in a truncated derivative chromosome 22 known as the Philadelphia chromosome. Approximately 90–95% of the CML population are Philadelphia chromosome positive (Ph+). A further 5% do not exhibit the characteristic Philadelphia chromosome, but have cryptic chromosomal rearrangements resulting in the BCR-ABL fusion gene. The resulting Bcr-Abl fusion protein is a constitutively active tyrosine kinase, resistant to apoptosis (programmed cell death). It phosphorylates numerous substrates, disrupting the regulation of intracellular signal transduction pathways, promoting proliferation and genetic instability.

CML has three phases: chronic (CP), accelerated (AP) and blast (BP), each corresponding to increasing leukaemic blast counts in the blood and bone marrow and clinical severity ([Pfizer submission] Table 3). Blast is a term which describes an immature blood cell of any type. Normally, a blast will develop into a mature blood cell, but in CML these cells are abnormal and do not fully develop, becoming known as leukaemic blasts.

Approximately 90% of patients are diagnosed while in CP, 9% in AP and 1% in the BP. If left untreated, the average time a patient would remain in CP, AP and BP is 3–5 years, 6–24 months and 6 months, respectively.

(Source: Pfizer submission, p23)

2.1.2 Epidemiology

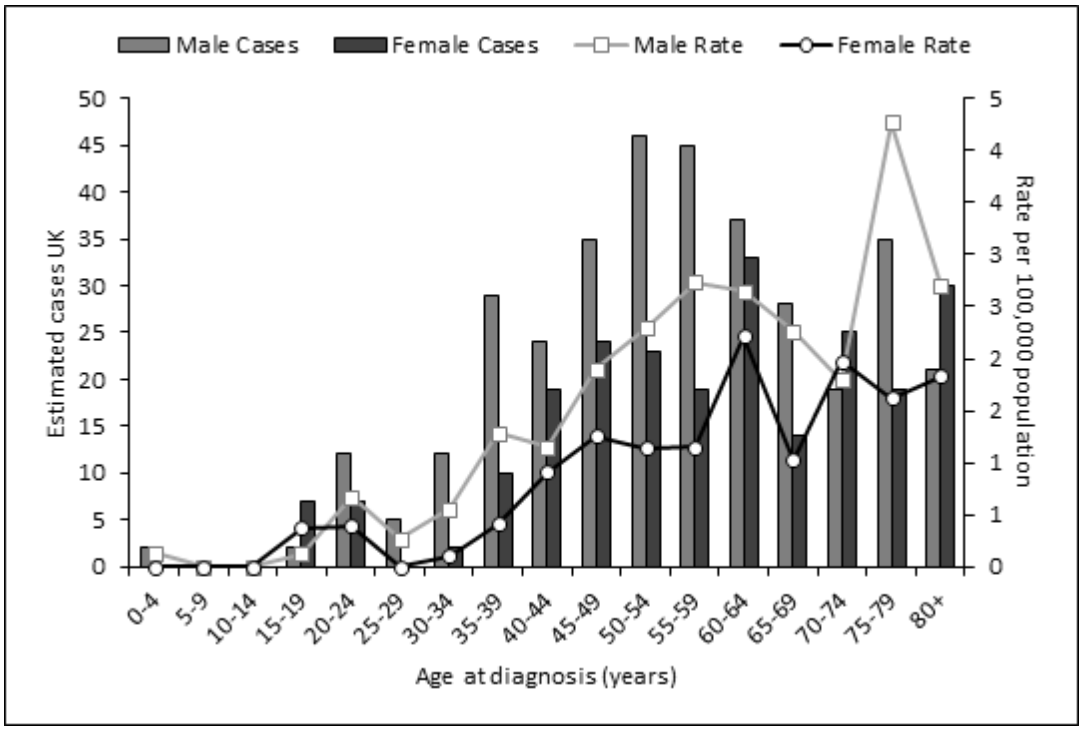
CML occurs in all age groups, but is most common in older adults and the median age at diagnosis is 59.1 years. A French study has shown that the prevalence of CML is increasing. In the pre-imatinib era, prevalence increased 4.1% annually (from 1998 to 2002), however, since the introduction of imatinib a mean annual increase of 9.3% has been observed (from 2003 to 2007). Apart from the impact of imatinib, better diagnosis and an aging population may play a part in increasing prevalence.

In 2003, the prevalence of CML in England and Wales was estimated at 2,660. Therefore, assuming a mean annual increase in cases of 9.3% since then, current prevalence of CML in England and Wales is estimated at 5,922.

(Source: Pfizer submission, p24)

Figure 2 shows the HMRN gender and age specific incidence estimates for CML.

Figure 2. Estimated age-specific incidence of CML[19]



Pfizer's estimates of the annual incidence of patients in the unmet need population at each phase of CML are given in Appendix A. In summary, they assume that bosutinib will be used mostly 4th-line, after 3 previous lines of TKIs: 12 patients p.a. 2nd-line, 19 p.a. 3rd-line and 49 p.a. 4th-line.

2.1.3 Prognosis

> If left untreated CML will typically progress from the CP to the AP in 3-5 years, and then to BP within 6-24 months. Median survival in the BP, without treatment, is around 6 months. As such, the typical life expectancy for a CML patient diagnosed in CP is around 4-7 years without treatment.
>
> The majority (>90%) of patients are diagnosed with CML in CP. Imatinib currently represents the established first-line treatment for these CP CML patients in clinical practice, having replaced interferon alpha upon its introduction. This new treatment paradigm has led to a dramatic improvement in the prognosis for patients diagnosed with CP CML. The estimated median survival with imatinib exceeds 25 years with median age of diagnosis of almost 60 years.
>
> Patients who respond well to standard-dose imatinib treatment (approximately 55% of patients) will often continue to receive this treatment for life and have a normal life expectancy.

(Source: Pfizer submission, p24)

We agree with Pfizer's statement above. However, our clinical advisor suggests that whilst imatinib used to be the 1st-line treatment of choice, nilotinib is now preferred given the recent NICE TA251 guidance. Treatments and clinical pathways are discussed in detail in Section 2.2.1, p43.

Two prognostic staging scores, developed prior TKI treatments, are available: the Sokal[20] and the Hasford[21] scores. Risk factors are used to determine if a patient is at a low, intermediate or high risk of death. In addition, The European Treatment and Outcome Study (EUTOS) prognostic scoring system was developed after the first TKI was introduced.[22] Although the Sokal and Hasford scores were briefly mentioned in the submission (Pfizer submission, p24), no risk factors were reported for Study 200 participants. While risk factors may allow comparisons across studies, our clinical advisor suggests they are not used to make treatment decisions.

2.1.4 Quality of life

We agree with Pfizer's description of HRQL for CML patients:

> Patients in the CP may experience mild and non-specific symptoms such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss. Approximately 40% of CP patients are asymptomatic and diagnosed as a result of a routine blood test. Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising,

bleeding and infections. In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.

Health-Related Quality of Life (HRQL) for CML patients can vary greatly, depending on the treatment regime used. The introduction of effective therapies such as those of the TKI class has led to improvements in the HRQL of CML patients. In contrast, there is some evidence that CML patients treated long-term with interferon alpha may experience reduced HRQL.

(Source: Pfizer submission, p23)

2.1.5 Rationale for bosutinib

Treatment options are limited for patients who have previously tried all three currently available TKIs (i.e. fourth-line patients) or second- and third-line patients for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. There is a clear unmet need for an effective treatment for these patients, the majority of who will currently be managed with hydroxycarbamide, which represents best supportive care (BSC).

(Source: Pfizer submission, p25)

Mutations in the BCR-ABL kinase domain often lead to imatinib resistance, particularly secondary resistance, and are often responsible for treatment failure:

The proposed indication for bosutinib is as a treatment for patients who have been previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are inappropriate. In some cases, a patient may be inappropriate for one of these TKIs as a result of the presence of Bcr-Abl mutations that confer resistance to currently available TKIs. Bosutinib has demonstrated clinical activity in CML patients with mutations that confer resistance to currently available TKIs. In a study of CP CML patients, treatment with bosutinib in the third-line setting resulted in complete haematological responses and major cytogenetic responses across a broad range of Bcr-Abl mutants, including those conferring clinical resistance to nilotinib (Y253H, E255K/V, F359C/I/V) and dasatinib (F317L). Efficacy of bosutinib in CML patients with a broad range of Bcr-Abl mutations have also been demonstrated for bosutinib in a second-line setting. Bosutinib is therefore innovative in its potential to treat a patient group, with unmet needs, which is identifiable by its genetic characteristics: Bcr-Abl kinase mutations conferring resistance to current TKIs.

(Source: Pfizer submission, p33)

Unfortunately Bosutinib was found to be ineffective in patients with the T315I gatekeeper mutation.[23]

2.2 Critique of manufacturer's overview of current service provision

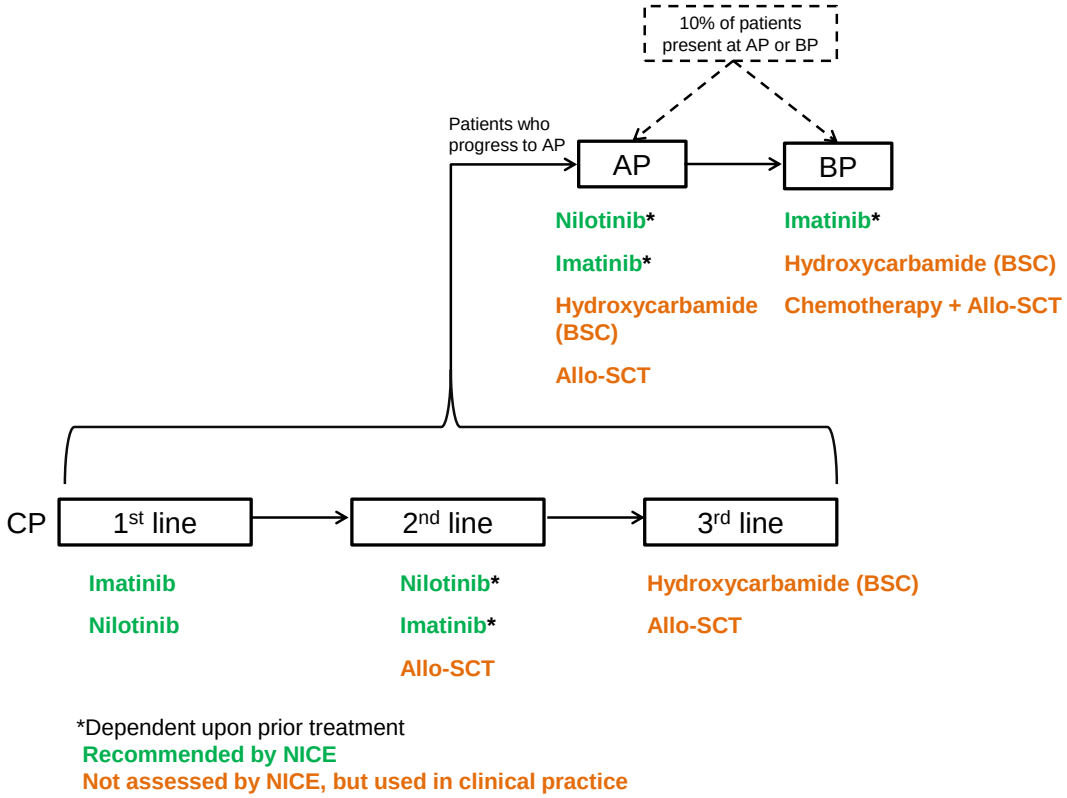
2.2.1 Current treatments for CML

We agree with Pfizer's assertion (Pfizer submission, p27) that the previous NICE technology appraisals that are relevant to the current appraisal are:

- TA251, 2012, 'Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)'.
- TA241, 2012, 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review TA70) and dasatinib and nilotinib for people with chronic myeloid leukaemia for whom treatment with imatinib has failed because of intolerance'.
- TA70, 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia. This guidance has now been partially updated by TA241 and TA251.

We further agree with Pfizer's summary of NICE recommended treatments for Ph+ CML, as shown in Figure 3 and in the text below (p28 Pfizer submission, p28).

Figure 3. NICE recommended clinical pathway of care



(Source: Pfizer submission, Figure A2)

NICE recommendations for 1st-line treatment are as follows (Figure 3):

- Nilotinib and standard-dose imatinib in CP CML (TA251).
- Dasatinib is not recommended for 1St-line use in CP, despite having an EMA marketing authorisation (TA251).
- Imatinib for CML that initially presents in AP or BP or that initially presents in CP and then progresses to AP or BP if imatinib has not been used previously.

NICE recommendations for 2nd-line treatment are as follows (Figure 3):

- Nilotinib for the treatment of CP or AP that is resistant or intolerant to standard dose imatinib (TA241).
- Dasatinib is not recommended for 2nd-line use for any phase of CML, despite having an EMA marketing authorisation (TA241).
- High-dose imatinib is not recommended for 2nd-line use for any phase of CML (TA241).
- NICE recommendations allow for the use of standard-dose imatinib 2nd-line after treatment with 1st-line nilotinib.
- NICE does not make any recommendations for treatment of patients in BP that is resistant or intolerant to standard-dose imatinib.

The following claim from Pfizer (Pfizer submission, p29) seems reasonable:

> There remains significant unmet need in the treatment of CP, AP and BP CML. Development of resistance, progression of disease despite treatment and intolerance to the currently recommended TKIs (imatinib, nilotinib and dasatinib) pose a significant challenge in the treatment of these patients and may cause withdrawal of therapy and can adversely affect compliance and outcomes. Furthermore, the presence of specific mutations or co-morbidities may render current therapies inappropriate. Hydroxycarbamide represents the main option in this patient population and therefore equates to best supportive care (BSC) for these patients. Given the limited efficacy of hydroxycarbamide (BSC), these patients represent a population of significant unmet need, for whom bosutinib offers an effective alternative.

We also agree with Pfizer's statements concerning the use of allogeneic stem cell transplantation (SCT) as follows (Pfizer submission, pp30–31):

> SCT is a treatment option for patients in CP, AP and BP and may be used in patients who have failed (due to lack of efficacy or tolerability) on currently available TKIs or for whom TKIs are inappropriate. In BP, SCT is typically preceded by treatment with acute leukaemia-style chemotherapy to try and establish haematological control. Bosutinib may therefore be considered as an alternative to SCT in CP, AP and BP patients, however as noted in Section 2.3 [Pfizer submission],

SCT is restricted by the number of matched donors available and is associated with high levels of morbidity and mortality.

The probability of success of this procedure is influenced by many factors, including (but not limited to): patient age, timing of the transplant, availability of a matched donor and level of progression of the disease. Therefore, SCT does not occupy a single, well-defined space in the CML pathway of care and could be applied at various stages of this pathway depending upon a complement of patient-related factors and the preference of the responsible physicians. This tends to be reflected in the evidence base for SCT, whereby the population is frequently heterogeneous including patients at different lines of treatment and even phases of CML. Additionally, its use in patients who are not suitable for or who have failed on all currently available TKIs is not known.

2.2.2 Bosutinib use in 2nd-, 3rd- and 4th-line treatment

Here we discuss the likely relative use of bosutinib across 2nd-, 3rd- and 4th-line lines of treatment. This is important because this dictates the most relevant clinical data to use in the economic model.

Pfizer assume that bosutinib will be used mostly 4th-line, after 3 previous lines of TKIs. In particular, they assume 12 patients p.a. 2nd-line, 19 p.a. 3rd-line and 49 p.a. 4th-line (Appendix A). For their economic model, Pfizer use clinical data from 3rd-line bosutinib as justified below:

With regards to the use of bosutinib in CP in practice, very few second-line patients are likely to be unsuitable for imatinib, nilotinib and dasatinib. As such, the third-line cohort from Study 200 is the focus for this submission as this is more likely to be representative of the patients expected in clinical practice, the majority of whom will likely be at least third-line. Data from the second-line CP CML patient population are only presented in Appendix 10.15 [Pfizer submission] for completeness.

(Source: Pfizer submission, p46)

Pfizer indicate that if 4th-line data were available from Study 200, they would have used this in their model (Pfizer submission, Section 7.2.1, p108).

Pfizer assume that most patients will receive imatinib 1st-line, and that dasatinib will be available in England & Wales, despite not being recommended by NICE in TA241 and TA251. They justify this by its current use under the Cancer Drugs Fund or individual funding requests (IFR).

By contrast, we believe that, if recommended by NICE, bosutinib will be used most often either as 2nd- or 3rd-line treatment, but rarely 4th-line.

Both imatinib and nilotinib, but not dasatinib, are recommended by NICE as 1st- and 2nd-line treatments in CP. Since NICE's TA251 recommendations, we understand that nilotinib has replaced imatinib as the 1st-line TKI of choice because it is similar in action to, but more potent than imatinib. Further, we understand that clinicians would be unlikely to use imatinib after nilotinib failure for the same reason. Dr Byrne, representing the Royal College of Pathologists and the BSH, appears to agree, stating (in a statement to NICE for this appraisal):

> Since an increasing number of patients are now receiving Nilotinib as a 1st-line treatment, this limits its usefulness as a 2nd-line agent in these patients. Furthermore as Nilotinib is generally accepted as a more potent bcr-abl inhibitor than Imatinib, with activity in many but not all the known mutations, there is little point in switching patients who have failed Nilotinib to Imatinib. However, Imatinib may be useful as a 2nd-line agent for patients experiencing toxicity on Nilotinib.

In contrast to Pfizer, we assume that dasatinib will be used only rarely from 2014 because we understand that the Cancer Drugs Fund is due either to end completely or to be scaled down in 2014, and because NICE have not recommended it for 1st- or 2nd-line use.

We imagine that if bosutinib were recommended by NICE in this appraisal, it will be used most heavily 2nd-line, after nilotinib, given that clinicians would be disinclined to use imatinib 2nd-line as it is less potent than nilotinib and given that dasatinib would not be available. However, it is possible that, at least initially, clinicians may prefer to delay use of bosutinib because they will be unfamiliar with it and because of the rather high treatment discontinuation rates. In this case, the preferred treatment sequence may be nilotinib then imatinib then bosutinib, i.e. bosutinib 3rd-line.

Bosutinib has a licence for patients who are unsuitable for imatinib, nilotinib and dasatinib. If it did not have this restriction, we imagine that it would be the 2nd-line treatment of choice after nilotinib. In particular, it is possible that most of the predicted 234 p.a. patients who Pfizer predict to fail on a 1st-line TKI would be treated with bosutinib 2nd-line. However, most patients who fail on 1st-line nilotinib will be suited to either imatinib or dasatinib. Given the restriction of the licence for bosutinib, these patients would then not be eligible for bosutinib, and they would instead likely receive 2nd-line imatinib, HU or SCT.

[redacted]. However, for the reasons given above, we imagine these sequences of treatment will be less likely to be relevant from 2014, given

that now most patients receive 1st-line nilotinib and we predict that dasatinib will rarely be used from 2014.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency (see Section 3.2 below).

The clinical evidence for bosutinib is taken entirely from Study 200, a single arm trial. The fitness of patients in this trial, as measured by ECOG, is representative of patients in clinical practice in England & Wales. However, the main weakness in the relevance of this evidence to the patient population in question is that most patients in this trial were suited to imatinib, nilotinib or dasatinib. Indeed, only 52 out of a total of 546 patients in Study 200 were not suited to all TKIs.

Other, probably more minor, weakness of Study 200 are that: (a) approx. 40% of patients had previously taken IFN, but IFN is now virtually never given for CML in the UK and (b) all patients had previously been treated with imatinib, but we understand that since TA251, 1st-line treatment for CML is now usually nilotinib.

3.2 Intervention

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

Pfizer state (Pfizer submission, p18):

> European Medicines Agency (EMA) filing originally occurred on 29th July 2011 for the indication stated below. This application was initially based on data from a pivotal phase III study, 3160A4-3000-WW (Study 3000). This was a randomised, open-label study comparison with imatinib. At this time the proposed indication applied for was:
>
> Bosutinib is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph^+ CML) in chronic phase (CP).

In this RCT, bosutinib failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib. Furthermore, toxicity with bosutinib was more pronounced than with imatinib. (EMA assessment report for bosutinib, Jan 2013).

Pfizer continue (p18 submission):

> Following ongoing discussions with the EMA, Pfizer agreed to revise the indication for bosutinib to:
>
> Bosutinib is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
>
> On the 17th January 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for bosutinib in this indication.
>
> In addition, the COMP adopted a positive opinion on the maintenance of orphan designation for bosutinib in EU in this indication on February 13th 2013

The final EPAR is now available on the EMA website.

3.3 Comparators

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML),
- Hydroxycarbamide,
- Interferon alpha,
- Best supportive care.

The comparators in the submission are as in the Scope, but without "best supportive care". Pfizer justify this by saying that hydroxycarbamide is accepted as best supportive care (Pfizer submission, p31), and we agree.

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 2.2.2, p45).

3.4 Outcomes

The outcomes in the Final Scope are as follows:

- overall survival,
- event-free survival,
- progression-free survival,
- time to progression,
- response rates: cytogenetic, haematological and molecular, including time to response and duration of response
- time to treatment failure
- adverse effects of treatment
- health-related quality of life

Pfizer consider all these outcomes in their submission. In addition, they consider rates of transformation from CP to AP/BP CML.

One important limitation of Pfizer's economic analysis is that, given that overall survival (OS) is immature for CP patients in Study 200, they estimate OS using a surrogate relationship based on the rate of major cytogenetic response.

The EQ-5D was used in Study 200, which is NICE's preferred instrument for measured health-related quality of life.

3.5 Other relevant factors

Pfizer present a discussion on matters of equity (Pfizer submission, p33) in which they state:

> There are no specific equality issues relating to bosutinib itself, however, the inclusion of bosutinib as an additional treatment option in the clinical pathway of care may help to address some of the equality issues associated with SCT, […]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

We validated the search strategy, critically appraised the systematic reviews described in Pfizer submission and critically appraised both the single arm phase I/II trial Study 200, the base of clinical effectiveness for bosutinib, as well as the studies with comparator data evidence. The power calculations for Study 200 were also re-run. The work has been undertaken between 11 March and 15 May 2013.

4.1.1 Searches

Pfizer provided detailed information on the search strategy. The complete search strategy (as included in Pfizer submission) is presented in Appendix B. In summary, the following search approach was used in Pfizer submission:

The following electronic databases were searched:

Medline (R) In-Process & Other Non-Indexed Citations
(searched from 1946 to January 21st 2013)
Ovid MEDLINE (R) 1946 to present (via OVID; searched from 1946 to January 21st 2013)
EMBASE, 1980 to present (via OVID; searched from 1974 to January 18th 2013)
The Cochrane Library (via OVID), searching the following databases:
The Cochrane Central Register of Controlled Trials (CENTRAL; searched to December 2012)
The Cochrane Database of Systematic Reviews (Cochrane Reviews; searches from 2005 to December 2012)
The Database of Abstracts of Reviews of Effects (DARE; searched 4th Quarter 2012)
The Health Technology Assessment Database (HTA; searched 4th Quarter 2012)
NHS Economic Evaluation Database (searched 4th Quarter 2012)

The following conference proceedings were searched (2010-2012):

American Society of Haematology (ASH)
American Society of Clinical Oncology (ASCO)
European Haematology Association (EHA)

(Source: Pfizer submission, adapted from Appendix 2, p201)

The searches were run in January 2013. The search strategy for the electronic databases took terms for CML and combined this with terms for imatinib (though this was restricted to incidences of intolerance, failure or resistance), hydroxycarbamide, stem cell transplantation, interferon, and bosutinib. A limit to systematic reviews and trials was used for this search. No separate searches were conducted for adverse event (AE). This could have compromised AE information.

In summary, the literature searching and search methods were found appropriate to the research question.

4.1.2 Inclusion criteria

Because of the lack of RCT evidence, the submission included separate clinical evidence for bosutinib and bosutinib comparators. The following study designs were included:

No RCTs were identified in the systematic review that specifically matched the licensed population for bosutinib. The data on which the license has been derived comes from a single-arm study, Study 200. The Study 200 Clinical Study Report (CSR), provides data across four cohorts of patients recruited separately into the study. In addition, a number of publications and conference abstracts/posters based on Study 200 are also available and are presented in this submission.

(Source: Pfizer submission, p44)

Comparators

No studies specifically evaluating comparator treatments in patients for whom imatinib, nilotinib and dasatinib are unsuitable were found. However, the systematic review identified 13 comparator studies that, like bosutinib, considered the use of the comparators in the broad second-line or later populations, in CP, AP and BP.

(Source: Pfizer submission, p48)

Inclusion and exclusion criteria as described in Table 12 are appropriate.

Table 12. Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years) with CP, AP and/or BP CML who have failed imatinib treatment	
Interventions/Comparators	• Bosutinib • Interferon alpha • Hydroxycarbamide (hydroxyurea) • SCT	
Outcomes	Efficacy: • Treatment response rates (including molecular, cytogenetic and haematological responses) • Time to- and duration of response • Overall survival • Event-free survival • Progression-free survival • Time to treatment failure • Health-related quality of life Safety/Tolerability: • Adverse events (all grades) • Incidence of serious adverse events	
Study design	• Prospective randomised controlled trials (RCTs) • Observational studies	Single case studies
Language	English abstracts of foreign language publications	Non-English publications

(Source: Pfizer submission, Table B1, p43)

4.1.3 Critique of data extraction

The submission explains the processes used in study selection and data extraction which is in line with the standard review process. The screening of the literature was performed by one reviewer and inclusion and exclusion criteria were verified by a second reviewer. Any disputes were resolved by a third party. The following data extraction strategy was used:

> Results from database searches were downloaded into a bespoke Access® database, which was used to manage citation screening. Following full-text review and identification of studies to be included, data was extracted into a Data Extraction Table (DET). The DET included, but was not limited to, the following column headings:

- Country
- Study design
- Number of patients
- Key inclusion and exclusion criteria including subgroups
- Baseline characteristics
- Outcomes reported as summarised on page 6
- Likelihood of bias (quality components)

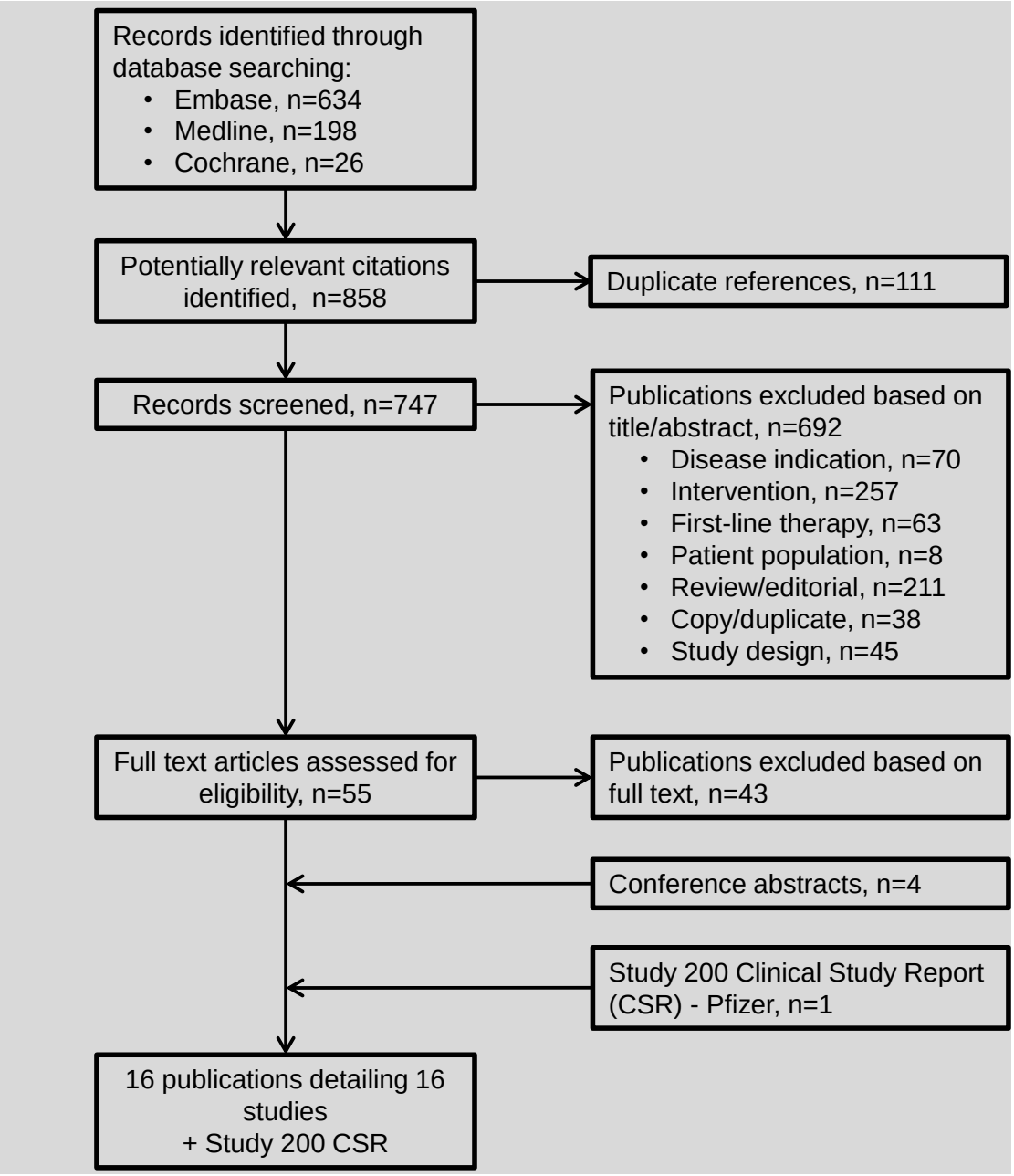
This data extraction was performed by one reviewer and verified by a second party.

(Source: Pfizer submission, Appendix 10.2.7, p212)

Overall, 16 studies were identified (Figure 4, p55), of these 13[3-15] reported on comparator treatments, and three[24-26] reported on bosutinib. All bosutinib studies are related to phase I/II Study 200 (NCT00261846; 3160A4-200). Further information on Study 200 was extracted from the Pfizer CSR,[27] and two conference posters based on Study 200 were identified.[1, 28] In addition, a similar on-going phase I/II study trial (NCT00811070; 3160A4-2203) evaluating bosutinib in Japanese subjects is expected to be completed in September 2014. Both Study 200 and the trial evaluating bosutinib in Japanese subjects, are Pfizer funded studies.

[redacted] Pfizer did not supply us with any information about the results from the Japanese trial. However, we found that some information on this phase I/II trial was reported in the EMA assessment report for Bosulif.[29] Given that Study 200 is a large multi-centre trial (conducted in North America, the European Union, Eastern Europe, Africa and Asia), and includes patients in all stages of CML, we believe that the lack of the results from the Japanese population (N=53) is not a significant weakness of the submission. In addition, one more study based on Study 200 and not identified in the submission, a study reporting baseline HRQL,[30] was identified.

Figure 4. Flow diagram of included studies



(Source: Pfizer submission, Figure B1, p44)

4.1.4 Quality assessment

We will now discuss Study 200, the clinical evidence for the comparator treatments is discussed in 4.3 (p95). Pfizer's quality assessment of Study 200 was performed according to the Chambers (2009) criteria for case series studies.[16] Further information on the quality assessment criteria can be found in Appendix C.

The most challenging aspect of the Study 200 quality assessment critique is its non-randomised single arm design. The design of single-arm studies makes it difficult to assess and generalise results. Results from non-randomised studies may differ from RCT evidence and case series design is considered to be the weakest source of clinical effectiveness evidence in the hierarchy of study designs. Interestingly, case series evidence was considered in 14 out of 47 Heath Technology Assessment reports.[31] While RCTs are designed to maximise internal validity, it can be argued that large, prospective and comprehensive case series may achieve high external validity. Study 200 was a multicentre trial and recruited people consecutively, which could reduce the risk of bias. There is no agreed 'gold standard' appraisal tool for the assessment of non-randomised studies.[32] The Cochrane handbook suggests that reviewers should select and modify or develop a tool that is most appropriate to their topic and the study design.[33] Similarly, the Centre for Reviews and Dissemination (CRD)[34] recommends considering the appropriateness of study design to the research objective, risk of bias, other issues related to study quality, choice of outcome measure, statistical issues, quality of reporting, quality of the intervention and generalizability in a quality assessment of any study. Therefore we will comment on both internal and external validity of Study 200 in addition to the Chambers (2009) criteria.[16] Details of the manufacturer's critical appraisal of Study 200 alongside our critique can be seen in Table 13.

Table 13. Quality assessment of Study 200 using Chambers (2009)[16] criteria

Study	1. Eligibility criteria adequately reported?	2. Study population representative of a normal population?	3. An appropriate measure of variability reported?	4. Loss to follow-up reported or explained?	5. At least 90% included at baseline followed-up?	6. Were patients recruited prospectively?	7. Were patients recruited consecutively?	8. Did the study report relevant prognostic factors?	Quality score
Bosutinib, advanced disease study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 2nd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 3rd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
PenTAG comment	Yes	Yes	Yes	Partially, see section below for more details.	Yes	Yes.	Yes, based on information in this table.	Partially, no risk factors reported.	Good, assuming "partially" is "yes".

4.1.4.1 Internal validity

Selection bias

Full details of Study 200 recruitment procedures are not given. It is not clear whether all eligible patients were invited, or if investigators' discretion affected those included. However, Pfizer states that participants were recruited consecutively in the quality assessment of Study 200 (Pfizer submission, p246) and details for recruited participants are given. Analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. Table 14 shows the difference between recruited and evaluable populations for CML disease phases at different snapshots.

The eligibility criteria allowed investigators to exclude participants if they were considered unable to take daily oral medication reliably. While this is reasonable, it may have allowed some potential for investigators to influence which participants were included.

Table 14. Recruited and evaluable population in Study 200

Population	**CP2L (N=288)**		**CP3L (N=118)**		**AP(N=76)**	**BP(N=64)**
Outcome	March 2011 snapshot evaluable population	February 2012 snapshot evaluable population	March 2011 snapshot evaluable population	February 2012 snapshot evaluable population	March 2011 snapshot evaluable population	March 2011 snapshot evaluable population
Cytogenetic	266	264	108	110	69	54
Haematological	288	285	116	115	69	60
Molecular	200	NR	105[a]	NR	NR	NR

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, N = number of participants, NR = not reported

a Excluded 13 subjects from China, India, Russia and South Africa, where molecular assessment was not performed due to logistical constraints

Performance bias

The dosage of bosutinib in Study 200 was 500mg once daily. Escalation to 600mg in case of haematological or cytological resistance, or reduction to 400 mg and 300mg once daily in case of AE was possible and the protocol for drug dosage was described. Eighty five subjects (15.2%) who started treatment at ≤ 500 mg (n=558) received dose escalations to 600 mg. Detailed information on treatment interruption was requested by PenTAG (Table 15). However, only some information is given for bosutinib dose reduction.

Table 15. Mean days of treatment interruption in Study 200

	CP2L (N=288)	CP3L (N=118)	AP (N=76)	BP (N=64)
Patients with an interruption [N (%)]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days interrupted [Mean (SD)]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Pfizer clarifications, question B5)

Patients were allowed to receive hydroxycarbamide and anagrelide while taking part in Study 200. In addition, patients after SCT or with previous interferon alpha therapy were eligible to take a part. It is not clear if anagrelide or previous SCT and interferon alpha treatment may have an effect on the expected outcomes in Study 200. In fact, 52% of 3rd-line CP patients and 32% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy. Since other than as a bridge to SCT, interferon alpha therapy is hardly used in England and Wales, it increases the uncertainty of Study 200 relevance to the expected clinical population.

Only some data were available on patient compliance with the treatment regiments. One participant (1%) was excluded based on protocol violation in the third line CP CML population.

Detection and reporting bias

No blinding was reported; investigators, care providers and patients were aware that bosutinib was the test drug. This could influence outcomes reporting, especially AE and HRQL, reflecting an understandable enthusiasm for a new drug therapy. However, since the main outcomes are measured objectively, they are less likely to be affected.

Attrition bias

Only 2 patients (0.7%) were lost to follow up in the March 2011 snapshot of second line CP CML patients. Similarly, 2 patients (2%) were lost to follow up in the March 2011 snapshot of third line CP CML patients. At the same snapshot, 3 participants requested treatment discontinuation in third line CP CML. No data are available on the numbers of patients lost to follow up in advanced phase CML.

4.1.4.2 External validity

Patients' characteristics

The full baseline characteristics are discussed in Section 4.2.5 (p69); here we discuss potential threats to external validity. Firstly, Study 200 was not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate (population of unmet clinical need appropriate for

this appraisal). The submission assumes that Study 200 is representative of the population expected in clinical practice. Although based on EMA recommendation, post-hoc analyses of the population of unmet clinical need are available; only 52 patients from Study 200 were eligible. In addition, the submission assumes that mostly third and fourth line patients would be eligible, thus the cost-effectiveness model is based on third-line CP, and combined second-line and multiple TKI AP and BP Study 200 sub-populations. However, we believe that based on current practice, if recommended, bosutinib would be mostly used in second and third line setting (see Section 2.2.2, p45).

Secondly, all patients in Study 200 had previously taken imatinib. Pfizer report the median duration of previous imatinib in the 2nd-line bosutinib chronic phase population as 2.6 years for imatinib-resistant people and as 1.5 years for imatinib-intolerant people (Pfizer submission, p350). Similarly, they report the median duration of previous imatinib in the 3rd-line CP population as 2.7 years (Pfizer submission, p54). However, these durations are much lower than the median of 8 years on 1st-line imatinib in the IRIS trial.[17] We are unable to account for this large discrepancy. We believe that if patients in Study 200 were truly representative of people who fail on imatinib, their median duration of imatinib should be approximately 8 years.

In addition, in third line CP CML, 37 patients were resistant to dasatinib, 50 were intolerant to dasatinib, 27 were resistant to nilotinib and only 1 was intolerant to nilotinib. The patients' characteristics for the third line CP subgroups were similar (Section 4.2.5, p69) to those of all patients in Study 200 (Table 16). We cannot explain why there was only 1 third line patient intolerant to nilotinib. While we cannot comment on treatment effects for nilotinib resistant patients in third line CP CML, the lack of participants in the nilotinib resistant sub-group may have been due to a small sample size.

Table 16. Baseline characteristics for Study 200

	CP2L (N=288)	**CP3L (N=118)**	**AP (N=76)**	**BP (N=64)**	**Unmet clinical need (N=52)**
Age (years) [Median (range)]	53 (18–91)	56 (20–79)	50.5 (18–83)	48.5 (19–82)	58 (19–81)
Male [N (%)]	154 (53%)	53 (45%)	42 (55%)	41 (64%)	31 (60)
Duration of CML disease (years) [Median (range)]	3.6 (0.1–15.1)	6.7 (0.6–18.3)	5.06 (1.11–22.06)	3.08 (0.35–14.46)	NR

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, N = number of participants, NR = not reported

Unsuitability was determined based on Bcr-Abl kinase domain mutations that would be reasonably expected to confer resistance to dasatinib (F317, E255) or nilotinib (E255, Y253, F359) and expected to have sensitivity to bosutinib, or the presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatinib therapy (for more details see Appendix G). Although Pfizer does not propose bosutinib use in patients with T315I mutation, no exclusion criteria for bosutinib use in CML patients was included in the submission.

Mutations T315I and V299L appear to be resistant to bosutinib,[23] Pfizer acknowledged this (Pfizer submission, p14). Indeed, patients with a documented history of prior T315I Bcr-Abl mutation were excluded from Study 200 as of 10 June 2008 due to a lack of efficacy in this group. This change in eligibility criteria resulted in inclusion of some participants with T315I mutation in Study 200. In addition, some participants with V299L may have been included. In fact, 2 participants with V299L were identified in third line CP CML population. Table 17 summarises the efficacy based on the different mutations. Although the numbers of recruited patients with a baseline T315I mutation were small (Appendix H), it may have caused more stringent efficacy estimates.

Table 17. Efficacy in full Study 200 evaluable populations versus those with a baseline T315I and V299L mutations

	Evaluable population		**T315I subpopulation**		**V299L subpopulation**	
	CHR	*MCyR*	*CHR*	*MCyR*	*CHR*	*MCyR*
CP2L	85.0%	53.4%	22.2%	22.2%	50%	0%
CP3L	73.3%	38.9%	28.6%	0%	NA	NA
Advanced phase	25.6%	32.5%	0%	7.7%	NA	NA

Abbreviations: CHR = Complete Haematological Response, MCyR = Major Cytogenetic Response, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable (no patients with V299L mutation identified)
(Source: Pfizer clarifications, question A2; Pfizer submission, Table B19, p71)

Co-morbidity

Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 were excluded from CP CML population and patients with a score of 3 were excluded from advanced phase leukaemia population. Thus 74% and 77% patients were ECOG 0 and 26% and 23% were ECOG 1 in third and second line CP CML respectively. Similarly, in accelerated phase, 54% were ECOG 0, 43% ECOG 1, 3% ECOG 2, and in blast phase, 34% were ECOG 0, 44% ECOG 1, 22% ECOG 2. Our clinical expert believes that these values are similar to those expected in clinical population. Patients

with liver, kidney and severe cardiac disease were excluded; for details on co-morbidities exclusion criteria see Appendix D.

Duration of response

The length of follow up for patients in Study 200 varied. Patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, whereas all patients still on bosutinib were followed up whilst on bosutinib. Thus the OS may be over-estimated because of selective censoring of patients, and this is acknowledged by Pfizer (Pfizer submission, p119).

Statistical analyses

For all populations (disease phases), analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. Intention-to-treat analyses were not reported; this may have resulted in more generous response estimates. PFS and OS were calculated based on all enrolled patients who received at least one dose of bosutinib. All patients who received at least 1 dose of bosutinib (the all-treated population) were also included in the analysis of safety. In addition, no adjustments for multiple comparisons were made for secondary or exploratory analyses (Pfizer response to clarification question A4).

4.2 Critique of clinical evidence for bosutinib

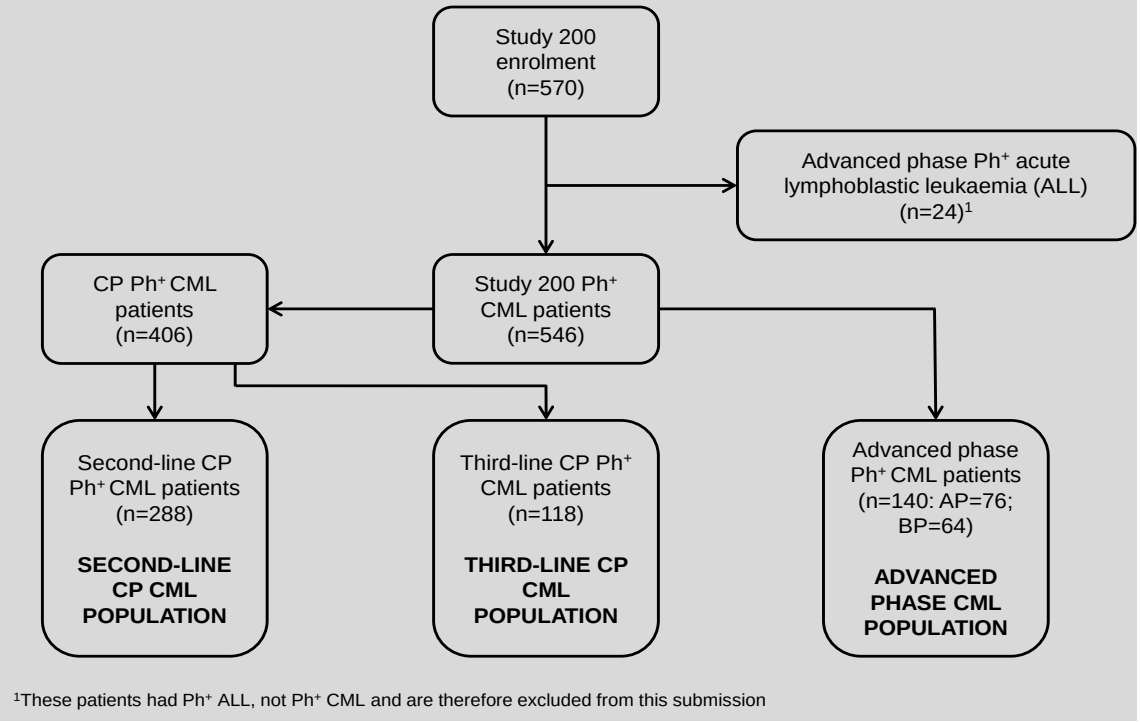
The search results presented by the manufacturer did not identify any randomised controlled trials directly comparing bosutinib with an appropriate comparator. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML:

- **Phase I** of this study defined the maximum tolerated dose of bosutinib in 18 Chronic Phase (CP) CML patients refractory to imatinib
- **Phase II** (n=570, including 18 patients enrolled in Phase I) investigates the efficacy and safety of bosutinib 500mg daily in four clinical sub-populations:
    - Second-line CP CML: Patients in CP CML with imatinib resistance or intolerance (n=288)
    - Third-line CP CML: Patients with imatinib resistance/intolerance followed by dasatinib resistance/intolerance or nilotinib resistance/intolerance or both dasatinib and nilotinib resistance/intolerance (n=118). This population also includes 3 patients who had prior exposure to imatinib, dasatinib and nilotinib, thus received bosutinib in fourth-line setting.

- Advanced phase CML: Patients with imatinib resistance/intolerance or resistance/intolerance to imatinib, dasatinib and/or nilotinib (n=140). This population includes patients receiving bosutinib second line or later:
  - Second line AP CML (n=45)
  - Multi TKI AP CML (n=31)
  - Second line BP CML (n=35)
  - Multi TKI BP CML (n=29)
- Acute lymphoblastic leukaemia: Patients with imatinib resistance or intolerance (n=24)

Figure 5 represents participants' flow in Study 200.

Figure 5. Study 200 participant flow diagram



(Source: Pfizer submission, Figure B2, p50)

Pfizer submission acknowledges that Study 200 was not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate (population of unmet clinical need). However, Study 200 is the only study that evaluates bosutinib in patients who have tried one or more prior TKI therapy (i.e. received bosutinib at second-line or later). The Committee for Medicinal Products for Human Use (CHMP) accepted Study 200 to be representative of the population of unmet clinical need. In addition, based on EMA (European Medicines Agency) recommendations, post-hoc analyses of patients with unmet clinical need from Study 200 were performed.

We agree that after excluding Phase I and the sub-population of acute lymphoblastic leukaemia (Phase II), the results from Study 200 are relevant to the research question. For participant flow of the sub-populations please see Appendix F. A total of 52 patients were eligible for inclusion in the post-hoc analysis of unmet clinical need population based on the presence of a mutation, a medical condition, or prior toxicities that may predispose patients to be unsuitable to nilotinib or dasatinib therapy (Appendix F).

Even though there is only one study assessed in the clinical effectiveness review, multiple references and various data snapshots of Study 200 are available (Table 18).

Table 18. Data sources for Study 200 populations

Third-line CP CML population	Second-line CP CML population	Advanced phase population (AP and BP)
Data snapshot 28 Mar 2011 (minimum/median follow-up: 12/28.5 months): • Khoury (2012)[25] • CSR[27] Data snapshot 15 Feb 2012 (minimum/median follow-up: 24/31.4 months): • Khoury (2012)[28]	Data snapshot 3rd June 2010 (24.2 months median follow-up): • Cortes (2011)[24] Data snapshot 28th March 2011 (24 month minimum follow-up): • CSR[27] Data snapshot 15th May 2012 (36 month minimum follow-up update): • Cortes (2012)[1] HRQL data • Trask (2012)[26]	Data snapshot 28 Mar 2011 (minimum follow-up: 12 months for AP; 18 months for BP): • CSR[27]
Baseline HRQL data • Trask (2013)[30]		

4.2.1 Eligibility criteria

Study 200 evaluates bosutinib in patients who have tried one or more prior TKI therapy. Appendix D lists the Study 200 eligibility criteria. The difference between the Study 200 population and the population defined in Pfizer submission (population of unmet clinical need) was already noted. In addition, criteria that we felt may have an effect on the generalizability of the Study 200 results to the population expected in clinical practice were discussed in Section 4.1.4.2 (p59).

The similarity and differences between the Study 200 and population of the unmet clinical need subpopulation (Appendix G) are discussed in Section 4.2.6 (p72).

4.2.2 Outcomes

Table 19 (p66) summarises primary and secondary outcomes for the three clinical sub-populations considered. Study 200 outcomes definitions are presented in Appendix E. The primary outcome for second and third line CP CML population was the rate of major cytogenetic response (MCyR) by 24 weeks, while the rate of overall haematological response (OHR) by 48 weeks was the primary outcome for the advanced phase populations. Cytogenetic responses (MCyR, CyR), haematological responses (mainly CHR), survival (mainly OS), HRQL and safety outcome (AE) at the March 2011 snapshot and at longer follow up are discussed. No data are available on patients' treatment after bosutinib failure, which adds to the uncertainty in the relevance of the OS data from Study 200.

Table 19. Summary of the methodology applied to Study 200 populations

	Second-line CP CML population (n=288)	Third-line CP CML population (n=118)	Advanced phase CML population (n=140; AP=76, BP=64)
Location	Multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. The 5 countries enrolling the most patients were the United States (147), Russia (66), Italy (53), China (43) and Germany (39).		
Design	Patients were treated with bosutinib 500mg once-daily until disease progression, unacceptable toxicity or withdrawal of consent. Dose escalation to bosutinib 600 mg once daily was permitted in cases of lack of efficacy (CHR not reached by week 8 or CCyR not reached by week 12) and dosage could be reduced in increments of 100 mg, as necessary in accordance with observed toxicities, down to a minimum of 300 mg/day. The dosing regimen used in Study 200 is reflective of the SPC recommendations, discussed in Table 1 [Pfizer submission]. Study 200 was a single-arm trial with no randomisation or blinding procedures. The only intervention was bosutinib 500mg once daily. There were no comparators.		
Duration of study	Study 200 began in January 2006 and is currently still on-going. Patients remain in the trial until death or lost to follow-up.		
Primary outcomes	Rate of MCyR by 24 weeks		Rate of attainment or maintenance of OHR by Week 48
Secondary outcomes	• Further response rates for efficacy endpoints: CCyR, CHR, MMR and CMR • Median duration of MCyR and CHR • Median time to MCyR and CHR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • Transformation Rate • HRQL: FACT-Leu & EQ-5D Safety outcomes were also considered: • Incidence rate of any AEs	• Further response rates for efficacy endpoints: CCyR, MiCyR, CHR, CMR and MMR • Median duration of MCyR, CCyR and CHR • Median time to MCyR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • HRQL: FACT-Leu & EQ-5D Safety outcomes were also considered • Incidence rate of any AEs • Incidence rate of Grade 3/4 AEs • Rate of patient deaths	• Duration of OHR, CHR and MCyR • Median time to confirmed (attained or maintained) OHR and CHR • Cumulative haematological response (for OHR, MHR and CHR) • Cumulative MCyR • BP transformation rate • PFS at 1 year and 2 years • OS at 1 year and 2 years • Time to treatment failure • HRQL: FACT-Leu & EQ-5D

4.2.3 Sample size calculation

The manufacturer used Simon two-stage design for sample size calculation which is often used for phase II cancer clinical trials.[35] The first stage requires a small sample size and sets a benchmark number of successes above which the trial enters the second stage.[36] The power calculations were determined separately for different patient populations, dependent upon their experience with prior TKI therapy and disease progression. The sample size calculation was based on primary outcomes; the rate of MCyR by 24 weeks for second and third line CP CML population and the rate of OHR by 48 weeks for the advanced phase populations (Appendix I). The MCyR rates for third line CP CML populations were based on clinical estimates, and the MCyR rates for second line CP CML as well as the OHR rates for AP and BP populations were based on published dasatinib and nilotinib data. We requested further information on the source of the OHR and MCyR rates used in the sample size calculation:

Due to the paucity of data available in the third line CP CML population when the study was designed, we were unable to provide sample size estimates based on specific clinical trial data. Although the original expectations for the treatment effect for this heavily pre-treated population were based on 2L clinical experience, the response rates observed were considered clinically meaningful within this heavily pre-treated cohort.

The published dasatinib data upon which the accelerated phase sample size calculation was based was taken from the three references below, whilst the blast phase sub-group estimates were based on the first two publications.

1. Talpaz M, Apperley JF, Kim DW, et al. Dasatinib (D) in patients with accelerated phase chronic myeloid leukemia (AP-CML) who are resistant or intolerant to imatinib: Results of the CA180005 'START-A' study. J Clin Oncol. 2006;24: 6526

2. Cortes JE, Kim DW, Rosti G, et al. Dasatinib (D) in patients (pts) with chronic myelogenous leukemia (CML) in myeloid blast crisis (MBC) who are imatinib-resistant (IM-R) or IM intolerant (IM-I): Results of the CA180006 'START-B' study. J Clin Oncol. 2006;24:6529

3. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or –intolerant accelerated-phase chronic myelogenous leukemia. Blood. 2008;111:1834 -1839

(Source: Pfizer clarifications, response to question A4)

It is not clear how Pfizer arrived at the rates of MCyR and OHR used in the sample size calculation. However based on the results of a systematic review of clinical effectiveness of dasatinib and nilotinib,[2] the estimates used in the submission appear to be within the range of reported results.

Interestingly, while no sample size calculation for imatinib and nilotinib intolerant third line CP CML patients was included in the submission, the response to clarification questions states that no statistical analyses of these patients were planned (Appendix J). Also no post-hoc sample size calculation for the unmet clinical need population was provided.

Study 200 recruitment was closed without reaching planned sample sizes for AP and BP CML patients due to slow accrual. Patients in second and third line CP CML were over-recruited because of a change in the evaluable population definition.

4.2.4 Statistical analysis

As already mentioned in Section 4.1.4, analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. Table 14 (p58) showed the difference between recruited and evaluable populations for CML disease phases at different snapshots. OS and AE were calculated for all patients who received at least 1 dose of bosutinib (the all-treated population). No intention-to-treat analyses or adjustments for multiple comparisons were reported.

Importantly, the analyses defined in the protocol have changed. The protocol pre-defined analyses considered patients with baseline MCyR or CCyR as non-responders. The new analyses consider patients who maintained or achieved a cytogenetic or haematological response as responders. Using the two approaches, 32%, or 38.9% of third-line CP CML patients, achieved, or attained and achieved MCyR at 12 months minimum follow up respectively. The results of the post-hoc analyses, with higher response rates, when both achieved and maintained response are considered to be a response, were reported in Pfizer submission, and are used in the cost-effectiveness model.

Of note is that the definition of evaluable patients has changed, from all treated patients with a valid baseline and post-baseline measurement or early death or progression, to all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. The first definition was found to produce a biased analysis, as subjects who discontinued early due to adverse events are ‘unevaluable’.

The outcomes used in the cost effectiveness model: MCyR, OHR, overall survival (OS), treatment discontinuation, HRQL and adverse events (AE) rates, are discussed in Section 4.2.6 (p72). The

results are described separately for the Study 200 sub-populations, and the post hoc analyses of patients that may have an unmet clinical need according to the proposed EMA indication.

4.2.5 Baseline characteristics

Study 200 baseline characteristics are summarised in Table 20 (p70). The full characteristics as supplied by Pfizer are included in Appendix K. We discussed some of the participants' characteristics in Section 4.1.4. ECOG performance status of Study 200 appears to be similar to the one expected in clinical population. The median age seems to be close to 50 years for all subpopulations, with the exception of second line BP patients. The post imatinib BP population (n=35) median age is 37 years (range 19–79), which is particularly low probably due to a small sample size. The proportion of male patients differs from 38% to 69% across the Study 200 subpopulations.

Baseline mutation status was recorded for 210 second-line CP, 117 third-line CP and 86 advanced phase CML patients. Based on May 2011 snapshot evaluable population, 78 (37%) second-line CP participants had ≥1 of 42 unique Bcr-Abl kinase domain mutations, of these 9 (4%) with the T315I mutation. Similarly, 65 (55.6%) third-line CP participants had Bcr-Abl kinase domain mutations, of these 15 (12.8%) with the T315I mutation. Forty (47%) advanced phase participants had ≥1 of 19 unique Bcr-Abl kinase domain mutations, including 7 (8%) with the T315I mutation. Information on cytogenetic and haematological response by baseline mutation status is included in Appendix L.

An important comparison is between the complete Study 200 population with the population of unmet clinical need (Appendix G). The results of the Study 200 populations and the population of the unmet clinical need sub population are discussed in Section 4.2.6 (p72).

Table 20. Study 200, baseline characteristics

Population		Age (years) [Median (range)]	Male [N (%)]	CML duration (years) [Median (range)]	IM duration (years) [Median (range)]	ECOG Performance Status [N (%)]		
						0	*1*	*2*
CP2L (N=288)	IM-R CP2L (N=200)	51.0 (18–86)	116 (58%)	4.0 (0.1–15.1)	2.6 (0.4–8.8)	151[a] (77%)	44[a] (23%)	0[a] (0%)
	IM-I CP2L (N=88)	54.5 (23–91)	38 (43%)	2.8 (0.1–13.6)	1.5 (<0.1–8.3)	68[a] (76%)	21[a] (23%)	1[a] (1%)
	Total CP2L (N=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	IM + DAS resistant CP3L (N=37)	54.0 (23–69)	14 (38%)	7.5 (1.2–17.6)	2.6 (0.02–6.4)	28 (76%)	9 (24%)	NA
	IM + DAS intolerant CP3L (N=50)	58.0 (25–79)	23 (46%)	5.6 (0.6–18.3)	3.3 (0.1–6.6)	31 (62%)	18 (36%)	NA
	IM + NI resistant CP3L (N=27)	52.0 (20–79)	14 (52%)	5.9 (1.2–16.3)	2.5 (0.7–5.9)	25 (93%)	2 (7%)	NA
	IM + DAS ± NI CP3L (N=4)	54.5 (31–62)	2 (50%)	11.7 (2.2–11.9)	3.0 (1.4–6.4)	2 (50%)	2 (50%)	NA
	Total CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	AP IM only (N=45)	47.0 (18–73)	24 (53%)	3.85 (1.1–22.1)	NR	26 (58%)	18 (40%)	1 (3%)
	AP Multi TKI (N=31)	56.0 (21–83)	18 (58%)	8.25 (1.5–19.2)	NR	15 (48%)	15 (48%)	1 (3%)
	AP Total (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.1–22.1)	NR	16 (46%)	10 (29%)	9 (26%)
BP (N=64)	BP IM only (N=35)	37.0 (19–75)	24 (69%)	1.75 (0.4–5.6)	NR	16 (46%)	10 (29%)	9 (26%)
	BP Multi TKI	53.0 (22–82)	17 (59%)	5.75 (1.1–14.6)	NR	6 (21%)	18 (62%)	5 (17%)

	(N=29)							
	BP Total (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.4–14.5)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need[b](N=52)	CP2L (N=15)	65 (24-81)	10 (67%)	NR	NR	6 (40%)	9 (60%)	0
	CP3L (N=21)	58 (30-79)	11 (52%)	NR	NR	13 (62%)	8 (38%)	0
	AP (N=5)	66 (48-73)	6 (60%)	NR	NR	1 (20%)	4 (80%)	0
	BP (N=11)	51 (19-80)	7 (64%)	NR	NR	2 (18%)	6 (55%)	3 (27%)
	Total (N=52)	58 (19-81)	31 (60%)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

4.2.6 Results

4.2.6.1 Cytogenetic response

As mentioned in Section 4.2.4 (p68), the protocol pre-defined analyses considering patients with baseline MCyR or CCyR as non-responders were not used. The post-hoc analyses (when both achieved and maintained MCyR or CCyR are considered to be a response) were used. The MCyR in the third line CP population was used in the cost-effectiveness model to estimate OS for bosutinib in CP CML. Because of the number of snapshots available and the multiple results reported, we collated the various results and calculated 95% Clopper-Pearson confidence intervals using Stata v.12[37] (Table 21). The cytogenetic response tables supplied in the submission are included in Appendix M. The rate of MCyR and CCyR increases only slightly as the duration of minimum follow-up increases, and the rate decreases with disease progression (Table 21). The imatinib resistant population seems to achieve similar rates as imatinib intolerant second line CP CML population (Appendix M), while dasatinib and nilotinib resistant patients seem to have slightly lower response rates than dasatinib intolerant third line CP CML patients (Appendix M).

It is interesting to compare the different sup-populations with the unmet clinical need sub-groups. It seems that apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical population. This would act to give a conservative estimate of the cost-effectiveness of bosutinib use in CP, given that Pfizer estimate OS for bosutinib in CP based on MCyR. However due to the very small numbers of participant in the unmet clinical need populations, any assumptions based on the unmet clinical need result have a high degree of uncertainty.

Table 21. Cytogenetic responses for all subpopulations at different snapshots

Population		Responding/N	MCyR% (95%CI)	Responding/N	CCyR% (95%CI)
CP2L	CP2L June 2010[24]	140/266[a]	52.6%[a] (46.4, 58.8)	110/266[a]	41.4%[a] (35.4, 47.5)
	CP2L March 2011[27]	142/266	53.4% (47.2, 59.5)	114/266	42.9 (36.8, 49.0)
	CP2L February 2012[27][b]	168/286	58.7% (52.8, 64.5)	141/286	49.3% (43.4, 55.3)
	CP2L May 2012[1]	155/264	58.7% (52.5, 64.7)	130/264	49.3% (43.1, 55.4)
	CP2L unmet clinical need population[27]	9/15	60% (32.3, 83.7)	8/15	53.3% (26.6, 78.7)
CP3L	CP3L March 2011[25, 27]	42/108	38.9%[c] (29.7, 48.7)	33/108	30.6%[d] (22.1, 40.2)
	CP3L February 2012[27, 28]	45/110	40.9%[e] (31.6, 50.7)	35/110	31.8%[f] (23.3, 41.4)
	CP3L unmet clinical need population[27]	9/21	42.9%[g] (21.8, 66.0)	7/21	33.3% (14.6, 57.0)
AP	AP March 2011[27]	24/69	34.8% (23.7, 47.2)	17/69	24.6% (15.1, 36.5)
	AP February 2012[27][b]	30/77	39.0% (28.0, 50.8)	23/77	29.9% (20.0, 41.4)
	AP unmet clinical need population[27]	3/5	60.0% (14.7, 94.7)	3/5	60.0% (14.7, 94.7)
BP	BP March 2011[27]	16/54	29.6% (18.0, 43.6)	11/54	20.4% (10.6, 33.5)
	BP February 2012[27][b]	21/64	32.8% (21.6, 45.7)	16/64	25% (15.0, 37.4)
	BP unmet clinical need population[27]	2/11	18.2%[h] (2.3, 51.8)	2/11	18.2% (2.3, 51.8)

Abbreviations: AP = accelerated phase, BP= blast phase, CP2L= second line chronic phase, CP3L= third line chronic phase

a Only patients attaining cytogenetic response counted as responders, not directly comparable with the rest of the table (protocol pre-specified analyses)

b Information extracted from the cost-effectiveness model supplied with the submission

c Results for the protocol pre-specified analysis for MCyR were 32.4% (23.7, 42.1)

d Results for the protocol pre-specified analysis for CCyR were 24.1% (16.4, 33.3)

e Different results found in Pfizer's economic model: 41.2% (32.1, 50.6)

f Different results found in Pfizer's economic model: 32.8% (24.4, 42.0)

g Different results found in Pfizer's economic model: 47.6% (25.7, 70.2)

h Different results found in Pfizer's economic model: 36.4% (10.9, 69.2)

4.2.6.2 Haematological response

Similarly to cytogenetic responses, not the protocol pre-defined analyses considering patients with baseline CHR as non-responders, but new analyses when both, achieved and maintained response, are considered to be a response, are discussed. Because of the number of snapshots available and the multiple results reported, we collated the various results and calculated 95% Clopper-Pearson confidence intervals using Stata v.12[37] (Table 22). The haematological response tables supplied in the submission are included in Appendix N. While the rate of CHR does not seem to change with increased duration of minimum follow-up, the rates decrease with disease progression. Again, it seems that the results of the post-hoc unmet clinical need population show slightly higher response rates. However, due to the very small numbers of participant in the unmet clinical need populations, any assumptions based on the unmet clinical need result have a high degree of uncertainty.

Table 22. Haematological responses for all sub-populations at different snapshots

Population		Responding/N	CHR% (95%CI)
CP2L	CP2L June 2010[24]	247/287	86.1% (81.5, 89.9)
	CP2L March 2011[27]	244/288	84.7% (80.0, 88.7)
	CP2L February 2012[27][a]	245/286	85.7% (81.1, 89.5)
	CP2L May 2012[1]	244/285	85.6%[b] (81.0, 89.5)
	CP2L unmet clinical need population[27][a]	12/15	80% (51.9, 95.7)
CP3L	CP3L March 2011[25, 27]	85/116	73.3% (64.3, 81.1)
	CP3L February 2012[27]	87/119	73.1% (64.2, 80.8)
	CP3L February 2012[27, 28]	84/115	73.0% (64.0, 80.9)
	CP3L unmet clinical need population[27]	18/21	85.7%[c] (63.7, 97.0)
AP	AP March 2011[27]	24/69	34.8% (23.7-47.2)
	AP unmet clinical need population[27]	4/5	80% (28.4, 99.5)
BP	BP March 2011[27]	9/60	15% (7.1, 26.6)
	BP unmet clinical need population[27]	3/11	27.3% (6.0, 61.0)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a Information extracted from Pfizer's economic model

b Reported in submission as 85%

c Different results found in Pfizer's economic model: 81.0% (58.1, 94.6)

4.2.6.3 Overall survival

Overall survival (OS) results were based on all enrolled patients who received at least one dose of bosutinib. Table 23, Table 24 and Table 25 detail the Kaplan-Meier (K-M) estimates of Study 200 subpopulations based on different snapshots. As expected, the estimated OS is shorter for more advanced disease phases. The OS tables supplied in the submission are included in Appendix O. In addition, as mentioned earlier, patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, while patients on bosutinib were followed up whilst on bosutinib. Thus the OS may be overestimated beyond 2 years because of selective censoring of patients.

Table 23. Kaplan-Meier estimate of overall survival in CP2L subpopulation at different snapshots

CP2L	**OS at 1 year (95%CI)**			**OS at 2 years (95%CI)**		
	Total N	**IM resistant N**	**IM intolerant N**	**Total N**	**IM resistant N**	**IM intolerant N**
June 2010[24]	97% 288	NR	NR	92% 288	92% 200	98% 88
March 2011[27[a]]	96.8% (94.0, 98.3) 288	95.9% (92.0, 97.9) 200	87.6% (82.1, 91.5) 88	90.6% (86.5, 93.5) 288	98.8% (92.0, 99.8) 200	97.6% (90.9, 99.4) 88
May 2012[1]	NR	NR	NR	NR 286	88% (83, 92) 195	98% (91, 99) 91
Unmet clinical need[27]	NR	NR	NR	NR	NR	NR

Abbreviations: CP2L = second line chronic phase, OS = overall survival, CI = confidence interval, IM = imatinib, N = number of participants, NR = not reported

a Source: Pfizer clarifications

Table 24. Kaplan-Meier estimate of overall survival in CP3L subpopulation at different snapshots

CP3L	OS at 1 year (95%CI)				OS at 2 years (95%CI)			
	Total N	IM + DAS resistant N	IM + DAS intolerant N	IM + NI resistant N	Total N	IM + DAS resistant N	IM + DAS intolerant N	IM + NI intolerant N
March 2011[25, 27]	91.2% (84.3, 95.2) 118	82.8% (65.6, 91.9) 37	93.9% (82.3, 98.0) 50	96.3% (76.5, 99.5) 27	82.9% (74.1, 88.9) 118	75.2% (56.1, 86.9) 37	85.4% (71.7, 92.8) 50	91.7% (70.5, 97.5) 27
February 2012[27, 28]	91.4% (84.6, 95.3) 119	83.6% (67.0, 92.3) 38	93.9% (82.3, 98.0) 50	96.3% (76.5, 99.5) 27	84.0% (75.8, 89.6) 119	77.4% (59.7, 88.0) 38	85.4% (71.7, 92.8) 50	92.4% (73.0, 98.1) 27
Unmet clinical need[27]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CP3L = third line chronic phase, OS = overall survival, CI = confidence interval, IM = imatinib, DAS = dasatinib, NI = nilotinib, N = number of participants, NR = not reported

Table 25. Kaplan-Meier estimate of overall survival in AP and BP subpopulations at different snapshots

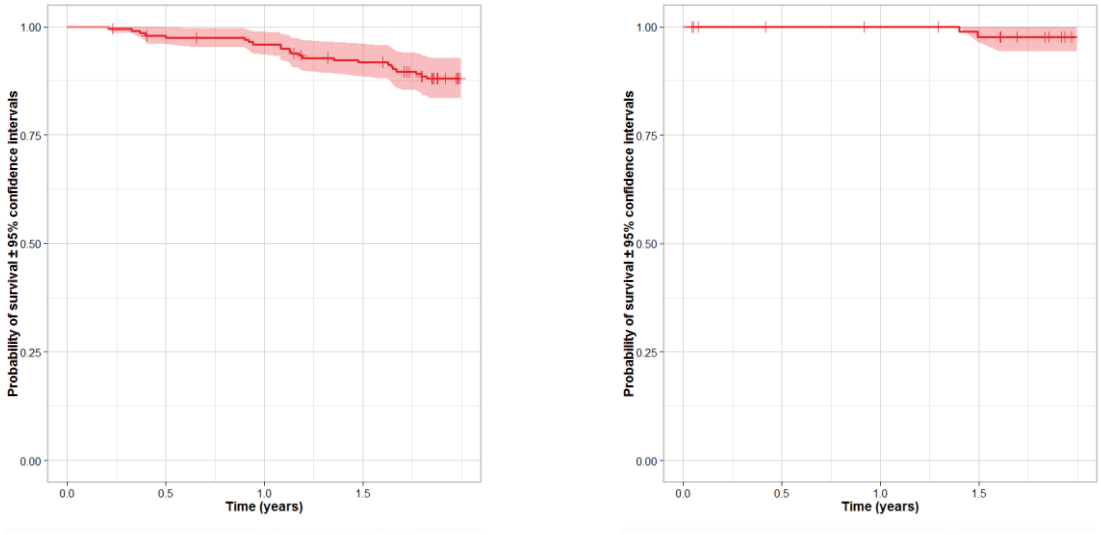
AP and BP	OS at 1 year (95%CI)			OS at 2 years (95%CI)		
	Total N	IM N	Multi TKI N	Total N	IM N	Multi TKI N
AP March 2011[27]	76.0% (64.7, 84.2) 76	NA	NA	65.6% (53.4, 75.4) 76	NA	NA
AP unmet clinical need[27]	NR	NR	NR	NR	NR	NR
BP March 2011[27]	43.8% (31.3, 55.6) 64	NA	NA	35.4% (23.8, 47.3) 64	NA	NA
BP unmet clinical need[27]	NR	NR	NR	NR	NR	NR

Abbreviations: AP = accelerated phase, BP = blast phase, OS = overall survival, CI = confidence interval, IM = imatinib, TKI = tyrosine kinase inhibitor, N = number of participants, NR = not reported

The imatinib-intolerant population seems to achieve better OS than the imatinib-resistant second line CP CML population. The nilotinib-resistant population seems to have the highest, while dasatinib-resistant populations seem to have the lowest OS estimates in third line CP CML population. Figure

6, Figure 7 and Figure 8 show the K-M estimates of OS for all three subpopulations (as included in Pfizer submission and Pfizer response to clarification questions).

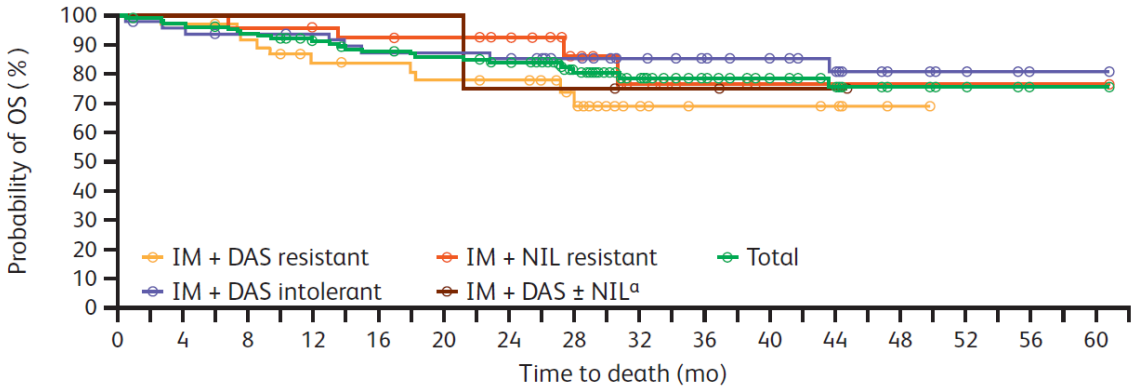
Figure 6. Kaplan-Meier estimates of overall survival for the 2nd-line CP all-treated population



Imatinib-resistant Imatinib-intolerant

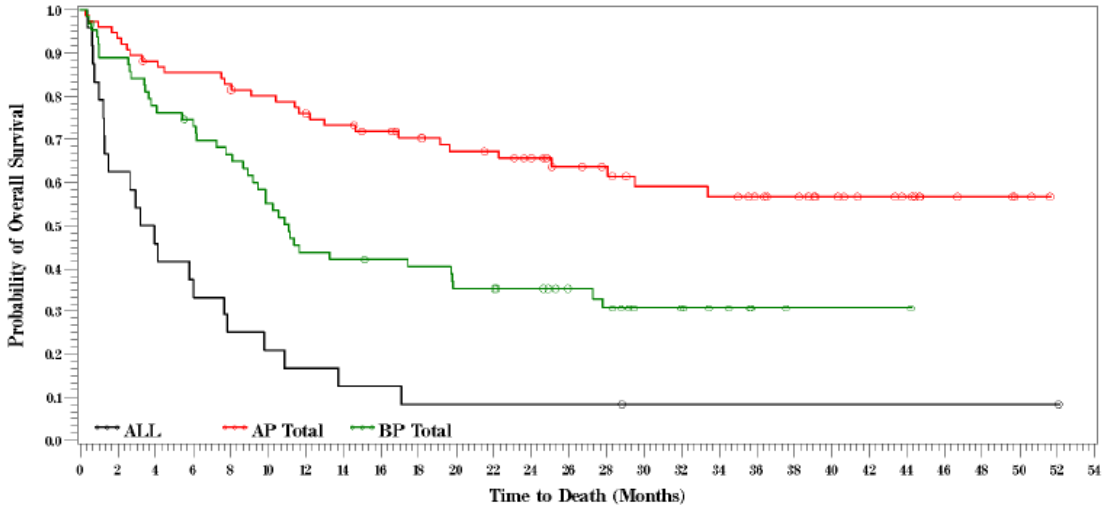
(Source: Pfizer response to clarification question B3)

Figure 7. Kaplan-Meier estimate of overall survival for the 3rd-line CP all-treated population (15 Feb 2012 snapshot)



(Source: Pfizer submission, Figure B12, p70)

Figure 8. Overall survival for the advanced phase CML population (28 Mar 2011 snapshot)



(Source: Pfizer submission, Figure B12, p79)

4.2.6.4 Treatment discontinuation and adverse events

All toxicities, up to 30 days after the last dose of bosutinib, were assessed according the National Cancer Institute Common Terminology for Adverse Events Version 3.0. We have already mentioned that no separate searches were conducted to search for adverse events evidence. However safety data are also available from a Phase III Study 3000 (NCT00574873; 3160A4-3000), a two-arm, randomized, open-label trial designed to evaluate the efficacy and safety of bosutinib compared to imatinib in subjects newly diagnosed with chronic phase CML (bosutinib n=248 and imatinib N=251). In addition, the Summary of Product Characteristics (SPC) for bosutinib combined evaluation of AE from the following three studies: Study 300 (248 patients treated with bosutinib), Study 200 (n=570, including 24 patients with acute CML) and 53 patients in the Japanese phase I/II trial (a dose-escalation study in CP CML patients followed with an evaluation study of safety and efficacy of the maximum tolerated dose in CML patients); all patients received at least 1 dose of single agent bosutinib. A summary of the three efficacy and safety studies is in Appendix P.

The treatment discontinuation and adverse events tables as supplied in the submission and response to clarification questions (including results from Study 3000) are presented in Appendix Q. Table 26 summarises reasons for treatment discontinuation in Study 200, the results reported are medians, not Kaplan-Meier estimates. While Table 27 and Table 28 summarise AE reported in Study 200 for different subpopulations. Finally Table 29 shows the combined AE from the three efficacy studies as reported in SPC. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (CP3L subgroup, n=4).

Adverse events were mainly restricted to gastrointestinal toxicities in both the chronic and advanced phases of the disease and in the majority of cases these toxicities were mild in severity. Overall, grade 3–4 non-haematological AE appear rare; diarrhoea was reported in patients in all lines of treatment: imatinib resistant CP2L 9%, imatinib intolerant CP2L 11%, CP3L 8.5%, AP 3.9% and BP 6.3%. Similarly rash was reported in imatinib resistant CP2L 8%, imatinib intolerant CP2L 12%, CP3L 4.2%, AP 3.9% and BP patients 3.1%. In addition, vomiting was reported in imatinib resistant CP2L 2%, imatinib intolerant CP2L 9%, AP 3.9% and BP 3.1%, but not among CP3L patients. In the advanced phases, fatigue (3.9 % and 3.1 % for AP and BP respectively), pleural effusion (5.3 % and 3.1 % for AP and BP respectively), and dyspnoea (7.9 % and 2.3 % for AP and BP respectively) were also reported. Fatigue was also reported in CP 2L; imatinib resistant CP2L 1%, imatinib intolerant CP2L 2%. The most common haematological events were thrombocytopaenia, neutropaenia and anaemia. In comparison with other TKIs, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] While the most commonly reported nilotinib AEs were thrombopenia, neutropenia , anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase, and bilirubin. In addition, the FDA has stipulated that nilotinib carry a 'black box' warning for possible heart problems that may lead to an irregular heart beat and possibly sudden death.[2]

Table 26. Treatment discontinuation in Study 200

Reason for discontinued treatment	Second line CP[a]			Third line CP[b]					Advanced CML[c]		Unmet clinical need population[d]
	15 May 2012 snapshot			15 February 2012 snapshot					28 March 2011 snapshot		28 March 2011 snapshot
	IM-R (n=200)	IM-I (n=88)	Total (n=288)	IM + DAS resistant (n=38)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NIL[a] (n=4)	Total (n=119)	AP CML (n=76)	BP CML (n=64)	Total (n=52)
Discontinued treatment, n (%)	109 (56)	57 (63)	166 (58)	32 (84)	37 (74)	18 (67)	3 (75)	90 (76)	61 (80)	61 (95)	NR
AE	35 (18)	6 (7)	66 (23)	6 (16)	17 (34)	3 (11)	0	26 (22)	18 (23.7)	6 (9.4)	13 (25)
Lack of efficacy	19 (10)	5 (6)	24 (8)	12 (32)	7 (14)	5 (19)	1 (25)	25 (21)	NR	NR	NR
Disease progression	35 (18)	6 (7)	41 (14)	7 (18)	4 (8)	7 (26)	2 (50)	20 (17)	NR	NR	NR
Patient request	11 (6)	6 (7)	17 (6)	2 (5)	3 (6)	1 (4)	0	6 (5)	NR	NR	NR
Death	6 (3)	0	6 (2)	2 (5)	2 (4)	0	0	4 (3)	NR	NR	NR
Investigator Request	2 (1)	0	2 (1)	0	0	2 (7)	0	2 (2)	NR	NR	NR
Lost to follow-up	2 (1)	0	2 (1)	2 (5)	0	0	0	2 (2)	NR	NR	NR
Protocol violation	NR	NR	NR	0	1 (2)	0	0	1 (1)	NR	NR	NR
Other	4 (2)	4 (4)	8 (3)	1 (3)	3 (6)	0	0	4 (3)	NR	NR	NR

Abbreviations: CP = chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

a Pfizer response to clarification questions A1

b Pfizer submission, Table B19, p73

c Pfizer response to clarification questions A6 and Pfizer submission Table B21, p74

d Pfizer submission Table B110, p366

Table 27. Non-haematological bosutinib AEs for all sub-populations at different snapshots

Population		Diarrhoea % (n/N)	Nausea % (n/N)	Vomiting % (n/N)	Rash % (n/N)	Dose reduction due to AE % (n/N)	Treatment discontinuation due to AE % (n/N) [% of participants with treatment discontinuation (n/N)]
CP2L	CP2L Total	85.3%* (244/286)	45.5%* (130/286)	36.7%* (105/286)	36%* (103/286)	47%[g] (135/288)	23%[a] (66/286) [58% (168/286)]
	CP2L IM-R	85%* (165/195)	43%* (83/195)	36%* (70/195)	32%* (63/195)	43%[g] (86/200)	15%[a] (30/195) [56% (109/195)]
	CP2L IM-I	87%* (79/91)	52%* (47/91)	39%* (35/91)	44%* (40/91)	56%[g] (49/88)	40%[a] (36/91) [63% (578/91)]
CP3L	CP3L total	82.4%[b] (98/119)	48.7%[b] (58/119)	39.5%[b] (47/119)	26.9%[b] (32/119)	63%[f]	22%[e] (26/119) [76% (90/119)]
	CP3L IM+NI resistant	85.2%[b] (23/27)	48.1%[b] (13/27)	29.6%[b] (8/27)	11.1%[b] (3/27)	NR	11%[e] (3/27) [67% (18/27)]
	CP3L IM+DAS resistant	78.9%[b] (30/38)	55.3%[b] (21/38)	39.5%[b] (15/38)	23.7%[b] (9/38)	NR	16%[e] (6/38) [84% (32/38)]
	CP3L IM+DAS intolerant	82%[b] (41/50)	44%[b] (22/50)	48%[b] (24/50)	38%[b] (19/50)	NR	34%[e] (17/50) [74% (37/50)]

AP	AP total	85.5%[c] (65/76)	44.7%[c] (34/76)	44.7%[c] (34/76)	32.9%[c] (25/76)	40.8%[c] (31/76)	23.7%[c] (18/76)
	AP IM	84.4%[c] (38/45)	37.8%[c] (17/45)	51.1%[c] (23/45)	35.6%[c] (16/45)	37.8%[c] (17/45)	25.8%[c] (10/45)
	AP Multi TKI	87.1%[c] (27/31)	54.8%[c] (17/31)	35.5%[c] (11/31)	29%[c] (9/31)	45.2%[c] (14/31)	29%[c] (8/31)
BP	BP total	65.6%[c] (42/64)	50%[c] (32/64)	39.1%[c] (25/64)	31.3%[c] (20/64)	26.6%[c] (17/64)	9.4%[c] (6/64)
	BP IM	65.7%[c] (23/35)	51.4%[c] (18/35)	31.4%[c] (11/35)	28.6%[c] (10/35)	31.4%[c] (11/35)	2.9%[c] (1/35)
	BP Multi TKI	65.5%[c] (19/29)	48.3%[c] (14/29)	48.3%[c] (14/29)	34.5%[c] (10/29)	20.7%[c] (6/29)	17.2%[c] (5/29)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

* Subjects reporting ≥20% treatment-emergent adverse events (Pfizer submission table B108, p359)

a May 2012 snapshot (Pfizer response to clarification questions A7)

b Subjects reporting ≥10% treatment-emergent adverse events, Feb 2012 snapshot (Pfizer response to clarification questions A5)

c Subjects reporting ≥10% treatment-emergent adverse events (Pfizer response to clarification questions A6)

d Patients with an interruption (Pfizer response to clarification question B5)

e Treatment discontinuation, February 2012 snapshot (Pfizer submission, Table B19, p73)

Table 28. Haematological bosutinib adverse effects for all subpopulations at different snapshots

Population		Thrombocytopenia	Neutropenia	Anaemia	Thrombocytopenia Grade 3/4	Neutropenia Grade 3/4	Anaemia Grade 3/4
CP2L	CP2L Total	66%[a] (191/288)	40%[a] (116/288)	90%[a] (258/288)	24%[a] (68/288)	18%[a] (53/288)	13%[a] (36/288)
	CP2L IM-R	68%[a] (60/88)	48%[a] (42/88)	86%[a] (76/88)	33%[a] (29/88)	28%[a] (25/88)	18%[a] (16/88)
	CP2L IM-I	66%[a] (131/200)	37%[a] (74/200)	91%[a] (182/200)	20%[a] (39/200)	14%[a] (28/200)	10%[a] (20/200)
CP3L	CP3L Total	34.7%[b] (41/118)	17.8%[b] (21/118)	15.3%[b] (18/118)	25.4%[b] (30/118)	14.4%[b] (17/118)	5.1%[b] (6/118)
	CP3L IM+NI resistant CP3L IM+DAS resistant CP3L IM+DAS intolerant	NR					
AP	AP Total	42.1%[c] (32/76)	15.8%[c] (12/76)	42.1%[c] (32/76)	32.9%[c] (25/76)	14.5%[c] (11/76)	30.3%[c] (23/76)
	AP IM / Multi TKI	NR					
BP	BP total	28.1%[c] (18/64)	20.3%[c] (13/64)	28.1%[c] (18/64)	26.6%[c] (17/64)	20.3%[c] (13/64)	18.8%[c] (12/64)
	BP IM / Multi TKI	NR					

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor, NR = not reported, subjects reporting ≥10% treatment-emergent adverse events, and subjects reporting ≥5% treatment-emergent adverse events

a Cortes (2011)

b March snapshot (Pfizer submission, Table B27, p81)

c March snapshot (Pfizer submission, Table B29, p81)

Table 29. Adverse reactions for bosutinib from SPC

System Organ Class	Frequency	Adverse reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations	Very common	Respiratory tract infection[a]	99 (11.4)	4 (0.5)	0
	Common	Pneumonia[b]	45 (5.2)	21 (2.4)	5 (0.6)
		Influenza	47 (5.4)	2 (0.2)	0
		Bronchitis	27 (3.1)	1 (0.1)	0
		Nasopharyngitis	81 (9.3)	0	0
Blood and lymphatic system disorders	Very common	Thrombocytopenia	335 (38.5)	127 (14.6)	94 (10.8)
		Neutropenia	141 (16.2)	67 (7.7)	33 (3.8)
		Anaemia	238 (27.4)	82 (9.4)	25 (2.9)
		Leukopenia	94 (10.8)	31 (3.6)	8 (0.9)
	Common	Febrile Neutropenia	13 (1.5)	8 (0.9)	3 (0.3)
	Uncommon	Granulocytopenia	2 (0.2)	0	2 (0.2)
Immune system disorders	Common	Drug hypersensitivity	12 (1.4)	7 (0.8)	0
	Uncommon	Anaphylactic shock	2 (0.2)	0	2 (0.2)
Metabolism and nutrition disorders	Very Common	Decreased appetite	109 (12.5)	4 (0.5)	0
	Common	Dehydration	20 (2.3)	2 (0.2)	0
		Hyperkalaemia	23 (2.6)	2 (0.2)	1 (0.1)
		Hypophosphataemia	54 (6.2)	18 (2.1)	0
Nervous system disorders	Very common	Headache	148 (17.0)	9 (1.0)	3 (0.3)
	Common	Dizziness	74 (8.5)	2 (0.2)	0
		Dysgeusia	18 (2.1)	0	0
Ear and labyrinth disorders	Uncommon	Tinnitus	8 (0.9)	0	0
Cardiac disorders	Common	Pericardial effusion	16 (1.8)	2 (0.2)	1 (0.1)
		Electrocardiogram QT prolonged[c]	10 (1.1)	1 (0.1)	0
	Uncommon	Pericarditis	1 (0.1)	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	125 (14.4)	0	0
	Common	Dyspnoea	82 (9.4)	15 (1.7)	3 (0.3)
		Pleural effusion	52 (6.0)	14 (1.6)	1 (0.1)
	Uncommon	Respiratory failure	5 (0.6)	1 (0.1)	1 (0.1)
		Acute pulmonary oedema	3 (0.3)	1 (0.1)	1 (0.1)
		Pulmonary hypertension	4 (0.5)	1 (0.1)	0

Gastrointestinal disorders	Very common	Diarrhoea	683 (78.5)	78 (9.0)	1 (0.1)
		Vomiting	323 (37.1)	25 (2.9)	0
		Nausea	366 (42.1)	10 (1.1)	0
		Abdominal pain[d]	291 (33.4)	15 (1.7)	0
	Common	Gastritis	25 (2.9)	3 (0.3)	1 (0.1)
	Uncommon	Acute pancreatitis	3 (0.3)	2 (0.2)	1 (0.1)
		Gastrointestinal haemorrhage[e]	6 (0.7)	5 (0.6)	0
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	194 (22.3)	79 (9.1)	10 (1.1)
		Aspartate aminotransferase increased	160 (18.4)	41 (4.7)	3 (0.3)
	Common	Hepatotoxicity[f]	15 (1.7)	5 (0.6)	1 (0.1)
		Hepatic function abnormal	27 (3.1)	8 (0.9)	3 (0.3)
		Blood bilirubin increased	33 (3.8)	8 (0.9)	0
		Gamma-glutamyltransferase increased	29 (3.3)	7 (0.8)	0
	Uncommon	Liver Injury	2 (0.2)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	Very common	Rash[g]	282 (32.4)	51 (5.9)	2 (0.2)
	Common	Urticaria	26 (3.0)	2 (0.2)	1 (0.1)
		Acne	25 (2.9)	0	0
		Pruritus	71 (8.2)	3 (0.3)	0
	Uncommon	Erythema multiforme	1 (0.1)	0	1 (0.1)
		Exfoliative rash	6 (0.7)	1 (0.1)	0
		Drug eruption	5 (0.6)	1 (0.1)	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	96 (11.0)	3 (0.3)	0
	Common	Myalgia	49 (5.6)	3 (0.3)	0
		Back pain	72 (8.3)	7 (0.8)	1 (0.1)
Renal and urinary disorders	Common	Renal failure	13 (1.5)	2 (0.2)	1 (0.1)
	Uncommon	Renal failure acute	7 (0.8)	3 (0.3)	1 (0.1)
		Renal impairment	8 (0.9)	1 (0.1)	0
General disorders and administration site conditions	Very common	Pyrexia	204 (23.4)	6 (0.7)	1 (0.1)
		Oedema[h]	100 (11.5)	1 (0.1)	0
		Fatigue[i]	169 (19.4)	14 (1.6)	1 (0.1)
	Common	Chest pain[j]	61 (7.0)	4 (0.5)	1 (0.1)
		Pain	41 (4.7)	5 (0.6)	0

		Asthenia	86 (9.9)	7 (0.8)	2.(0.2)
Investigations	Common	Lipase increased	76 (8.7)	41 (4.7)	4 (0.5)
		Blood creatinine increased	42 (4.8)	2 (0.2)	0
		Blood amylase increased	31 (3.6)	7 (0.8)	0
		Blood creatine phosphokinase increased	28 (3.2)	3 (0.3)	2 (0.2)

The following terms have been combined:

a Respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral
b Pneumonia, bronchopneumonia, primary atypical pneumonia, lobar pneumonia
c Electrocardiogram QT prolonged, long QT syndrome
d Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain
e Gastrointestinal haemorrhage, gastric haemorrhage, upper gastrointestinal haemorrhage
f Hepatotoxicity, toxic hepatitis, cytolytic hepatitis
g Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash
h Oedema, face oedema, localized oedema, peripheral oedema
i Fatigue, malaise
j Chest pain, chest discomfort

(Source: Pfizer response to clarification question A1)

Cross-intolerance and cross-resistance

The reported cross-intolerance between bosutinib and dasatinib showed that 8% patients discontinued treatment with bosutinib as a result of same AE:

> This study included a retrospective evaluation of cross-intolerance between dasatinib and bosutinib. This retrospective evaluation provides an indication of how likely it is that the reason(s) for inappropriateness of dasatinib may also render bosutinib inappropriate, where the reason(s) are based on intolerance due to adverse events. This is therefore highly relevant to the scope of this submission, since the indication for bosutinib includes patients for whom dasatinib is not appropriate.
>
> Of 50 patients with dasatinib intolerance, 11 (22%) were found to experience the same adverse event as a grade 3/4 event when treated with bosutinib. Of 50 patients, 4 (8%) discontinued treatment with bosutinib as a result of the same AE.

(Source: Pfizer submission, p83)

No data on bosutinib and nilotinib cross-intolerance are available (only 1 third line patient intolerant to nilotinib was recruited in Study 200). However, the EMA highlighted a high degree of cross-resistance between bosutinib and dasatinib or nilotinib.[29] The reported MCyR for CP 3L dasatinib

intolerant subgroup was 47.7%, in comparison dasatinib resistant and nilotinib resistant patients achieved 33.3% and 38.5% respectively. Advanced phase patients treated with bosutinib at second line reported better MCyR than patients receiving bosutinib at third line or later. In fact, AP patients achieved 47.6% and 14.8% MCyR at second line and multi TKI respectively, while BP patients achieved 44.8% and 12.6% MCyR at second line and multi TKI respectively (March 2011 snapshot). We can argue, that at least some of the difference between the results could be explained by cross-resistance between second generation TKIs. The results of the retrospective evaluation of dasatinib cross-intolerance are presented in Table 30.

Table 30. Cross-intolerance between dasatinib and bosutinib for third-line CP CML population

AE, n (%)[a]	Dasatinib intolerant	Grade 3/4 event	Discontinued bosutinib because of event
Any AE	50	11 (22)	4 (8)
Haematological events	20	8 (40)	2 (10)
Thrombocytopaenia	8	6 (75)	1 (13)
Pancytopenia	5	0	0
Neutropaenia	4	4 (100)	1 (25)
Haematoxicity	3	0	0
Cardiovascular events	3	0	1 (33)
Gastrointestinal events	6	0	0
Diarrhoea	3	0	0
Musculoskeletal events	4	0	0
Respiratory events	23	3 (13)	1 (4)
Pleural effusion	19	2 (11)	0
Dyspnoea	3	1 (33)	1 (33)
Skin disorders	5	0	0

a Includes all AEs with ≥3 patients categorized as intolerant on prior dasatinib
(Source: Pfizer submission, Table B28, p83)

4.2.6.5 Quality of life

Tyrosine kinase inhibitors have revolutionised the treatment of CML and led to improvements in HRQL:

CML is a chronic disease and unless a patient is able to receive a SCT, patients remain on medication for many years. The estimated median survival with imatinib exceeds 25 years in patients with a median age of diagnosis of almost 60 years. Quality of life is not significantly impaired in the chronic phase of CML compared to those of a similar age without CML, indeed approximately 40% of CP

patients are asymptomatic and diagnosed as a result of a routine blood test. For those that do experience symptoms in the chronic phase they tend to be mild and non-specific, such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss.

Although quality of life is not assumed to be very different for CML patients on and off treatment, low grade chronic AEs can be debilitating, particularly if experienced over long periods of time, such as fatigue, oedema, muscle aches, rash or diarrhoea. Some more serious AEs may have a more significant impact on quality of life and may require intervention, for example a pleural effusion requiring steroids, pleural taps or pleural drains, PAOD requiring surgical bypass or balloon angioplasty or pulmonary HTN requiring cardiac catheterisation and medication.

Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising, bleeding and infections.18 In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease. For patients, symptoms such as breathlessness, tiredness, bleeding and infections can seriously affect patients' quality of life.

Please describe how a patient's HRQL is likely to change over the course of the condition.

Quality of life is expected to worsen as the disease progresses from chronic phase to accelerated phase and again to blast crisis phase.

In the chronic phase of the disease, previous studies have found that quality of life is not seriously impaired compared to those of a similar age without CML. In the advanced phases, HRQL is expected to be significantly worse.

(Source: Pfizer submission, p130)

A disease specific, The Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale, and a general, European Quality of Life- 5 Dimensions questionnaire (EQ-5D), were reported in Study 200. Since EQ-5D is NICE's preferred instrument, the submission commented on these results only. The EQ-5D was valued using the UK tariff.

The mean EQ-5D for CP patients across the trial was [redacted] and [redacted] (estimated by us from data on p357-8 Pfizer submission) for second and third- line for patients respectively. The mean utility values at screening were [redacted] and [redacted] for second and third-line respectively. Similarly, the mean EQ-5D for advanced phase patients across the trial was [redacted] and [redacted] for AP and BP for patients respectively. The mean utility values at screening were [redacted] and [redacted] for AP and BP respectively. In comparison, the average utility used in TA251 and TA241 for first and second- line CP patients

(based on IRIS study) was 0.85 (SE 0.004) at diagnosis (Pfizer submission, p135). Interestingly, the mean EQ-5D values did not differ much across the disease phases.

Pfizer reports improvements in HRQL in all disease phases at the March 2011 snapshot:

> Improvements in overall health status as assessed by the EQ-5D were observed for second-line CP patients over the course of treatment, as of 28 Mar 2011 snapshot.
>
> Imatinib-resistant subjects experienced a significant improvement in overall health status from baseline starting at Week 8 ($p<0.05$) and continuing at each subsequent assessment until Week 48 (all $p<0.001$). Imatinib-intolerant subjects experienced significant improvement from baseline by Week 24 ($p<0.001$) that continued until Week 48 ($p<0.001$).

(Source: Pfizer submission, p 357)

> *3L CP:*
>
> Improvements or maintenance of baseline levels of overall health status as assessed by the EQ-5D was observed for dasatinib-intolerant, dasatinib-resistant and nilotinib-resistant patients over the course of treatment, as of the 28 March 2011 snapshot. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (n=4).

(Source: Pfizer submission, p 72)

> Improvements in overall health status as assessed by the EQ-5D were observed for the AP CML and BP CML subjects over the course of treatment, as of the 28 Mar 2011 snapshot.
>
> The mean and median EQ-5D scores, and the number of patients with an EQ-5D score at each observation, are presented along with cost-effectiveness data in Section 7.4.3 [Pfizer submission].

(Source: Pfizer submission, p 79)

However as can be seen in the following tables (Table 31, Table 32, Table 33 and Table 34), the numbers of patients reporting at each week varied significantly.

Table 31. Summary of EQ-5D results by visit for second-line CP patients, n=288 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					

(Source: Pfizer submission, Table B107, p357)

Table 32. Summary of EQ-5D results by visit for third-line CP CML patients, n=118 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					

(Source: Pfizer submission, Table B39, p131)

Table 33. Summary of EQ-5D results by visit for AP patients, n=76 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]		

(Source: Pfizer submission, Table B40, p131)

Table 34. Summary of EQ-5D results by visit for BP patients, n=64 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
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[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

(Source: Pfizer submission, Table B42, p132)

4.3 Critique of the clinical evidence for comparator treatments

As previously mentioned – because of the lack of RCT evidence – the submission included separate studies to inform clinical effectiveness for bosutinib and bosutinib comparators. The following comparators were considered in the literature searches:

- Hydroxycarbamide (HU; as a proxy for best supportive care)
- Allogeneic stem cell transplantation (SCT)
- Interferon alpha

The submission identified 13 non-RCT comparator studies (Table 35). Again we cannot emphasize enough, that the naïve comparison of single arm Study 200 with non-randomised comparator studies is strongly susceptible to bias. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] The submission did not identify any studies reporting on interferon alpha in a refractory setting (post-TKI or post-other treatments). The submission further excluded 5 SCT studies from the review as they did not stratify results according to CML disease phase.[5, 8, 9, 11, 15] Studies that reported combined results for AP and BP CML patients were included in the Pfizer submission.[6, 10, 13]

Table 35. Summary of studies of hydroxycarbamide and stem cell transplant

Study	Patients (Disease phase at transplantation)	Survival	Response	Safety	Pfizer analysis	PenTAG comments
Benedicte (2010)[5]* Median follow-up: 27 months (range 1.2-50.2).	N=31 (median age 39.8 years), (CP 21 (including second CP), AP 10) Received SCT at: • 3rd-line (imatinib and dasatinib or nilotinib) • 4th-line (imatinib, dasatinib and nilotinib)	**OS:** CP and AP combined • 1 year: 79.2% (95% CI 64.3-94.1) Estimated: • 2 years: 55.5% (95% CI 35.0-75.9)	NR	**GVHD** CP and AP combined Grade 2–4: 37.9% Grade 3–4: 20.6% Chronic: 60%	Excluded: Mixed phases.	Only abstract with limited information available. Combined results for CP and AP CML patients.
Bornhäuser (2006)[6] Median follow-up: 18 months (range 2–62).	N=61 (CP 47 (including second CP), AP 8, BP 6), (mean age=45, 57% male) Received SCT at: • 2nd-line (imatinib)	**OS** CP, AP and BP combined (N=61) • 18 months: 37% **Disease Free Survival at 18 months:** CP (N=47) = 34.6% AP and BP combined (N=14) = 29.4% CP, AP and BP combined (N=61) = 33.0%	CP, AP and BP combined Molecular response recorded in 25 from 26 participants alive at last follow up: molecular remission achieved in 19 participants.	**GVHD** CP AP and BP combined Grade 2–4: 66% Grade 3–4: 38% Chronic: 29%	Included: Second-line (post-imatinib failure)	Although 32 (50%) patients were at high risk for transplant-related deaths Gratwohl score of 5-7, 47(77%) patients were in chronic phase at the time of transplantation.
Holroyd (2010)[7]* Median follow-up: NR.	N=43, (CP 17 (including second CP), AP 24, BP 2), (median age 40.8 years) Received SCT at: • 2nd-line: 35	**OS** Estimated: CP (N=17) • 1 year: 49.4%	11 patients relapsed post SCT.	**GVHD** CP, AP and BP combined Grade 2–4: 24%	Included: Multiple lines.	Only abstract with limited information available. Small numbers of participants in all disease cohorts.

	participants (34 imatinib and 1 dasatinib) • 3rd-line: 6 participants (imatininb and dasatinib) • 4th-line: 2 participants (imatinib, dasatinib and nilotinib) Some patients received chemotherapy.	• 3 years: 29.6% <u>AP (N=24)</u> • 1 year: 54.2% • 3 years: 50% <u>BP (N=2)</u> • 1 year: 0% • 3 years: 0% The impact of maximal disease stage, AP(n=23) vs. BP (n=20): • 3 years: 61% and 33% respectively.		Chronic: 54%		
Ibrahim (2011)[4] Median follow-up: 50.4 months (range 2-202)	N=293 (57.3 % male) Subpopulation of interferon alpha versus chemotherapy RCT for CP CML[38]. 247 patients failed to response to interferon alpha. Of these, 117 CP patients received HU after: • interferon alpha treatment failure.	**OS** Estimated: <u>CP(N=246)</u> • 7 years: 34.4 %	NR	NR	Included: Second-line (post-IFN failure)	Results given for all 246 patients who failed to response to interferon alpha; of these only 117 received HU, 122 remained on interferon alpha till disease progression and 7 received bosutinib.
Jabbour (2006)[9] Median follow-up: 19 months (range 13-24).	N=10 (CP 3, AP 4, BP 2, acute 1), (median age 44 years, 80% male) Received SCT at: • 2nd-line: 10 participants (imatinib)	**OS** <u>CP, AP and BP combined</u> • 1 year: 70%	<u>CP, AP and BP combined</u> 2 patients relapsed post SCT. CMR=66.7% MMR=77.8%	**GVHD** <u>CP, AP and BP combined</u> Acute: 44% Chronic: 60%	Excluded: Mixed phases.	Very small study (N=10). Results are reported for all participants, including the one acute CML patient.

Jabbour (2007)[8]	N=12 (CP 7 (including second CP), AP 1, BP 4), (median age 41 years, 58% male) Received SCT at: • 2nd-line: 9 participants (dasatinib (2) and nilotinib (7)) • 3rd-line: 3 participants (dasatinib and nilotinib)	**OS** CP, AP and BP combined • Median follow up of 6 months (2, 11): 58%	CP, AP and BP combined Median follow-up: 10 months: Molecular response in 58% participants.	**GVHD** CP, AP and BP combined Acute: 58.3% Chronic: 50%	Excluded: Mixed phases.	Very small study (N=12).
Jabbour (2011)[10] Median follow-up: 22 months (range 5–53).	N= 47 (CP 26 (10 second CP), AP 12, BP 9), (median age 44 years; 57% male) Received SCT • 2nd-line: 18 (38%) patients received imatinib only • 3rd-line: 29 (62%) patients received imatinib and nilotinib (13), dasatinib (13) or bosutinib (30) • 4th-line: 5 (11%) patients received imatinib and two more TKIs	**OS** CP(N=16) • 2 years: 72% (95% CI 49–96) Advanced (N=31; include 10 second CP patients) • 2 years: 59% (95% CI 41–77) ALL combined (N=47) • 2 years: 63% (95% CI 49–78)	**CMR** CP (N=16) 87.5% Advanced (including second CP) (N=31) 54.8% All combined (N=47) 66% **CCyR** CP (N=16) 6.25% Advanced (including second CP) (N=31) 32.3% CP, AP and BP combined (N=47)	**GVHD** CP, AP and BP combined (N=47) Grade 2–4: 42% Grade 3–4: 17% Chronic: 46%	Included: Multiple lines. Pfizer Base case:	Small study, only 16 patients in CP and advanced phase cohort (N=31) included 10 second CP patients. Submission (p384) shows OS is very immature, therefore poor data source.

			23%			
Kantarjian (2007)[3]	N=574 (CP 321, AP 161, BP 92) participants who discontinued imatinib therapy. Results reported for 104 CP CML participants post-imatinib failure who received: • SCT (n=8) • TKI (n=35) • Other treatment, (n=61), of these 12 participants received HU. Outcome for 127 participants is missing	**OS** Estimated: <u>CP SCT cohort (N=8)</u> • 2 years: 60.0 % • 3 years: 45.0 % <u>CP other treatment cohort (N=61)</u> • 2 years: 77.0 % • 3 years: 70.0 % **Mortality** <u>CP SCT cohort (N=8)</u> CP: 4/10 (40%) AP: 1/5 (20%) BP: 5/8 (63%) <u>Other treatment cohort (N=61):</u> CP: 24/68 (35%) AP: 53/64 (83%) BP: 85/95 (90%)	NR	NR	Included: Second-line (post-imatinib failure)	Data for large number of patients are missing (N=127). A very small SCT cohort (N=8), and in the HU cohort (N=61) only 12 patients received HU.
Markiewicz (2011)[11]*	N= 48 (NR), (median age 33 years) Received SCT at: • 2nd-line: 39 Imatinib (37), dasatinib (2) • 3rd-line: 6 Imatinib and dasatinib or nilotinib	**OS:** Estimated •5 years: 79%	NR	**GVHD** <u>Disease progression NR</u> Grade 3–4: 6.25% Chronic, limited: 35.4% Chronic, extensive: 18.75%	Excluded: Mixed phases.	Only abstract with limited information available. Disease stage not reported.

	• 4th-line: 3 patients, imatinib and dasatinib and nilotinib					
Oehler (2007)[12]	N= 145 (CP 72, AP (or second CP) 60, BP 13), (median age= 40.1; 64% male) Received SCT at: • 2nd-line: after imatinib (not after imatinib failure, 23 patients had previous INF)	**OS:** Estimated: <u>CP(N=72)</u> • 3 years: 78.0 % <u>AP and second CP(N=60)</u> • 3 years: 48.0 % **Mortality** <u>BP</u> 6/12 (follow up 542-1593 days) **Mortality** **by response to imatinib:** <u>69 CP patients with available data:</u> *Suboptimal/loss of response to prior imatinib:* 26% (8/31), i.e. OS = 74% *Good response to prior imatinib:* 5% (2/38), i.e. i.e. OS = 95% <u>Advanced phases</u> *Disease progressed from CP whilst on imatinib:* 45% (19/42), i.e. OS = 55%	NR	Results only reported as HR and OR compared with a historical cohort of patient who underwent SCT without previous imatinib treatment	Included: Second-line (post-imatinib failure)	**OS** of the CP cohort (N=72) was not reported in the submission; however mortality by response to imatinib were recorded. Large trial in comparison with the rest of comparator studies.

		Patients in advanced phases with no prior response to imatinib: 35% (6/17), i.e. OS = 65%				
Saussele (2010)[13] Median follow-up: 26 months (range 1-50) for CP, and 24 months (range 0-50) for advanced phase.	N= 65 (CP 37 , AP 3, BP 25; 11 of advanced patients achieved second and 1 patient achieved third CP before SCT), (mean age=38; 57% male in CP and 79% in AP & BP). Received SCT at: CP: • 2nd-line: 32 patients • 3rd-line or 4th-line: 5 patients AP and BP: • 2nd-line: 22 patients • 3rd-line or 4th-line: 6 patients • 22 patients treated with chemotherapy	**OS:** Estimated: CP (N=37) • 3 years: 94.1% (95% CI 83.8–99.4%) AP and BP combined (N=28) • 3 years: 58.8% (95% CI 38.6-77.5%)	**CMR** CP(N=37) 89% AP and BP combined (N=28) 93%	**GVHD** CP(N=37) Grade 3–4: 19% Chronic: 36% AP and BP combined (N=28) Grade 3–4: 35% Chronic: 21%	Included: Multiple lines.	Results for CP reported (N=37).
Schleuning (2010)[14]* Median follow-up: 19 months.	N=56 (first CP 21, second or higher CP 20, AP or BP 15) Had nilotinib and/or dasatinib (had not received first-line imatinib) prior to SCT.	**OS** Estimated: First CP(N=21) • 2 years: 85%. AP,CP, BP combined (N=56) Estimated non relapse mortality at 2 years: 33%	NR	NR	Included: Multiple lines.	Only abstract with limited information available. Small numbers of patients in first CP phase (N=21).

		and relapse incidence 15%.				
Weisser (2007)[15]	N=30 (second or higher CP; 10 and 20 patients had history of BP and AP respectively) (median age =51, 60% male) Received SCT at: • 2nd-line: after imatinib (imatinib given after IFN failure)	**OS** Estimated: <u>Second or higher CP</u> • 3 years: <35% BCR-ABL positive nuclei (N=13, 11 censored, median survival not reached): 81%; ≥35% BCR-ABL positive nuclei (N=17, 6 censored, median survival 101 days): 28%[a] **Mortality** at 1 year: 30%	<u>Second or higher CP</u> Cytogenetical relapse in 20%	**GVHD** <u>Second or higher CP(N=30)</u> Grade 3–4: 40%	Excluded: Mixed phases.	Although all patients are in the same phase, (second or higher CP), OS data are reported separately for patients with <35% and ≥35% BCR-ABL positive nuclei in bone marrow. Small study.

Abbreviations: AP = accelerated phase, BP = blast phase, CMR = Complete molecular response, CP = chronic phase, GVHD = Graft versus host disease, N = number of participants, NR = not reported, OS = overall survival

* Abstract presented at the Annual Meeting of ASH (2010-2011); no full publication is available for these sources, hence the data presented is limited to that present in the abstract

a Results estimated from figures

4.3.1 Hydroxycarbamide

Only two studies, Ibrahim (2011) and Kantarjian (2007) reported using HU in a refractory setting (Table 35).[3, 4] Ibrahim (2011)[4] used data from an interferon-failure sub-population in The UK Medical Research Council CML-III randomised trial of interferon alpha versus chemotherapy in CP CML patients.[38] In the Allan (1995) RCT,[38] 293 patients received interferon alpha and 294 patients received chemotherapy (with busulphan or hydroxyurea) treatment. In addition, all patients received a course of chemotherapy for tumour reduction as an induction treatment, and some patients also received chemotherapy while on interferon alpha. There were 278 Philadelphia positive CP CML patients in both the interferon alpha, and the no interferon alpha arm. The actual survival rates at 5 years for Philadelphia positive CP CML patients were, 36% (SD 3.8), and 54% (SD 3.7) for no interferon alpha and interferon alpha arms respectively. Ibrahim (2011)[4] reported data on 246 patients who failed interferon therapy (in the interferon alpha arm). However, of these, only 117 actually received HU; 122 remained on interferon alpha till disease progression and 7 received busulfan. The estimated 7 years overall survival for the interferon-failure sub-population was 34.4%. It may be that these results include a small proportion of Philadelphia negative CP CML patients. Pfizer did not consider this population in the submission because patients did not receive any TKI prior to HU treatment.

Kantarjian (2007)[3] is a retrospective study of 420 CML patients, who received first line imatinib treatment. One hundred and four patients were identified with imatinib failure in CP CML. The post-imatinib failure treatment was either SCT (8 patients), dasatinib/nilotinib (35 patients) or other treatment (61 patients). Out of the 61 patients receiving other treatment, only 12 received HU; remaining treatments included tipifarnib, lonafarnib, cytarabine, homohorringtonine, decitabine, homoharringtonine, interferon alpha and others. The estimated 2 and 3 years OS for CP CML patients receiving "other" treatment was 77% and 70% respectively. Based on Hoyle (2011) report,[17] the submission used the estimated OS from the "other" treatment group in their model. Hoyle (2011)[17] assumed that survival when taking HU is the same as that of the "other" treatment arm for imatinib resistant patients. However, they also acknowledged that based on this assumption, the OS estimates for HU following TKI failure are uncertain.

4.3.2 Allogeneic stem cell transplantation

Eight studies[3, 6, 8-10, 12, 13, 15] and four conference abstracts[5, 7, 11, 14] reported on SCT in a refractory setting. Table 35 summarises results of all comparator studies.

4.3.3 Interferon alpha

Considering the highly unlikely usage of interferon (other than as a bridge to SCT, interferon alpha therapy is hardly used in England and Wales) and of the lack of suitable data, we did not consider clinical data on interferon alpha further here.

4.3.4 Quality assessment

Similarly to the quality appraisal of Study 200, comparator studies were assessed according to the Chambers (2009) criteria.[16] We have already emphasised the weakness of using a single arm study design as the only source for clinical evidence. We have also highlighted the further difficulties arising from comparing results from different single arms studies. Finding suitable comparator studies is very challenging, not least in terms of potential differences in the populations studied, the variable completeness of follow-up, publication bias, and lack of blinding throughout the literature.

Thirteen comparator studies[3-15] were identified. However, four of these are available only as conference abstracts,[5, 7, 11, 14] thus only limited information on quality assessment is available. Earlier in this section we commented on some of the weaknesses (Table 35) of the comparator studies, thus only our assessment of the Chambers (2009) criteria[16] is included in Table 36.

Table 36. Quality assessment of comparator non-RCTs identified by the systematic review

Study	Comparator	Eligibility criteria adequately reported?	Study population representative of a normal population?	An appropriate measure of variability reported?	Loss to follow-up reported or explained?	At least 90% included at baseline followed-up?	Were patients recruited prospectively?	Were patients recruited consecutively?	Did the study report relevant prognostic factors?	Pfizer Quality score	PenTAG comment
Benedicte (2010)[5]	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Bornhäuser (2006)[6]	SCT	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Poor	OK
Holroyd (2010)[7]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Ibrahim (2011)[4]	HU	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Jabbour (2006)[9]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Jabbour (2007)[8]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Jabbour (2011)[10]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Kantarjian (2007)[3]	SCT, HU	Yes	Yes	Yes	Yes	No[b]	No	Yes	Yes	Poor	OK
Markiewicz (2011)[11]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Oehler (2007)[12]	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Saussele (2010)[13]	SCT	Yes	Yes	Yes	Yes	Yes[c]	Yes	Yes	Yes	Good	OK
Schleuning	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK

(2010)[14]											
Weisser (2007)[15]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK

a >50% of patients (n=32) were at high risk for transplant-related deaths (Gratwold scores of 5–7)

b Of the 574 patients analysed, the outcome of 127 could not be retrieved in detail in relation to subsequent therapies or survival. The next analysis concentrated only on patients in whom imatinib therapy was discontinued for either clear cut resistance or recurrence (n=374) or for imatinib. toxicities (n=46)

c Follow-up was reported in the 84 patients who underwent transplantation

(Source: Pfizer submission, adapted from Table B83, p216)

4.4 Conclusions of the clinical effectiveness section

Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI. Bosutinib was also found to have an acceptable safety profile across all phases of the disease. Adverse events were restricted primarily to gastrointestinal toxicities (Table 4, p26).

The main two weaknesses of the clinical effectiveness evidence are, that Study 200 is a non-randomised single arm trial, and that while the licence is intended for treatment of adult patients with Ph^+ CML previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, the clinical evidence for bosutinib is taken entirely from Study 200, in which the great majority of patients were suited to either imatinib, nilotinib or dasatinib. Secondly, the clinical effectiveness evidence for the comparator treatments is very poor. Any comparison between Study 200 and comparator studies is highly prone to bias. In addition, OS data from Study 200 for CP patients is very immature.

Other, minor weaknesses of Study 200 are that approximately 40% of patients had previously taken IFN, while IFN is a very rare CML treatment in England and Wales, the fact that all patients had previously been treated with imatinib while the current first line treatment is nilotinib, the discrepancy between the duration of imatinib treatment reported in Study 200 and in IRIS trial, and the fact that only one participant with nilotinib intolerance was recruited in third line CP CML subpopulation.

On the other hand, the strength of the submitted evidence is that Study 200 is a large, multi-centre, consecutively recruited trial, with patients representative of population expected the in clinical practice in England and Wales (based on ECOG scores).

5 COST-EFFECTIVENESS

5.1 Manufacturer's review of cost-effectiveness evidence

5.1.1 Objective

The objective of the manufacturer's cost-effectiveness review was to identify cost-effectiveness studies in CML patients previously treated by one or more TKIs. It was assumed this population would include and be representative of the indicated population (patients for whom imatinib, nilotinib and dasatinib would be inappropriate).

We believe the objective of the cost-effectiveness review was appropriate for identifying existing answers to the decision problem, but note that by excluding studies of first-line TKIs possible sources of economic evidence to inform the *de novo* analysis could be missed.

5.1.2 Search strategy

Pfizer conducted two sets of searches to locate cost-effectiveness studies for this submission.

The first search (Pfizer submission, Section 10.10, p218) took terms for CML or Philadelphia Chromosome combined with methodological limits to economics/cost studies (see Pfizer submission, Section 10.10.4, p218 for full search strategy). These searches were run 2nd October 2012 and were performed in the databases listed in Table 37.

Table 37. Electronic databases searched by Pfizer for cost-effectiveness review (run from database inception; Source: Pfizer submission, Section 10.10, p218)

Database	Searched via
Ovid MEDLINE®	Ovid
EMBASE	Ovid
MEDLINE® In-Progress	Ovid
EconLit	Ovid
NHS EED	Cochrane Library and Centre for Reviews and Dissemination
Cochrane Library	Ovid

Pfizer state that search results were limited to Dasatinib, Nilotinib, Imatinib, Bosutinib, Stem-Cell, Hydroxycarbamide, Interferon, or Standard Care (Pfizer submission, Section 10.10.4, p220). It is not clear from the submission how this was achieved.

Pfizer additionally searched proceedings of selected conferences (Table 38) in February 2013 and NICE HTAs. Pfizer report that horizon scans were performed using the Google search engine (Pfizer submission, Section 10.10.5, p221).

Table 38. Conferences searched by Pfizer (Source: Pfizer submission, Section 10.10.5, p221)

Conference
International Society for Pharmacoeconomics and Outcomes (ISPOR)
International Congress on Leukemia Lymphoma Myeloma (ICLLM)
ESMA[a]
American Society of Clinical Oncology (ASCO)
American Society of Hematology (ASH)

a We were unable to identify this conference, but we believe, as does our clinical expert, Dr Rudin, that it probably refers to ESMO (European Society of Medical Oncology)

5.1.2.1 Update searches

In clarification, Pfizer confirmed they had updated the submission searches from 2nd October 2012 to April 2013. We are happy to accept these update searches in place of the horizon scanning.

5.1.2.2 ERG comment on search strategy

The searches performed were appropriate to the task.

5.1.3 Inclusion and exclusion criteria used in the study selection

Inclusion and exclusion criteria in the cost-effectiveness review are shown in Table 39. By excluding studies of first-line TKIs and excluding cost- (without assessment of effectiveness) it is possible that studies capable of informing the *de novo* model would be missed, but we note in Section 5.2.9.1 (p127) that an additional search was conducted in which the study type criteria were dropped. We believe the inclusion and exclusion criteria were appropriate to the objective of the cost-effectiveness review.

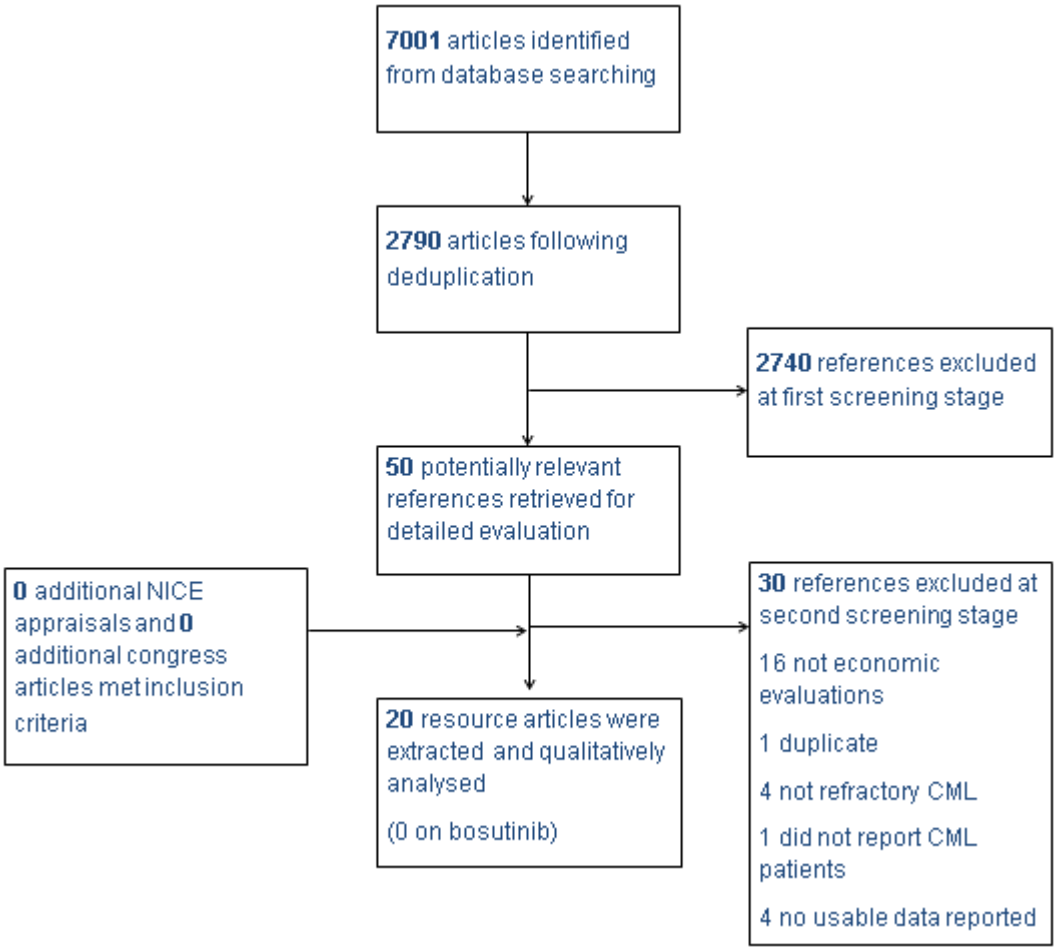
Table 39. Inclusion and exclusion criteria for systematic review of economic evidence

Category	Include	Exclude
Population	Adult patients with refractory CP, AP or BP Ph^+ CML (treated with at least one prior TKI)	Studies that did not report adult patients Studies that did not report patients with refractory Ph^+ CML
Intervention	Include but not limited to bosutinib, dasatinib, nilotinib and imatinib	
Comparators	Hydroxycarbamide, interferon, SCT, best supportive care, dasatinib, nilotinib, imatinib	
Outcomes	Incremental costs and QALYs Any other measure of effectiveness reported together with costs	
Study type	Full economic evaluation (including cost-consequence, cost-minimisation, cost-effectiveness, cost-utility, cost-benefit) comparing two or more interventions	
Publication type		Letters, editorials, reviews of economic articles (although reference lists of these would be hand searched)
Other	Reported in sufficient detail to assess methodological quality and extract data and results	

5.1.4 Results

Figure 9 shows the study flow diagram for the cost-effectiveness review. Searching identified 7,001 articles, which corresponded to 2,790 articles following de-duplication. Fifty articles were retrieved for detailed evaluation, of which 20 were included and 30 were excluded from the final set of studies for extraction and quality assessment. Details of the excluded studies were not given, and the reasons for exclusion are given for at most 26 of the 30 articles. We would have preferred to have access to the set of articles excluded after full paper retrieval but this was not provided by Pfizer.

Figure 9. Study flow diagram for systematic review of economic evidence



(Source: Pfizer submission, Section 7.1.1, p107)

The key included studies were Hoyle and colleagues (2011),[39] Rogers and colleagues (2012)[2] and Loveman and colleagues (2012),[40] which are all publications based on TA241 (Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance). These studies are most relevant to the decision problem as they study refractory CML in adults in the UK treated by TKIs. These studies also included details of submissions by Novartis and Bristol-Myers Squibb on the cost-effectiveness of nilotinib and dasatinib.

No studies were identified which investigated the cost-effectiveness of bosutinib in refractory CML.

5.1.5 Conclusions and ERG critique

Pfizer did not identify any economic evaluations of bosutinib in refractory CML. As such no conclusions were drawn from the systematic review regarding the decision problem. An additional

review was conducted by Pfizer (see Section 5.2.9.1, p127) to identify inputs for the *de novo* model, which relaxed inclusion criteria.

We believe the review of cost-effectiveness evidence was appropriate and accept that there are no economic evaluations of bosutinib in refractory CML.

5.2 Summary of the manufacturer's submitted evaluation

5.2.1 History of submission

Table 40 details the history of the Pfizer model submission. This report references the latest version of the model and report (received 22/04/2013).

Table 40. History of Pfizer model submission

Date	Detail
14/03/2013	PenTAG receive Pfizer model from NICE
19/04/2013–22/04/2013	PenTAG receive updated Pfizer model and supplementary report with corrections to errors highlighted by PenTAG in questions for clarification[a]

a PenTAG identified that the hazard ratio for OS in bosutinib CP patients was not implemented correctly. When Pfizer corrected the error the CP model base case ICER for bosutinib decreased from [redacted] per QALY to [redacted] per QALY.

5.2.2 Model structure

The submission includes three cohort models (for patients starting in CP, AP and BP). In each model bosutinib is compared with hydroxycarbamide, interferon (CP model only) and SCT. The models are described as "semi-Markov models" but there are no transition probabilities as would be expected from a Markov model.[41, 42] The membership of each state is calculated in a manner similar to that which would be expected in an area-under-the-curve model.

Cycles in the models last one month and a half-cycle correction was not applied.

Bosutinib patients receive bosutinib until they discontinue treatment due to intolerance or resistance, progress to a later disease stage (AP or BP for those in CP, BP for those in AP, not applicable for those in BP), or die. Bosutinib patients receive hydroxycarbamide following bosutinib discontinuation until death (even in the case of further disease progression).

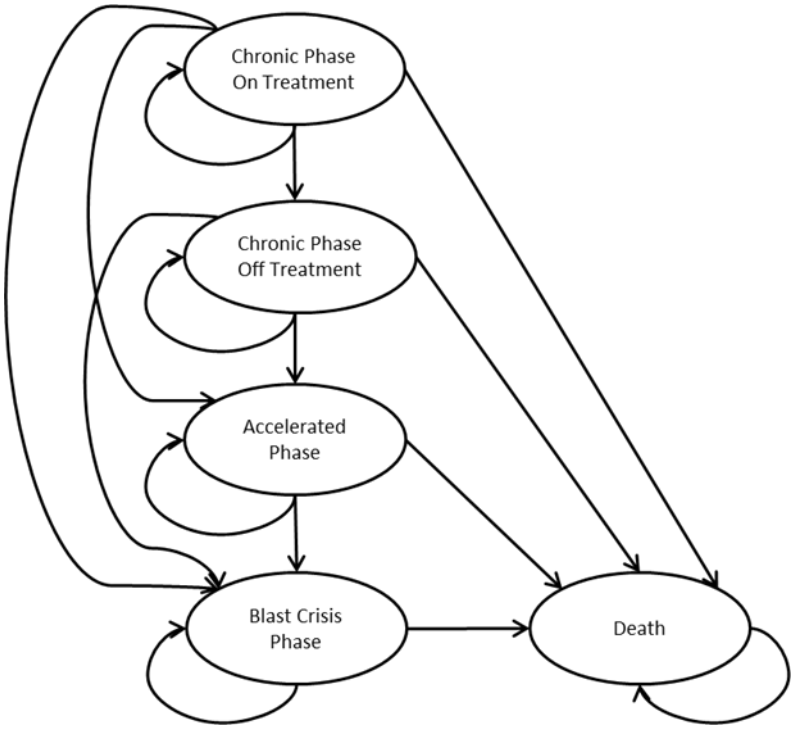
Hydroxycarbamide patients receive hydroxycarbamide regardless of disease progression until death.

Interferon patients receive interferon until they discontinue treatment (similarly to bosutinib patients), progress to a later disease stage (AP or BP), or die. Interferon patients receive hydroxycarbamide following bosutinib discontinuation until death (even in the case of further disease progression).

SCT patients receive SCT and are thereafter regarded as cured in the base case analysis and so do not progress to later disease stages and do not receive drug treatment after SCT.

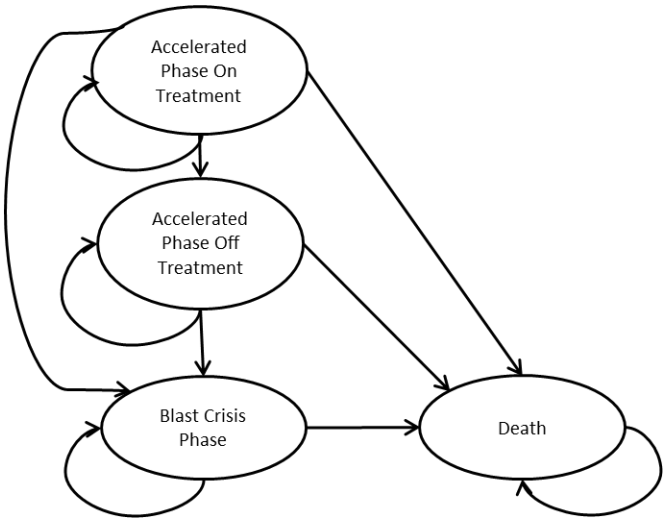
The models are structured similarly, with time on and off treatment in the initial phase, later disease phases (if applicable) and death. Figure 10 shows the CP model structure, Figure 11 shows the AP model structure and Figure 12 shows the BP model structure.

Figure 10. Chronic phase (CP) model structure



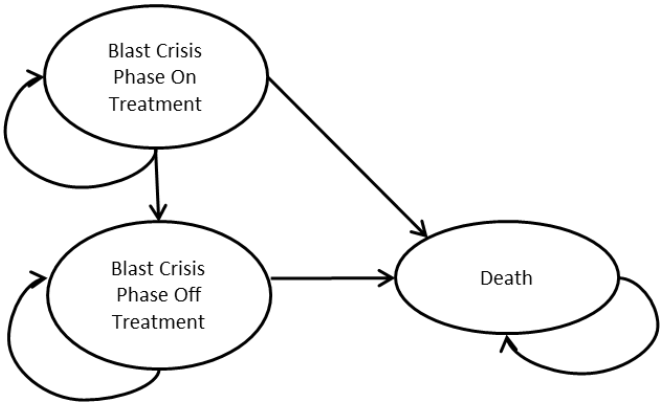
(Source: Pfizer submission, Section 7.2.2, p109)

Figure 11. Accelerated phase (AP) model structure



(Source: Pfizer submission, Section 7.2.2, p110)

Figure 12. Blast phase (BP) model structure



(Source: Pfizer submission, Section 7.2.2, p110)

5.2.2.1 State membership in the CP model

The proportion of the cohort in each state in the CP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)
2. The proportion in the Blast Crisis Phase state is set so that patients spend 6 months in the blast crisis phase
3. The proportion in the Accelerated Phase state is set so that patients spend 10 months in the accelerated phase

4. The proportion in the Chronic Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive or the proportion in the Blast Crisis Phase and Accelerated Phase states
5. The remainder of the population is in the Chronic Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Chronic Phase Off Treatment state is always zero.

Patients receiving a stem cell transplant are assumed to be cured and hence do not progress to the accelerated and blast crisis phases. Therefore the proportions in the Blast Crisis Phase, Accelerated Phase and Chronic Phase Off Treatment states are zero and the proportion in the Chronic Phase On Treatment state is set equal to the relevant overall survival curve.

5.2.2.2 State membership in the AP model

The proportion of the cohort in each state in the AP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)
2. The proportion in the Blast Crisis Phase state is set so that patients spend 6 months in the blast crisis phase
3. The proportion in the Accelerated Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive or the proportion in the Blast Crisis Phase state
4. The remainder of the population is in the Accelerated Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Accelerated Phase Off Treatment state is always zero.

Patients receiving a stem cell transplant are assumed to be cured and hence do not progress to the blast crisis phase. Therefore the proportions in the Blast Crisis Phase and Accelerated Phase Off Treatment states are zero and the proportion in the Accelerated Phase On Treatment state is set equal to the relevant overall survival curve.

5.2.2.3 State membership in the BP model

The proportion of the cohort in each state in the BP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)

2. The proportion in the Blast Crisis Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive
3. The remainder of the population is in the Blast Crisis Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Blast Crisis Phase Off Treatment state is always zero. Patients receiving a stem cell transplant are assumed to be cured; therefore the proportion in the Blast Crisis Phase Off Treatment state is always zero.

5.2.3 Population

Bosutinib is indicated for patients with Ph^+ CML in the chronic, accelerated or blast phase who have failed one or more TKIs and for whom imatinib, nilotinib and dasatinib are considered inappropriate.

Pfizer estimate that each year, 80 of the 631 annual CML cases in England and Wales will be eligible to receive bosutinib, and of these 12 (15%) will be eligible to receive it second-line (following imatinib failure), 19 (24%) will be eligible to receive it third-line (following failure of imatinib and nilotinib), and 49 (61%) will be eligible to receive it fourth-line (Pfizer submission, Section 8.1, pp188-189).

Pfizer suggest that the third-line chronic phase cohort in Study 200 is most representative of the intended population, and hence this forms the basis of the population in the CP model and for many other parameters in the CP model.

All patients in the CP model were assumed to start treatment at age 54 years, which was the mean baseline age in the third-line CP cohort of Study 200 (Pfizer submission, Section 7.3.2, p124). All patients in the AP and BP models were assumed to start treatment aged 50 and 47 years respectively, which were the mean baseline ages in the AP and BP cohorts of Study 200 (Pfizer submission, Section 7.3.2, p124).

Pfizer assumed equal proportions of males and females in the patient population.

No assumptions were made in the model about previous treatments, although Study 200 evaluated patients who received imatinib first-line, followed by nilotinib and/or dasatinib. Some patients in Study 200 had previous interferon use (52% of third-line CP cohort, 50% of AP cohort and 30% of BP cohort) and some patients had previously received stem cell transplants (8% of third-line CP cohort, 9% of AP cohort and 6% of BP cohort).

There were no subgroups in any of the models.

5.2.4 Intervention and comparators

The intervention is bosutinib given until any of the following occur:

- progression to later phase CML,
- patient has/develops resistance to bosutinib,
- patient no longer tolerates bosutinib, or
- patient dies.

Following bosutinib discontinuation patients receive hydroxycarbamide until death.

The comparator treatments are:

- Hydroxycarbamide (patients receive until death)
- Interferon alpha (patients may discontinue treatment and then receive hydroxycarbamide until death)
- Allogeneic stem cell transplant (one-off treatment followed by medical management)

Interferon alpha is only considered as a comparator in the CP model because effectiveness estimates were not available for interferon alpha in the advanced and blast phases.

5.2.5 Perspective, time horizon and discounting

The Pfizer submission adopts the perspective of the NHS. Costs of drug acquisition, drug administration, medical management, adverse events and death are included. Impacts on costs outside the NHS budget (e.g., Personal Social Services) were not included as they were not expected to be affected significantly. Wider societal costs are not included. Health benefits are only included from the patient population being treated. Wider societal benefits are not included.

The time horizon is 50 years. As the patients start aged 47–54 years, this means the time horizon is to age 97–104 years.

Costs and QALYs are discounted at 3.5% per annum.[43] Life years are not discounted.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Overall survival

Overall survival (OS) is one of the most clinically relevant measures of treatment effectiveness and is also a key driver of cost-effectiveness.

Pfizer used results from Study 200 to inform the OS of bosutinib and estimated OS of hydroxycarbamide, interferon and SCT from published literature. Table 41 shows the methods which were used to calculate OS in the CP, AP and BP models, both in the base case and in a number of scenario analyses.

Overall survival of bosutinib is extrapolated in all three models, but most significantly in the CP model. Due to study protocol the OS after two years is biased (since patients are only followed up for two years after treatment discontinuation) and hence OS is only available from Study 200 up to two years. In the CP-3L cohort OS at two years (calculated by the Kaplan-Meier method) was 84%, so significant extrapolation takes place in the model. In the AP cohort OS at two years was 65.6%, again requiring significant extrapolation. In the BP cohort OS at two years was 35.4%, with median OS of 11.1 months, so some extrapolation was still necessary, but not to the same extent as for the CP and AP models.

Table 41. Methods used to calculate overall survival (OS) in Pfizer submission base case and scenario analyses

Model	Treatment	Base case OS	Scenario analysis OS
CP	Bosutinib	MCyR surrogate relationship based on Jabbour and colleagues (2009)[44] (see p119)	MCyR surrogate with different hazard ratio for OS Exponential distribution fitted to third line CP cohort from Study 200 "Cumulative survival approach" (see p121)
	Hydroxycarbamide	Exponential distribution with mean OS = 3.5 years following Kantarjian (2007)[3]	Exponential distribution with different mean OS
	Interferon	Exponential distribution with mean OS = 3.6 years following Loveman (2012)[40]	*None*
	SCT	Exponential distribution fitted to Jabbour (2011)[10]	Weibull distribution fitted to Jabbour (2011)[10] Exponential distribution fitted to Oehler (2007)[12]
AP	Bosutinib	Exponential distribution fitted to AP cohort OS in Study 200	Extreme value distribution fitted to AP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 16 months to match length of time spent in AP and BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Jabbour (2011)[10]
BP	Bosutinib	Exponential distribution fitted to OS in Study 200	Weibull distribution fitted to BP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 6 months to match length of time spent in BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Saussele (2010)[13]

MCyR surrogate overall survival

Overall survival for bosutinib patients in the CP model was estimated using a MCyR surrogate approach. This approach was not used for OS for bosutinib patients in the AP and BP models as sufficiently mature OS data was available from Study 200 to fit parametric curves. A very similar MCyR approach has been used in a previous assessment, TA241,[2] which investigated nilotinib, dasatinib and high-dose imatinib for treatment of Ph^+ imatinib-resistant or imatinib-intolerant CML patients.

Following Rogers and colleagues (2012)[2] Pfizer assume a hazard ratio of overall mortality of 0.370 for patients achieving a MCyR versus those not achieving a MCyR. Pfizer assumed that the same hazard ratio would apply for patients achieving a MCyR using bosutinib as bosutinib is a TKI with a similar mode of action to imatinib.

Pfizer first extracted individual patient OS data from Jabbour and colleagues (2009),[44] which investigates the effectiveness of high-dose imatinib in patients after cytogenetic failure on standard-dose imatinib. Pfizer then fitted an exponential curve to the OS data using the maximum likelihood method. This curve, adjusted for general mortality, was then used as the basis for fitting a new curve with two components: survival for responders and survival for non-responders. These two components were both exponential curves with scale factors set such that the hazard ratio between matched 0.370. It was then assumed that the MCyR rate in Jabbour and colleagues (2009)[44] would be 41.7%, so that the overall survival in Jabbour would be equal to 41.7% × (OS for MCyR) + (100% − 41.7%) × (OS for no MCyR). The exponential parameters were chosen to achieve the best fit to the adjusted exponential curve fitted to the Jabbour OS data.

Finally OS for bosutinib was estimated by using the MCyR rate of 38.9%, which corresponds to the best cumulative response at a minimum follow up of 12 months for the entire 3rd-line population (not the post-hoc unmet clinical need population), i.e., 38.9% is the proportion of patients achieving a MCyR at any time or maintaining a MCyR present at baseline, with all patients followed up for at least 12 months (median follow-up 28.5 months).

Fitting parametric distributions to overall survival data

For bosutinib patients in the AP and BP models exponential distributions were fitted to individual patient data from the relevant cohorts in Study 200. The entire AP and BP cohorts were used (i.e., no post-hoc "unmet need" subpopulation was considered, nor were cohorts divided into imatinib-failure patients and multiple TKI-failure patients), but analysis was restricted to the first two years, since the study protocol stated that patients would only be followed up for two years post-discontinuation. In addition an exponential distribution was fitted to the CP cohort for a scenario analysis. Pfizer do not state explicitly that maximum likelihood methodology is used but it is very likely that this is the case.

For SCT patients in the CP model individual patient data was extracted from the relevant overall survival curve in Jabbour and colleagues (2011)[10] and an exponential distribution was fitted to this OS data. Again it is likely, but not explicitly stated, that the maximum likelihood methodology was used. The same methodology was used in the AP and BP models but fitted to OS data from Oehler and colleagues (2007).[12]

Choosing exponential distributions with desired mean overall survival

The method of moments was used to choose exponential distributions with desired mean OS for hydroxycarbamide in all three models and for interferon in the CP model. The method of moments involves simply setting the rate parameter λ to 1/(Mean OS).

Pfizer "cumulative survival approach"

Pfizer developed a "cumulative survival approach" for bosutinib overall survival in a scenario analysis of the CP model which they describe as similar to the cumulative survival approach used in TA251. Their approach involves estimating OS as PFS + 10 months in AP + 6 months in BP. We do not believe it is correct to describe this method as similar to the approach in TA251 as the cumulative survival approach in TA251 involved estimating OS as the sum of time spent on treatments, which is a different structural assumption.

Death due to non-CML mortality

Death due to non-CML mortality was originally calculated as follows for all treatments in the CP, AP and BP models, except for bosutinib in the CP model (Pfizer submission, Section 7.3.2, p124):

> For all three models, for all comparators, background mortality was incorporated into the model, to ensure that parametric curve fits did not over predict survival as patients aged.
>
> Background mortality was applied in the model by subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200), and adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012). The starting age in the AP and BP models are 50 and 47 respectively, so these ages are used to adjust for background mortality.
>
> As this component of mortality increases over time, it has the effect of ensuring survival curves do not asymptote to 0, estimating survival beyond what can be expected in clinical practice, where patients are likely to experience co-morbidities and competing risks.

The method for incorporating non-CML mortality for bosutinib in the CP model was changed following clarifications from the manufacturer in which they corrected an error in calculating CML mortality from the MCyR surrogate relationship (p119). Rather than using the above method, CML mortality was estimated accounting for general mortality (see p119) and then general mortality is added to CML mortality in a manner similar to that used in TA241 and described by Rogers and colleagues (2012).[2]

5.2.6.2 Time on treatment

Time on treatment has clinical relevance because treatments can reduce or improve health related quality of life. It is also very relevant to cost-effectiveness because higher drug acquisition costs are incurred while patients are on bosutinib or interferon rather than hydroxycarbamide.

Bosutinib and interferon are both discontinued when disease progresses (or the patient dies), the patient does not tolerate them or the technology is not efficacious. Hydroxycarbamide is received until death and is not discontinued; therefore for hydroxycarbamide time on treatment is equal to overall survival. Stem cell transplant patients have a one-off procedure followed by medical management, with medical management continuing until death.

Time on bosutinib

Time on bosutinib is incorporated into the model by fitting a lognormal distribution to the individual patient data for discontinuation in Study 200 for the relevant cohort, i.e., in the CP model the CP-3L cohort is used (Figure 13), in the AP model the AP cohort is used (

Figure 14) and in the BP model the BP cohort is used (

Figure 15).

Figure 13. [redacted]

Figure 14. [redacted]

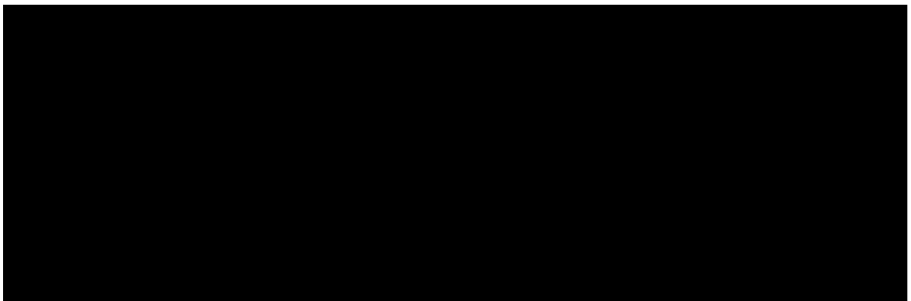


Figure 15. [redacted]

Time on interferon

Time on interferon is incorporated into the model using an exponential distribution, chosen such that the mean time on treatment (ignoring the effect of non-CML mortality) would be 0.5 years.[40] This estimate was not taken from any study, but on the basis of expert opinion.

5.2.7 Health related quality of life

5.2.7.1 Utilities in CP CML

For CP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. From patients on 1st-line imatinib in the IRIS RCT of imatinib vs. IFN. These values were reported in Reed and colleagues (2004),[45] and are estimated from a large sample of patients, using the EQ-5D, which is preferred in the NICE reference case. The mean utility is 0.85 at age 50. In TA251, we, PenTAG, applied this value to the utility for all 1st-line TKIs: imatinib, nilotinib and dasatinib in CP, given the lack of relevant high-quality utility data for these treatments, and based on clinical opinion and the similarity of the incidence of adverse events across treatments.
2. From patients in Study 200 of people on bosutinib. The weighted average utility for 3rd-line patients, mostly over the first two years of treatment, was [redacted] (p131 Pfizer submission). At baseline, [redacted] of 3rd-line CP patients completed the EQ-5D. The weighted average utility for 2nd-line patients also mostly over the first two years of treatment, was [redacted] (estimated by us from data on pp357-8 Pfizer submission). At baseline, [redacted] of 2nd-line CP patients completed the EQ-5D.

For their base case, Pfizer used the estimate from the IRIS trial.

Next, Pfizer found no relevant studies to estimate the utility for patients on HU in CP. They therefore assumed the same utility as for bosutinib. In TA251, we also found no relevant data for the utility for patients on HU in CP. We also set this value to equal the utility for the TKIs.

Next, Pfizer found two sources for utilities for patients after SCT in CP:

1. They correctly cite our TA251 analysis where we assumed a disutility vs. the general population of 0.041 for the 75% of patients in a "low risk" population and a disutility of 0.079 for the remaining 25% of patients in a "high risk" population. For details of our analysis, see our TA251 report.[17] In brief, the disutility of 0.079 was in respect of chronic graft-versus-host disease and was elicited from 12 US clinicians familiar with bone marrow transplantation. This therefore gave a mean utility at age 54 of 0.81 for patients in the "low risk" population and 0.76 for patients in the "high risk" population, giving a weighted mean of 0.80.
2. They cite utilities after SCT in CP of 0.60 from the BMS submission in TA241 and 0.81 from the Novartis submission in TA251 (p135 Pfizer submission). However, they give no further details on how these were estimated.

In their base case, Pfizer estimate a utility after SCT in CP of 0.71 at age 54.

Next, Pfizer assume a utility for patients on IFN in CP of 0.71, which they took from our analysis in TA241 (IFN was not a treatment in our TA251 analysis).

As in our TA251 analysis, all utilities are assumed to decrease gradually with age.

5.2.7.2 Utilities in AP CML

For AP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. 0.73 at age 54. We used this value in TA251 for treatment with HU (we did not model treatment with TKIs in AP). This value was originally reported in Dalziel and colleagues (2004).[46]
2. From patients in Study 200 of people on bosutinib. The weighted average utility, [redacted]. At baseline, [redacted] of AP patients completed the EQ-5D.

For their base case, Pfizer used the first value.

Next, Pfizer assumed the same value of 0.73 for patients on HU in AP.

Finally, for patients after SCT in AP, Pfizer assume a utility of 0.71 for patients age 54, the same as for patients after SCT in CP.

5.2.7.3 Utilities in BP CML

For AP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. 0.52 at age 54. We used this value in TA251 for treatment with HU (we did not model treatment with TKIs in BP). This value was originally reported in Dalziel and colleagues (2004).[46]
2. From patients in Study 200 of people on bosutinib. The weighted average utility, [redacted], was [redacted] (p132 Pfizer submission), which is only slightly less than the averages for 3rd-line CP and AP in Study 200. At baseline, [redacted] of BP patients completed the EQ-5D.

For their base case, Pfizer used the first value.

Next, Pfizer assumed the same value of 0.52 for patients in BP on HU and after SCT.

Table 42. Comparison of utilities used in TA251, used by Pfizer and measured in Study 200

Phase	Treatment	TA251	Study 200	Pfizer
CP	**Bosutinib**	For TKIs[a], 0.84 age 54, declining with age.	[redacted] at age [redacted] for 3rd-line, [redacted] for 2nd-line[d]	0.85 age 54, declining with age
	HU	0.84 age 54, declining with age	n/a	0.85 age 54, declining with age
	SCT	0.80 age 54, declining with age [b]		0.71 age 54, declining with age
	IFN	0.71, independent of age 51[c]		0.71 age 54, declining with age
AP	**Bosutinib**	n/a	[redacted]	0.73 age 54, declining with age
	HU	0.73 (declining with age from age 78)	n/a	0.73 age 54, declining with age
	SCT	n/a		0.71 age 54, declining with age
BP	**Bosutinib**	n/a	[redacted]	0.52 age 54, declining with age
	HU	0.52 (independent of age)	n/a	
	SCT	n/a		

a Bosutinib not modelled in TA251
b See text for derivation.
c From TA241; not modelled in TA251
d [redacted] calculated by PenTAG from data on p358 Pfizer submission

5.2.8 Adverse events

Adverse events are included only for bosutinib and are assumed to incur costs but not affect quality of life in any way not already reflected by utility values as specified in Section 5.2.7 (p124). Adverse events are assumed to occur in the first cycle only.

Resource use and costs associated with adverse events are discussed in Section 5.2.9.6 (p130).

5.2.9 Resources and costs

Resource use and cost data were drawn from multiple sources. Resource use data were largely drawn from TA251[17] (which were in turn based on a survey by Oxford Outcomes on behalf of Bristol-Myers Squibb), with most costs derived from the Department of Health National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts.[47]

5.2.9.1 Resource use systematic review

Pfizer conducted a systematic review for relevant resource use and cost data. The search was performed in October/November 2012 and used the same search strategy, inclusion and exclusion criteria as in Section 5.1 (p108), but with the study type criteria broadened to include any study that reported cost or resource data from the UK.

Abstracts were assessed by two reviewers for full paper retrieval. Full papers were obtained and assessed by two reviewers. Data extraction was conducted by one reviewer and checked by a second party.

Pfizer felt that insufficient resource use data had been identified and so sought data from first-line studies. As a result they included resource use and cost data from TA251.[17] Pfizer state that first-line data are appropriate as resource use is expected to be driven primarily by phase of disease rather than line of treatment (Pfizer submission, Section 7.4.18, p141).

Figure 16 shows the flow diagram of articles in the systematic review, and Table 43 shows the included studies.

Figure 16. Study flow diagram for resource use systematic review

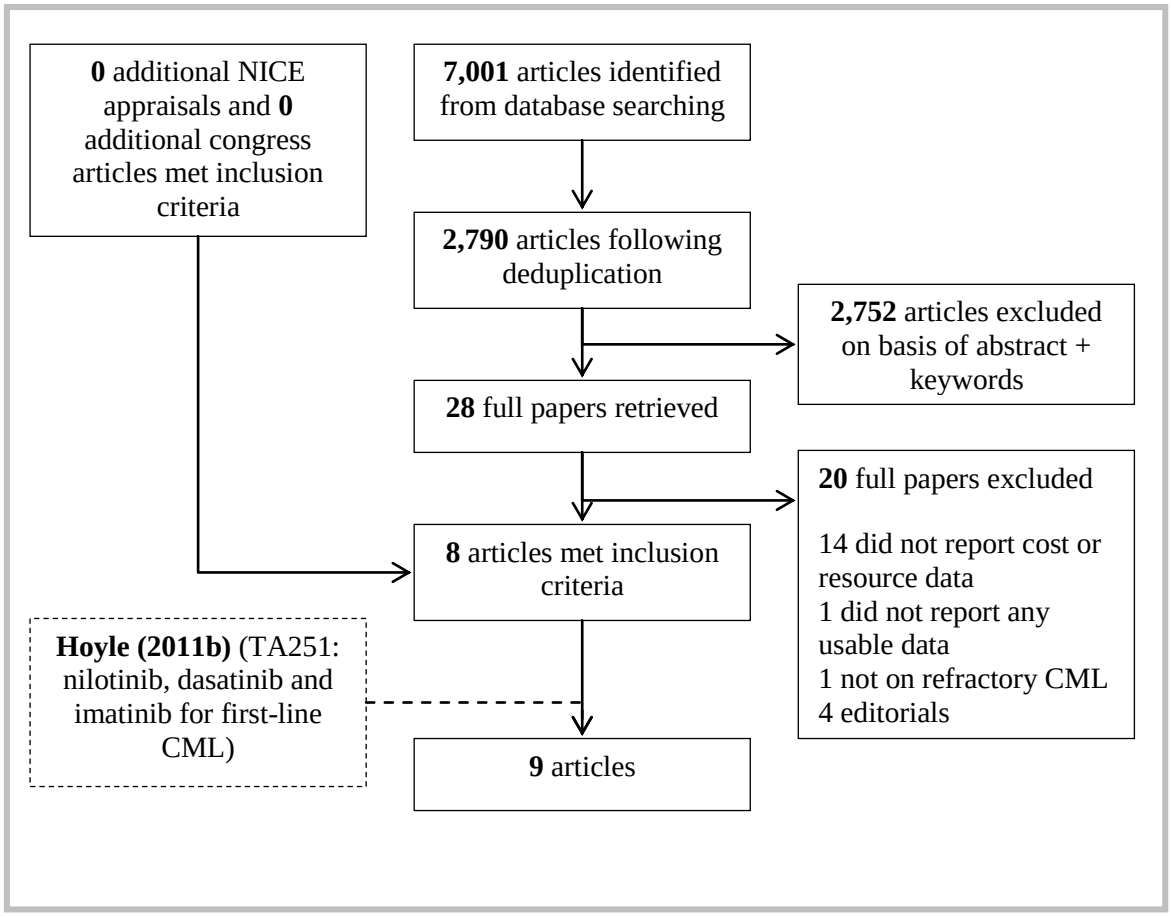


Table 43. Included studies in systematic review of resource use and cost data

Study	Resource use/cost included in Pfizer model base case	Notes
Hoyle (2011a)[39] Rogers (2012)[2] Loveman (2012)[40]	Interferon patients requiring assistance with injection Hydroxycarbamide and interferon dosing	TA241
Hoyle (2011b)[17]	Nurse-led outpatient appointments Consultant-led outpatient appointments Tests (various) Hospital inpatient bed days Hospital inpatient ICU days Adverse events	TA251
Darbà (2012)[48]	*None*	Not English language
Szabo (2009)[49]	*None*	Conference abstract
Taylor (2009a)[50]	*None*	Conference abstract
Taylor (2009b)[51]	*None*	Conference abstract
Warren (2004)[52]	*None*	

5.2.9.2 Drug acquisition

Drug acquisition costs per monthly model cycle were calculated by multiplying the expected dosage across the cycle by the drug cost per unit, to give monthly costs (costs per cycle) as shown in Table 44. Costs of stem cell transplant are discussed in Section 5.2.9.7 (p131).

Table 44. Costs per month of bosutinib, hydroxycarbamide and interferon

Intervention	Cost per month	Units per month	Source	Unit cost	Source
Bosutinib	£3,735.84	30.44	Recommended daily dose 500mg	£122.74	£3,436.67 for 28 tablet pack
Hydroxycarbamide	£12.75	121.75	Loveman (2012)[40]	£0.10	BNF 63[b]
Interferon	£1,296.03[a]	60.88	Rogers (2012)[2]	£21.29	BNF 63

a The Pfizer report states that the monthly cost of interferon including nurse assistance with injection for some patients is £648. We believe this assumes one unit daily, i.e., 30.44 units per month, and does not include the cost of nurse assistance. The Pfizer model assumes two injections per day.

b The Pfizer model cites the source as BNF 63 while the report cites the source as BNF 64

5.2.9.3 Drug administration

Pfizer assumed no drug administration costs for bosutinib and hydroxycarbamide. Pfizer assumed that 25% of interferon patients would require assistance with injection, following an assumption made by Rogers and colleagues (2012),[2] and that this would require a district nurse visit, each costing £39.[53]

The Pfizer model includes one nurse visit per cycle (i.e., per month) in drug administration costs for patients requiring assistance.

Stem cell transplant administration costs are discussed in Section 5.2.9.7 (p131).

5.2.9.4 Medical management, monitoring and tests

Pfizer included medical management costs as shown in Table 45 and a cost of palliative care before death (discussed in Section 5.2.9.5, p129). Medical management costs relating to stem cell transplant are discussed in Section 5.2.9.7 (p131).

Table 45. On-going medical management costs for patients on bosutinib, HU or IFN in Pfizer model

Item	Cost / month	Units / month[17]	Unit cost[47]
Chronic Phase			
Nurse-led outpatient appointment	£42	0.40	£106[a]
Consultant-led outpatient appointment	£111	0.90	£124[b]
Hospital inpatient ward day	£0	0.00	£322[c]
Hospital inpatient ward day	£0	0.00	£1,109[d]
Total	**£154**		
Accelerated Phase and Blast Crisis Phase			
Nurse-led outpatient appointment	£53	0.50	£106[a]
Consultant-led outpatient appointment	£161	1.30	£124[b]
Hospital inpatient ward day	£554	1.72	£322[c]
Hospital inpatient ward day	£111	0.10	£1,109[d]
Total	**£878**		

a Outpatient medical oncology - Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face
b Outpatient medical oncology - Consultant Led: Follow up Attendance Non-Admitted Face to Face
c Average of excess bed day – Non-elective inpatient - Malignant Disorders of Lymphatic or Haematological Systems, with/without CC
d Average of critical care unit costs – adult critical care (weighted by number of critical care periods)

Pfizer included costs of CML related tests (mostly bone marrow aspirations), separately for CP and for AP/BP, which were inflated from TA251[17] using the HCHS Pay and Prices index[53] to inflate from 2008/09 to 2011/12 prices. The resulting costs per cycle of tests in CP, AP and BP were £231, £377 and £377 respectively.

5.2.9.5 Palliative care

Pfizer used a cost of £6,004 for death based on a cost of £5,401 reported by Addicott and Dewar (2008)[54] and inflated from 2007/08 prices. The cost of £5,401 includes costs incurred in the acute and

community health sectors and is derived from 40 patients accessing a new programme of end of life choice.

5.2.9.6 Adverse events

Costs of adverse events were included for bosutinib but not for comparators. Pfizer state that this is in order to present a conservative estimate of the costs associated with bosutinib treatment. Frequencies of adverse events were estimated from the third-line CP cohort of Study 200 and included "treatment-emergent adverse events of grade 3 or 4 that occurred in 5% or more of the subpopulations contained within the third-line cohort of Study 200".

Table 46 shows the costs of adverse events for bosutinib in the Pfizer model, which are used for the CP model and also the AP and BP models. A one-off cost of £506.25 is assumed in the first cycle.

Table 46. Costs of adverse events for bosutinib in Pfizer model

AE	Proportion of patients (Study 200 CP-3L cohort, 28 March 2011 snapshot)	Cost per event	Cost source
Thrombocytopenia	25.4%	£503.99	TA251[17]
Neutropenia	14.4%	£506.13	
Anaemia	5.1%	£346.69	
Cardiac disorders	4.2%	£169.81	
Gastrointestinal disorders[a]	13.6%	£281.07	Erlotinib ERG report[55]
Hepatobiliary disorders	4.2%	£215.85	DH Reference costs 2011-12[47]
Infections and infestations	3.4%	£933.23	
Investigations	9.3%	£31.02	
Metabolism and nutrition disorders	3.4%	£1,576.37	
Musculoskeletal and connective tissue disorders	5.9%	£717.03	
Neoplasms benign, malignant and unspecified	3.4%	£1,570.14	
Nervous system disorders	4.2%	£1,091.02	
Respiratory, thoracic and mediastinal disorders[b]	2.5%	£32.10	TA251[17]
Skin and subcutaneous tissue disorders	1.7%	£138.76	Erlotinib ERG report[55]
Weighted average	**100%**	**£506.25**	

a Assumed to be diarrhoea
b Assumed to be pleural effusion

5.2.9.7 Stem cell transplant

Stem cell transplant costs were mainly drawn from the economic analysis performed for the NHS Blood and Transplant service[56] which estimated the upfront costs of SCT and the costs for three follow-up periods (1-6 months, 7-12 months and 13-24 months).

These costs were based on resource use in a Dutch cost study by van Agthoven and colleagues (2002)[57] into the costs of three forms of stem cell transplant for acute myeloid leukaemia and acute lymphoblastic leukaemia. The three forms were:

- BMT – Bone marrow transplant; stem cell graft harvested from the bone marrow of an HLA-identical sibling
- PBSCT – Peripheral blood stem cell transplant; stem cell graft harvested from the peripheral blood of an HLA-identical sibling
- MUD – Matched unrelated donor; stem cell graft from the bone marrow or peripheral blood of a voluntary matched unrelated donor

The study included direct medical costs for Personnel, Transplantation and Follow-up (two years), which importantly included outpatient clinic attendances and diagnostic tests during follow-up. The results of the study are shown in Table 47.

Table 47. Costs of stem cell transplant (1998 EUR, €) from van Agthoven and colleagues (2002)[57]

	BMT			**MUD**			**PBSCT**		
	Average cost per living patient	% alive	Average cost per transplant patient	Average cost per living patient	% alive	Average cost per transplant patient	Average cost per living patient	% alive	Average cost per transplant patient
Personnel	26,543		26,543	26,543		26,543	26,543		26,543
Transplantation	42,129	100	42,129	84,948	100	84,948	45,734	100	45,734
Follow-up phase 1 (1–6 months)	16,587	98	16,255	30,292	90	27,263	15,051	92	13,847
Follow-up phase 2 (7–12 months)	10,157	81	8,227	18,473	48	8,867	12,265	77	9,444
Follow-up phase 3 (13–24 months)	8,093	64	5,180	13,331	31	4,133	6,313	54	3,409
Total	**103,509**		**98,334**	**173,587**		**151,754**	**105,906**		**98,977**

In the economic analysis performed for the NHS Blood and Transplant service[56] unit costs were replaced with NHS costs (2009 prices) where possible, and where not possible were converted using the 1999 pound sterling / euro exchange rate and inflated at 3% per annum (Table 48).

Table 48. Costs of stem cell transplant (2009 GDP, £) from NHS Blood and Transplant service[56]

	Average cost per living patient	% alive	Weighted cost per transplant patient
Personnel	31,409	100	31,409
Transplantation	40,140	100	40,140
Follow-up phase 1 (1–6 months)	29,713	90	26,742
Follow-up phase 2 (7–12 months)	18,119	48	8,697
Follow-up phase 3 (13–24 months)	13,075	31	4,053
Total	**132,456**		**111,041**

The adaptation to NHS costs is not described in sufficient detail to be reproducible, but the researchers note that the weighted cost per transplant patient (£111k) is reassuringly close to the commissioning price (£101k).

Costs were then inflated by Pfizer using the HCHS Pay and Prices Index.[53]

Longer term follow-up was assumed to consist of 100 mg of ciclosporin twice daily. Costs per month used in Pfizer's model are presented in Table 49.

Table 49. Pfizer assumed costs associated with stem cell transplant

Item	Cost / month	Units / month	Unit cost
Initial treatment	£76,560	1	£76,560
Follow-up 1-6 months	£5,299	1	£5,299
Follow-up 7-12 months	£3,231	1	£3,231
Follow-up 13-24 months	£1,166	1	£1,166
Follow-up 25+ months	£140	60.88	£2.30

Patients receiving SCT in the blast crisis phase (i.e., SCT patients in the BP model) are assumed to receive two cycles of the FLAG-IDA chemotherapy regime before SCT, at a cost of £29,212. Table 50 gives a summary of costs for two cycles of the FLAG-IDA regime (further details available in Pfizer submission, Section 10.20, pp393-395).

Table 50. Summary of FLAG-IDA chemotherapy costs

Item	Item cost	Units	Unit cost
Drug acquisition			
Fludarabine	£1,471	10	£147.07
Cytarabine	£780	20	£39.00
Idarubicin	£1,048	12	£87.36
G-CSF	£1,922	Various	Various
Medical management			
Haematology tests	£3	1	£3.09
AML without CC: Elective inpatient stay	£4,866	1	£4,866
AML without CC: Elective excess bed day	£4,515	14	£322.34
Total (two cycles)	**£29,212**		

Abbreviations AML – acute myeloid leukaemia; CC – comorbidities and complications

5.2.9.8 Summary of costs

Table 51. Summary of costs per month in CP model

Intervention	Bosutinib	Hydroxy-carbamide	Interferon	SCT
Chronic Phase On Treatment				
Drug acquisition	£3,736	£13	£1,296	
Drug administration	£0	£0	£10	
Medical management	£154	£154	£154	£154
Tests	£231	£231	£231	£231
Adverse events	£506 first cycle only			
SCT costs				Month 0: £76,560 Months 1-6: £5,299 per month (p.m). Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£4,627** first cycle **£4,121** thereafter	**£398**	**£1,691**	Month 0: **£76,945** Months 1-6: **£5,684** p.m. Months 7-12: **£3,616** p.m. Months 13-24: **£1,551** p.m. Months 25+: **£525** p.m.
Chronic Phase Off Treatment				
Drug acquisition	£13		£13	
Drug administration	£0		£0	
Medical management	£154		£154	
Tests	£231		£231	
Total	**£398**		**£398**	
Accelerated & Blast Phases				
Drug acquisition	£13	£13	£13	
Drug administration	£0	£0	£0	
Medical management	£878	£878	£878	
Tests	£377	£377	£377	
Total	**£1,268**	**£1,268**	**£1,268**	
Death	**£6,004**	**£6,004**	**£6,004**	**£6,004**

Table 52. Summary of costs per month in AP model

Intervention	Bosutinib	Hydroxycarbamide	SCT
Accelerated Phase On Treatment			
Drug acquisition	**£3,736**	**£13**	
Drug administration	**£0**	**£0**	
Medical management	**£878**	**£878**	£878
Tests	**£377**	**£377**	£377
Adverse events	**£506 first cycle only**		
SCT costs			Month 0: £76,560 Months 1-6: £5,299 p.m. Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£5,498** first cycle **£4,991** thereafter	**£1,268**	Month 0: **£77,815** Months 1-6: **£6,554** p.m. Months 7-12: **£4,487** p.m. Months 13-24: **£2,421** p.m. Months 25+: **£1,396** p.m.
Accelerated Phase Off Treatment			
Drug acquisition	£13		
Drug administration	£0		
Medical management	**£878**		
Tests	**£377**		
Total	**£1,268**		
Blast Crisis Phase			
Drug acquisition	£13	£13	
Drug administration	£0	£0	
Medical management	**£878**	**£878**	
Tests	**£377**	**£377**	
Total	**£1,268**	**£1,268**	
Death	**£6,004**	**£6,004**	**£6,004**

Table 53. Summary of costs per month in BP model

Intervention	Bosutinib	Hydroxy-carbamide	SCT
Blast Crisis Phase On Treatment			
Drug acquisition	**£3,736**	**£13**	
Drug administration	**£0**	**£0**	
Medical management	**£878**	**£878**	£878
Tests	**£377**	**£377**	£377
Adverse events	**£506 first cycle only**		
SCT costs (including FLAG-IDA)			Month 0: £105,772 Months 1-6: £5,299 p.m. Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£5,498** first cycle **£4,991** thereafter	**£1,268**	Month 0: **£107,027** Months 1-6: **£6,554** p.m. Months 7-12: **£4,487** p.m. Months 13-24: **£2,421** p.m. Months 25+: **£1,396** p.m.
Blast Crisis Phase Off Treatment			
Drug acquisition	£13		
Drug administration	£0		
Medical management	**£878**		
Tests	**£377**		
Total	**£1,268**		
Death	**£6,004**	**£6,004**	**£6,004**

5.2.10 Cost-effectiveness results

This section presents the deterministic base case cost-effectiveness results.

Unless otherwise stated, positive Incremental cost-effectiveness ratios (ICERs) mean that the intervention is more costly and more effective than the comparator. Negative ICERs are not shown but instead it is stated whether the intervention "dominates" the comparator (is less costly and more effective) or is "dominated" by the comparator (is more costly and less effective).

Incremental net health benefits (INHBs) are also presented in units of QALYs. Incremental net health benefit is calculated as $INHB = \Delta QALYs - \Delta Costs/\lambda$ for a willingness-to-pay threshold λ. We present INHB at willingness-to-pay thresholds of £20,000 and £30,000 per QALY for all models, as well as INHB at willingness-to-pay threshold of £50,000 per QALY for the AP and BP models as Pfizer propose that bosutinib meets the end-of-life criteria in these patients. INHB are always shown relative to bosutinib, such that positive INHB for hydroxycarbamide (for example) means that hydroxycarbamide is cost-effective compared to bosutinib.

5.2.10.1 CP model deterministic results

Deterministic base case cost-effectiveness results from the CP model are shown in Table 54 (p138) and Figure 17 (p138). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 4.83 QALY (9.23 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted] (costs and QALYs discounted at 3.5% per annum, life years not discounted). The extra costs of bosutinib are mainly from drug acquisition, with smaller increases also due to additional medical management during the prolonged life expectancy. Interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib. Bosutinib is the most effective treatment, providing 3.56 QALYs more than the next most effective treatment, SCT.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000 and £30,000 per QALY are [redacted] and [redacted] QALYs respectively. At a willingness-to-pay threshold of £20,000 per QALY hydroxycarbamide gives the greatest expected net health benefit while at £30,000 per QALY bosutinib gives the greatest expected net health benefit.

Bosutinib patients spend longer in the chronic phase than other patients (11.54 years versus 2.58 for hydroxycarbamide, 2.67 for interferon and 6.60 for SCT) and also accrue more discounted QALYs in the chronic phase (6.77 QALYs versus 1.93 for hydroxycarbamide, 1.92 for interferon and 3.70 for SCT). Bosutinib patients also spend longer in the accelerated and blast phases than hydroxycarbamide and interferon patients (SCT patients are cured and do not progress to AP or BP), and accrue more discounted QALYs in the accelerated phase as a result, but not in the blast phase (due to greater discounting as BP is reached at a later time).

Bosutinib patients spend [redacted] life years in the CP off treatment state, in which they are treated with hydroxycarbamide.

[redacted]

Table 54. Deterministic CP model results

	Bosutinib	Hydroxycarbamide	Interferon	SCT
Life years (undiscounted)				
CP on treatment	[redacted]	2.58	0.54	6.60
CP off treatment	[redacted]	n/a	2.12	n/a
AP	0.73	0.51	0.52	n/a
BP	0.48	0.43	0.44	n/a
Total	**12.75**	**3.52**	**3.62**	**6.60**
Discounted QALYs				
CP on treatment	[redacted]	1.93	0.38	3.70
CP off treatment	[redacted]	n/a	1.53	n/a
AP	0.33	0.31	0.31	n/a
BP	0.16	0.19	0.19	n/a
Total	**7.26**	**2.43**	**2.42**	**3.70**
Discounted costs				
Technology cost	[redacted]	£490	£8,461	£141,132
Hydroxycarbamide following discontinuation	£1,053	n/a	£419	n/a
Monitoring	£24,372	£13,195	£13,386	£10,163
Tests	£27,315	£10,352	£10,583	£15,283
Palliative care	£4,174	£5,436	£5,419	£4,961
Adverse events	£506	n/a	n/a	n/a
Total	[redacted]	**£29,473**	**£38,268**	**£171,539**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified				
vs. hydroxycarbamide	[redacted]			
vs. interferon	[redacted]	Dominant		
vs. SCT	Dominant	111,511[a]	103,662[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)				
WTP £20,000/QALY	**n/a**	[redacted]	[redacted]	[redacted]
WTP £30,000/QALY	**n/a**	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 17. Cost-effectiveness plane in CP model, Pfizer base case

Note that (IFN, HU) and (Bosutinib, HU) denote that interferon and bosutinib are followed by hydroxycarbamide

5.2.10.2 AP model deterministic results

Deterministic base case cost-effectiveness results from the AP model are shown in Table 55 (p140) and

Figure 18 (p140). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 1.86 QALY (3.11 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted]. The extra costs of bosutinib are mainly drug acquisition and also due to additional medical management during the prolonged life expectancy. SCT is dominated by bosutinib as it is less effective and more costly. Bosutinib is the most effective intervention, providing a 0.80 QALY (1.45 life year) gain per patient over the next most effective intervention, SCT.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY are [redacted] QALYs respectively. At all three willingness-to-pay thresholds hydroxycarbamide therefore gives the greatest expected net benefit.

Bosutinib patients spend longer in the accelerated phase than patients receiving hydroxycarbamide and SCT (4.03 life years for bosutinib versus 1.02 life years for hydroxycarbamide and 3.02 life years for SCT), and accrue more discounted QALYs in the accelerated phase as well (2.56 QALYs for bosutinib versus 0.72 QALYs for hydroxycarbamide and 1.96 QALYs for SCT). Bosutinib patients spend slightly longer in the blast crisis phase than do hydroxycarbamide patients (0.45 versus 0.35 life

years; SCT patients do not transform to BP), and also accrue slightly more discounted QALYs in BP (0.20 versus 0.18).

Bosutinib patients spend [redacted] life years in the AP off treatment state, in which they are treated with hydroxycarbamide.

[redacted]

Table 55. Deterministic AP model results

	Bosutinib	Hydroxycarbamide	SCT
Life years (undiscounted)			
AP on treatment	[redacted]	1.02	3.02
AP off treatment	[redacted]	n/a	n/a
BP	0.45	0.35	n/a
Total	**4.48**	**1.37**	**3.02**
Discounted QALYs			
AP on treatment	[redacted]	0.72	1.96
AP off treatment	[redacted]	n/a	n/a
BP	0.20	0.18	n/a
Total	**2.76**	**0.90**	**1.96**
Discounted costs			
Technology cost	[redacted]	£204	£130,528
Hydroxycarbamide following discontinuation	£297	n/a	n/a
Monitoring	£41,726	£14,032	£29,414
Tests	£17,916	£6,025	£12,630
Palliative care	£5,280	£5,817	£5,520
Adverse events	£506	n/a	n/a
Total	[redacted]	**£26,078**	**£178,093**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified			
vs. hydroxycarbamide	[redacted]		
vs. SCT	Dominant	142,982[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)			
WTP £20,000/QALY	**n/a**	[redacted]	[redacted]
WTP £30,000/QALY	**n/a**	[redacted]	[redacted]
WTP £50,000/QALY	**n/a**	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 18. Cost-effectiveness plane in AP model, Pfizer base case

5.2.10.3 BP model deterministic results

Deterministic base case cost-effectiveness results from the BP model are shown in Table 56 (p142) and

Figure 19 (p142). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 0.60 QALY (1.23 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted]. The extra costs of bosutinib are drug acquisition and additional medical management during the prolonged life expectancy. SCT is more costly than bosutinib but more effective. The ICER for SCT versus bosutinib is [redacted] per QALY. SCT is the most effective intervention, providing a 0.40 QALY (0.87 life year) gain per patient over the next most effective intervention, bosutinib.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY are [redacted] QALYs respectively. The INHBs of SCT versus bosutinib at the same thresholds are [redacted] QALYs respectively.

Across all three willingness-to-pay thresholds hydroxycarbamide therefore gives the greatest expected net benefit.

Bosutinib patients spend [redacted] life years in the BP off treatment state, in which they are treated with hydroxycarbamide.

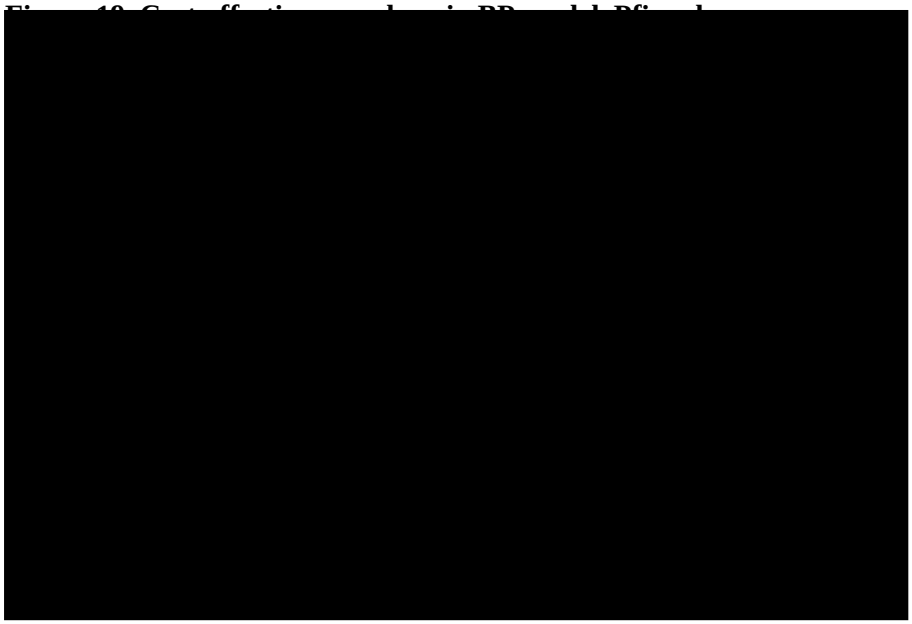
[redacted]

Table 56. Deterministic BP model results

	Bosutinib	Hydroxycarbamide	SCT
Life years (undiscounted)			
BP on treatment	[redacted]	0.54	2.64
BP off treatment	[redacted]	n/a	n/a
Total	**1.77**	**0.54**	**2.64**
Discounted QALYs			
BP on treatment	[redacted]	0.28	1.28
BP off treatment	[redacted]	n/a	n/a
Total	**0.88**	**0.28**	**1.28**
Discounted costs			
Technology cost	[redacted]	£82	£157,759
Hydroxycarbamide following discontinuation	£169	n/a	n/a
Monitoring	£17,935	£5,681	£26,011
Tests	£7,701	£2,439	£11,169
Palliative care	£5,743	£5,967	£5,586
Adverse events	£506	n/a	n/a
Total	[redacted]	**£14,170**	**£200,526**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified			
vs. hydroxycarbamide	[redacted]		
vs. SCT	[redacted]	186,265[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)			
WTP £20,000/QALY	**0.0**	[redacted]	[redacted]
WTP £30,000/QALY	**0.0**	[redacted]	[redacted]
WTP £50,000/QALY	**0.0**	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 19: Cost-effectiveness scatterplot in PBS model: Pfizer



5.2.11 Sensitivity analyses

5.2.11.1 One-way sensitivity analyses

Extensive one-way sensitivity analyses were not performed as Pfizer believed structural uncertainties were greater than parameter uncertainties. Scenario analyses were performed instead (see Section 5.2.11.3, p146).

5.2.11.2 Probabilistic sensitivity analysis

Pfizer conducted a probabilistic sensitivity analysis but cautioned that it could not capture all the uncertainty in the decision problems addressed by the economic models due to several sources of structural uncertainty.

Pfizer did not record the parameter values associated with probabilistic outputs and therefore no value of information analyses could be conducted.

CP model PSA

Table 57 gives a comparison of the key CP model deterministic and probabilistic results. The deterministic and mean probabilistic results are very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented graphically in the Pfizer report).

Further results are presented in Appendix R.

Table 57. Comparison of key CP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	Interferon	SCT
Deterministic results				
Total discounted QALYs	7.26	2.43	2.42	3.70
Total discounted costs	[redacted]	£29,473	£38,268	£171,539
ICER vs. hydroxycarbamide	[redacted]			
ICER vs. interferon	[redacted]	Dominant		
ICER vs. SCT	Dominant	111,511[a]	103,662[a]	
Probabilistic results				
Total discounted QALYs	7.15	2.43	2.39	3.84
Total discounted costs	[redacted]	£29,389	£36,091	£173,948
ICER vs. hydroxycarbamide	[redacted]			
ICER vs. interferon	[redacted]	Dominant		
ICER vs. SCT	Dominant	102,524[a]	104,118[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report

AP model PSA

Table 58 gives a comparison of the key AP model deterministic and probabilistic results. Deterministic results and mean probabilistic results were very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY, £30,000/QALY and £50,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented in the Pfizer report).

Further results are presented in Appendix R.

Table 58. Comparison of key AP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	SCT
Deterministic results			
Total discounted QALYs	2.76	0.90	1.96
Total discounted costs	[redacted]	£26,078	£178,093
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	Dominant	142,982[a]	
Probabilistic results			
Total discounted QALYs	2.75	0.91	1.95
Total discounted costs	[redacted]	£26,095	£175,420
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	Dominant	143,454[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	100.0%	0.0%
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £50,000/QALY[b]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report

BP model PSA

Table 59 gives a comparison of the key BP model deterministic and probabilistic results.

Deterministic results and mean probabilistic results were very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY, £30,000/QALY and £50,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented in the Pfizer report).

Further results are presented in Appendix R.

Table 59. Comparison of key BP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	SCT
Deterministic results			
Total discounted QALYs	0.88	0.28	1.28
Total discounted costs	[redacted]	£14,170	£200,526
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	[redacted]	186,265[a]	
Probabilistic results			
Total discounted QALYs	0.89	0.32	1.29
Total discounted costs	[redacted]	£15,262	£201,228
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	[redacted]	192,016[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	100.0%	0.0%
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £50,000/QALY[b]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report
c Note that in the Pfizer submission this was reported as [redacted]/QALY

5.2.11.3 Scenario analyses

Pfizer conducted a number of scenario analyses for each of the models. Some of these are parameter changes and would normally be considered one-way sensitivity analyses, while others are structural changes to the model. Here, we simply report the results of the analyses. Later (Section 5.3, p159), we comment on the appropriateness of the analyses.

[redacted]. Note that shading does not indicate whether bosutinib is more or less costly or more or less effective than the comparator.

Table 60. Shading used to denote cost-effectiveness of bosutinib

White background	[redacted]
Grey background	[redacted]
Black background	

CP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 61 (p148). In most scenarios interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib. Where this is not the case additional results are presented. Further details of scenario analyses can be found in the Pfizer submission, Section 10.22, pp467-476.

In most analyses interferon is dominated by hydroxycarbamide, which Pfizer state is in keeping with clinical practice. When bosutinib is compared to hydroxycarbamide, bosutinib is always more expensive, and more effective, with ICERs ranging from [redacted] per QALY. There were four scenarios where the ICER of bosutinib versus hydroxycarbamide was substantially reduced:

- Patient population set to second line for bosutinib
- Hydroxycarbamide overall survival set to two years
- Resource use from TA241 is assumed
- Hazard ratio for survival in MCyR surrogate method of 0.876 used

Pfizer suggest that resource use from TA241 may be more appropriate than resource use from TA251 (the base case) because TA241 and this decision problem involve patients who have failed imatinib treatment.

In most analyses bosutinib dominates SCT. When the time on bosutinib treatment is calculated using a similar method to TA241 SCT becomes cheaper than bosutinib but also less effective, with an ICER of [redacted] per QALY. When the cost per month in CP post-discontinuation is increased to £1,040 for bosutinib, SCT becomes cheaper than bosutinib but also less effective, with an ICER of [redacted] per QALY.

Table 61. Scenario analyses applied to CP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	Dominant
Patient population				
Bosutinib patient population	CP-3L from Study 200	CP-3L post-hoc "unmet need" subpopulation	[redacted]	Dominant
		CP-2L population	[redacted]	Dominant
		CP post-hoc "unmet need" subpopulation	[redacted]	Dominant
Cohort starting age	54 years (mean age in CP-3L Study 200)	49 years (−10%)	[redacted]	Dominant
		59 years (+10%)	[redacted]	Dominant
Overall survival				
Bosutinib overall survival	MCyR using hazard ratio for survival of 0.37[2]	MCyR using hazard ratio for survival of 0.156 (lower bound of 95% CI)	[redacted]	Dominant
		MCyR using hazard ratio for survival of 0.876 (upper bound of 95% CI)	[redacted]	Dominant
		Exponential curve fitted to CP-3L OS	[redacted]	Dominant
		"Cumulative survival approach" (OS = PFS + 10 months AP + 6 months BP)	[redacted]	Dominant
SCT overall survival	Exponential curve fitted to Jabbour (2011)[10]	Weibull curve fitted to Jabbour (2011)[10]	Unchanged	Dominant
		Exponential curve fitted to Oehler (2007)[12]	Unchanged	Dominant
Hydroxycarba-mide overall survival	Mean OS = 42 months	Mean OS = 38 months (see Pfizer submission, Section 10.22, pp469-470 for justification)	[redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		Mean OS = 24 months (lower bound of plausible range in Rogers 2012)[2]	[redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged
		Mean OS = 78 months (upper bound of plausible range in Rogers 2012)[2]	[redacted]	Unchanged
Transformation to AP and BP				
Time in blast phase	6 months	13 months[2]	[redacted]	Dominant
		3 months	[redacted]	Dominant
Transformation following SCT	Patients cannot transform to AP and BP, but remain in CP	Patients transform to AP and BP for 10 and 6 months respectively before death	[redacted]	Dominant
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to CP-3L cohort of Study 200	Loglogistic curve	[redacted]	Dominant
		Time on treatment equal to PFS minus discontinuation due to AEs[2]	[redacted]	[redacted]
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	Dominant
Costs				
Resource use	Medical management from TA251[17]	Medical management from TA241	[redacted]	Dominant
Cost of CP off treatment health state	Patients receive hydroxycarba-mide, costing £12.75 per month	Patients receive further treatment post-discontinuation in CP (e.g., other TKIs or SCT) costing £1,040 per month (similar to TA241)	[redacted]	[redacted]
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP & BP £2,536/month (doubled)[c]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		AP only doubled	[redacted]	Dominant
		BP only doubled	[redacted]	Dominant
Cost of death	£6,004	£569[17]	[redacted]	Dominant
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarba-mide arm only	[redacted]	Dominant
		Additional cost of £100/month in all arms wherever patients receive hydroxycarba-mide	[redacted]	Dominant
Utility values				
Source of utility for CP patients on bosutinib or hydr-oxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility at screening for CP-3L cohort in Study 200 used for all patients in CP on bosutinib and hydroxy-carbamide	[redacted]	Not reported
		Utility at screening for CP-3L cohort in Study 200 used for patients in CP on bosutinib only	[redacted]	Dominant
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251	Unchanged	Dominant
Interferon on-treatment utility value	Decrement to HRQL from interferon treatment	No decrement to HRQL from interferon treatment	Unchanged [redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged
Utility values varying by age	Utility values adjusted to account for patient aging	No adjustment for aging	[redacted]	Dominant
Model settings				
Time horizon	50 years	2 years	[redacted]	Dominant
		5 years	[redacted]	Dominant
		10 years	[redacted]	Dominant
		25 years	[redacted]	Dominant

a In these scenarios interferon is not dominated by hydroxycarbamide
b In these scenarios SCT is cheaper than bosutinib
c Analysis conducted by PenTAG

AP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 62 (p152). In most scenarios (including the base case) bosutinib dominated SCT (i.e., bosutinib was cheaper and more effective than SCT). The ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] to [redacted] per QALY (ignoring scenario analyses where the time horizon is shortened). The ICERs for SCT versus hydroxycarbamide ranged from £98,279 to £195,626 per QALY (again, ignoring scenario analyses where the time horizon is shortened).

Notable scenarios in terms of impact on ICERs included:

- Increasing the time spent in BP to 13 months (as used in Rogers and colleagues 2012[2]) increases the ICERs of both bosutinib and SCT versus hydroxycarbamide to [redacted] and £195,626 per QALY respectively.
- Setting the time on bosutinib treatment equal to PFS from Study 200 results in bosutinib becoming more expensive than SCT. In this scenario the ICER of SCT versus hydroxycarbamide is unchanged at £142,982 per QALY and the ICER of bosutinib versus hydroxycarbamide is [redacted] per QALY. The ICER of bosutinib versus SCT is [redacted] per QALY but SCT would be deemed extended dominated by hydroxycarbamide and bosutinib and hence SCT would not be viewed as a proper comparator.
- Using medical management costs from TA241 instead of TA251 results in an ICER for bosutinib versus hydroxycarbamide of [redacted] per QALY.
- Doubling the cost per cycle of AP results in an increased ICER for bosutinib versus hydroxycarbamide of [redacted] per QALY.

Further details of scenario analyses can be found in the Pfizer submission, Section 10.23, pp477-483.

Table 62. Scenario analyses applied to AP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	Dominant
Patient population				
Cohort starting age	50 years (mean age in Study 200 AP cohort)	45 years (−10%)	[redacted]	Dominant
		55 years (+10%)	[redacted]	Dominant
Overall survival				
Bosutinib overall survival	Exponential curve fitted to Study 200 AP cohort OS	Extreme value curve fitted to Study 200 AP cohort OS (15 Feb 2012 snapshot)	[redacted]	Dominant
Stem cell transplant overall survival	Exponential curve fitted to AP cohort in Oehler (2007)[12]	Weibull curve fitted to AP cohort in Oehler (2007)[12]	Unchanged	Dominant
		Exponential curve fitted to AP cohort in Jabbour (2011)[10]	Unchanged	Dominant
Time spent in BP				
Time spent in blast phase	6 months	13 months[2]	[redacted]	Dominant
		3 months	[redacted]	Dominant
Transformation following SCT				
Transformation following SCT	Patients cannot transform to BP, but remain in AP	Patients transform to BP 6 months before death	[redacted]	Dominant
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200 AP cohort	Time on treatment equal to PFS from Study 200 (AP to BP)[a]	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 AP cohort	[redacted]	Dominant
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	Dominant
Costs				
Resource use	Medical management in TA251	Medical management in TA241	[redacted]	Dominant

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP and BP £2,536 (doubled)[b]	[redacted]	Dominant
		AP only doubled[c]	[redacted]	Dominant
		BP only doubled	[redacted]	Dominant
Cost of death	£6,004	£569[17]	[redacted]	Dominant
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	Dominant
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	Dominant
Utility values				
Source of utility for AP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for AP and BP cohorts from Study 200 used for all patients in AP and BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	Not reported
		Utility for AP in Study 200 only used for AP patients on bosutinib in the model (remainder as per base-case)	[redacted]	Dominant
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251[17]	Unchanged	Dominant
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	Dominant
Model settings				
Time horizon	50 years	2 years	[redacted]	Dominant
		5 years	[redacted]	Dominant
		10 years	[redacted]	Dominant

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		25 years	[redacted]	Dominant

a In these scenarios SCT was cheaper than bosutinib
b Analysis conducted by PenTAG
c Pfizer reported an ICER of £136,703/QALY for SCT vs. hydroxycarbamide, PenTAG calculated a different ICER of £168,310/QALY

BP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 63 (p155). In all scenarios SCT is more effective and more costly than bosutinib, which is in turn more costly and more effective than hydroxycarbamide. The ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] per QALY. The scenarios in which the ICER was lowest (i.e., in which bosutinib was most cost-effective) were:

- Utility values from Study 200 used for bosutinib (± hydroxycarbamide) patients (instead of IRIS trial utilities)
- Extreme value distribution used for bosutinib OS instead of exponential distribution

The scenarios in which the ICER for bosutinib versus hydroxycarbamide was highest were:

- Time spent in BP set to 13 months
- Time on treatment equal to PFS from Study 200
- Cost of BP health state doubled

The ICER for SCT versus bosutinib varied from [redacted] per QALY.

Further details of scenario analyses can be found in the Pfizer submission, Section 10.24, pp483-489.

Table 63. Scenario analyses applied to BP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	[redacted]
Patient population				
Cohort starting age	47 years (mean age in Study 200 BP cohort)	42 years (−10%)	[redacted]	[redacted]
		52 years (+10%)	[redacted]	[redacted]
Overall survival				
Bosutinib overall survival	Exponential curve fitted to Study 200 BP cohort OS	OS estimated by fitting 2nd best fitting curve (Weibull) to BP cohort from Study 200	[redacted]	[redacted]
Stem cell transplant overall survival	Exponential curve fitted to BP cohort in Oehler (2007)[12]	Weibull curve fitted to BP cohort in Oehler (2007)[12]	[redacted] Unchanged	[redacted]
		Exponential curve fitted to "advanced phase" cohort in Saussele (2010)[13]	[redacted] Unchanged	[redacted]
Time spent in BP				
Time spent in blast phase	6 months	13 months[2]	[redacted]	Unchanged
		3 months	[redacted]	Unchanged
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200 BP cohort	Time on treatment equal to PFS from Study 200	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 BP cohort	[redacted]	[redacted]
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	[redacted]
Costs				
Resource use	Medical management in TA251	Medical management in TA241	[redacted]	[redacted]
Cost of BP health state	BP £1,268/month	BP £2,536 (doubled)[b]	[redacted]	[redacted]
Cost of death	£6,004	£569[17]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	Unchanged (reported as [redacted] in Pfizer report)
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	[redacted] (reported as [redacted] in Pfizer report)
Cost of SCT	All patients incur cost of FLAG-IDA at £29,212	FLAG-IDA cost removed	Unchanged	[redacted]
Utility values				
Source of utility for BP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for BP cohort from Study 200 used for all patients in BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	Not reported
		Utility for BP in Study 200 only used for BP patients on bosutinib in the model (remainder as per base-case)	[redacted]	[redacted]
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251[17]	Unchanged	[redacted]
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	[redacted]
Model settings				
Time horizon	50 years	2 years	[redacted]	[redacted]
		5 years	[redacted]	[redacted]
		10 years	[redacted]	[redacted]
		25 years	[redacted]	[redacted]

a A wiring error was discovered in Pfizer's model meaning that the log-logistic curve for AP patients was used instead of the curve for BP patients. This gave an original erroneous ICER of [redacted] per QALY.

5.2.12 Model validation and face validity check

Pfizer describe the following model validation and face validity checks (Pfizer submission, Section 7.8.1, p185).

Model design

At the design stage of the model, it was presented to a leading clinician currently treating CML patients in the UK (October 2012), in order to ensure the model has face validity, and matched clinical practice. The key issues around the economic modelling such as time horizon, comparators, survival analysis, adverse events, and utility measures were discussed with other experts using at an advisory meeting in December 2012.

The subsequent model design and shell were then presented to a senior UK economist (and former member of the NICE appraisal committee), whose comments were then incorporated. After this the full economic model was developed, and a first draft of the submission document produced.

Model accuracy and calculations

A number of steps were taken to validate the technical accuracy of the model and submission.

Firstly, estimates of time on treatment and overall survival from the final model were checked against values calculated in a separate spreadsheet – results were the same.

Secondly, extensive one-way sensitivity analyses were conducted on all model inputs and results were reviewed to ensure that changes in cost and effectiveness measures were consistent with expectations.

Thirdly, random checks were made on model inputs compared with source data.

As a last step in the model validation process, the model was reviewed by a senior health economist not involved with the project, using the Drummond checklist, as well as a proprietary internal checklist from BresMed (who developed the model). Following this review a report was produced, with discussions held and changes made to the model and documented accordingly

Finally, in terms of internal validity, as discussed in Section 7.2.2 [of Pfizer submission] the survival functions used to generate estimates of time on treatment and overall survival for bosutinib, hydroxycarbamide and stem cell transplant are very close to those obtained based on the empirical (Kaplan-Meier) survival distributions (see Section 7.3.1 [of Pfizer submission]), and results seen in published NICE technology appraisals (TA241, TA251).

External review

Following the development of the model, the model and submission were reviewed by an independent UK economist not thus far involved with the project. This economist works in a department of a leading centre for health economics in the UK, and part of an Evidence Review Group. The economist reviewed the submission, highlighting areas for improvement and clarification, as well as any assumptions they did not agree with. Following this review, further changes were made (as well as amendments made to answers questions they raised), ahead of submission to NICE.

5.3 Critique of manufacturer's submitted evidence

5.3.1 Checking wiring of Pfizer's model

We checked the wiring of Pfizer's model in the following three ways:

- We built an independent, simplified version of Pfizer's model. This model did not use discrete model cycles. Instead, QALYs and costs were estimated by applying unit costs and utilities to the undiscounted life year estimates for each treatment in each arm in Pfizer's model. The results of the simplified model (e.g. total discounted costs and QALYs, ICERs) were similar to those from Pfizer's model. For example, the ICER for bosutinib vs. HU in CP was estimated as [redacted] vs. [redacted] from Pfizer's model. This provides strong evidence that there are no serious wiring errors in Pfizer's model in addition to the error we found in the original version of the model.
- We checked the key formulae in Pfizer's model.
- We checked that the model outputs were correct when input parameters were set to extreme values.

5.3.2 NICE reference case checklist

NICE reference case[43] requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	P	Population changed to reflect revised indication from the EMA for bosutinib. Population limited to include only patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	P	Does not include SCT following bosutinib (see Section 5.3.6, p162)
Perspective on costs	NHS and PSS	Y	See Section 5.3.7.1, p164
Perspective on outcomes	All health effects on individuals	Y	
Type of economic evaluation	Cost-effectiveness analysis	Y	
Synthesis of evidence on outcomes	Based on a systematic review	Y	
Measure of health benefits	QALYs	Y	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Y	*For bosutinib, hydroxycarbamide and interferon:* RCT of imatinib vs. combination of IFN-α and cytarabine. *For SCT:* Submissions to TA241 from Bristol-Myers Squibb and Novartis.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Y	
Discount rate	3.5% p.a. for costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	

Y – Yes; N – No; U – Unclear; P – Partially

5.3.3 Critical appraisal frameworks

Table 64. Critical appraisal checklist from Drummond and colleagues (1997)[58]

Item	Critical appraisal	Reviewer comment
Is there a well-defined question?	Y	
Is there a clear description of alternatives (i.e., who did what to whom, where and how often)?	Y	
Has the correct patient group / population of interest been clearly stated?	Y	
Is the correct comparator used?	P	Believe more appropriate to include SCT following bosutinib failure (see Section 5.3.6, p162)
Is the study type reasonable?	Y	
Is the perspective of the analysis clearly stated?	P	See Section 5.3.7.1, p164
Is the perspective employed appropriate?	Y	
Is effectiveness of the intervention established?	P	No evidence from RCT for specified population. Non-randomised evidence suggests bosutinib is capable of achieving cytogenetic response in some patients but no mature data on overall survival.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	Y	
Are the costs and consequences consistent with the perspective employed?	P	See Section 5.3.7.1, p164
Is differential timing considered?	Y	Discount rates for costs and QALYs 3.5% in line with NICE reference case
Is incremental analysis performed?	Y	
Is sensitivity analysis undertaken and presented clearly?	Y	

Y – Yes; N – No; U – Unclear; P – Partially

5.3.4 Model structure

The model structure chosen by Pfizer for bosutinib is very similar to the structure we, PenTAG, used in TA241[2] and importantly includes chronic phase states both on and off treatment and accelerated and blast crisis phase states. We believe the model structure is appropriate for the treatment sequence bosutinib followed by hydroxycarbamide, although in Section 5.3.6 (p162) we discuss how appropriate the selected treatment sequences are.

We also believe the model structure is appropriate for hydroxycarbamide and interferon.

The model structure for SCT is effectively a two state model with two states, alive and dead. SCT is assumed to be curative and therefore not followed by treatments expected in the event of SCT failure, i.e., TKI, hydroxycarbamide.

We believe the cycle length of one month is appropriate for the CP model. A shorter cycle length may have been marginally more appropriate for the AP model and would probably have been more appropriate for the BP model, however we doubt this would significantly impact on cost-effectiveness and changing the cycle length would require a great deal of work.

5.3.5 Population

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used as 2nd-line. However, as we say in Section 2.2.2 (p45), we believe that bosutinib will be used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis assumes 3rd-line use of bosutinib, and we consider the cost-effectiveness of bosutinib for use as 2nd-line in an important scenario analysis.

5.3.6 Intervention and comparators

As stated in Section 5.2.4, p117, Pfizer consider the following treatment sequences in the CP model:

- (Bosutinib, HU)
- HU
- SCT
- (IFN, HU)

The focus of our critique is on the first three sequences, as we understand that IFN is now virtually never used for CML in England & Wales due to poor quality of life.

For the AP and BP models, Pfizer consider the same treatment sequences with the exception of (IFN, HU), because they say that appropriate clinical effectiveness evidence is lacking.

Pfizer seem unsure whether HU or SCT is the main comparator for bosutinib. They say: "*It has been noted by clinicians that hydroxycarbamide is rarely, if ever used in CML patients and therefore SCT may be a more appropriate comparator*" (Pfizer submission, p104). This is later contradicted: "*No data was found on the uptake of SCT versus hydroxycarbamide (BSC) in the patient population under consideration in this license. Clinical experts have estimated that only 30% of this population would be eligible for SCT given the strict eligibility criteria and availability of donors, it is assumed that the rest will receive hydroxycarbamide*" (Pfizer submission, p190).

Our clinical expert, Dr Rudin, agrees with the second statement. We imagine that the actual proportion of patients who have a SCT may be less than 30% because this is a major operation which we assume some patients will not wish undergo. Furthermore, Pfizer later say "*Nonetheless, SCT remains the only 'cure' for CML and bosutinib is not expected to replace SCT for the minority of patients who are eligible to receive a SCT and who have a match*." (Pfizer submission, p192).

For all these reasons, we believe that HU is clearly the most important comparator treatment.

Pfizer assume that after patients become resistant or intolerant to bosutinib (as either 2nd-, 3rd- or 4th-line), they are then treated with HU until death. We agree that this is reasonable for those patients who are unsuitable for SCT or for those who are suitable for, but do not want SCT. However, our understanding is that patients who are suitable for and want a SCT may either proceed directly to transplant, or may try bosutinib first, and then when they become resistant or intolerant to bosutinib, they will likely then try SCT. Given that patients are predicted to take 3rd-line bosutinib for only about [redacted], we understand that if a patient is eligible for SCT before bosutinib treatment, they are very likely still to be eligible for SCT only [redacted] later. Indeed, Pfizer acknowledge this: "*However, in practice the impact of introducing another effective TKI option may result in a reduction in the numbers of SCT since patients or clinicians may prefer to try another TKI before or instead of SCT given the considerable cost, morbidity and mortality impact associated with SCT*" (Pfizer submission, p192).

In summary, we assume the following comparators for CP:

- (Bosutinib, HU)
- (Bosutinib, SCT) (only for those eligible for SCT)
- HU
- SCT (only for those eligible for SCT)
- (IFN, HU)

In other words, for those patients unsuited to SCT, the relevant comparators are:

- (Bosutinib, HU)
- HU
- (IFN, HU)

And for those suited to SCT, the main comparators are:

- (Bosutinib, SCT)
- SCT

But for completeness, we also model the following comparators:

- (Bosutinib, HU)
- HU
- (IFN, HU)

For AP and BP, we believe exactly the same arguments apply as for CP, except we do not model (IFN, HU).

In theory, it would be possible to additionally model the treatment sequence (IFN, SCT). However, we do not do this because IFN is rarely used now in England & Wales.

5.3.7 Perspective, time horizon and discounting

5.3.7.1 Perspective

Pfizer state (Section 5, p37) that a NHS/PSS perspective for costs is adopted in line with the NICE reference case, and this is reiterated on p39. In Section 7.2.6, p114, however it is stated that only NHS costs are included as "In this disease area there are not expected to be significant impacts on costs outside the NHS budget".

We believe that certain costs included in the economic analysis include costs incurred by PSS rather than NICE, e.g., the cost of palliative care prior to death is taken from Addicott and Dewar (2008)[54] and just over half of the cost is incurred in the community sector.

We do not believe that significant PSS costs have been excluded from the analysis and are therefore satisfied that the perspective adopted is appropriate, although reported inconsistently.

5.3.7.2 Time horizon

We are satisfied that a time horizon of 50 years is sufficient to account for all costs and benefits relevant to the decision problem.

5.3.7.3 Discounting

Discounting is applied at 3.5% per annum as per the NICE reference case.[43] We note that the discount factor is calculated on the basis of integer years from commencing treatment rather than months, which we feel would have been more appropriate and technically simple to implement. This however did not significantly impact on cost-effectiveness so we are satisfied that discounting is appropriate.

5.3.8 Treatment effectiveness and extrapolation

5.3.8.1 Overall survival (OS)

For the CP model, Pfizer's methods of estimating OS are not consistent across the four comparator treatments. OS for the bosutinib arm is estimated using a surrogate relationship using MCyR measured at minimum follow-up of 12 months in Study 200. This relationship was estimated as explained in Section 5.2.6.1 (p119). OS for the comparators: HU, SCT and IFN is estimated either by extrapolation directly from single arm trials (HU and SCT), or expert opinion (IFN) (Section 5.2.6.1, p118).

We believe that there are serious problems with Pfizer's methods of estimating OS for the four treatments because they involve numerous assumptions, for many of which there is little supporting evidence. Instead, we suggest that there is a superior method of estimating OS for all comparator treatments, which we describe as the Cumulative Survival method, not just in the CP model, but also in the AP and BP models. This is explained in detail in Section 6.1, p190.

Key assumptions underlying Pfizer's method of estimating OS for all comparators in CP are given in Table 65 below. All assumptions are important.

Table 65. Assumptions underlying Pfizer's methods of estimating OS for treatments in CP

Assumption	Description	Evidence to support
1. Lack of randomisation	Given that clinical effectiveness evidence is not randomised across treatments, we assume that estimated clinical effectiveness is similar to that which would be observed in a randomised trial of all treatments. This requires that many factors are similar across the single arm studies, e.g. patient baseline characteristics, medical management.	None given
2. Inconsistency in methods of estimated OS by treatment	OS is estimated using different methods across treatments: by a surrogate MCyR relationship for bosutinib and by extrapolating OS for HU, SCT and IFN. Assume that the MCyR surrogate relationship yields similar OS as extrapolation of mature OS for bosutinib	Very little
3. MCyR in model should refer to unmet need population	The MCyR value of 38.9% used to estimate OS for bosutinib in CP is taken from the whole population of Study 200. Pfizer report the corresponding MCyR value for the unmet need population as 43%. They say it is appropriate to use MCyR from the whole population because this is similar to the unmet need value. However, MCyR for the unmet need population is based on a sample of only 21 patients.	Some evidence, but limited due to small sample.
4. Validity of MCyR surrogate relationship:	The MCyR surrogate relationship is crucially dependent on MCyR and OS observed in a trial of patients on high-	Jabbour (2009)[44]

subsequent treatments	dose imatinib.[44] In particular, for the surrogate relationship to apply to bosutinib, Pfizer assume that all patients in Jabbour (2009) received only HU after high-dose imatinib, as they assume that all patients received HU after bosutinib. Furthermore, as explained in Section 5.3.6, p162, we believe it is appropriate to consider the treatment sequence (bosutinib, HU) for some patients and (bosutinib, SCT) for others.	
5. Validity of MCyR surrogate relationship: OS a function of MCyR only	Pfizer assume that OS is purely a function of MCyR. In particular OS is assumed independent of the duration and depth of response, and independent of treatment. In particular, the MCyR surrogate relationship is based on patients taking high-dose imatinib. However, Pfizer apply the relationship to MCyR achieved for patients taking bosutinib.	Unknown
6.Validity of MCyR surrogate relationship: unmet need population	The MCyR surrogate relationship estimated from Jabbour (2009)[44] is for patients who are both suited and unsuited to TKIs. However, Pfizer apply the relationship only to patients unsuited to TKIs.	Very little
7. 2nd-line OS from Jabbour (2009) appropriate for estimating OS for 3rd-line bosutinib	The MCyR surrogate relationship calibrates OS for 3rd-line using in CP for bosutinib to OS from Jabbour (2009)[44], but this is for a 2nd-line line population (after imatinib). OS for bosutinib is therefore probably over-estimated.	None

Pfizer claim that bosutinib OS estimated by MCyR is similar to that obtained by extrapolating bosutinib OS from Study 200 (Pfizer clarifications, Figure 7, p28; see also Appendix V). They then say that this validates their estimated bosutinib OS. However, we consider that the extrapolated OS is likely to be misleading for the following four reasons:

1. OS for bosutinib in CP is extremely immature, with approximately 85% patients still alive at 2 years. Any extrapolation of such immature OS data means that the estimated mean OS is extremely uncertain.
2. Whilst we require OS for bosutinib for patients unsuited to TKIs, most patients in Study 200 were suitable for TKIs. However, Pfizer estimate OS for bosutinib by extrapolating OS from Study 200.
3. Pfizer's model assumes that all patients in the bosutinib arm subsequently receive HU. However, Pfizer do not tell us the nature of subsequent treatments in Study 200. Given that the bosutinib OS data relates mostly to people who are suited to TKIs in Study 200, and not to those patients unsuited to TKIs (as required), these patients may have been treated with TKIs after bosutinib treatment. If so, this would likely lead to an over-estimate of OS for the bosutinib arm, as such subsequent TKIs are likely to extend OS.

4. As Pfizer acknowledge, OS for bosutinib in Study 200 may be over-estimated because of selective censoring of patients. In particular, patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, whereas all patients still on bosutinib were followed up whilst on bosutinib (Pfizer submission, p119).

In the current HTA, we believe that Pfizer's methods for estimating OS for treatments in CP result in the highly implausible result that the mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm and the time on 4th-line HU in the (IFN, HU) arm ([redacted] vs. 2.6 vs. 2.1 years respectively) (shown in Figure 20 below). We believe, and clinical expert advice has agreed, that this is unreasonable. Furthermore, this assumption acts dramatically in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU and (Bosutinib, HU) vs. (IFN, HU), because the price of HU is negligible. In Section 6.1, p190, we show how we correct for this under the Cumulative Survival method.

Figure 20.

[redacted]

Pfizer's surrogate relationship between MCyR and OS is very similar to the relationship that we, PenTAG, derived for TA241, to estimate OS for 2nd-line high-dose imatinib, nilotinib, dasatinib and IFN after imatinib failure for patients starting in CP CML. We believe that it was more appropriate to use the MCyR relationship in TA241 than in the current appraisal because fewer Assumptions were required in TA241. Specifically, although Assumptions 1, 4 and 5 above were required, Assumptions 2, 3, 6 and 7 were not. In particular, the crucial Assumption 2, was not required, i.e. the same method (MCyR) was used to estimate OS for all treatments. Nonetheless, with hindsight and with the experience of two previous HTAs in CML, we believe that it would have been useful to have

performed the Cumulative Survival method, at least as a sensitivity analysis, if not as the base case analysis.

By contrast, OS for bosutinib for the AP and BP models is not estimated using a MCyR relationship. Instead, it is extrapolated directly from OS from Study 200. Therefore, for the AP and BP models, the methods of estimating OS for the three treatments: bosutinib, HU and SCT are consistent. Furthermore, Assumptions 2–7 (Table 65, p165) are not required. However, we identify the following six criticisms with Pfizer's method of estimating OS for all treatments in the AP model:

1. Importantly, Assumption 1 still applies, i.e. randomisation is still lacking between comparator treatments.
2. OS for bosutinib in the AP model is very immature, with 65% of patients still alive at maximum follow up (Pfizer submission, p122). The means that the estimated mean OS in the bosutinib arm is highly uncertain.
3. Whilst we require OS for bosutinib for patients unsuited to TKIs, most patients in Study 200 were suitable for TKIs. However, Pfizer estimate OS for bosutinib by extrapolating OS from Study 200.
4. In their model, Pfizer assume that all patients receive HU after bosutinib failure. However, Pfizer do not state the nature of treatments after bosutinib failure in Study 200. Given that most patients in Study 200 were suited to TKIs, some patients may have had other TKIs after bosutinib failure, and this would likely increase their OS and hence lead to an over-estimate of OS for bosutinib for patients unsuited to TKIs.
5. As stated above when discussing CP, as Pfizer acknowledge, OS for bosutinib in Study 200 may be over-estimated because of selective censoring of patients.
6. In the AP model, as in the CP model, Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 1.0 years respectively) (Figure 21). As in CP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 21.

Similarly, in the BP model, the six criticisms for AP above also apply, although Criticism 2 is less of a problem between OS for bosutinib for BP (35% alive at maximum follow-up of 2 years) is more mature than for AP (65% alive). Criticism 6 again applies. Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm (vs. 0.5 years respectively) (Figure 22). As in CP and AP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 22.

Under the Cumulative Survival method, we again correct for these imbalances, in an analogous way as for CP CML, described in Section 6.1 (p190).

Estimation of OS for bosutinib in CP using MCyR surrogate relationship

In addition to our belief that the use of a MCyR surrogate relationship to estimate OS for bosutinib patients in CP is inappropriate (as stated above), we also note some issues with the methodology used by Pfizer, although these do not significantly impact cost-effectiveness (see Appendix S).

Briefly, rather than fitting to data from Jabbour and colleagues (2009),[44] Pfizer instead fitted to an exponential curve fitted to the study. Pfizer also assumed a lower MCyR rate from Jabbour and colleagues (2009)[44] to the rate used in TA241.[2] Pfizer also use an inappropriate formula to calculate the monthly probability of death from non-CML causes. None of these shortcomings were judged significant enough to warrant changing Pfizer's base case and our objections to Pfizer's methodology as described above (p165) still stand.

Non-CML mortality

We identified a number of shortcomings with Pfizer's method of incorporating non-CML mortality but did not judge that these were significant enough to warrant significant changes to the model. See Appendix S for further details.

5.3.8.2 OS for HU in CP

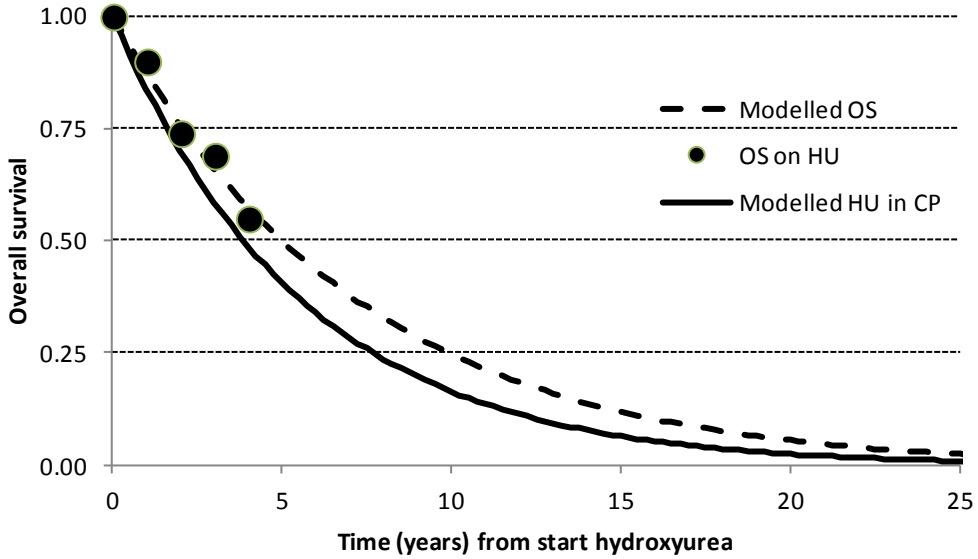
As stated in Section 5.2.6.1, p118, Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] Pfizer say that this study was used for the same purpose in TA241 and TA251 (Pfizer submission, p121). We agree that we, PenTAG, and Novartis, the manufacturer of nilotinib and imatinib used this study for this purpose in TA251. Furthermore, Novartis used this study for this purpose in TA241 (Novartis TA241 submission, p36). Our review of the literature at the time of TA251 suggested that this study was most appropriate for estimating OS for HU in CP.

This study enrolled patients in the USA from 1999 to 2005 who had failed on imatinib. Most (89%) were resistant to imatinib, but some (11%) were intolerant. For patients starting in CP, 8 subsequently received treatment with SCT, 35 with dasatinib/nilotinib and 61 'other' treatments. Of the 'other' treatment group, only 12 of the 61 patients received HU. The remaining patients received regimens including tipifarnib, ionafarnib, decitabine, cytarabine, homoharringtonine and IFN. The median age was 54 years, coincidentally and appropriately the same age as assumed in Pfizer's current model.

We also agree with Pfizer when they say that OS in the CP "other" treatment cohort was 77% at 2 years and 70% at 3 years (p94 Pfizer submission).

We agree with Pfizer when they state that an exponential curve was fitted to OS for CP HU in TA251 (Pfizer submission, p121). However, we disagree when they claim that the resulting mean OS was 3.5 years (Pfizer submission, p121). Instead, Novartis assumed a mean time on HU in CP (not OS) of 3.5 years (Novartis response document, 18th Oct 2011). Using Pfizer's estimated mean times in AP of 10 months and BP of 6 months, gives an estimated OS for HU of 3.5 + 0.8 + 0.5 = 4.8 years. Furthermore, we, PenTAG, estimated a mean OS for HU of 7.0 years (Hoyle and colleagues (2011),[17] p164). Below (Figure 23), we reproduce our exponential fit to the empirical data from Kantarjian and colleagues (2007)[3], taken from our TA251 Assessment report.[17]

Figure 23. PenTAG TA251 fit to CP HU OS data from Kantarjian and colleagues (2007)[3]



(Source: PenTAG TA251 submission,[17] Figure 29, p165)

From this figure, we can see clearly that Pfizer's estimate of OS on HU in CP of 3.5 years is far lower than indicated from Kantarjian and colleagues (2007).[3]

Clearly, the quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available to inform this parameter. We further note that clinical experts who advised Novartis in TA241 suggested that it was reasonable to assume that OS for HU is the same as OS for the "other" treatment group given the lack of available relevant data on HU in this setting (p164[17]).

Pfizer state that OS for HU in CP from Kantarjian and colleagues (2007)[3] should be viewed as an upper bound for the purposes of the current appraisal, given that the data from this study is for 2nd-line CML, whereas Pfizer's base case analysis is for 3rd-line, and we might expect OS to be lower for 3rd-line HU compared to 2nd-line HU. We agree that this is true for a 3rd-line analysis. However, as

stated in Section 5.3.5, p162, there is uncertainty as to whether bosutinib would be more likely to be used 2nd- or 3rd-line in England & Wales were it approved by NICE. If it is more likely to be used 2nd-line, then OS from Kantarjian and colleagues (2007)[3] is then appropriate.

Interestingly, our estimated mean OS of 7.0 years for HU in CP from TA251 is similar to Pfizer's base case estimate of [redacted] years for the mean survival on HU after bosutinib. Whilst this observation could be seen to corroborate our estimate of 7.0 years, we caution that we disagree with the derivation of Pfizer's estimate (Section 5.3.8.1, p165).

We adjust Pfizer's model to allow for a mean OS in the HU arm in CP of 7.0 years by changing the mean OS for HU, parameter "hu_cp_os" (cell E38 in worksheet "Efficacy") from 42 to 85 months. Note that we do not set this to 7.0 × 12 = 84 months, because Pfizer apply additional mortality due to background causes. Here, we do not change the mean times on HU after bosutinib or IFN failure. The ICERs are then as shown in Table 67 below. As explained above, we believe that the key comparison is (Bosutinib, HU) vs. HU, indicated in bold.

[redacted]

Note that shading does not indicate whether bosutinib is more or less costly or more or less effective than the comparator.

Table 66. Shading used to denote cost-effectiveness of bosutinib

Table 67. Pfizer's base case ICERs for CP CML adjusted for mean time in HU arm

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
Mean OS in HU arm increased from 3.5 to 7.0 years	[redacted]	Unchanged	Unchanged

5.3.8.3 OS for SCT in CP

Pfizer performed a literature review for studies that report OS after SCT. The results of this review suggest that relevant data for patients in CP is sparse. This is unfortunate since the cost-effectiveness of the comparison (bosutinib, HU) vs. SCT is strongly influenced by this parameter. There is substantial uncertainty in mean OS after SCT in CP because:

- OS for SCT is very immature, with maximum follow-up of 2 or 3 years, at which time at least 70% of patients are still alive. By contrast, mean OS is several years.
- This assessment concerns patients unsuited to TKIs other than bosutinib. However, all trial data refers to patients both suited and unsuited to TKIs.
- All trials of SCT have very small patient populations, in particular, all less than 100 patients.

As stated in Section 5.2.6.1, p118, Pfizer's base case estimate of OS after SCT for patients in CP was based on data from Jabbour and colleagues (2011).[10] Pfizer state that they chose this study "*because it was a full publication (rather than abstract), included the most comparable patient population (majority were third line) and presented OS curves.*" (Pfizer submission, p121) We agree with Pfizer that the Jabbour and colleagues (2011) patient population is mostly appropriate for the current HTA, given that patients were resistant to a TKI.[10] We further agree that most patients were 3rd-line, having previously received two TKIs. However, the sample size is extremely small, with only 16 CP patients (see Figure 3B of Jabbour and colleagues (2011)[10]) contributing to the estimates of OS, which is reflected in a very wide 95% confidence interval in the estimated 2-year OS of 72% (49%–96%). Also, the median age of 44 in this study is rather lower than that 54 years assumed in Pfizer's CP model.

Pfizer say that they digitised the OS data from Jabbour and colleagues (2011)[10] and then reconstructed the underlying patient level data. The exponential function fitted the patient level data best. Pfizer's fit to the Kaplan-Meier OS data from Jabbour and colleagues (2011)[10] appears reasonable. For example, the Kaplan-Meier estimate at 2 years of 72% is close to the 74% in the model.

Pfizer state (Pfizer submission, p121): "*The only other full-publication that reported OS in a format that was useable for our economic evaluation was Oehler 2007, but this was in a second-line population only and therefore deemed to be less relevant. Nonetheless, this is considered in a sensitivity analysis.*" In Oehler and colleagues (2007),[12] 145 patients in the US who received imatinib before allogeneic hematopoietic cell transplantation was retrospectively compared to 231 historical cohort patients who did not receive imatinib. Henceforth, we consider only the patients who previously received imatinib, as this is relevant to the current appraisal. As in Jabbour and colleagues (2011),[10] the median age (40 years) was lower than the starting age of 54 in Pfizer's CP model.

However, the sample size of 72 patients that informed the estimate of OS was far greater than the tiny sample of 16 patients in Jabbour and colleagues (2011).[10]

OS for CP patients was estimated as 78% at 3 years in Oehler and colleagues (2007).[12] Pfizer states that this study is less relevant than Jabbour and colleagues (2011)[10] because it concerns 2nd-line treatment, whereas Jabbour and colleagues (2011)[10] is mostly for 3rd-line treatment. However, as stated in Section 5.3.5, p162, we believe that bosutinib may be used for 2nd-line treatment and hence it is relevant to estimate OS for SCT in 2nd-line.

In addition, two further studies that report OS after SCT for patients starting in CP CML satisfy Pfizer's inclusion criteria (Pfizer submission, p90): Saussele and colleagues (2010)[13] and Schleuning and colleagues (2010).[14]

All patients in the study by Saussele and colleagues (2010)[13] had previously been treated with imatinib. Of the 37 CP patients, most, 32, were 2nd-line (after imatinib), and 5 were 3rd or 4th-line. The median age at transplantation was 37. OS at 3 years after SCT was 94.1% (95% CI 83.8–99.4%) in the 37 CP patients.

The retrospective registry study of Schleuning and colleagues (2010)[14] is published in abstract form only. All patients had been treated with nilotinib and/or dasatinib. Twenty-one patients were in CP and 20 patients in second or higher CP at the time of transplant. OS at 2 years was greater than 85% for the 15 patients in first CP.

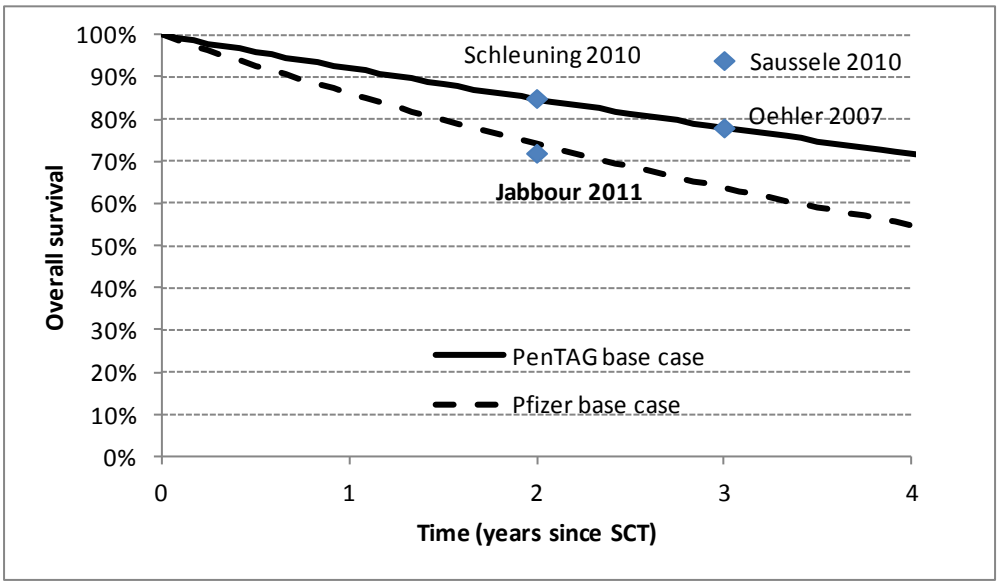
Whilst we acknowledge that there is no obviously superior source of data to estimate OS for SCT in CP, we believe that it is more appropriate to use the data from Oehler and colleagues (2007)[12] in preference to data from Jabbour and colleagues (2011),[10] which is Pfizer's preference, because:

- The sample size of 72 patients in Oehler and colleagues (2007)[12] that informs the estimate of OS is far greater than the tiny sample of 16 patients in Jabbour and colleagues (2011).[10]
- Whilst there is debate about the most appropriate line of treatment, we believe that it is reasonable to use the mostly 2nd-line data from Oehler and colleagues (2007)[12] as opposed to the mostly 3rd-line data from Jabbour and colleagues (2011).[10]
- The OS data from Oehler and colleagues (2007)[12] is clearly more consistent with that from Schleuning and colleagues (2010)[14] and Saussele and colleagues (2010)[13] (see Figure 24)

In summary, the PenTAG base case uses OS data from Oehler and colleagues (2007).[12]

In Figure 24, we can see clearly that Pfizer's base case estimate of OS after SCT in CP, shown by the dotted line, and which based on data from Jabbour and colleagues (2011),[10] is at the lower extreme of the data available, whereas our estimate of OS is more central (continuous line).

Figure 24. OS after SCT in CP



In Pfizer's model, we change the log(scale) parameter of the exponential distribution, cell E4 in worksheet "SCT parametric curves" from 1.897 to 2.491. The mean OS after SCT in CP then increases substantially, from 6.6 to 11.6 years. We notice that Pfizer estimate the log(scale) parameter of the exponential distribution using data from Oehler and colleagues (2007)[12] as 1.915, which is substantially different to our estimate of 2.491. However, it is impossible for us to reconstruct their analysis which led to this estimate. We do however note that the KM OS curve that Pfizer present on p381 appears inconsistent with the Kaplan-Meier curve shown in Figure 1A of Oehler and colleagues (2007).[12] In particular, Pfizer's figure shows OS at 3 years of approximately 0.72, whereas the figure from Oehler and colleagues (2007) is 0.78.[12]

The impact of our revised estimate of OS for SCT in CP on cost-effectiveness is given in Table 68 below. Note that while (Bosutinib, HU) continues to dominate SCT, the incremental costs and QALYs do change, as shown in Table 69.

Table 68. Pfizer's base case ICERs for CP CML adjusted for PenTAG preferred OS SCT

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
Mean OS in SCT arm increased from 6.6 to 11.6 years	Unchanged	Dominant	Unchanged

Table 69. Effect of PenTAG preferred OS on incremental outcomes, (Bosutinib, HU) vs. SCT

	Incremental discounted costs	Incremental discounted QALYs	INHB at WTP £20,000/QALY	INHB at WTP £30,000/QALY
Pfizer base case	[redacted]	+3.56	[redacted]	[redacted]
Mean OS of SCT increased to 11.6 years	[redacted]	+1.54	[redacted]	[redacted]

5.3.8.4 Time on treatment

The cost-effectiveness of bosutinib treatment sequences is very sensitive to the time on bosutinib treatment in all CML phase models. As stated in Section 5.2.6.2, p122, Pfizer estimate the time on bosutinib for all CML phases from Study 200. For 3rd-line CP CML, Pfizer fitted a log-normal distribution to the time on bosutinib treatment, and this appears reasonable. They estimate the mean time on 3rd-line bosutinib as [redacted] years. Fortunately, time on 3rd-line bosutinib data in Study 200 is rather mature, and so little extrapolation is required. However, this data is for the whole 3rd-line population in Study 200, whereas we are concerned with patients unsuited to TKIs. This therefore adds some uncertainty to the estimated time on bosutinib treatment.

Given that we believe that bosutinib may be used 2nd-line at least as often as 3rd-line, we asked Pfizer to provide Kaplan-Meier data for time on 2nd-line CP bosutinib. They agree, see Figure 25 below.

Figure 25. [redacted]

(a) Imatinib resistant (b) Imatinib intolerant

(Source: Pfizer clarifications, p35)

Later, we show that we estimate the mean time on 2nd-line bosutinib as approximately [redacted] years, far longer than the [redacted] years for 3rd-line treatment. This is a key parameter in our estimation of the cost-effectiveness of bosutinib treatment sequences in 2nd-line (Section 6.3.1, p214).

Our clinical advisor, Dr Rudin, believes that patients may often remain on bosutinib for the entire duration of CP in clinical practice. This would be in contrast to Study 200, where it appears that patients typically stopped bosutinib treatment well before progression to AP or BP. We consider this scenario in a sensitivity analysis (Section 6.3.1, p214).

Now turning to bosutinib use in AP, the time on bosutinib treatment is also rather mature, with approximately [redacted] of patients still on bosutinib at maximum follow-up (

Figure 14, p122). Therefore, little extrapolation is required. Pfizer again fitted a log-normal distribution to the time on bosutinib treatment, and this appears reasonable. They estimate the mean time on bosutinib in AP as [redacted] years.

The time on bosutinib treatment in BP is almost completely run off (

Figure 15, p123). Pfizer again fitted a log-normal distribution to the time on treatment, and this appears reasonable. They estimate the mean time on bosutinib in BP as [redacted] years.

Pfizer assume that HU is taken until death, which is appropriate.

As stated in Section 5.2.6.2, p123, Pfizer estimate the mean time on IFN was estimated as 0.5 years, on clinical advice. We believe this is a reasonable assumption.

5.3.9 Health related quality of life

Relevant sources for utility data, and Pfizer's base case utilities are given in Table 42, p126. First we note that there is uncertainty due to the fact that all sources of utilities were taken from patients who are both suited and unsuited to TKIs other than bosutinib, whereas we are interested in values appropriate for patients who are unsuited to TKIs.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 (Table 42, p126). In addition, they assume a utility for IFN in CP of 0.71, which is the same as our assumption in TA241. Their only departure from our previous assumptions is their estimate of the utility after SCT in CP, where they assume 0.71, versus our TA251 estimate of 0.80.

Importantly, Pfizer prefer the utilities that we have used previously to those from their Study 200. They justify this decision as follows (Pfizer submission, p137):

"*Whilst values taken directly from the intervention clinical trial is often more appropriate, the values in previous appraisals are from the IRIS study. This study collected arrange of utilities, in a large cohort of patients, including the utility of patients who progressed to AP and BP whilst not on active*

treatment. These utilities, though vital for modelling, are not available from Study 200. In addition the use of the IRIS values provides consistency with previous technology appraisals."

We agree that it is generally preferable to take utilities directly from the clinical trial of the intervention in question, in this case Study 200. Furthermore, the only source of utilities for bosutinib is Study 200 (IRIS gives utilities for imatinib), and this Study used the EQ-5D, which is preferred by NICE, and Study 200 is in the appropriate lines of treatment (2nd and 3rd-line vs. 1st-line in IRIS). But in this case, we are satisfied with Pfizer's decision because:

- Pfizer's utility of 0.85 for bosutinib in CP is only slightly higher than the Study 200 value of [redacted] for 3rd-line treatment. Furthermore, the Study 200 mean utility for 2nd-line [redacted] Pfizer's estimate of 0.85. As stated in Section 5.3.5, p162, the most relevant line of treatment for this appraisal is uncertain.
- Ideally, we would like a trial-based estimate of the utility of patients on bosutinib over the entire duration of treatment ([redacted]). However, utility measurements were heavily biased towards the start of bosutinib treatment. Therefore, this arguably limits the usefulness of the utilities from Study 200.
- The estimated utility of 0.85 for CP imatinib is based on a much larger study than Study 200.
- The mean utility from Study 200 for AP of [redacted] is the same as for 3rd-line CP. However, it is well know that quality of life is lower in AP. Therefore, arguably the Study 200 AP estimated utility lacks face validity.

We do not agree with Pfizer's justification of consistency with previous technology appraisals.

However, given that there is a reasonable argument to use utilities from Study 200, we perform the following sensitivity analysis:

- Utility bosutinib = [redacted] at age 54 (Study 200 value),
- Utility HU = Utility bosutinib = [redacted], and
- SCT, IFN unchanged from Pfizer base case.

Next, as stated above, Pfizer's only departure from our previous assumptions is their estimate of the utility after SCT in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Having inspected the source of our estimate, we believe that there is insufficient evidence to have a clear preference for our 0.80, and Pfizer's estimate is not unreasonable. Therefore, we accept Pfizer's base case estimate of 0.71, but we perform the following sensitivity analysis:

- Utility SCT = 0.80 at age 0.54 (increased from Pfizer base case 0.71),

- Utility bosutinib, HU, IFN = unchanged from Pfizer base case.

5.3.10 Adverse events

We are satisfied that using adverse event data from Study 200 is appropriate to the decision problem.

5.3.11 Resource use and costs

5.3.11.1 Resource use systematic review

Pfizer's systematic review of resource use and costs did not include first-line CML, but Pfizer include TA251[17] on the basis that they did not get sufficient data in their systematic review. It would have been more appropriate to conduct another systematic review but we are satisfied that TA251 should include the most relevant UK resource use and costs for first-line CML.

5.3.11.2 Drug acquisition

Pfizer have provided us with the acquisition cost of bosutinib (Table 44, p128) of £3,735.84 per month, or approximately £123 per day. We assume that this is indeed the price that the NHS would pay. In their base case analysis, Pfizer assume that all patients receive the licensed dose of bosutinib of 500mg per day, i.e. a dose intensity of 100%, in all CML phases. However, patients may increase the dose up to 600mg per day, or reduce the dose to 400mg or 300mg daily (Pfizer submission, p472), or may have dose interruptions. In short, we investigated Pfizer's assumption of a dose intensity of 100%, and we found it to be appropriate given the available data. The details are as follows.

Pfizer appropriately investigated the observed dose adjustments in Study 200. Specifically, they allowed for the proportion of Study 200 patients that received increased or decreased doses. As the duration of time at the new dose and time to new dose is not reported, they assumed that all patients received the adjusted dose for the entire duration of treatment with bosutinib. Given this, they estimated the mean daily cost for 3rd-line CP as [redacted] (Pfizer submission, p473), for AP as [redacted], and BP [redacted] and we agree with their calculations. Given that these costs are virtually identical to the mean cost assuming no dose adjustments, Pfizer assumed a dose intensity of 100% for all phases of CML.

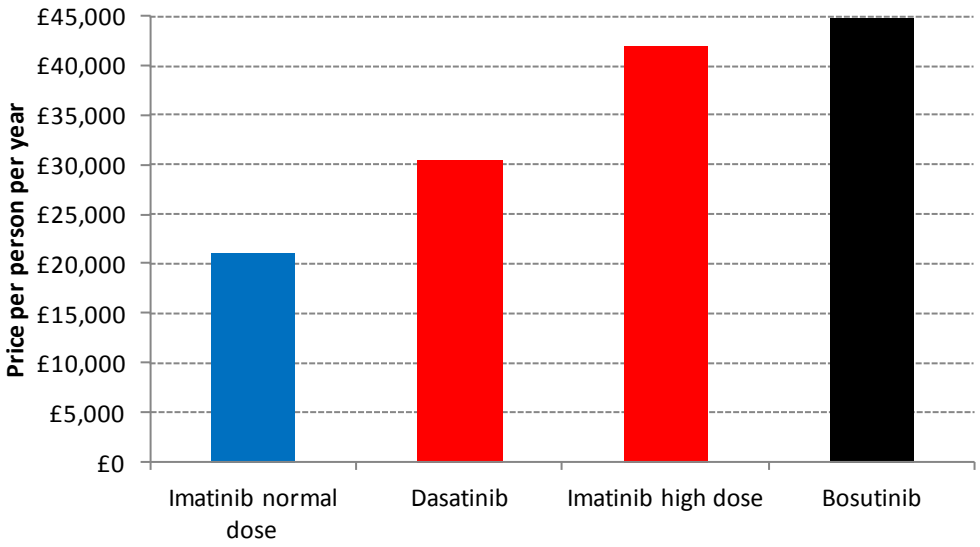
However, Pfizer's dose intensity calculation ignores (a) the possibility that people changed dose more than once and (b) treatment interruptions. Indeed, treatment interruptions are indicated for non-haematological adverse reactions (Pfizer submission, Table A1, p21), and some patients did have treatment with bosutinib interrupted due to adverse events (Pfizer submission, p359). We asked Pfizer to provide an indication of the mean time that patients were not receiving bosutinib due to dose interruptions. In response, they stated that in CP, approximately [redacted] of patients had at least one interruption of bosutinib treatment, and that for these patients, the mean total interruption period was

approximately [redacted]. The effect of modelling this is that the cost-effectiveness of bosutinib treatment sequences improves, but only incrementally. Specifically, the effect is to reduce the mean per patient cost in the bosutinib arms by approximately [redacted] × £44,830 / 12 = [redacted], where the annual acquisition cost of bosutinib is £44,830. Pfizer's base case ICER of (bosutinib, HU) vs. HU then improves very slightly, but still remains at [redacted] per QALY after rounding. The improvement in the ICERs for (bosutinib, HU) vs. HU in AP and BP are also slight. Given this, and given that the dose intensity of bosutinib whilst patients are actually taking the drug is slightly greater than 100%, we agree with Pfizer's assumption of a dose intensity of bosutinib of 100% for all phases of CML.

Given that bosutinib is given in packs of 28 tablets, there is scope for wastage. However, we estimate that if we allow for a plausible amount of wastage at the time the patient stops taking bosutinib, the ICERs for the bosutinib treatment sequences worsen only incrementally for all CML phases. Therefore, henceforth, we ignore wastage of bosutinib.

Figure 26 below shows the prices per person per year of TKI drugs for CML that have been assessed by NICE in the past and the price of bosutinib in this assessment. We are unable to cite the Patient Access price of nilotinib for reasons of confidentiality. Normal dose imatinib (blue shading) and nilotinib were recommended by NICE in TA251 and TA241 for 1st- and 2nd-line use. TKIs not recommended by NICE (red shading) are dasatinib for 1st- and 2nd-line use (TA251 and TA241) and high-dose imatinib for 2nd-line use (TA241). The price per patient per year is greatest for bosutinib (£44,830). The prices of the other TKIs are: normal dose imatinib = £20,994, dasatinib = £30,498, high dose imatinib = £41,989.

Figure 26. Prices of TKI drugs for CML assessed by NICE



Next, we are satisfied with Pfizer's estimation of the cost of HU as £12.75 per month (Table 44, p128). It is important to note that HU is extremely cheap.

We are also satisfied with Pfizer's estimation of the cost of IFN of £1,296 per month (Table 44, p128). We do however caution that the price that hospitals pay for IFN may be substantially lower due to discounted purchasing. However, we have no high quality evidence to support this claim, and so we accept Pfizer base case assumption. Furthermore, the cost-effectiveness of bosutinib versus IFN is rather insensitive to this parameter because Pfizer assume that IFN is taken for only about 0.5 years, far shorter than bosutinib, at about [redacted] years.

5.3.11.3 Stem cell transplant

As explained in Section 5.2.9.7, p131, Pfizer assume the cost of a SCT operation of £76,560, which was based on a 2010 NHS Blood and Transplant costing study,[56], which in turn was taken from van Agthoven and colleagues (2002).[57] In short, we are satisfied that the source of this cost and the cost itself are reasonable.

Pfizer also assume in the BP model that all patients receiving SCT first receive two cycles of FLAG-IDA chemotherapy. All patients are assumed to survive these cycles of chemotherapy and go on to incur SCT costs. The cost of FLAG-IDA was estimated based on Pastore and colleagues (2003),[59] in which 6.5% of patients died while undergoing one cycle of FLAG-IDA, which would suggest not all BP patients would go on to receive SCT. We investigated this and while the ICER for SCT versus bosutinib decreased it was not judged to have a significant impact.

5.3.11.4 Adverse events

Pfizer's assumptions regarding adverse events (i.e., adverse events incur costs but do not affect HRQL and are incurred in the first cycle) are broadly consistent with previous assessments of TKIs for CML. The PenTAG assessment in TA241[2] did not include costs for adverse events as these were expected to be low and could lend spurious accuracy. In previous assessments, adverse events have been used to estimate discontinuation rates, but this is not necessary in this assessment, as fairly mature discontinuation data is available from Study 200.

We note that the cost of adverse events in the AP and BP models are assumed to be the same as in the CP model. This is unrealistic as Table B29 of Pfizer's submission (Section 6.9.2, pp84-85) shows higher rates of adverse events for AP and BP patients than CP patients (Table B27, pp81-82). Using the same methodology as was used for CP to estimate a cost for AP and BP (combined) produced a value of £1,011 compared to the cost in CP of £506, i.e., the cost doubled. This however did not have a significant impact on cost-effectiveness.

We believe that adverse events are unlikely to have a significant impact on cost-effectiveness and are therefore satisfied by Pfizer's methodology.

5.3.11.5 Drug administration

Drug administration costs are incurred for interferon. We found an error in the calculation of the drug administration costs (see Appendix S) but it did not significantly impact cost-effectiveness.

5.3.11.6 Medical management, monitoring and tests

First, as explained in Section 5.2.9.7, p131, Pfizer assume the following follow-up costs after SCT: monthly costs for months 1–6 of £5,299, monthly costs for months 7–12 of £3,231 and monthly costs for months 13–24 of £1,166. In months 25 onwards, patients are assumed to receive 100mg of ciclosporin twice daily, giving a monthly cost of £140 (Pfizer submission, p145). As explained in Section 5.2.9.7, p131, these costs are taken from a NHS Blood and Transplant costing study,[56]. The underlying resource use for this study was taken from van Agthoven and colleagues (2002).[57] In short, we are satisfied that the source of these costs and the costs themselves are reasonable.

Pfizer's assumptions for medical management, monitoring and testing are given in Section 5.2.9.4, p129. These assumptions were based on those that we used originally in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey of 6 UK-based CML clinicians. However, Pfizer seem unaware that in TA251, our assumptions for medical management, monitoring and testing were challenged by Novartis, the manufacturer of nilotinib. In particular, in their response to our Assessment Report for TA251, Novartis submitted a response document, dated 18th October 2011, in which they stated that we over-estimated the frequencies of some resource use items. In response, we amended some of our assumptions for resource use in CP CML, as shown in Table 70.

Table 70. Selected resource use assumptions for CP CML

	Treatment	Nurse visits / month	Haematologist visits / month	Bone marrow aspirations / month
Pfizer current HTA	Bosutinib	0.4	0.9	0.3
	HU, IFN	0.4	0.9	0.3
	SCT	0.4	0.9	0.3
PenTAG TA251	Imatinib, dasatinib, nilotinib	0	0.33	0
	HU	0	0.72	0
	SCT	0	0	0
PenTAG current HTA	Bosutinib	0	0.33 per month, plus 2 at t = 0	0
	HU, IFN	0	0.72	0
	SCT	0	Many visits in months 0–24 included in ongoing costs from van Agthoven (2002)[57] 0.31 visits per month for month 24 onwards	0

Appendix U gives the full text of our response to Novartis' criticism of our original resource use assumptions in TA251. The NICE appraisal committee for TA251 were satisfied with our revised assumptions.

In April 2013, we asked our clinical expert, Claudius Rudin, to comment on our revised TA251 assumptions. His view of resource use whilst patients take TKIs is unchanged. However, as shown in Table 70 above, whilst patients are taking bosutinib, we now additionally include two haematologist visits at time zero. As stated in Appendix U, Dr Rudin believes that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly, i.e., there would be two more visits in the first three months than in subsequent three month periods. In TA251, we ignored the costs of the visits at 2, week 4, month 2 and month 4, because that appraisal was for 1st-line use of TKIs, and these costs cancelled between treatments almost exactly. In the current appraisal, we cost for these visits because a TKI, bosutinib, is used in just one treatment arm, and hence these costs do not cancel out in the other arms, HU and SCT. Also, we assume that all patients remain on bosutinib treatment, given that Pfizer's model predicts that [redacted] of patients are still on bosutinib treatment at 4 months.

Dr Rudin is still satisfied with our assumptions for patients whilst taking HU. Further, he believes that these are also appropriate for treatment whilst on IFN.

In TA251, we assumed no nurse visits, haematologist visits or bone marrow aspirations for patients after SCT. Dr Rudin agrees with the assumptions of no nurse visits or bone marrow aspirations, but disagrees with our assumption for frequency of haematologist visits after SCT. Specifically, he suggests that there are many such appointments in the first 100 days after SCT: twice a week after discharge at approximately day 28 until approximately day 60, then weekly until day 100, then monthly for the first year and if all goes well approximately every second month in the 2nd year, gradually extending to yearly after the 4th or 5th year. He advised that there would be much more frequent consultant-led clinic appointments, every 2 months if there is chronic graft versus host disease (cGvHD). Further, he agrees with the assumption that we and Novartis used in TA251 that 54% of patients get cGvHD after SCT.

We note that the follow-up costs assumed by Pfizer after SCT reflect a similar number of haematologist visits in the first 2 years as suggested by Dr Rudin. Specifically, in the period 0–6 months after transplant, patients visited an outpatient clinic an average of approximately 20 times, from 6–12 months after transplant, approximately 11 times, and from 12–24 months, approximately 10 times.[57] Therefore, on the basis of the suggested frequency of haematologist visits from Dr Rudin and the additional costs assumed by Pfizer after SCT, we first assume no haematologist visits in the first 2 years in addition to those already costs from the monthly follow up costs above. Second, we assume that all patients incur a background 0.31 visits per month from month 24 onwards, which is a weighted average of 0.50 per month for patients with cGvHD and the long term 0.08 per month for patients without cGvHD, with the weight being 54% of patients with cGvHD.

Note that whilst our estimate of consultant appointments in TA251 was incorrect, the cost-effectiveness of the 1st-line TKIs in this appraisal would have changed only marginally given the assumptions we now use in the current HTA. This is because SCT treatment was modelled as a downstream treatment in TA251, and costs of SCT largely cancelled between treatment arms. This is not the case in the current appraisal because SCT is one of the initial treatments.

As shown in Table 70 above, we assume no bone marrow aspirations. In TA251, we originally allowed for 0.3 bone marrow aspirations per month for all treatments. This constituted 94% of our estimated costs for tests of £216 per month. Pfizer's estimated cost for tests of £231 was based on the £216 per inflated to 2011/12 prices. Given that bone marrow aspirations constituted almost all test costs, in the current HTA, we assume zero test costs for all treatments.

When we alter Pfizer's model to reflect our preferred resource use assumptions shown in Table 70 above (see Appendix W for details), the cost-effectiveness of bosutinib improves versus hydroxycarbamide: Pfizer's ICER decreases from [redacted] per QALY. The costs of

bosutinib and SCT both decrease, although the costs of bosutinib decrease farther; as a result bosutinib continues to dominate SCT (Table 71).

Table 71. Pfizer's base case ICERs for CP CML adjusted for resource use assumptions preferred by PenTAG

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
PenTAG resource use assumptions in Table 49, p184.	[redacted]	Dominant	[redacted]

5.3.12 Cost-effectiveness results

We are satisfied that the results presented by Pfizer match those from the model supplied.

5.3.13 Sensitivity analyses

5.3.13.1 One-way sensitivity analyses

Pfizer conduct a number of one-way sensitivity analyses but by no means on all parameters. Tornado diagrams are not provided. Pfizer group their one-way sensitivity analyses along with explorations of structural uncertainty in Section 5.2.11.3, p146.

5.3.13.2 Probabilistic sensitivity analysis

We agree with Pfizer that probabilistic sensitivity analyses are not particularly useful as they do not account for the significant structural uncertainties in the decision problems, and we have therefore not critiqued the probabilistic sensitivity analyses in detail.

5.3.13.3 Scenario analyses

2nd-line use of bosutinib in CP patients

Pfizer's base case analysis assumes that bosutinib is used 3rd-line, but we feel it is likely that bosutinib will be used 2nd-line rather than 3rd-line due to the approval of nilotinib for 1st-line use, clinical opinion suggesting that imatinib is unlikely to be used in patients resistant to imatinib, and dasatinib not being approved 1st-line or post imatinib failure. Therefore as an important scenario analysis, we estimate the cost-effectiveness of bosutinib for 2nd-line CP. Pfizer did conduct a scenario analysis in which the 2nd-line cohort was used as the model population, however we do not believe that Pfizer's sensitivity analysis is appropriate as it includes only a change in the MCyR rate and does not include a change in the length of time patients spend on treatment – this biases the results in favour of cost-effectiveness of bosutinib.

We conduct our own scenario analysis based on treatment discontinuation curves provided by Pfizer in response to questions of clarification (Figure 25, p176) and on the MCyR rate for 2nd-line patients published in Cortes and colleagues (2011), in which the cumulative MCyR rate at a minimum follow-up of 12 months (median follow-up 24.2 months) was 140/266 = 52.6%.[24]

We estimated from Figure 25 (p176) that median time on 2nd-line bosutinib treatment would be [redacted] years for imatinib resistant patients and [redacted] years for imatinib intolerant patients. As there were 200 imatinib resistant patients versus 88 imatinib intolerant patients we estimated the median time on 2nd-line bosutinib treatment as (200 × [redacted] + 88 × [redacted]) / 288 = [redacted] years.

For simplicity, we then assumed an accelerated failure time model, i.e., the time to bosutinib treatment discontinuation for 2nd-line patients would be as for 3rd-line patients, but with time rescaled. This is achieved simply by adjusting the scale parameter μ of the log-normal distribution. The mean and median times on treatment are both scaled by the same factor. The median time on treatment from Study 200 in the 3rd-line CP cohort was 8.6 months = 0.72 years (15 February 2012 snapshot; Pfizer submission, Section 6.8.5, p72). We therefore estimated that the appropriate scaling factor was [redacted]/0.72 = [redacted].

To achieve the required [redacted] scaling of mean time on treatment we took mean time on treatment for 3rd-line patients from the model as [redacted] years and adjusted μ using Solver such that the mean time on 2nd-line treatment from the model was equal to [redacted] years when OS was adjusted using the MCyR rate of 52.6%, giving μ = [redacted].

Under this scenario analysis (and with no other alterations to the Pfizer model) we find that bosutinib is more costly and more effective than SCT and that the cost-effectiveness of bosutinib has worsened generally (see Table 72).

Table 72. Pfizer's base case ICERs for CP CML adjusted for 2nd-line patients

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
2nd-line CP cohort	[redacted]	[redacted]	[redacted]

It should be cautioned that, due to lack of evidence, no adjustments were made to survival or time on treatment for hydroxycarbamide and SCT to reflect the choice of a 2nd-line cohort (although the

estimate of effectiveness of hydroxycarbamide is already taken from a 2nd-line study), nor was the age adjusted for any patients.

Pfizer's "cumulative survival approach" to bosutinib OS in CP model

Pfizer present results of a "cumulative survival approach" in Table B64, Section 7.5.9, p160, and in Table B151, Section 10.22, p469. We believe this is a flawed analysis and that the methodology – while described as similar to an approach in TA251 – is not to be confused with the cumulative survival method we present in Section 6.1 (p190). Further discussion of this can be found in Section 6.1.4 (p202).

Bosutinib OS in BP model

We identified that there was a formula error in the scenario analysis where bosutinib OS in the BP model is based on fitting a Weibull distribution to Study 200 OS individual patient data. We corrected the formula error and re-fitted the Weibull distribution. The ICER for bosutinib versus hydroxycarbamide in this scenario increased from [redacted] per QALY.

5.4 Cost-effectiveness conclusions

No previous cost-effectiveness evaluations of bosutinib in refractory CML were identified in Pfizer's systematic review. The *de novo* economic evaluation submitted by Pfizer contains ICERs significantly lower than those calculated by PenTAG (see Section 6, p190), in which the following items were adjusted:

- The method of estimation of OS for all comparators using our "cumulative survival method"
- Mean overall survival on HU (CP model only)
- Mean overall survival after SCT (CP model only)
- Medical management resource use (CP model only)

The cumulative survival method also allows an estimation of the cost-effectiveness of bosutinib followed by SCT, which we believe is a relevant treatment sequence for patients able to receive SCT.

The cumulative survival method had the greatest impact on cost-effectiveness, with the additional items not affecting the cost-effectiveness of the PenTAG base case significantly (although some do affect the Pfizer base case significantly).

Table 73. Comparison of Pfizer and PenTAG base case ICERs

	Pfizer ICERs		**PenTAG ICERs**	
	(Bosutinib, HU) vs. HU	(Bosutinib, SCT) vs. SCT	(Bosutinib, HU) vs. HU	(Bosutinib, SCT) vs. SCT
CP model	[redacted]	n/a	[redacted]	[redacted]
AP model	[redacted]	n/a	[redacted]	[redacted]
BP model	[redacted]	n/a	[redacted]	[redacted]

n/a as not estimated by Pfizer

Although there is significant uncertainty regarding the effectiveness of HU and SCT and regarding which TKIs will be attempted before bosutinib, the PenTAG base case is fairly robust to these uncertainties as it is primarily driven by the drug acquisition cost of bosutinib.

6 ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Cumulative survival method

As explained in Section 5.3.8.1, p165 above, we believe that there are major problems with the methods Pfizer have used to estimate OS for all comparator treatments, especially for the CP model, but also for the AP and BP models. This leads to the implausible prediction that the mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm and the time on 4th-line HU in the (IFN, HU) arm for the CP, AP and BP models. Also as explained in Section 5.3.8.1, p165, in our base case, we have used a different method, the Cumulative Survival method, of estimating OS for all treatments in all model phases.

The Cumulative Survival method was used by us, PenTAG, in our base case analysis in TA251, of the cost-effectiveness of imatinib, nilotinib and dasatinib for 1st-line CML. In a sensitivity analysis, we estimated OS separately using a surrogate relationship based on CCyR and on MMR (major molecular response). In this appraisal, the method was also used by Novartis, the manufacturer of nilotinib. By contrast, Bristol-Myers Squibb, the manufacturer of dasatinib, estimated OS for all treatments using a surrogate relationship based on CCyR. In this appraisal, our base case analysis was accepted by the NICE Appraisal Committee as most appropriate.

6.1.1 Cumulative survival method CP

We first discuss the Cumulative Survival method applied to treatment starting in CP CML.

The motivation for performing the method in the CP is as follows. Pfizer estimate that the on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in arm and the time on 4th-line HU in the (IFN, HU) arm (versus 2.6 versus 2.1 years respectively) (

Figure 27). We believe, and clinical expert advice has agreed, that this is unreasonable. Furthermore, this assumption acts dramatically in favour of the cost-effectiveness of (Bosutinib, HU) versus HU and (Bosutinib, HU) versus (IFN, HU), because the price of HU is negligible.

Figure 27.

Under the Cumulative Survival method, we correct for this imbalance.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (IFN, HU) arm, the mean time, cost and QALY whilst on 3rd-line IFN treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

Clearly, not all patients in the (Bosutinib, HU) arm will survive to start 4th-line HU treatment. The key assumption of the Cumulative Survival method is that, in the (Bosutinib, HU) arm, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. None of Assumptions 1–7 (Table 65, p165), which are necessary for Pfizer's methods of estimating OS, are required.

Equivalently, we assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equals that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib. We believe that the life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib is probably an upper bound, as discussed in Section 6.1.4 (p202).

Similarly, in the (IFN, HU) arm, the life expectancy of those patients who start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm.

Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

In the next sections, we estimate the total life years, costs and QALYs for the (Bosutinib, HU), (IFN, HU) and (Bosutinib, SCT) treatment arms.

6.1.1.1 Cumulative survival method CP time on treatment

We denote T as the mean per patient undiscounted time. This is split in to four parts, corresponding to 3rd-line CP, 4th-line CP, AP and BP. Here, without loss of generality, we assume that all patients start 3rd-line treatment for CML. The notation of these time components is given in Table 74 below.

Table 74. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in CP.

	(Bosutinib, HU)	**HU**	**SCT**	**(IFN, HU)**	**(Bosutinib, SCT)**
3rd-line CP	$\mathrm{T}^{BOS\ 3}_{\mathrm{BOS,HU}}$	$\mathrm{T}^{\mathrm{HU}}_{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}^{IFN\ 3}_{\mathrm{IFN,HU}}$	$\mathrm{T}^{BOS\ 3}_{\mathrm{BOS,SCT}}$
4th-line CP	$\mathrm{T}^{HU\ 4}_{\mathrm{BOS,HU}}$	n/a		$\mathrm{T}^{HU\ 4}_{\mathrm{IFN,HU}}$	$\mathrm{T}^{SCT\ 4}_{\mathrm{BOS,SCT}}$
AP	$\mathrm{T}^{AP}_{\mathrm{BOS,HU}}$	$\mathrm{T}^{\mathrm{AP}}_{\mathrm{HU}}$		$\mathrm{T}^{AP}_{\mathrm{IFN,HU}}$	
BP	$\mathrm{T}^{BP}_{\mathrm{BOS,HU}}$	$\mathrm{T}^{\mathrm{BP}}_{\mathrm{HU}}$		$\mathrm{T}^{BP}_{\mathrm{IFN,HU}}$	

Then under the Cumulative Survival method, the component times are calculated as shown in Table 75, where S_{BOS} denotes the probability that a patient is still alive when he/she stops treatment with bosutinib, i.e. the probability that a patient in the (Bosutinib, HU) arm starts 4th-line HU treatment, which equals the probability that a patient in the (Bosutinib, SCT) arm starts 4th-line SCT treatment. S_{IFN} represents the analogous quantity for IFN.

Table 75. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in CP

	(Bosutinib, HU)	HU	SCT	(IFN, HU)	(Bosutinib, SCT)
3rd-line CP	unchanged	unchanged	unchanged	unchanged	unchanged
4th-line CP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$	
BP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$	

Unfortunately, S_{BOS} and S_{IFN} are not calculated in Pfizer's model. However, we estimate upper bounds for these quantities, 95.5% and 99.8% respectively, by assuming that the only mortality whilst patients are on bosutinib or IFN treatment is due to background causes. These estimates are based on Pfizer's base case estimates of time on 3rd-line bosutinib and 3rd-line IFN. These upper bounds in turn yield lower bounds for the ICERs of (Bosutinib, HU) versus HU and versus (IFN, HU).

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm and 4th-line HU in the (IFN, HU) arm are very similar (2.5 vs. 2.6 vs. 2.6 years respectively) (Figure 28). The mean time on HU in the (Bosutinib, HU) arm is slightly lower because not all patients (95.5%) reach HU treatment, whereas all patients start treatment in the HU arm and nearly all patients (99.8%) in the (IFN, HU) arm start HU treatment.

In addition, the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are very similar (6.3 vs. 6.6 years respectively) (Figure 28). Similarly, the time is slightly lower in the (Bosutinib, SCT) arm, again because only 95.5% reach SCT treatment.

Figure 28.

6.1.1.2 Cumulative survival method CP total costs and QALYs

Next, we denote C as the mean per patient discounted total costs. Then, as for T, this variable is split in to four parts, corresponding to 3rd-line CP, 4th-line CP, AP and BP, using exactly the same notation as for T, shown in Table 76, where d_{BOS} denotes the mean discount factor at the time of cessation of bosutinib treatment across all patients. Technically, this is the integral over all time of the probability density function of the bosutinib discontinuation function at time t multiplied by the discount factor at time t. d_{IFN} represents the analogous quantity for IFN.

d_{BOS} and d_{IFN} can be calculated directly from Pfizer's model and equal 93.0% and 99.4% respectively. These quantities are also based on Pfizer's base case estimates of time on 3rd-line bosutinib and 3rd-line IFN. They also assume a discount rate of 3.5% p.a.

Then under the cumulative survival method, the component costs are calculated as shown in Table 76.

Table 76. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in CP

	(Bosutinib, HU)	**HU**	**SCT**	**(IFN, HU)**	**(Bosutinib, SCT)**
3rd-line CP	unchanged	unchanged	unchanged	unchanged	unchanged
4th-line CP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{HU}}$	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{SCT}}$
AP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{AP}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{AP}}$	
BP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{BP}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{BP}}$	

The component QALYs are calculated in exactly the same way.

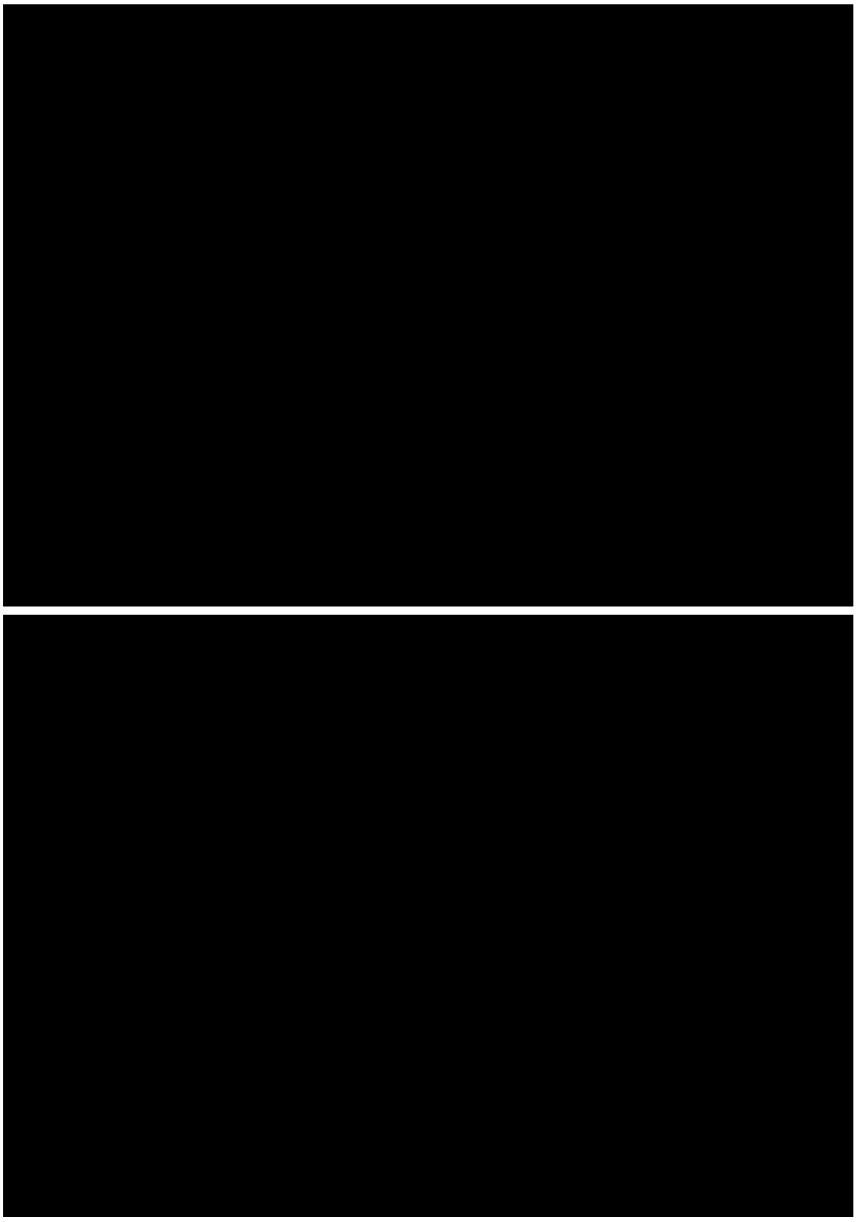
The ICERs are then as shown in Table 77 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT, indicated by bold font.

Table 77. PenTAG ICERs under the Cumulative Survival method for CP

Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

n/a as not estimated by Pfizer

Figure 29.



Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) and (IFN, HU) arms survive to start 4th-line HU treatment, i.e. $S_{\mathrm{BOS}} = S_{\mathrm{IFN}}$ = 100%, and
- no discounting of costs and QALYs, i.e. $d_{\mathrm{BOS}} = d_{\mathrm{IFN}}$ = 100%,

then the ICER for (Bosutinib, HU) versus HU is [redacted] per QALY and (Bosutinib, HU) versus (IFN, HU) is [redacted] per QALY. These ICERs only then depend on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm and IFN treatment in the (IFN, HU) arm. In other words, we ignore all costs and QALYs on HU treatment and in AP and BP in all arms, in particular ignoring all costs and QALYs in the entire HU arm.

Similarly, the ICER for (Bosutinib, SCT) versus SCT is [redacted] per QALY and then depends only on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, SCT) arm, i.e. ignoring all costs and QALYs in the entire SCT arm.

6.1.2 Cumulative survival method AP

We now discuss the Cumulative Survival method applied to treatment starting in AP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 1.0 years respectively) (Figure 30). As in CP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 30.

[redacted]

Under the Cumulative Survival method, we again correct for this imbalance, in an analogous way as for CP CML, described above. The details are given in Appendix T. The key assumptions are that the life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equals that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib, and in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm are very similar (1.01 vs. 1.02 years respectively) (Figure 31). The mean time on HU in the (Bosutinib, HU) arm is slightly lower because not all patients (98.9%) reach HU treatment, whereas all patients start treatment in the HU arm.

In addition, the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are very similar (2.99 vs. 3.02 years respectively) (Figure 31). Similarly, the time is slightly lower in the (Bosutinib, SCT) arm, again because only 98.9% reach SCT treatment.

Figure 31.

The ICERs are then as shown in Table 78 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT, indicated in bold.

Table 78. PenTAG ICERs under the Cumulative Survival method for AP CML

Intervention	(Bosutinib, HU) vs.	(Bosutinib, SCT) vs.

Comparator	***HU***	*SCT*	*HU*	***SCT***
Pfizer base case	[redacted]	Dominant	**n/a**	
Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]

n/a as not estimated by Pfizer

Figure 32.

[redacted]

Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) arm survival to start 4th-line HU treatment, i.e. S_{BOS} =100%, and
- no discounting of costs and QALYs, i.e. d_{BOS} = 100%,

then the ICERs for (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT are both [redacted] per QALY. This ICER only then depends on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm. In other words, we ignore all costs and QALYs on HU and SCT treatments in all arms, in particular ignoring all costs and QALYs in the entire HU and SCT arms.

6.1.3 Cumulative survival method BP

We now discuss the Cumulative Survival method applied to treatment starting in BP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 0.54 years respectively) (Figure 33). As in CP and AP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 33.

[redacted]

Under the Cumulative Survival method, we again correct for this imbalance, in an analogous way as for CP and AP CML. The details are given in Appendix T. The key assumptions are that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib, and in

the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm are virtually identical (0.54 vs. 0.54 years respectively) (Figure 34), and the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are virtually identical (2.64 vs. 2.64 years respectively) (Figure 34).

Figure 34.

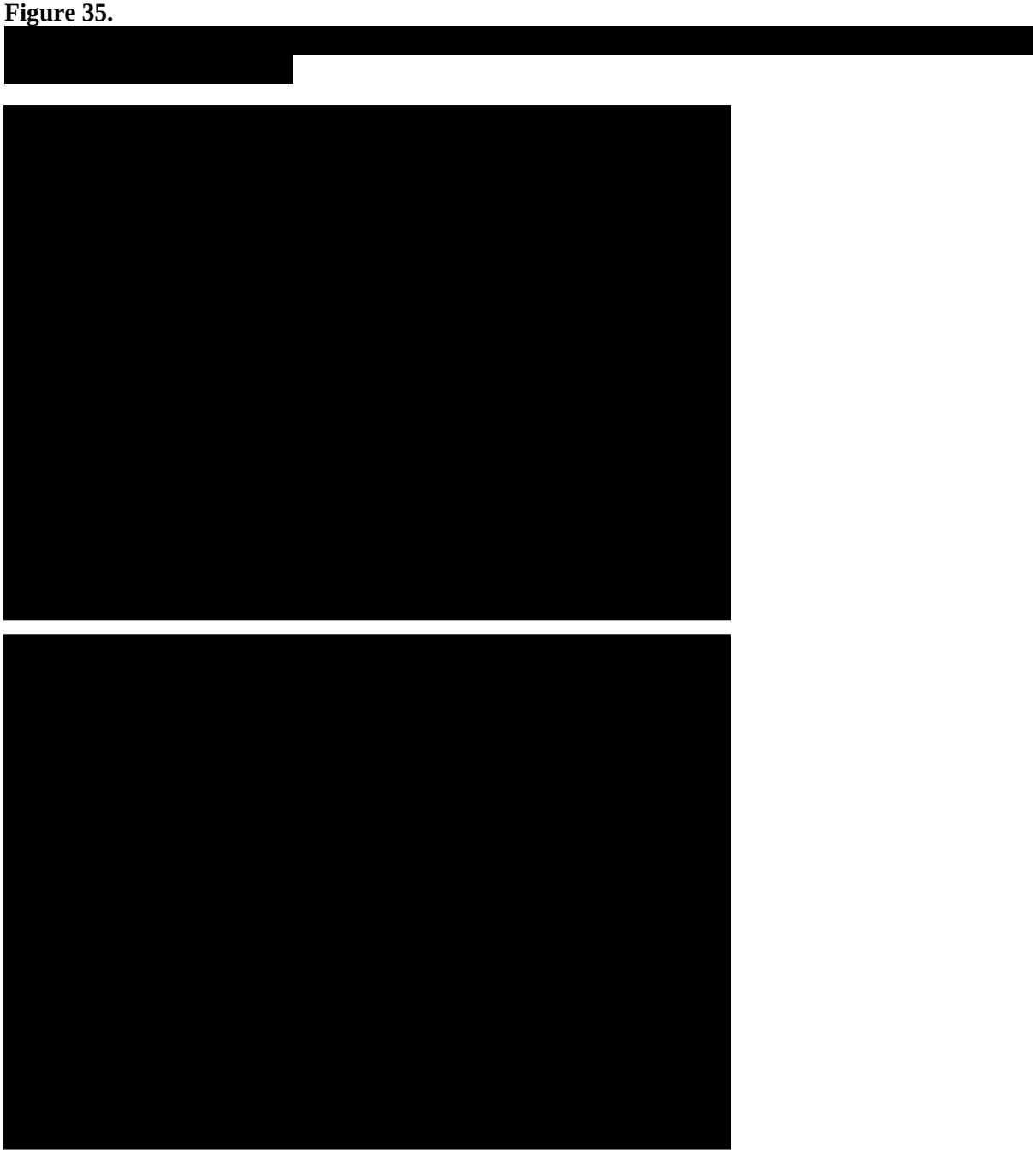
The ICERs are then as shown in Table 79 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT, indicated in bold.

Table 79. PenTAG ICERs under the Cumulative Survival method for BP CML

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
Pfizer base case			n/a	
Cumulative survival method				

n/a as not estimated by Pfizer
a (Bosutinib, HU) cheaper and less effective than SCT

Figure 35.



Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) arm survival to start 4th-line HU treatment, i.e. $S_{\mathrm{BOS}} = 100\%$, and
- no discounting of costs and QALYs, i.e. $d_{\mathrm{BOS}} = 100\%$,

then the ICERs for (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT are both [redacted] per QALY. This ICER only then depends on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm. In other words, we ignore all costs and QALYs on HU and SCT treatments in all arms, in particular ignoring all costs and QALYs in the entire HU and SCT arms.

6.1.4 Cumulative survival method discussion

We believe that the method to estimate OS for all treatments should be simple and parsimonious for the following reasons:

- Evidence for OS for all comparators is from single arm trials.
- The quality of evidence for OS for patients having failed a TKI for all comparators is poor.
- Worse still, there is no OS evidence whatsoever specifically for patients unsuited to TKIs for HU, SCT and IFN, and only limited evidence for bosutinib.

Pfizer's method for estimating OS involves numerous assumptions (Table 65, p165), for which there is little or no evidence. Furthermore, their results appear implausible. By contrast, the Cumulative Survival method requires just a single assumption and gives far more plausible estimates for the times on treatment. Therefore, we believe that the Cumulative Survival method should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The Cumulative Survival method additionally has the attractive property that the ICERs for the key comparisons of (bosutinib, HU) vs. HU and (bosutinib, SCT) vs. SCT depend almost exclusively on the costs and QALYs per unit time whilst patients are on bosutinib treatment. This leads to the following attractive predictions about the ICERs for the key comparisons of (bosutinib, HU) vs. HU and (bosutinib, SCT) vs. SCT under the Cumulative Survival method, none of which apply under Pfizer's method.

- They are very insensitive to the estimated mean time on HU and SCT. This is attractive because these quantities are highly uncertain due to the lack of quality clinical evidence.
- They are largely independent of line of treatment of bosutinib, as they are influenced heavily by the costs and QALYs on bosutinib per unit time, not over the entire duration of bosutinib treatment.
- They are insensitive to whether the clinical evidence relates just to those patients unsuited to TKIs or to all patients after imatinib failure.
- They are insensitive to the nature of subsequent treatments in the trials that inform OS for all comparator treatments.

Pfizer briefly mention a sensitivity analysis which they dub the "Cumulative survival approach" (p160 & p469) in which they estimate OS for bosutinib as PFS plus 10 months in AP and 6 months in BP. We agree with Pfizer that their "Cumulative survival approach" is "similar to the cumulative survival approach in TA251" (Pfizer submission, p469). We believe it is similar in that OS for bosutinib is not estimated by a surrogate approach, but instead is estimated as the sum of times in various health states. Nonetheless, their method is importantly different to the method we describe as the "Cumulative Survival" method for two main reasons. First, it is based on PFS, not on time on bosutinib treatment. Pfizer assume that OS is estimated as PFS plus time on AP plus time on BP. As we discussed in TA241, we disagree, because of the definition of progression. In Study 200, progression can indeed be due to progression to AP or BP, but also due to other events such as doubling of white blood cell count over at least 1 month with a second count >20 x 109/L confirmed at least 1 week later, loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss, loss of MCyR with an increase of ≥30% in Ph+ metaphases (p346 Pfizer submission). Therefore, we believe that Pfizer underestimate OS under their method. Second, Pfizer apply their "Cumulative survival approach" only to the bosutinib arm, not to the comparator arms. Therefore, the crucial Assumption 1 (Table 65, p165) remains, i.e. inconsistency in the method of estimating OS across comparators.

The Cumulative Survival method in the form we have just described is not mentioned by Pfizer in the current HTA. We find this puzzling, given that it was the accepted base case model structure in TA251 and given that Pfizer contrast their current analysis with the analyses from TA251 in great details in almost every other area, including choice of utilities, resource use and surrogate survival relationship.

If anything, the Cumulative survival method may slightly over-estimate OS in the bosutinib arm, and therefore is favourable to the cost-effectiveness of bosutinib, for three reasons.

First, the method assumes that the mean time on HU after bosutinib is approximately equal to the mean time on HU (without bosutinib). In other words, that the life expectancy on HU does not decrease at a later line of treatment. Conversely, life expectancy generally decreases with line of treatment.

Second, our estimate of S_{BOS}, the probability that a patient is still alive when he/she stops treatment with bosutinib, i.e. the probability that a patient in the (Bosutinib, HU) arm starts 4th-line HU treatment, which equals the probability that a patient in the (Bosutinib, SCT) arm starts 4th-line SCT treatment, is an upper bound since we assume that the only cause of mortality whilst patients are on bosutinib is background mortality, i.e. unrelated to CML. In reality, mortality is likely to be greater. In particular, an evidence-based estimate of the upper bound of S_{BOS} is 94.9%, which we derive as

follows. In the 3rd-line CP cohort of Study 200, by the 15th February 2012 snapshot, there had been 23 deaths overall, of which 6 occurred during bosutinib treatment or within 30 days of last dose, and 17 died more than 30 days after discontinuation of bosutinib (p83 Pfizer submission). Given that there were 118 3rd-line CP patients, if we assume that all patients were off bosutinib treatment at the data snapshot, this gives an upper bound of 100% − 6 / 118 = 94.9%. This is an upper bound because some patients were still taking bosutinib at the data cut off.

Third, the method does not allow for the fact that background mortality for patients starting 4th-line HU or SCT is slightly greater than for patients starting 3rd-line HU or SCT, reflecting an average time of [redacted] years on 3rd-line bosutinib in CP. However, we ignore this because exploratory calculations suggest that correcting this inaccuracy increases the ICER of bosutinib only very marginally.

Furthermore, we also do not allow for the fact that total QALYs on 4th-line HU will be slightly lower than on 3rd-line HU because utilities are assumed to reduce slightly with age. However, we ignore this for the same reason.

6.2 Derivation of PenTAG base case

In this section we present derivations of the PenTAG base cases in the CP, AP and BP models. The impacts of the individual components of our base case on cost-effectiveness are shown, as well as selected combinations of components and finally the base case which is composed of all components.

We also show more detailed results of the PenTAG base case and comparisons of the Pfizer and PenTAG base cases in the cost-effectiveness plane.

Unless otherwise stated, all ICERs lie in the first (NE) quadrant (i.e., the intervention is more costly and more effective than the comparator). We believe that the comparisons that are most relevant to the decision problem are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT. These ICERs are therefore highlighted in bold.

6.2.1 Derivation of PenTAG CP base case

Table 80 shows the derivation of the PenTAG base case in the CP model. Unless otherwise stated, IFN is dominated by HU.

Table 80. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
	Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	Dominant	[redacted]	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	[redacted]	n/a		
1+2[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+3[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+4[b]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+3+4		[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT
b Interferon is more costly and more effective than hydroxycarbamide

c Interferon is less costly and less effective than hydroxycarbamide

Our base case ICERs for (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT are [redacted] and [redacted] per QALY respectively. The cumulative survival method is the principal cause of the increase in the ICER for (Bosutinib, HU) versus HU from [redacted] per QALY, as individually it results in an ICER of [redacted] per QALY. The change in medical management costs improves the cost-effectiveness of bosutinib both when applied to Pfizer's base case and also as a component of the PenTAG base case. Increases in the overall survival for HU and SCT patients results in a significant worsening in the cost-effectiveness of bosutinib according to Pfizer's model but the change is less pronounced with the cumulative survival method as these OS gains are passed on to bosutinib patients also. Figure 36 shows the mean time on each treatment for each treatment arm in the PenTAG base case. Note that while SCT is now predicted to provide more life years than (Bosutinib, HU) (11.6 versus [redacted]), it is not predicted to provide more QALYs (5.7 versus [redacted]), although as stated before we believe the appropriate comparisons are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT.

Figure 36. [redacted]

The general effect of bosutinib in the PenTAG base case is to increase total QALYs by between [redacted] and [redacted] and increase discounted costs by around £100,000, as is shown in Figure 37. Comparisons of the cost-effectiveness planes in the Pfizer and PenTAG bases are shown in

Figure 38, in which it can be seen that HU and SCT become significantly more effective and marginally less costly. (Bosutinib, HU) by contrast becomes less effective and less costly. Further details are shown in Table 81.

Figure 37.

Figure 38.

Table 81. Life years, QALYs and costs in PenTAG CP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	(IFN, HU)	SCT
Life years (undiscounted)					
CP on treatment	[redacted]	[redacted]	5.87	0.54	11.59
CP off treatment	5.61	11.06	n/a	5.86	n/a
AP	0.62	n/a	0.65	0.65	n/a
BP	0.45	n/a	0.47	0.47	n/a
Total	[redacted]	[redacted]	**6.99**	**7.52**	**11.59**
Discounted QALYs					
CP on treatment	[redacted]	[redacted]	3.94	0.38	5.72
CP off treatment	3.50	5.08	n/a	3.90	n/a
AP	0.31	n/a	0.35	0.35	n/a
BP	0.16	n/a	0.18	0.18	n/a
Total	[redacted]	[redacted]	**4.47**	**4.82**	**5.72**
Discounted costs					
CP on treatment	[redacted]	[redacted]	£5,970	£9,038	£151,863
CP off treatment	£5,302	£134,862	n/a	£5,919	n/a
AP	£6,981	n/a	£7,861	£7,794	n/a
BP	£5,102	n/a	£5,745	£5,696	n/a
Palliative care	£4,356	£3,842	£4,905	£4,863	£4,326
Adverse events	£506	£506	n/a	n/a	n/a
Total	[redacted]	[redacted]	**£24,482**	**£33,311**	**£156,189**

6.2.2 Derivation of PenTAG AP base case

Table 82 shows the derivation of the PenTAG AP base case.

Table 82. Derivation of PenTAG base case AP CML

	Intervention	(Bosutinib, HU) vs.		(Bosutinib, SCT) vs.	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

[redacted]

The PenTAG AP base case is composed simply of the cumulative survival method. The effect of this change is to introduce the (Bosutinib, SCT) arm and to worsen slightly the cost-effectiveness of

(Bosutinib, HU) versus HU, with the ICER increasing from [redacted] per QALY. The ICER of (Bosutinib, SCT) versus SCT is estimated at [redacted] per QALY.

Figure 39 shows the mean time on each treatment in the PenTAG AP base case. It can be seen that the time spent on HU in AP in the (Bosutinib, HU) arm is similar to the time spent in AP in the HU arm, and likewise for SCT in the (Bosutinib, SCT) arm.

Figure 39.

[redacted]

Figure 40 shows the cost-effectiveness plane for the PenTAG AP base case. In this instance, bosutinib adds [redacted] QALYs and [redacted].

Figure 41 shows a comparison of the Pfizer and PenTAG base case cost-effectiveness planes, showing that the PenTAG base case reduces the effectiveness and cost of bosutinib and introduces the (Bosutinib, SCT) arm. Further details are shown in Table 83.

Figure 40.

Figure 41.

Table 83. Life years, QALYs and costs in PenTAG AP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	SCT
Life years (undiscounted)				
AP on treatment	[redacted]	[redacted]	1.02	3.02
AP off treatment	1.01	2.99	n/a	n/a
BP	0.35	n/a	0.35	n/a
Total	[redacted]	[redacted]	**1.37**	**3.02**
Discounted QALYs				
AP on treatment	[redacted]	[redacted]	0.72	1.96
AP off treatment	0.68	1.83	n/a	n/a
BP	0.16	n/a	0.18	n/a
Total	[redacted]	[redacted]	**0.90**	**1.96**
Discounted costs				
AP on treatment	[redacted]	[redacted]	£15,117	£172,572
AP off treatment	£14,129	£161,294	n/a	n/a
BP	£4,808	n/a	£5,144	n/a
Palliative care	£5,437	£5,160	£5,817	£5,520
Adverse events	£506	£506	n/a	n/a
Total	[redacted]	[redacted]	**£26,078**	**£178,093**

6.2.3 Derivation of PenTAG BP base case

Table 84 shows the derivation of the PenTAG BP base case. In both the Pfizer base case and PenTAG base case (Bosutinib, HU) is less costly and less effective than SCT.

Table 84. Derivation of PenTAG base case BP CML

	Intervention	(Bosutinib, HU) vs.		(Bosutinib, SCT) vs.	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

As in the AP model, the only change is the introduction of the cumulative survival method. This results in the additional intervention arm (Bosutinib, SCT). The PenTAG base case ICERs for (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT are [redacted] and [redacted] per QALY

respectively. The ICER for (Bosutinib, HU) versus HU is increased from [redacted] per QALY in the Pfizer model because costs and QALYs are reduced in this arm but QALYs are more heavily reduced.

The mean time on each treatment for each treatment arm in the PenTAG BP base case is shown in Figure 42, which demonstrates that bosutinib provides an extra [redacted] life years.

Figure 42.

[redacted]

The PenTAG base case cost-effectiveness plane is shown in Figure 43, and demonstrates that bosutinib provides an extra [redacted] QALYs for an extra cost of around [redacted]. The SCT arms give approximately [redacted] extra QALY at an extra cost of approximately [redacted].

Figure 44 shows a comparison of the Pfizer and PenTAG BP base cases in the cost-effectiveness plane and demonstrate that the PenTAG base case introduces the (Bosutinib, SCT) arm and reduces the costs and QALYs of the (Bosutinib, HU) arm. Further details are shown in Table 85.

Figure 43.

Figure 44.

Table 85. Life years, QALYs and costs in PenTAG BP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	SCT
Life years (undiscounted)				
BP on treatment	[redacted]	[redacted]	0.54	2.64
BP off treatment	0.54	2.64	n/a	n/a
Total	[redacted]	[redacted]	**0.54**	**2.64**
Discounted QALYs				
BP on treatment	[redacted]	[redacted]	0.28	1.28
BP off treatment	0.28	1.27	n/a	n/a
Total	[redacted]	[redacted]	**0.28**	**1.28**
Discounted costs				
BP on treatment	[redacted]	[redacted]	£8,203	£194,940
BP off treatment	£8,117	£192,892	n/a	n/a
Palliative care	£5,904	£5,528	£5,967	£5,586
Adverse events	£506	£506	n/a	n/a
Total	[redacted]	[redacted]	**£14,170**	**£200,526**

6.3 Key sensitivity analyses applied to PenTAG and Pfizer base cases

In this section we select scenario analyses which we regard as key analyses either as explorations of potentially valid alternative base cases or of uncertainty in key parameters.

6.3.1 Key sensitivity analyses CP

We conducted a number of scenario analyses on both the Pfizer base case and the PenTAG base case (see Table 86 and Table 87). Some of these were performed because they were potentially valid as base cases (e.g., 2nd-line cohort, utilities from Study 200) while others were to explore the effect of uncertainty in key parameters.

When applied to the PenTAG base case, none of the sensitivity analyses have a significant impact on the relevant ICERs of (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT; in all scenarios, (Bosutinib, HU) is not cost-effective versus HU at cost-effectiveness thresholds of £20,000 or £30,000 per QALY, and likewise for (Bosutinib, SCT) versus SCT.

When applied to the Pfizer base case, some of the sensitivity analyses have a significant impact on the ICER of (Bosutinib, HU) versus HU. In particular, if bosutinib is used in a 2nd-line cohort we predict an ICER of [redacted] per QALY using Pfizer's base case; if bosutinib is received until transformation to AP (as might be the case if bosutinib is the last available TKI for a patient) we predict an ICER of [redacted] per QALY. In these two scenarios, it is also worth noting that (Bosutinib, HU) is no longer

cost-effective versus SCT, although we feel that a more appropriate comparison is (Bosutinib, SCT) vs. SCT.

Table 86. Important scenario analyses applied to PenTAG base case for CP model

Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	[redacted]	[redacted]	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	[redacted]	[redacted]	[redacted]
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
SCT utility set to TA251 utility	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT

Table 87. Important scenario analyses applied to Pfizer base case CP model

Intervention	**(Bosutinib, HU) vs.**		
Comparator	***HU***	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]
Mean OS HU decreased from 3.5 to 1.8 years (−50%)	[redacted]	n/c	n/c
Mean OS HU increased from 3.5 to 5.2 years (+50%)	[redacted]	n/c	n/c
Mean OS for SCT decreased from 6.6 to 3.3 years (−50%)	**n/c**	[redacted]	n/c
Mean OS for SCT increased from 6.6 to 9.9 years (+50%)	**n/c**	Dominant	n/c
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]
Bosutinib and HU utility set to Study 200 utility	[redacted]	n/c	[redacted]
SCT utility set to TA251 utility	**n/c**	Dominant	n/c

n/c – Not changed from base case
Shading as in Table 86

6.3.2 Key sensitivity analyses AP

We performed two sensitivity analyses on both the PenTAG and Pfizer base cases. In the first analysis, we increased the overall survival of HU from 1.37 to [redacted] years to match the time spent in AP off bosutinib treatment in the (Bosutinib, HU) arm. In the second analysis, we used utilities from Study 200. In both the PenTAG and Pfizer base cases, these sensitivity analyses did not significantly impact on the ICERs. Using Study 200 utilities improves cost-effectiveness as the HRQL under bosutinib is improved, but the ICERs remain well above the £20,000, £30,000 and £50,000 per QALY thresholds, at [redacted] per QALY in the PenTAG and Pfizer models respectively.

Table 88. Important scenario analyses applied to PenTAG base case for AP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]
HU OS = Time in Bosutinib AP Off Treatment [redacted]	[redacted]	n/c	[redacted]	[redacted]
Study 200 utilities	[redacted]	Dominant	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 89. Important scenario analyses applied to Pfizer base case for AP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	Dominant
HU OS = Time in Bosutinib AP Off Treatment [redacted]	[redacted]	n/c
Study 200 utilities	[redacted]	Dominant

n/c – Not changed from base case
Shading as in Table 88

6.3.3 Key sensitivity analyses BP

We performed similar sensitivity analyses in the BP model as in the AP model. We found that increasing the OS of HU to match the time spent off bosutinib in the (Bosutinib, HU) arm significantly worsened cost-effectiveness in the Pfizer model but had very little effect in the PenTAG model, as expected. Use of Study 200 utilities improved cost-effectiveness, but the ICER of (Bosutinib, HU) versus HU remained high, at [redacted] per QALY in the PenTAG and Pfizer models respectively. (Bosutinib, HU) was consistently less costly and less effective than SCT, except when the Pfizer base case was adjusted for Study 200 utilities.

Table 90. Important scenario analyses applied to PenTAG base case for BP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	[redacted]	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 200 utilities	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 91. Important scenario analyses applied to Pfizer base case for BP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	n/c
Study 200 utilities	[redacted]	Dominated

n/c – Not changed from base case

[redacted]

7 END OF LIFE

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML.

We agree that there is clearly no case for CP CML because life expectancy under the comparator treatments of HU and SCT are far greater than the threshold of 2 years.

We believe that bosutinib does not meet the End of Life criteria in any phase of CML, as demonstrated in Table 92 and Table 93 below.

Table 92. End of Life criteria for bosutinib in AP

Criterion	Pfizer comments	PenTAG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Pfizer claim life expectancy is approx. 1.3 years (p103 Pfizer submission)	In summary, it seems likely that the life expectancy for patients on an appropriate comparator treatment is close to the threshold of 24 months, as follows: First, we believe that the relevant comparator for most people is HU rather than SCT. Pfizer estimate life expectancy under HU as 1.4 years and after SCT as 3.0 years. We have no alternative value for SCT. We believe that the estimate of 1.4 years for HU is based on weak evidence. Also, Pfizer estimate a mean time on HU after bosutinib of [redacted] years.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pfizer claim extension to life expectancy is approx. 1.7 years (p103 Pfizer submission)	We believe that this criterion is probably satisfied. We understand that Pfizer's base case claims extension to life of 3.1 years for (Bosutinib, HU) vs. HU and 1.5 years vs. SCT. Under our Cumulative Survival method, the extension to life is 2.3 years.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Pfizer claim patient population < 8 p.a. (p103 Pfizer submission)	We believe that this criterion is clearly satisfied. Pfizer's estimate is not unreasonable.
The estimates of the extension to life are robust and can be shown or reasonably inferred from	No discussion	We believe that this criterion is not satisfied for the numerous reasons given in Section 5.3.8.1, p165.

either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)		For example, estimates of OS are not randomised, the method of estimation of OS is not consistent across treatments, OS is estimated from very small sample sizes, and largely from people suited to TKIs (whereas they should be for people unsuited to TKIs), OS data is immature.
The assumptions used in the reference case economic modelling are plausible, objective and robust.	No discussion in relation to End of Life	This criterion is difficult to evaluate. Most assumptions for the AP model are plausible, but not robust.
Overall qualification for End of Life	**Yes**	**No**

Table 93. End of Life criteria for bosutinib in BP

Criterion	Pfizer comments	PenTAG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Pfizer claim life expectancy is approx. 0.5 years (p103 Pfizer submission)	In summary, it seems likely that this criterion is satisfied, as follows: First, we believe that the relevant comparator for most people is HU rather than SCT. Pfizer estimate life expectancy under HU as 0.5 years and after SCT as 2.6 years. We have no alternative value for SCT. We believe that the estimate of 0.5 years for HU is based on weak evidence. Also, Pfizer estimate a mean time on HU after bosutinib of [redacted] years
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pfizer claim extension to life expectancy is approx. 1.2 years (p103 Pfizer submission)	We believe that this criterion is probably satisfied. Pfizer's base case extension to life is 1.2 years for (Bosutinib, HU) vs. HU (the most relevant comparator), but (Bosutinib, HU) reduces life expectancy vs. SCT. Under our Cumulative Survival method, the extension to life is 0.6 years.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in	Pfizer claim patient population < 8 p.a. (p103 Pfizer submission)	We believe that this criterion is clearly satisfied. Pfizer's estimate is not unreasonable.

England.		
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	No discussion	We believe that this criterion is not satisfied for the same reasons given for AP (Table 92).
The assumptions used in the reference case economic modelling are plausible, objective and robust.	No discussion in relation to End of Life	This criterion is difficult to evaluate. Most assumptions for the BP model are plausible, but not robust.
Overall qualification for End of Life	**Yes**	**No**

8 IMPLICATIONS FOR RESEARCH

Research in to the following would be welcome:

- The EMA's marketing authorisation is conditional on the following trial to be conducted, with final clinical study report due 30th September 2018[29]:

  "a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options."

  We agree that this would improve our understanding of bosutinib in the unmet need population.
- However, better still would be a randomised trial of bosutinib versus the comparators HU or SCT in the unmet need population.
- More mature OS data for bosutinib in all phases, specifically for patients in the patient population appropriate to this appraisal, i.e., those after TKIs failure, unsuited to imatinib, nilotinib and dasatinib. This would allow us to test our default assumption under the Cumulative Survival method that bosutinib does not affect mortality once it is discontinued. We assume that this will be recorded from Study 200. However, a larger patient population would be welcome from the single-arm trial recommended by the EMA.
- High quality estimate of OS on HU in all phases of CML for 2nd-line patients, and also for patients in the population appropriate to this appraisal, ideally from the randomised trial we recommend above, would be useful for modelling the cost-effectiveness of bosutinib (or other new TKIs in the future) versus HU. But we understand that this data may not be collected due to ethical reasons, as HU is not a potent treatment for CML.
- Similarly for OS after SCT in CP.
- Utilities for patients after SCT.

REFERENCES

1. Cortes J, Kantarjian H, Kim DW, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib: 36-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.

2. Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:1-410.

3. Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer 2007;109:1556-60.

4. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. Haematologica 2011;96:1779-82.

5. Benedicte D, Emmanuel B, Nicole R, et al. Impact of prior second-generation tyrosine kinase inhibitors on the outcome of hematopoietic stem cell transplantation for chronic myeloid leukemia In 52nd Annual Meeting of the American Society of Hematology, 2010.

6. Bornhauser M, Kroger N, Schwerdtfeger R, et al. Allogeneic haematopoietic cell transplantation for chronic myelogenous leukaemia in the era of imatinib: a retrospective multicentre study. Eur J Haematol 2006;76:9-17.

7. Holroyd A, Philips E, Szydlo R, et al. Response to tyrosine kinase inhibitor therapy in patients undergoing allogeneic hematopoietic stem cell transplantation for advanced phase chronic myeloid leukemia, In 52nd Annual Meeting of the American Society of Hematology, 2010, 2010.

8. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. Cancer 2007;110:340-4.

9. Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after Bcr-Abl kinase mutation-related imatinib failure. Blood 2006;108:1421-3.

10. Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-7.

11. Markiewicz M, Dzierzak-Mietla M, Wisniewska-Piaty K, et al. The favorable results of allo-HSCT in TKI-resistant CML, In 53rd Annual Meeting of the American Society of Hematology, In 53rd Annual Meeting of the American Society of Hematology, 2011, 2011.

12. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-9.

13. Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-5.

14. Schleuning M, Scholten M, van Bienzen A, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia after prior treatment with nilotinib or dasatinib, In 52nd Annual Meeting of the American Society of Hematology, 2010.

15. Weisser M, Schleuning M, Haferlach C, et al. Allogeneic stem-cell transplantation provides excellent results in advanced stage chronic myeloid leukemia with major cytogenetic response to pre-transplant imatinib therapy. Leuk Lymphoma 2007;48:295-301.

16. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol 2009;62:1253-1260 e4.

17. Hoyle M, Pavey T, Ciani O, et al. Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. National Institute for Health and Clinical Excellence (NICE): Peninsula Technology Assessment Group (PenTAG), University of Exeter 2011.

18. Bhamidipati PK, Kantarjian H, Cortes J, et al. Management of imatinib-resistant patients with chronic myeloid leukemia. Ther Adv Hematol 2013;4:103-17.

19. Haematological Malignancy Research Network. Chronic myelogenous leukaemia http://www.hmrn.org/Statistics/Cancer_Info.aspx?id=1 (last accessed 13 May 2013), 2013.

20. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.

21. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-8.

22. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011;118:686-92.

23. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol 2009;27:469-71.

24. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.

25. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403-12.

26. Trask PC, Cella D, Besson N, et al. Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia. Leuk Res 2012;36:438-42.

27. Pfizer. Study 200 Clinical Study Report.

28. Khoury HJ, Gambacorti-Passerini C, Kantarjian H, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Failure with Imatinib Plus Dasatinib and/or

Nilotinib: 24-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.

29. European Medicines Agency. Assessment report: bosulif, 2013.

30. Trask PC, Cella D, Powell C, et al. Health-related quality of life in chronic myeloid leukemia. Leuk Res 2013;37:9-13.

31. Dalziel K, Round A, Stein K, et al. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess 2005;9:iii-iv, 1-146.

32. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii-x, 1-173.

33. Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions (Available from www.cochrane-handbook.org): The Cochrane Collaboration, 2011.

34. Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Healthcare, 2009.

35. Porcher R, Desseaux K. What inference for two-stage phase II trials? BMC Med Res Methodol 2012;12:117.

36. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.

37. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP, 2011.

38. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. Lancet 1995;345:1392-7.

39. Hoyle M, Rogers G, Moxham T, et al. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. Value Health 2011;14:1057-67.

40. Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:iii-xiii, 1-137.

41. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006.

42. Hawkins N, Sculpher M, Epstein D. Cost-effectiveness analysis of treatments for chronic disease: using R to incorporate time dependency of treatment response. Med Decis Making 2005;25:511-9.

43. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. Process and methods guides, 2013.

44. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 2009;113:2154-60.

45. Reed SD, Anstrom KJ, Ludmer JA, et al. Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2004;101:2574-83.

46. Dalziel K, Round A, Stein K, et al. Effectiveness and cost-effectiveness of imatinib for first-line treatment of

chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technol Assess 2004;8:iii, 1-120.

47. Department of Health. Reference costs 2011-12 (available from: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012), 2012.

48. Darbà J, Kaskens L. Análisis coste-efectividad de dasatinib frente a imatinib a dosis alta en el tratamiento de la leucemia mieloide crónica en pacientes resistentes a dosis estándar de imatinib. PharmacoEconomics Spanish Research Articles 2012;9:63-71.

49. Szabo SM, Davis C, Sidhu S, et al. Characterizing resource use and treatment costs for chronic myelogenous leukemia (CML) in the UK (UK). Value Health 2009;12:A268.

50. Taylor M, Saxby R, Davis C. Using short-term response to predict long-term outcomes in patients with imatinib-resistent or imatinib-intolerant chronic myeloid leukaemia. Value Health 2009;12:A50.

51. Taylor MJ, Saxby RC, Davis C. An Economic Evaluation of Dasatinib for the Treatment of Imatinib-Resistant Patients with Chronic Myelogenous Leukaemia. ASH Annual Meeting Abstracts 2009;114:A4535.

52. Warren E, Ward S, Gordois A, et al. Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. Clin Ther 2004;26:1924-33.

53. Curtis L. Unit Costs of Health and Social Care 2012: Personal Social Services Research Unit, 2012.

54. Addicott R, Dewar S. Improving choice at end of life: a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice programme in Lincolnshire. London: King's Fund, 2008.

55. Bagust A, Boland A, Dundar Y, et al. Erlotinib for the treatment of relapsed non-small-cell lung cancer: Liverpool Reviews and Implementation Group, 2006.

56. NHS Blood and Transplant. The future of unrelated donor stem cell transplantation in the UK (report of the UK Stem Cells Strategic Forum), 2010.

57. van Agthoven M, Groot MT, Verdonck LF, et al. Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow Transplant 2002;30:243-51.

58. Drummond MF. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1997.

59. Pastore D, Specchia G, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed acute myeloid leukemia: single-center experience. Ann Hematol 2003;82:231-5.

9 APPENDICES

9.1 Appendix A: Incident population for bosutinib treatment in England & Wales

The following table is reproduced from Table C1, p188 of Pfizer's submission.

Table C1: Estimated annual, incident population for bosutinib treatment in England and Wales

Population	Estimated incidence	Assumption	Reference
Cases of chronic myeloid leukaemia in England and Wales	631	596 people in England and 35 people in Wales diagnosed with CML in 2010. Assuming that incidence has been stable since 2010.	Office of National Statistics Cancer Statistics Registrations, England, 2010 Welsh Cancer Intelligence and Surveillance Unit, Annual Publication No. SA12/01
People with Ph+ CML and treated with a 1st-line TKI (imatinib)	599	95% of those diagnosed with CML are Ph+. All diagnosed patients are treated with a 1st-line TKI (imatinib).	Goldman, 2009 Assumption
People for whom 1st-line imatinib treatment is unsuccessful and are treated with a 2nd-line TKI	234	39% of 1st-line patients discontinued imatinib (excluding those who discontinued due to mortality or receipt of a SCT) and all are treated with a 2nd-line TKI (usually nilotinib)	Deininger, 2009 Assumption
2nd-line patients for whom current 2nd-line TKIs are inappropriate options and therefore **eligible for bosutinib at 2nd-line**	12	5% of imatinib-resistant patients from Study 200 may have been unsuitable for treatment with nilotinib and dasatinib at 2nd-line, due to the presence of mutations conferring resistance or co-morbidities	Draft EPAR
Patients for whom 2nd-line TKI treatment is unsuccessful and are treated with a 3rd-line TKI	107	48% of 2nd-line patients discontinued nilotinib due to lack of efficacy (progression) or intolerance (adverse events) and treated with a 3rd-line TKI	Kantarjian (2011)
3rd-line patients whom the remaining TKI is not an appropriate option and therefore **eligible for bosutinib at 3rd-line**	19	18% of third-line patients from Study 200 may have been unsuitable for treatment with nilotinib or dasatinib at third-line (depending on previous treatment), due to the presence of mutations conferring resistance or co-morbidities, and therefore may be eligible for bosutinib at 3rd-line.	Draft EPAR
Patients for whom all currently available TKIs have been unsuccessful at 3rd-line and are therefore **eligible for bosutinib at 4th-line**	49	56% of 3rd-line patients (nilotinib and dasatinib) discontinue treatment excluding those discontinued due to mortality or receipt of a SCT) and have therefore exhausted all TKI options currently available.	Garg (2009)
Total incident population eligible to receive bosutinib under its proposed licensed indication	**80**	**80 patients per year may be eligible for bosutinib.**	

9.2 Appendix B: Pfizer search strategy

Embase 1974 to January 18th 2013: accessed January 21st 2013

# ▲	Searches	Results
1	exp chronic myeloid leukemia/	28150
2	exp myeloid leukemia/	94931
3	chronic.mp. or exp CHRONIC DISEASE/	1137090
4	2 and 3	37637
5	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	36017
6	1 or 4 or 5	40870
7	imatinib.mp. or exp IMATINIB/	25210
8	(gleevec or glivec).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	7043
9	(STI-571 or STI571 or CGP-57148B or CGP57148B).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3450
10	imatinib mes?late.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3959
11	7 or 8 or 9 or 10	25381
12	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1825148
13	11 and 12	8632
14	((second or third or fourth) adj2 line).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18247
15	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20661

16	exp hydroxycarbamide/	18838
17	exp stem cell transplantation/	73805
18	(HSCT or SCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	16373
19	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	80164
20	(best adj2 support*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2980
21	BSC.mp.	1903
22	exp alpha interferon/	42290
23	("roferon-a" or "intron-a").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4127
24	(interferon adj2 alpha).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	58762
25	exp bosutinib/	768
26	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	785
27	13 or 14	26479
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	164462
29	exp Meta Analysis/	68526
30	((meta adj analy$) or metaanalys$).tw.	64279
31	(systematic adj (review$1 or overview$1)).tw.	49775
32	or/29-31	126912
33	cancerlit.ab.	667
34	cochrane.ab.	29194
35	embase.ab.	26182

36	(psychlit or psyclit).ab.	960
37	(psychinfo or psycinfo).ab.	6477
38	(cinahl or cinhal).ab.	8859
39	science citation index.ab.	1924
40	bids.ab.	426
41	or/33-40	44645
42	reference lists.ab.	8707
43	bibliograph$.ab.	13958
44	hand-search$.ab.	4023
45	manual search$.ab.	2311
46	relevant journals.ab.	733
47	or/42-46	26833
48	data extraction.ab.	10705
49	selection criteria.ab.	19538
50	48 or 49	28886
51	review.pt.	1927821
52	50 and 51	17160
53	letter.pt.	810639
54	editorial.pt.	423694
55	animal/	1814965
56	human/	14033665
57	55 not (55 and 56)	1358614
58	or/53-54,57	2579283

59	32 or 41 or 47 or 52	158341
60	59 not 58	152465
61	Clinical trial/	880466
62	Randomized controlled trial/	338298
63	Randomization/	60597
64	Single blind procedure/	16904
65	Double blind procedure/	115252
66	Crossover procedure/	36027
67	Placebo/	224651
68	Randomi?ed controlled trial$.tw.	83038
69	Rct.tw.	10825
70	Random allocation.tw.	1244
71	Randomly allocated.tw.	18468
72	Allocated randomly.tw.	1879
73	(allocated adj2 random).tw.	797
74	Single blind$.tw.	13248
75	Double blind$.tw.	140106
76	((treble or triple) adj blind$).tw.	322
77	Placebo$.tw.	189572
78	Prospective study/	223692
79	or/61-78	1323025
80	Case study/	18387
81	Case report.tw.	246829

82	Abstract report/ or letter/	874710
83	or/80-82	1135017
84	79 not 83	1286701
85	Clinical study/	89188
86	Case control study/	73451
87	Family study/	9857
88	Longitudinal study/	57858
89	Retrospective study/	305071
90	Prospective study/	223692
91	Randomized controlled trials/	25395
92	90 not 91	222997
93	Cohort analysis/	138791
94	(Cohort adj (study or studies)).mp.	93662
95	(Case control adj (study or studies)).tw.	66302
96	(follow up adj (study or studies)).tw.	43659
97	(observational adj (study or studies)).tw.	50576
98	(epidemiologic$ adj (study or studies)).tw.	70019
99	(cross sectional adj (study or studies)).tw.	68258
100	or/85-89,92-99	1060706
101	60 or 84 or 100	2135162
102	6 and 27 and 28 and 101	634

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed January 21st 2013

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	14336
2	exp Leukemia, Myeloid/	73716
3	exp Chronic Disease/ or chronic.mp.	866224
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	22855
5	2 and 3	21552
6	1 or 4 or 5	26689
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9340
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1329087
9	7 and 8	3386
10	((second or third or fourth) adj2 line).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	12295
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9716
12	exp Hydroxycarbamide/	6966
13	exp Hematopoietic Stem Cell Transplantation/	24548
14	(HSCT or SCT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9314
15	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	52708
16	("roferon-a" or "intron-a").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease	602

	supplementary concept, unique identifier]	
17	(interferon adj2 alpha).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	34862
18	exp Interferon-alpha/	22848
19	(best adj2 support*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1940
20	BSC.mp.	1393
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	159
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	101858
23	9 or 10	15527
24	Randomized controlled trials as Topic/	82308
25	Randomized controlled trial/	337940
26	Random allocation/	75868
27	Double blind method/	117051
28	Single blind method/	16860
29	Clinical trial/	472870
30	exp Clinical Trials as Topic/	259509
31	or/24-30	838537
32	(clinic$ adj trial$1).tw.	186641
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	118891
34	Placebos/	31156
35	Placebo$.tw.	144503
36	Randomly allocated.tw.	14961

37	(allocated adj2 random).tw.	690
38	or/32-37	374411
39	31 or 38	967127
40	Case report.tw.	185707
41	Letter/	775875
42	Historical article/	288376
43	Review of reported cases.pt.	0
44	Review, multicase.pt.	0
45	or/40-44	1239238
46	39 not 45	940466
47	Epidemiologic studies/	5506
48	exp case control studies/	577770
49	exp cohort studies/	1213923
50	Case control.tw.	66232
51	(cohort adj (study or studies)).tw.	68832
52	Cohort analy$.tw.	3047
53	(Follow up adj (study or studies)).tw.	34614
54	(observational adj (study or studies)).tw.	35931
55	Longitudinal.tw.	121664
56	Retrospective.tw.	236529
57	Cross sectional.tw.	139952
58	Cross-sectional studies/	148552
59	or/47-58	1671329

60	Meta-Analysis as Topic/	12349
61	meta analy$.tw.	47037
62	metaanaly$.tw.	1193
63	Meta-Analysis/	36590
64	(systematic adj (review$1 or overview$1)).tw.	39507
65	exp Review Literature as Topic/	6473
66	or/60-65	95085
67	cochrane.ab.	22972
68	embase.ab.	20860
69	(psychlit or psyclit).ab.	844
70	(psychinfo or psycinfo).ab.	8116
71	(cinahl or cinhal).ab.	7677
72	science citation index.ab.	1607
73	bids.ab.	331
74	cancerlit.ab.	546
75	or/67-74	38173
76	reference list$.ab.	7893
77	bibliograph$.ab.	10357
78	hand-search$.ab.	3325
79	relevant journals.ab.	572
80	manual search$.ab.	1965
81	or/76-80	21577
82	selection criteria.ab.	16585

83	data extraction.ab.	8165
84	82 or 83	23449
85	Review/	1735402
86	84 and 85	15340
87	Comment/	518398
88	Letter/	775875
89	Editorial/	318524
90	animal/	4993336
91	human/	12521330
92	90 not (90 and 91)	3656512
93	or/87-89,92	4819761
94	66 or 75 or 81 or 86	121442
95	94 not 93	113116
96	46 or 59 or 95	2475570
97	6 and 22 and 23 and 96	198

EBM Reviews - Cochrane Central Register of Controlled Trials December 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2012, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2012, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2012: accessed January 21st 2012

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ ?	243
2	exp Leukemia, Myeloid/ ?	1243

3	exp Chronic Disease/ or chronic.mp. ?	55159
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	663
5	2 and 3 ?	322
6	1 or 4 or 5 ?	711
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	398
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	66651
9	7 and 8 ?	119
10	((second or third or fourth) adj2 line).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	1784
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	602
12	exp Hydroxycarbamide/ ?	289
13	exp Hematopoietic Stem Cell Transplantation/ ?	779
14	(HSCT or SCT).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	538
15	(stem adj2 cell adj2 transplant*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	2329
16	("roferon-a" or "intron-a").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	258
17	(interferon adj2 alpha).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	4044

18	exp Interferon-alpha/ ?	2264
19	(best adj2 support*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	437
20	BSC.mp. ?	175
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	3
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ?	7700
23	9 or 10 ?	1896
24	6 and 22 and 23 ?	26

(Source: Pfizer submission, Appendix 2, p201)

9.3 Appendix C: Quality assessment tool

Chambers criteria for quality assessment of non-RCTs

Criteria used for quality assessment
1 Were selection/eligibility criteria adequately reported?
2 Was the selected population representative of that seen in normal practice?
3 Was an appropriate measure of variability reported?
4 Was loss to follow-up reported or explained?
5 Were at least 90% of those included at baseline followed-up?
6 Were patients recruited prospectively?
7 Were patients recruited consecutively?
8 Did the study report relevant prognostic factors?

Using the above criteria, a study's quality could be scored as good, satisfactory or poor; good, if the answer is 'yes' to all of criteria 1 to 8; satisfactory, if the answer is 'yes' to criteria 2 and 4-7; poor, if the answer is not 'yes' to one or more of the criteria listed for 'satisfactory'

(Source: Pfizer submission, Appendix 7, p215)

9.4 Appendix D: Eligibility criteria for Study 200

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Signed and dated informed consent prior to any protocol-specific screening procedures • Cytogenetic- or PCR- based diagnosis of any phase of Ph^+ CML or Ph^+ ALL whose disease was resistant to full-dose imatinib (≥600 mg) or was intolerant of any dose of imatinib (please see Appendix 10.14 for definitions of resistance/intolerance) • Adequate duration of prior imatinib therapy • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for CP patients and 0, 1 or 2 for advanced phase leukaemia patients • No antiproliferative or antileukaemia treatment within 7 days of the first dose of bosutinib (except hydroxycarbamide and anagrelide) • At least three months post allogeneic stem cell transplantation • Recovery to grade 0/1, or to baseline, from any toxicities of prior anticancer treatment (excluding alopecia) • Able to take daily oral capsules or tablets reliably • Adequate bone marrow function (for imatinib-resistant patients in chronic phase only) o Absolute neutrophil count (ANC) >1000/mm3 (>1 x109/L) o Platelets ≥100,000/mm3 (≥100 x 109/L) and absence of any platelet transfusions during the preceding 14 days • Adequate hepatic function o AST/ALT ≤2.5 x ULN or ≤5 x ULN if attributable to liver involvement of leukaemia o Total bilirubin ≤1.5 x ULN • Adequate renal function o Creatine ≤1.5 x ULN • Willingness to use reliable birth control (if applicable) throughout the study and 30 days after the last dose • Documented normal INR if not on oral anticoagulant therapy, or if on oral anticoagulant therapy, consistent target INR ≤3 **<u>Additional inclusion criteria specific to Study 200 populations</u>** <u>Third-line CP CML population</u> • Imatinib-resistant or imatinib-intolerant CP	• Ph negative leukaemia or Bcr-Abl negative leukaemia • Overt leptomeningeal leukaemia (free of CNS involvement for <2 months) • Extramedullary disease only • GVHD (treated or untreated) within 60 days of study start • Documented history of the T315I Bcr-Abl mutation (this criterion added as of 10th June 2008 based on lack of efficacy in this group) • Pregnant or breastfeeding • Major surgery within 14 days or radiotherapy within 7 days before the first dose of bosutinib (recovery from any previous surgery should have been completed before day 1) • History of clinically significant or uncontrolled cardiac disease including: o history of or active congestive heart failure o uncontrolled angina or hypertension within 3 months o myocardial infarction within 12 months o clinically significant ventricular arrhythmia o diagnosed or suspected congenital or acquired prolonged QT syndrome o unexplained syncope o history of prolonged corrected QT interval (QTc) • Prolonged QTc (>0.45 seconds, average of triplicate readings at screening) • Concomitant use of or need for medications known to prolong the QT interval • Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval • Recent (within 30 days of study entry) or ongoing clinically significant gastrointestinal disorder • Evidence of serious active infection, or significant medical or psychiatric illness • Known seropositivity to human immunodeficiency virus or current acute or chronic hepatitis B or hepatitis C (antigen positive), cirrhosis or clinically significant abnormal laboratory findings that would, in the investigator's judgement, make the patient inappropriate for this study

Ph+ CML also previously treated with dasatinib and/or nilotinib, to which the patient developed resistance or intolerance <u>Advanced phase CML population</u> • Advanced phase Ph+ CML previously treated with 1 or more TKIs (imatinib only or imatinib and dasatinib and/or nilotinib)	
<u>Second-line CP CML patient population</u>	
• Imatinib-resistant or imatinib-intolerant CP Ph^+ CML • QTc interval <470 msec at screening	

(Source: Pfizer submission, Table B6, p53 and Appendix 15, p 349)

9.5 Appendix E: Outcome definitions used in Study 200

Outcome	Description/details
Cytogenetic Response	At least 20 metaphases were required for post-baseline assessment. If fewer than 20 metaphases were available, fluorescence in situ hybridisation (FISH) analysis of bone marrow aspirate for the presence of Bcr-Abl fusion protein could be used, provided ≥200 cells were analysed. Cytogenetics were performed within 14 days of registration and every 3 months thereafter. After 2 years, assessments were performed every 6 months. For CP patients, disease status was assessed at baseline and every 12 weeks during the first 2 years of treatment, every 24 weeks thereafter, and at the time of treatment completion. For advanced phase patients, cytogenetic assessments were performed monthly until week 12, or until the patient's status returned to chronic phase (whichever came first) and at week 24
Major cytogenetic response (MCyR)	0%—35% Ph^+ metaphases (0%—35% positive cells by FISH) MCyR = CCyR + PCyR
Complete cytogenetic response (CCyR)	0% Ph^+ metaphases (<1% positive cells by FISH)
Partial cytogenetic response (PCyR)	1%—35% Ph^+ metaphases (1%—35% positive cells by FISH)
Minor Cytogenetic Response (MiCyR)	36%—65% Ph^+ metaphases (36%—65% positive cells by FISH)
Minimal Cytogenetic Response	66%—95% (66%—95% positive cells by FISH)
No Cytogenetic Response	>95% positive cell (>95% positive cells by FISH)
Haematological Response	Haematological responses were based upon peripheral blood assessments (complete blood count, including 5-part differential, platelet count, absolute neutrophil count), bone marrow assessments (differential, clonal evolution) and clinical assessments of extramedullary disease. Peripheral blood assessments were performed at screening, weeks 1, 2, 3, 4, 8, 12, every 12 weeks during the first 2 years of treatment, every 24 weeks beginning with the third year of treatment and at the final visit
Complete haematological response (CHR)	For a patient to be deemed to possess a CHR, they must have fulfilled all of the following haematological criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in blood • White blood cell count (WBC) ≤ institutional ULN • Platelets <450 x 10^9/L • <20% basophils in blood • No extramedullary involvement (including hepato- or

Outcome	Description/details
	splenomegaly) • Platelets ≥100 x 10^9/L (only applicable to advanced phase) • Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (only applicable to advanced phase) • ≤5% bone marrow blasts (only applicable to advanced phase)
Overall haematological response (OHR)	A patient was defined as having an OHR if they met the criteria for any one of: CHR, no evidence of leukaemia (NEL) or return to chronic phase (RCP). <u>CHR</u> See above for criteria <u>NEL</u> A patient was defined as having NEL if they met all of the following criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in the blood • WBC ≤ institutional ULN • 450 x 10^9/L> platelets ≥20 x 10^9/L • ANC ≥0.5 x 10^9/L • <20% basophils in blood • No extramedullary involvement • ≤5% bone marrow blasts (only applicable to advanced phase) <u>RCP</u> To be defined as having achieved RCP, a patient had to meet all of the below criteria, with the exception of patients with CP CML who were not required to have post-baseline bone marrow samples taken. Disappearance of features defining accelerated and blast phases, but still in chronic phase as noted by: • <15% blasts in both peripheral blood and bone marrow • <30% blasts and promyelocytes in both peripheral blood and bone marrow • <20% basophils in both peripheral blood and bone marrow • No extramedullary involvement other than liver/spleen
Major haematological response (MHR)	A patient was defined as having a MHR if they met the criteria for either a CHR or NEL (see above)
Molecular Response	Assessed with non-nested RT-PCR for the BcrAbl transcript performed at a central laboratory (Quest Diagnostics) monthly for the first 3 months, every 3 months through 2 years and every 6 months thereafter
Major molecular response (MMR)	≥ 3 log reduction from standardised baseline (baseline based upon the PCR data of 120 previously untreated CML patients) in ratio of Bcr-Abl to Abl transcripts
Complete molecular response (CMR)	Undetectable Bcr-Abl transcript, with a PCR sensitivity of ≥5 log
Progression-free survival (PFS)	Within Study 200, PFS was calculated as the time from start of bosutinib therapy to disease progression (as assessed by an investigator), treatment discontinuation due to death or death within 30 days of the last dose. For patients who were

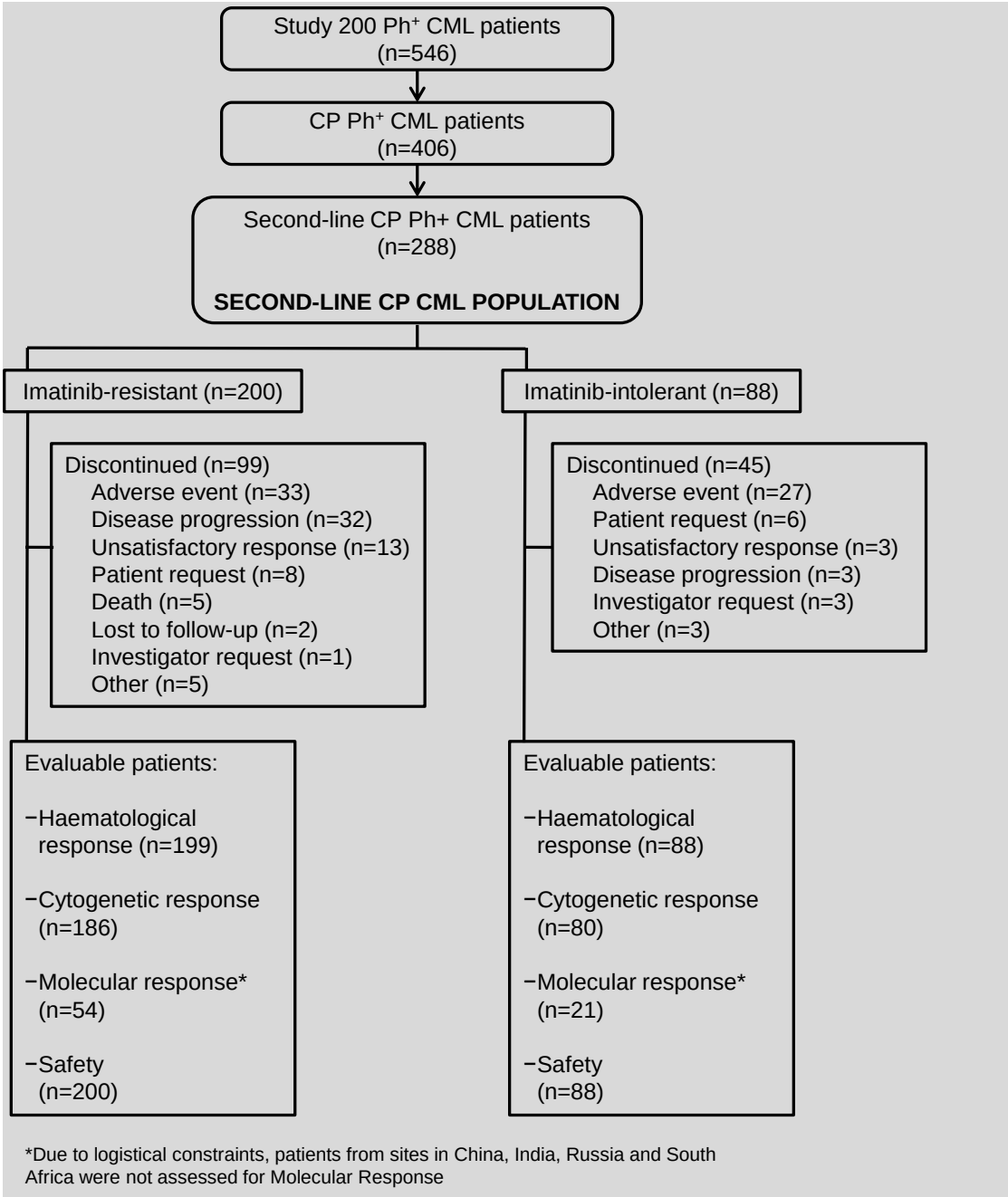
Outcome	Description/details
	last known to be alive and without progression, censoring was performed using the last date at which the patient was known to be progression free. Progression was defined by possession of any of the following criteria: • Entry in CP and clear progression to AP within the first 4 weeks of therapy (early progressor). To be considered a progressor to AP, a patient must have had an absolute increase of at least 10% in the count(s) qualifying the patient for accelerated phase • Evolution from initial CP, or from CP to which the patient returned, to AP or BP (evolution had to be measured on at least 2 consecutive assessments, at least 1 week apart) • Doubling of white blood cell count over at least 1 month with a second count >20 x 10^9/L confirmed at least 1 week later • Loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss • Loss of MCyR with an increase of ≥30% in Ph^+ metaphases
Overall survival (OS)	Overall survival was taken as the interval from the date of the first dose of bosutinib to the date of death, due to any cause. Patients who were not recorded as dead at the end of the study were censored at the last date at which they were known to be alive. The Study 200 protocol only required patients who discontinued treatment to be followed up for 24 months. It should therefore be noted that overall survival is truncated at 24 months for these patients and that this may bias the analysis with regards to this outcome
AP/BP Transformation Rate	Patients were considered to have undergone transformation if they experienced an evolution of disease from CP at study entry to AP or BP, or from AP at study entry to BP. This measure of transformation had to be present on 2 consecutive post-baseline assessments at least 1 week apart. In cases where the last haematological assessment did not confirm AP or BP status, then treatment discontinuation due to disease progression and death, or death within 30 days of last dose was considered a confirmation of transformation
FACT-Leu	The FACT-Leu is a 44-item, self-reported, reliable and valid assessment of health-related quality-of-life in patients with leukaemia. The FACT-Leu measures leukaemia specific health related quality of life and consists of 4 domains (27 items): • Physical well being (PWB) • Social well being (SWB) • Emotional well being (EWB) • Functional well being (FWB) The FACT-leu also measures a leukaemia subscale (LEUS) of additional concerns (17 items)

Outcome	Description/details
EQ-5D	EQ-5D is a patient-reported outcome which was obtained at screening, weeks 4, 8 and 12, every 12 weeks thereafter and at the end of treatment visit in countries where appropriate translations were available. EQ-5D assessments were also administered at the time of disease progression, grade 3 or 4 toxicitiy or at the time of early withdrawal. EQ-5D is a 5-item validated assessment of patient utility, consisting of: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Where each item takes an integral value from 1 (“no problems”) to 3 (“extreme problems”). The scores on these 5 items are summarised to create a single summary score. Since the questions may be answered differently in different countries/regions, for example due to different societal perspectives or customs, different weightings or tarrifs may be applied to the summary score. Study 200 EQ-5D data presented in this submission uses the UK summary score, such that the evidence is most relevant to the patient population covered in this submission i.e.patients in England and Wales. In addition, the EQ-5D has a general health visual anaolog scale (VAS): scores range from 0 to 100, where 0 is equivalent to the worst imaginable health state and 100 is equivalent to the best imaginable health state.
Adverse events (AEs)	Incidence and severity of AEs were reported at each study visit through 30 days after the last dose of bosutinib. Graded by use of the National Cancer Institute Common Terminology for Adverse Events Version 3.0[127]
Grade 3/4 adverse event	Unique clinical descriptions dictate the grading of each AE, but generally grade 3/4 AEs are considered severe (grade 3) or life-threatening or disabling (grade 4)

(Source: Pfizer submission, Appendix 14, p344)

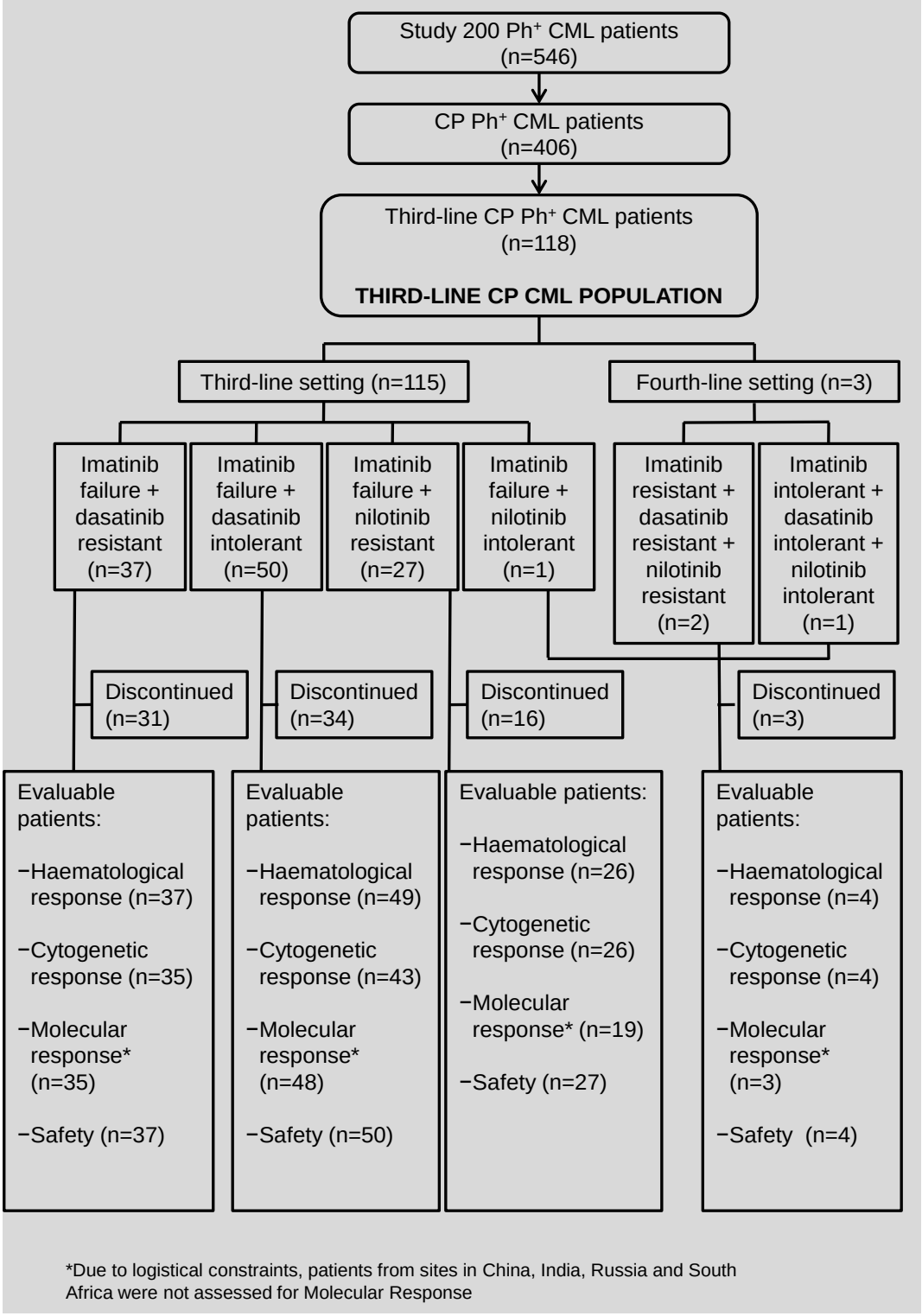
9.6 Appendix F: Participant flow diagrams

9.6.1 Participant flow for the second-line CP-CML population



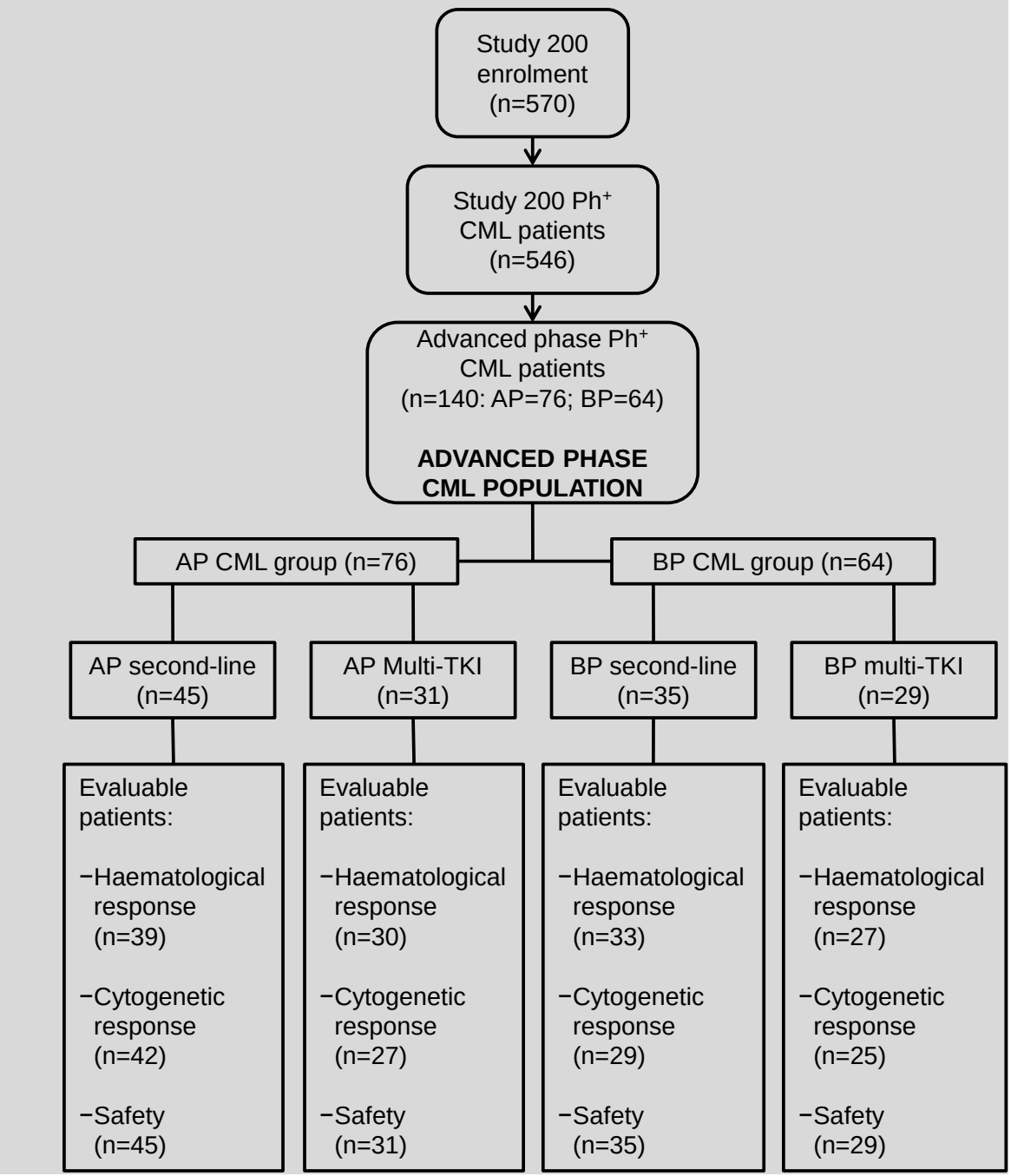
(Source: Pfizer submission, Figure B57, p352)

9.6.2 Participant flow for the third-line CP-CML population



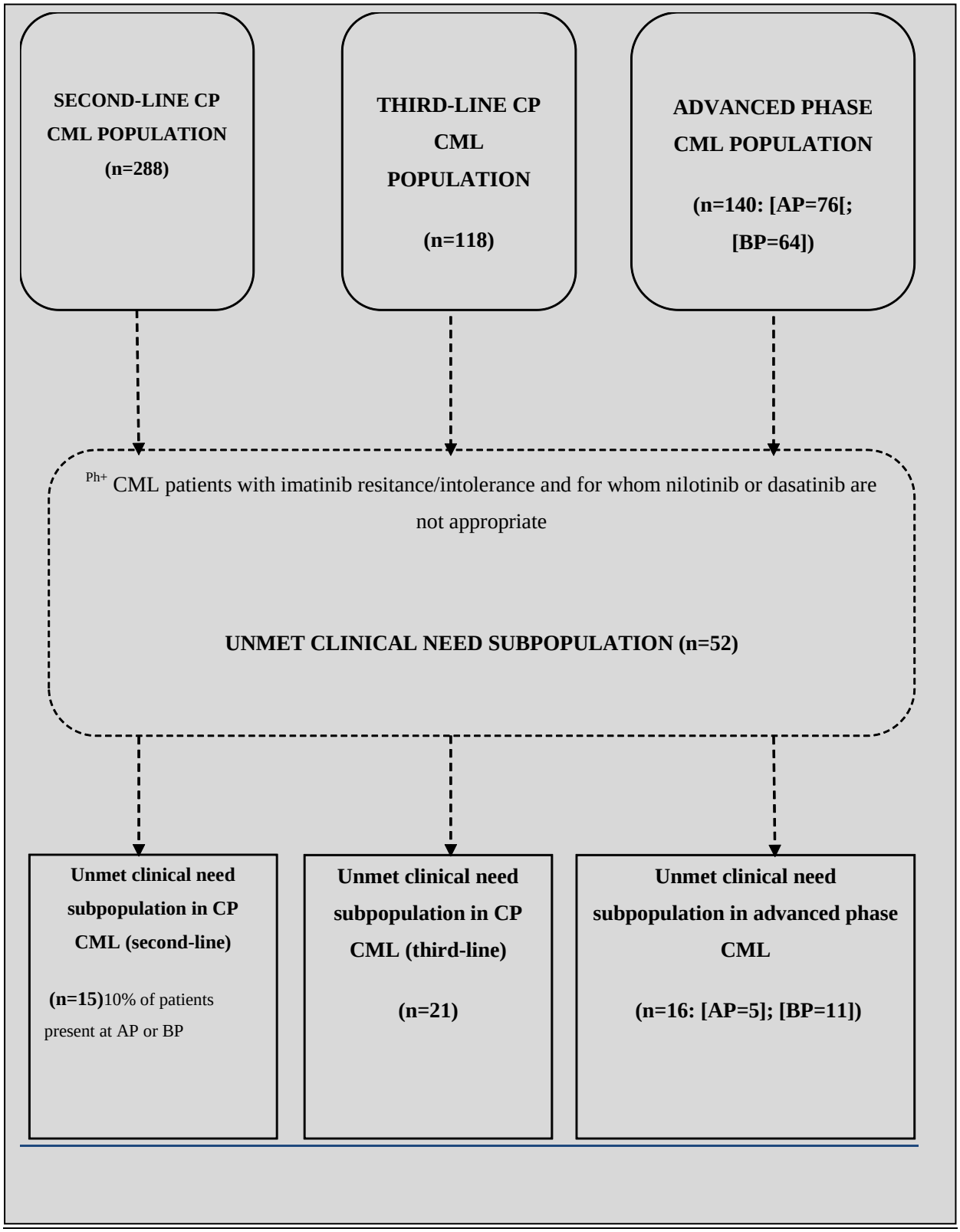
(Source: Pfizer submission, Figure B3, p60)

9.6.3 Participant flow for the advanced phases CML population



(Source: Pfizer submission, Figure B4, p61)

9.6.4 Participant flow for the unmet clinical need subpopulation



(Source: Pfizer submission, Figure B59, p362)

9.7 Appendix G: Unmet clinical need population eligibility; summary of mutations and medical conditions defining inappropriateness of nilotinib and dasatinib

	Nilotinib	**Dasatinib**
Mutation	Y253 E255 F359	F317 E255
Medical history or evidence of prior TKI intolerance	Coronary artery occlusion, coronary arterial stent insertion, arterial occlusive disease, coronary artery disease, arteriosclerosis, glucose tolerance impairment, coronary angioplasty, coronary artery bypass, hyperglycaemia, hypertriglyceridaemia, diabetes, pancreatitis	Pleural effusion, blood pressure increase, interstitial lung disease, chronic obstructive pulmonary disease, bronchitis chronic, pulmonary hypertension, pulmonary fibrosis, pulmonary oedema, emphysema, hypertension (Grade 3 or 4), cardiomyopathy, cardiac failure, ventricular failure, ventricular dysfunction, myocardial infarction., myocardial ischaemia, respiratory disorder

(Source: Pfizer submission, Table B109, p360)

9.8 Appendix H: Proportion of patients with T315I mutation at baseline

	N of patients assessed for mutations at baseline	**N of patients assessed with a T315I mutation at baseline**
CP2L	212/288 (74.6%)	9/212 (4.2%)
CP3L	83/118 (70.3%)	7/83 (8.4%)
Advanced phase	117/140 (83.6%)	15/117 (12.8%)

(Source: Pfizer response to clarification question A2)

9.9 Appendix I: Sample size calculations for Study 200

9.9.1 Sample size calculations for the second-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients resistant to imatinib and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a MCyR rate at 24 Weeks of 0.33 is of interest. Taking the interesting and uninteresting rates for MCyR rate at 24 Weeks to be p1=0.33 and p0=0.23, respectively, it was desired to test the null hypothesis of H0: p≤0.23 against the 1-sided alternative H1: p>0.23 Power calculation The hypothesis test was performed with a type I error rate of 0.05 and 80% power at p=0.33 Sample size calculation The design of the primary cohort incorporated a 4-stage group sequential design , requiring a maximum sample size of 167 evaluable patients, with a sample size of 82 expected under the null hypothesis, and a sample size of 115 expected when the true MCyR rate was p=0.33. Statistical analyses The test statistic, standardized using the empirical variance estimate, was assessed for efficacy at an overall 1-sided significance level of 0.05, and assessed for futility at an overall 1-sided significance level of 0.20. The decisions concerning stopping for efficacy or futility were based on the error spending functions at the actual number of enrolled patients at the interim analyses.
CP CML patients intolerant to imatinb and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a 73% MCyR rate at 24 Weeks was of interest. Taking the interesting and uninteresting MCyR rates at 24 Weeks to be p1=0.73 and p0=0.56, respectively, the null hypothesis H0: p ≤p0 was tested against the alternative H1: p≥p1. Sample size calculation The optimum Simon 2-stage design for alpha=0.05, beta=0.20, required a maximum of n=55 patients with 16 in the first stage. If the response rate was no greater than 9/16=0.56 at stage 1, consideration was given to early termination. The expected sample size under the null was 31.5 and probability of early termination under the null was 0.60.

(Source: Pfizer submission, Table B102, p351)

9.9.2 Sample size calculations for the third-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients previously treated with imatinib and who were resistant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.30 and p0=0.10 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=29 patients with 10 in the first stage. If the response rate was no greater than 1/10 at stage 1, consideration was given to early termination. The expected sample size under the null was 15.0 and probability of early termination under the null was 0.74.
CP CML patients previously treated with imatinib and who were intolerant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.37 and p0=0.17 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=35 patients with 12 in the first stage. If the response rate was no greater than 2/12=0.17 at stage 1, consideration was given to early termination. The expected sample size under the null was 19.7 and probability of early termination under the null was 0.67.
CP CML patients previously treated with imatinib who were resistant to nilotinib	Sample size calculation This cohort was sized using the same statistical considerations as in the dasatinib-resistant cohort, yielding a sample size of n=29 and an identical Simon 2-stage design. . Patients previously treated with imatinib who were either nilotinib intolerant or treated with both nilotinib and dasatinib were described. No testing was planned for this group.

(Source: Pfizer submission, Table B10, p58)

9.9.3 Sample size calculations for the advanced phase CML population

TKI exposure history	Statistical analysis details
Imatinib-resistant/intolerant CML patients in AP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.61 and p0=0.43 based on published nilotinib and dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=49 patients with 42 in the first stage. If the response rate was no greater than 22/42 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 42.6 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant patients in BP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.48 and p0=0.30 based on published dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=45 patients with 41 in the first stage. If the response rate was no greater than 16/41 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 41.3 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant CML patients, exposed to other TKIs	Both AP and BP patient populations fitting this description were analysed descriptively.

(Source: Pfizer submission, Table B11, p59)

9.10 Appendix J: Number of planned and enrolled patients

Subject Group Study Cohort	Planned	Expected Evaluable	Enrolled
Chronic Phase Second-line (Prior Imatinib)			
Imatinib Resistant	186	167	200
Imatinib Intolerant	61	55	88
Chronic Phase Third line (Prior Imatinib + ≥1 Additional TKI)			
IM + NI-Intolerant or IM + D and NI	Descriptively analysed – no testing planned		4
IM + D-Resistant	32	29	37
IM + D-Intolerant	39	35	50
IM + NI-Resistant	32	29	27
Advanced Leukaemia (≥1 Prior TKI)[a]			
AP CML – 2nd Line	55	49	45
BP CML – 2nd Line	50	45	35
AP/BP – Multi-TKI	Descriptively analysed – no testing planned		60

Abbreviations: AP=accelerated phase, BP=blast phase, CML=chronic myelogenous leukaemia, D=dasatinib, IM=imatinib, NA=not applicable, NI=nilotinib, Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukaemia, TKI=tyrosine kinase inhibitor

All subjects in the advanced leukaemia group received imatinib; some subjects also received at least 1 additional TKI. Date of Snapshot: 28MAR11

(Source: Pfizer response to clarification questions A4)

9.11 Appendix K: Baseline characteristics for Study 200

9.11.1 Second-line CP CML

Characteristic	Imatinib-resistant (n=200)	Imatinib-intolerant (n=88)	Total
Age, y			
Median	51.0	54.5	53.0
Range	18-86	23-91	18-91
Sex, n (%)			
Female	84 (42%)	50 (57%)	134 (47%)
Male	116 (58%)	38 (43%)	154 (53%)
Haematological analysis, 10^9/L			
White blood cell count			
Median	6.7	5.9	6.5
Range	2.1-151	2.1-160.7	2.1-151
Platelet count			
Median	261.5	202.5	237.5
Range	47-2436	48-2251	47-2436
Duration of disease, y			
Median	4.0	2.8	3.6
Range	0.1-15.1	0.1-13.6	0.1-15.1
Treatment history			
No. of previous therapies*, n (%)			
1	131 (66%)	65 (74%)	196 (68%)
2	69 (35%)	23 (26%)	92 (32%)
Previous IFN	69 (35%)	23 (26%)	92 (32%)
Previous SCT	6 (3%)	2 (2%)	8 (3%)
Features of imatinib treatment			
Duration of previous imatinib treatment, y			
Median	2.6	1.5	2.2
Range	0.4-8.8	<0.1-8.3	<0.1-8.8
Previous CHR with imatinib, n (%)	164 (82%)	55 (63%)	219 (76%)
Reason for stopping imatinib, n (%)			
Adverse event (intolerance)†	1 (1%)	86 (98%)	87 (33%)
Disease progression	163 (92%)	1 (1%)	164 (62%)
Regimen completed	7 (4%)	0 (0%)	8 (3%)
Other	7 (4%)	1 (1%)	7 (3%)
Missing‡	22	0	22
1 or more Bcr-Abl mutations detected§	57/83 (69%)	8/32 (25%)	65/115 (57%)

*Includes previous tyrosine kinase inhibitor therapies. Percentages may not total 100% because of rounding
†Patients simultaneously meeting the protocol definitions for imatinib resistance and imatinib intolerance are categorized as having imatinib resistance
‡The reason for stopping imatinib was not reported
§Total of 83 imatinib-resistant and 32 imatinib-intolerant patients assessed for mutation status at baseline
(Source: Pfizer submission, Table B101, p350)

9.11.2 Third-line CP CML

Characteristic	IM + DAS resistant (n=37)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NI (n=4)*	Total (n=118)
Median age, y (range)	54.0 (23-69)	58.0 (25-79)	52.0 (20-73)	54.5 (31-62)	56.0 (20-79)
Sex, n (%)					
Female	23 (62)	27 (54)	13 (48)	2 (50)	65 (55)
Male	14 (38)	23 (46)	14 (52)	2 (50)	53 (45)
Race, n (%)					
White	27 (73)	38 (76)	17 (63)	3 (75)	85 (72)
Asian	4 (11)	9 (18)	3 (11)	0	16 (14)
Other	6 (16)	3 (6)	7 (26)	1 (25)	17 (14)
Median duration of CML disease, y (range)	7.5 (1.2-17.6)	5.6 (0.6-18.3)	5.9 (1.2-16.3)	11.7 (2.2-11.9)	6.7 (0.6-18.3)
ECOG Performance Status, n (%)†					
0	28 (76)	31 (62)	25 (93)	2 (50)	86 (74)
1	9 (24)	18 (36)	2 (7)	2 (50)	31 (26)
Median duration of prior therapy, (range)					
Imatinib, years	2.6 (0.02-6.4)	3.3 (0.1-6.6)	2.5 (0.7-5.9)	3.0 (1.4-6.4)	2.7 (0.02-6.6)
Dasatinib, months	18.3 (1.7-47.9)	17.3 (1.1-35.7)	0	4.1 (1.3-6.9)	17.7 (1.1-47.9)
Nilotinib, months	0	0	12.7 (1.7-38.9)	5.4 (0.8-6.1)	9.2 (0.8-38.9)
Additional prior therapies, n (%)					
Interferon	25 (68)	24 (48)	10 (37)	2 (50)	61 (52)
SCT	2 (5)	5 (10)	0	2 (50)	9 (8)

IM = Imatinib; DAS = Dasatinib; NI = Nilotinib; ECOG = Eastern Cooperative Oncology Group
*Includes 3 patients who previously received all 3 inhibitors (2 DAS + NI resistant; 1 DAS + NI intolerant) and 1 patient with NI intolerance
†ECOG Performance Status at baseline was missing for 1 patient with DAS intolerance
(Source: Pfizer submission, Table B7, p54)

9.11.3 Advanced phase CML

Characteristic	**AP IM only (n=45)**	**AP Multi TKI (n=31)**	**AP Total (n=76)**	**BP IM only (n=35)**	**BP Multi TKI (n=29)**	**BP Total (n=64)**
Age, y						
Median	47.00	56.00	50. 50	37.00	53.00	48.50
Range	18.00-73.00	21.00-83.00	18.00-83.00	19.00-75.00	22.00-82.00	19.00-82.00
Sex, n (%)						
Female	21 (47)	13 (42)	34 (45)	11 (31)	12 (41)	23 (36)
Male	24 (53)	18 (58)	42 (55)	24 (69)	17 (59)	41 (64)
Race, n (%)						
Asian	15 (33)	5 (16)	20 (26)	12 (34)	2 (7)	14 (22)
Black	3 (7)	2 (6)	5 (7)	5 (14)	6 (21)	11 (17)

Characteristic	AP IM only (n=45)	AP Multi TKI (n=31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Other*	3 (7)	2 (6)	5 (7)	0	1 (3)	1 (2)
White	24 (53)	22 (71)	46 (61)	18 (51)	20 (69)	38 (59)
Duration of CML						
N	41	29	70	34	29	63
Median	3.85	8.25	5.06	1.75	5.75	3.08
Range	1.11-22.06	1.5 - 19.22	1.11-22.06	0.35 - 5.56	1.05 - 14.46	0.35-14.46
ECOG Performance Status, n (%)						
0	26 (58)	15 (48)	41 (54)	16 (46)	6 (21)	22 (34)
1	18 (40)	15 (48)	33 (43)	10 (29)	18 (62)	28 (44)
2	1 (2)	1 (3)	2 (3)	9 (26)	5 (17)	14 (22)
Number of prior therapies						
1	29 (64)	0	29 (38)	30 (86)	0	30 (47)
2	16 (36)	6 (19)	22 (29)	5 (14)	11 (38)	16 (25)
3	0	19 (61)	19 (25)	0	16 (55)	16 (25)
4	0	6 (19)	6 (8)	0	2 (7)	2 (3)
Prior interferon therapy						
No	29 (64)	9 (29)	38 (50)	30 (86)	15 (52)	45 (70)
Yes	16 (36)	22 (71)	38 (50)	5 (14)	14 (48)	19 (30)
Prior imatinib†						
Yes	45 (100)	31 (100)	76 (100)	35 (100)	29 (100)	64 (100)
Prior dasatinib†						
No	45 (100)	6 (19)	51 (67)	35 (100)	6 (21)	41 (64)
Yes	0	25 (81)	25 (33)	0	23 (79)	23 (36)
Prior nilotinib†						
No	45 (100)	16 (52)	61 (80)	35 (100)	17 (59)	52 (81)
Yes	0	15 (48)	15 (20)	0	12 (41)	12 (19)
Prior stem cell transplant						
No	41 (91)	28 (90)	69 (91)	34 (97)	26 (90)	60 (94)
Yes	4 (9)	3 (10)	7 (9)	1 (3)	3 (10)	4 (6)
Reasons for stopping imatinib						
Adverse event (intolerance)	3 (7)	6 (19)	9 (12)	5 (14)	7 (24)	12 (19)
Disease progression/ Inadequate response	41 (91)	24 (77)	65 (86)	30 (86)	22 (76)	52 (81)
Other‡	0	1 (3)	1 (1)	0	0	0
Regimen completed	1 (2)	0	1 (1)	0	0	0

IM only= only prior TKI exposure is to imatinib; Multi TKI = Multiple TKI exposure
*Race Other: Afghan (1), Hispanic (7), Turkish (1)
†If a patient received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the patient is only counted once for the respective treatment
‡Other reason for discontinuing imatinib: Unknown
(Source: Adapted from Pfizer submission, Table B8, p55 and Pfizer response to clarification questions A3)

9.12 Appendix L: Response by baseline mutation status, Study 200

9.12.1 Response by baseline mutation status in the second-line CP evaluable population (15 May 2012 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)	
		CHR	MCyR
No mutation	132	119/132 (90)	70/120 (58)
≥1 mutation	78	65/77 (84)	44/77 (57)
≥2 mutations	11	8/11 (73)	3/10 (30)
Most common individual mutations[b]			
T315I[c,d]	9	2/9 (22)	2/9 (22)
M351T	9	9/9 (100)	8/9 (89)
F359V[d]	9	8/9 (89)	4/9 (44)
G250E	6	5/6 (83)	3/5 (60)
M244V	6	6/6 (100)	3/6 (50)
L248V	5	5/5 (100)	3/5 (60)
F317L[c]	4	4/4 (100)	3/4 (75)
E255K[d]	3	0/2	2/3 (67)
Y253H[d]	2	2/2 (100)	2/2 (100)
E255V[d]	2	2/2 (100)	1/2 (50)
F311I	2	2/2 (100)	1/2 (50)
F311L	2	2/2 (100)	2/2 (100)
E355G	2	2/2 (100)	1/2 (50)
H396P	2	2/2 (100)	2/2 (100)
H396R	2	1/2 (50)	0/2

[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint
[b] Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
(Source: Pfizer submission, Table B105, p356)

9.12.2 Response by baseline mutation status in the third-line CP CML population

	17 May 2011 snapshot			15 February 2012 snapshot		
Bcr-Abl mutation status	**n**	**Cumulative response, n/n evaluable[a] (%)**		**n**	**Cumulative response, n/n evaluable[a] (%)**	
		CHR	**MCyR**		**CHR**	**MCyR**
No mutation	44	34/44 (77)	15/43 (35)	46	35/45 (78)	18/45 (40)
≥1 mutation	39	26/39 (67)	11/35 (31)	40	26/39 (67)	14/37 (38)
≥2 mutations	9	3/9 (33)	2/9 (22)	9	3/9 (33)	2/9 (22)
Most common individual mutations[b]						
F317L[c]	8	4/8 (50)	1/7 (14)	8	4/8 (50)	1/7 (14)
T315I[c,d]	7	2/7 (29)	0/6	7	2/7 (29)	1/7 (14)[e]
G250E	6	3/6 (50)	0/5	6	3/6 (50)	0/5
Y253H[d]	6	5/6 (83)	4/6 (67)	6	5/6 (83)	5/6 (83)
M244V	3	3/3 (100)	2/3 (67)	3	3/3 (100)	2/3 (67)
F359V[d]	2	0/2	1/2 (50)	3	1/3 (33)	2/3 (67)
V299L[c]	2	1/2 (50)	0/2	2	1/2 (50)	0/2
F359C[d]	2	2/2 (100)	1/2 (50)	2	1/1 (100)	1/2 (50)
F359I	2	2/2 (100)	2/2 (100)	2	2/2 (100)	2/2 (100)

[a]Evaluable patient had received ≥1 bosutinib dose and had a valid baseline disease assessment for the corresponding endpoint
[b]Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
[e]The patient with the T315I mutation at baseline who responded with a MCyR had a PCyR at baseline that was maintained at Week 12 allowing the patient to be counted as a responder. The patient discontinued treatment due to an AE around Week 24 and did not have any further cytogenetic assessments

(Source: Pfizer submission, Table B19, p71)

9.12.3 Response by baseline mutation status in the advanced phase CML population (17 May 2011 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)		
		CHR	OHR	MCyR
No mutation	52	19/49 (38.8)	23/49 (46.9)	16/43 (37.2)
≥1 mutation	65	10/59 (16.9)	21/59 (35.6)	13/55 (23.6)
Most common individual mutations[b]				
T315I[c,d]	15	0/13	1/13 (7.69)	1/13 (7.69)
F317L[c]	9	0/9	2/9 (22.2)	0/6
G250E	7	4/6 (66.7)	4/6 (66.7)	2/7 (28.6)
Y253H[d]	7	1/7 (14.3)	2/7 (28.6)	2/7 (28.6)
E255V[d]	5	0/4	0/4	1/3 (33.3)
M351T	5	2/5 (40.0)	3/5 (60.0)	1/4 (25.0)
E255K[d]	4	0/4	1/4 (25.0)	1/3 (33.3)
M244V	3	1/2 (50.0)	2/2 (100)	1/2 (50.0)
F359I	2	0/2	1/2 (50.0)	1/2 (50.0)
F359V[d]	2	0/2	1/2 (50.0)	0/2
F486S	2	1/2 (50.0)	1/2 (50.0)	2/2 (100)

[a]The evaluable population includes patients who had a valid baseline disease assessment
[b]Includes all mutations reported for ≥2 patients assessed at baseline
(Source: Pfizer submission, Table B26, p77)

9.13 Appendix M: Cytogenetic response rates, Study 200

9.13.1 Cytogenetic response rates for the second-line CP CML population

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]
Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.
(Source: Pfizer response to clarification questions A7)

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
(Source: Pfizer response to clarification questions A7)

9.13.2 Cytogenetic response rates for the third-line CP CML population

	12 months minimum follow-up 28 Mar 2011 Snapshot			24 months minimum follow up-15 February 2012 Snapshot		
Cohort	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**
Post-hoc analysis: patients who attained a response or maintained a response present at BL[c]						
IM + D resistant	35	12 (34.3) (19.1, 52.2)	6 (17.1) (6.6, 33.7)	36	12 (33.3) (18.6, 51.0)	7 (19.4) (8.2, 36.0)
IM + D intolerant	43	19 (44.2) (29.1, 60.1)	18 (41.9) (27.0, 57.9)	44	21 (47.7) (32.5, 63.3)	19 (43.2) (28.4, 59.0)
IM + NI resistant	26	9 (34.6) (17.2, 55.7)	7 (26.9) (11.6, 47.8)	26	10 (38.5) (20.2, 59.4)	7 (26.9) (11.6, 47.8)
IM + (NI + D) or IM + NI intolerant*	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)
Total	**108**	**42 (38.9) (29.7, 48.8)**	**33 (30.6) (22.1, 40.2)**	**110[d]**	**45 (40.9) (31.6, 50.7)**	**35 (31.8) (23.3, 41.4)**

Abbreviations: CI=confidence interval; CCyR= complete cytogenetic response; D=dasatinib; IM=imatinib; MCyR=major cytogenetic response; n=number of patients; NI=nilotinib; BL = baseline
*Includes 3 patients who previously received all 3 inhibitors and 1 patient with NI intolerance
[a]Evaluable patients had a baseline disease assessment
[c]Note: Percentages are based on number of patients in each analysis. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with MCYR at baseline who were allowed to maintain best response post-baseline.
[d]Includes Patients 200-060-001446 and 200-075-001612. Patient 200-075-001612 had a valid baseline cytogenetic assessment in 15FEB2012 but not 28MAR2011

(Source: Pfizer submission, adapted Table B13, p54)

9.13.3 Cytogenetic response rates for the advanced phase population

Cytogenetic response rates for the advanced phase CML population (28 Mar 2011 snapshot)

Cytogenetic response, n (%)	Accelerated phase			Blast phase		
	Second-line (n=42)	Multi-TKI (n=27)	Total (n=69)	Second-line (n=29)	Multi-TKI (n=25)	Total (n=54)
MCyR	20 (47.6)	4 (14.8)	24 (34.8)	13 (44.8)	3 (12.0)	16 (29.6)
CCyR	14 (33.3)	3 (11.1)	17 (24.6)	9 (31.0)	2 (8.0)	11 (20.4)
PCyR	6 (14.3)	1 (3.7)	7 (10.1)	4 (13.8)	1 (4.0)	5 (9.3)

(Source: Pfizer submission, Table B23, p75)

9.14 Appendix N: Haematological response rates, Study 200

9.14.1 CHR rates for the second-line CP CML population

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]
Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.
(Source: Pfizer response to clarification questions A7)

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
(Source: Pfizer response to clarification questions A7)

9.14.2 CHR rates for the third-line CP CML population

Cohort	28 Mar 2011 Snapshot n	28 Mar 2011 Snapshot CHR N (%) (95% CI)	15 February 2012 Snapshot n	15 February 2012 Snapshot CHR N (%) (95% CI)
CHR including subjects with CHR at baseline[a,b]				
IM + (NI + D) or IM + NI Intolerant	4	3 (75.0) (19.4, 99.4)	4	3 (75.0) (19.4, 99.4)
IM + D Resistant	37	23 (62.2) (44.8, 77.5)	37	23 (62.2) (44.8, 77.5)
IM + D Intolerant	49	39 (79.6) (65.7, 89.8)	49	39 (79.6) (65.7, 89.8)
IM + NI Resistant	26	20 (76.9) (56.4, 91.0)	25	19 (76.0) (54.9, 90.6)
Total	**116**	**85 (73.3) (64.3, 81.1)**	**115[c]**	**84 (73.0) (64.0, 80.9)**

Abbreviations: CHR=major hematologic response; CI=confidence interval; D=dasatinib; IM=imatinib; n=number of patients; NI=nilotinib.
[a]Analysis includes patients who have a valid baseline hematologic measurement.
[b]Subjects with CHR at baseline are eligible for response post-baseline. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with CHR at baseline who were allowed to maintain best response post-baseline.
[c]Analysis includes Patient 200-060-001446 but excludes Patients 200-093-002244 and 200-093-002246 due to missing baseline hematologic assessment in 15 February 2012

(Source: Pfizer submission, Table B14, p65)

9.14.3 CHR rates for the advanced phase CML population (28 Mar 2011 snapshot)

Haematological response, n (%) [95% CI]	Accelerated phase			Blast phase		
	Second-line (n=39)	Multi-TKI (n=30)	Total (n=69)	Second-line (n=33)	Multi-TKI (n=27)	Total (n=60)
OHR	25 (64.1) [47.2-78.8]	13 (43.3) [25.5-62.6]	38 (55.1) [42.6-67.1]	12 (36.4) [20.4-54.9]	5 (18.5) [6.3-38.1]	17 (28.3) [17.5-41.4]
MHR	21 (53.9) [37.2-69.9]	11 (36.7) [19.9-56.1]	32 (46.4) [34.3-58.8]	8 (24.2) [11.1-42.3]	3 (11.1) [2.4-29.2]	11 (18.3) [9.5-30.4]
CHR	16 (41.0) [25.6-57.9]	8 (26.7) [12.3-45.9]	24 (34.8) [23.7-47.2]	8 (24.2) [11.1-42.3]	1 (3.7) [0.1-19.0]	9 (15.0) [7.1-26.6]

(Source: Pfizer submission, Table B22, p75)

9.15 Appendix O: Overall survival, Study 200

9.15.1 OS second-line CP CML population

Kaplan-Meier Estimate of Overall Survival Chronic Phase Second-line All-treated Population, 28 March 2011 snapshot

OS, K-M estimates, % (95%CI)	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Year 1	96.8 (94.0,98.3)	95.9 (92.0,97.9)	98.8 (92.0,99.8)
Year 2	90.6 (86.5,93.5)	87.6 (82.1,91.5)	97.6 (90.9,99.4)

(Source: Pfizer response to clarification questions A7)

9.15.2 OS third-line CP CML population

K-M estimate of OS in third-line CP all-treated population

	28 March 2011 Snapshot			15 February 2012 Snapshot		
Cohort	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**
IM + (NI + D) or IM + NI Intolerant	4	N/A	N/A	4	N/A	N/A
IM + D Resistant	37	82.8 (65.6, 91.9)	75.2 (56.1, 86.9)	38	83.6 (67.0, 92.3)	77.4 (59.7, 88.0)
IM + D Intolerant	50	93.9 (82.3, 98.0)	85.4 (71,7, 92.8)	50	93.9 (82.3, 98.0)	85.4 (71.7, 92.8)
IM + NI Resistant	27	96.3 (76.5, 99.5)	91.7 (70.5, 97.9)	27	96.3 (76.5, 99.5)	92.4 (73.0, 98.1)
Total	**118**	**91.2 (84.3, 95.2)**	**82.9 (74.1, 88.9)**	**119**	**91.4 (84.6, 95.3)**	**84.0 (75.8, 89.6)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; N/A=not applicable; n=number of patients; NI=nilotinib.
a. The sample size is too small to suggest accurate estimates.
Note: One year is assumed to have 12 months.

(Source: Pfizer submission, Table B18, p70)

9.16 Appendix P: Efficacy and safety studies

Protocol number	Study design	Treatment groups	No of subjects	Demographics	Duration of treatment
Phase I/II Study 200 (NCT00261846; 3160A4-200).	Phase 1/2 open-label 2-part study in subjects with Ph+ leukemia. Part 1: dose escalation. Part 2: efficacy study at the selected Phase 2 dose. To determine safety, tolerability, MTD, PK, PD, and efficacy in subjects with chronic phase and advanced phase Ph+ leukaemias. To explore pharmacogenomic effects.	Parts 1 and 2: bosutinib 100-mg capsules or 100-mg tablets Part 1: Dose levels studied were 400, 500, and 600 mg Part 2: selected dose=500 mg.	Randomised: 571 Treated: 570 - 18 in Part 1 - 553 in Part 2		QD until disease progression, unacceptable toxicity, or withdrawal of consent.
		CP CML Second line	288	Sex: 135F/153M Mean Age (min/max): 52 (18/91) years Race, % W/B/A/O: 64/5/19/12	
		CP CML Third line	118	Sex: 65F/53M Mean Age (min/max): 54 (20/79) years Race, % W/B/A/O: 72/3/11/14	
		Advanced phase Ph+ leukaemias (AP and BP CML; Ph+ ALL)	164	Sex: 69F/95M Mean Age (min/max): 50 (18/84) years Race, % W/B/A/O: 63/11/13/13	
Phase III Study 3000 (NCT00574873; 3160A4-3000)	Phase 3 randomised open-label trial. 1/ to compare the efficacy (rate of CCyR at 1 year) of bosutinib vs imatinib in subjects with chronic phase (CP) CML. 2/ to compare MMR at 1 year, duration of CCyR, CHR, and MMR, time to transformation to	Bosutinib 500 mg QD (100-mg tablets).	Randomised: 250 Treated: 248	Sex: 101F/149M Mean Age (min/max): 47 (19/91) years Race, % W/B/A/O: 64.5/1.0/24.15/ 10.4	QD until completion of 8 years or early discontinuation due to treatment failure, unacceptable toxicity, death, or withdrawal of consent
		matinib 400 mg QD (100-mg and/or 400-mg tablets).	Randomised: 252 Treated: 251	Sex: 117F/135M Mean Age (min/max): 46 (18/89) years Race, % W/B/A/O: 65/1/23/11	

	AP and BP; to assess the population PK; to assess the comparative safety of bosutinib vs imatinib.		Total: Randomised: 502 Treated: 499	Sex: 218F/284M Mean Age (min/max): 47 (18/91) years Race, % W/B/A/O: 65/1/24/10	
Phase I/II in Japanese subjects (NCT00811070; 3160A4-2203)	Phase 1/2 open-label, continuous daily dose administration, 2-part study in subjects with Ph+ leukaemia. To determine safety, tolerability, MTD, PK, PD, and efficacy of bosutinib in Japanese subjects with Ph+ leukaemias.	Part 1: bosutinib capsules (100 mg). Part 2: bosutinib tablet (100 mg). Part 1: Starting dose of 400 mg (up to max. 600 mg). Part 2: MTD=500 mg. Continuous oral dose administration from Day 1 onwards.	Part 1 Treated: 17 Part 2 Treated: 35	Sex: 20F /32M Mean Age (min/max): 54 (78/20) years Race, %: A: 100	QD until disease progression, unacceptable toxicity, or withdrawal of consent.

Note: Table information taken from Bosulif EMA assessment report,[29] study status is as of 15 Nov 2010. A=Asian; AP=Accelerated phase; B = Black; BA =Bioavailability; BE = Bioequivalence; BID = Twice daily; BMI=Body mass index; BP = Blast phase; CCyR=Complete cytogenetic response; CHR=Complete haematologic response; CML=Chronic myelogenous leukaemia; CP=chronic phase; CYP3A=Cytochrome P450 isoenzyme 3A; DB = Double-blind; ER=estrogen receptor; erbB2=epidermal growth factor receptor 2; F = Female; FR=fast release; HRQoL=health-related quality of life; M = Male; MBC=metastatic breast cancer; MMR=Major molecular response; MTD = Maximum tolerated dose; No = Number; O=other; ORR= objective response rate; OS= overall survival; PC = Placebo-controlled; PD = Pharmacodynamic; PG = Parallel-group; PgR=progesterone receptor; Ph+ = Philadelphia chromosome positive; PK = Pharmacokinetic; PFS=progression-free survival; QD=once a day; SR=low-release; TR=target release; vs = versus; "+" = Positive (for receptors);"-" = Negative (for receptors); W = White.

9.17 Appendix Q: Treatment discontinuation and adverse effects, Study 200

9.17.1 Second-line CP CML population

Treatment discontinuation in the second-line CP CML population, 28 March 2011 snapshot

Reason for discontinued treatment[a]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Discontinued treatment, n (%)	159 (55.2)	108 (54.0)	51 (58.0)
AE	64 (22.2)	33 (16.5)	31 (35.2)
Disease progression	41 (14.2)	35 (17.5)	6 (6.8)
Lack of efficacy	21 (7.3)	17 (8.5)	4 (4.5)
Patient request	18 (6.3)	11 (5.5)	7 (8.0)
Death	5 (1.7)	5 (2.5)	0
Investigator Request	1 (0.3)	1 (0.5)	0
Lost to follow-up	2 (0.7)	2 (1.0)	0
Other[b]	7 (2.4)	4 (2.0)	3 (3.4)

(a) Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
(b) Other: For imatinib resistant: no CCyR at Week 48 (1 subject), non-compliance (1 subject), T315I mutation (1 subject), no CCyR, investigator/subject request, loss of CCyR, and increasing transcript levels (1 subject); For imatinib intolerant: transplant (2 subjects), non-compliance (1 subject).

(Source: Pfizer response to clarification questions A7)

Treatment discontinuation in the second-line CP CML population, 15 May 2012 snapshot

Reason for discontinued treatment	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Discontinued treatment, n (%)	166 (58)	109 (56)	57 (63)
AE	66 (23)	30 (15)	36 (40)
Disease progression	41 (14)	35 (18)	6 (7)
Lack of efficacy	24 (8)	19 (10)	5 (6)
Patient request	17 (6)	11 (6)	6 (7)
Death	6 (2)	6 (3)	0
Investigator Request	2 (1)	2 (1)	0
Lost to follow-up	2 (1)	2 (1)	0
Other	8 (3)	4 (2)	4 (4)

(Source: Pfizer response to clarification questions A7)

Rates of most common (≥20%) adverse events in the second-line CP CML population

AE[a], n (%)	IM-R (n=195)		IM-I (n=91)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhoea	165 (85)	18 (9)	79 (87)	10 (11)
Nausea	83 (43)	1 (1)	47 (52)	3 (3)
Rash	63 (32)	16 (8)	40 (44)	11 (12)
Vomiting	70 (36)	3 (2)	35 (39)	8 (9)
Pyrexia	57 (29)	1 (1)	16 (18)	1 (1)
Fatigue	47 (24)	1 (1)	23 (25)	2 (2)
Abdominal pain	46 (24)	2 (1)	24 (26)	2 (2)
Cough	44 (23)	0	17 (19)	0
Elevated ALT	41(21)	14 (7)	22 (24)	8 (9)
Upper abdominal pain	40 (21)	1 (1)	17 (19)	0
Elevated AST	36 (19)	7 (4)	19 (21)	5 (6)
Headache	34 (17)	0	18 (20)	0

IM-R = imatinib-resistant; IM-I = imatinib-intolerant; ALT = alanine aminotransferase; AST = aspartate aminotransferase

(Source: Pfizer submission, Table B108, p 359)

9.17.2 Third-line CP CML population

Rates of TEAEs (all grades) occurring in ≥10% and of TEAEs (grade 3/4) occurring in ≥5% of the third-line CP CML population

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
Any adverse event	118 (100)	74 (62.7)
Blood and lymphatic system disorders	58 (49.2)	35 (29.7)
Thrombocytopaenia	41 (34.7)	30 (25.4)
Neutropaenia	21 (17.8)	17 (14.4)
Anaemia	18 (15.3)	6 (5.1)
Cardiac disorders	13 (11.0)	5 (4.2)
Eye disorders	14 (11.9)	-
Gastrointestinal disorders	111 (94.1)	16 (13.6)
Diarrhoea	98 (83.1)	10 (8.5)
Nausea	56 (47.5)	-
Vomiting	46 (39.0)	-
Abdominal pain	23 (19.5)	-
Abdominal pain upper	20 (16.9)	-
Constipation	15 (12.7)	-
General disorders and administration site conditions	59 (50.0)	-
Fatigue	28 (23.7)	-
Pyrexia	18 (15.3)	-
Oedema peripheral	12 (10.2)	-
Hepatobiliary disorders	-	5 (4.2)
Infections and infestations	46 (39.0)	4 (3.4)
Injury, poisoning and procedural complications	15 (12.7)	-
Investigations	45 (38.1)	11 (9.3)
Alanine aminotransferase increased	18 (15.3)	8 (6.8)
Lipase increased	-	4 (3.4)
Aspartate aminotransferase increased	-	3 (2.5)
Metabolism and nutrition disorders	38 (32.2)	4 (3.4)
Decreased appetite	14 (11.9)	-
Musculoskeletal and connective tissue	50 (42.4)	7 (5.9)

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
disorders		
Arthralgia	17 (14.4)	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	-	4 (3.4)
Nervous system disorders	43 (36.4)	5 (4.2)
Headache	30 (25.4)	-
Dizziness	15 (12.7)	-
Psychiatric disorders	13 (11.0)	-
Respiratory, thoracic and mediastinal disorders	47 (39.8)	5 (4.2)
Cough	20 (16.9)	-
Pleural effusion	12 (10.2)	-
Skin and subcutaneous tissue disorders	59 (50.0)	8 (6.8)
Rash	34 (28.8)	5 (4.2)
Pruritus	17 (14.4)	-
Vascular disorders	12 (10.2)	-

[a]Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA)
[1]For 'All grades' adverse events, the incidence threshold of ≥10% was applied to the entire third-line CP CML population (n=118)
[1]For 'All grades' adverse events, only adverse events occurring in ≥10% of the entire third-line CP cohort (n=118)
[2] For grade 3/4 adverse events, adverse events occurring in ≥5% of any of the constituent subpopulations

(Source: Pfizer submission, Table B27, p 81)

Number (%) of Subjects Reporting ≥10% TEAEs (CP3L Safety Population) (15 Feb 2012 snapshot)

System Organ Class a Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	4 (100)	38 (100)	50 (100)	27 (100)	119 (100)
Blood and lymphatic system disorders	2 (50.0)	20 (52.6)	23 (46.0)	14 (51.9)	59 (49.6)
Thrombocytopenia	2 (50.0)	9 (23.7)	18 (36.0)	12 (44.4)	41 (34.5)
Neutropenia	1 (25.0)	8 (21.1)	7 (14.0)	7 (25.9)	23 (19.3)
Anaemia	1 (25.0)	7 (18.4)	7 (14.0)	6 (22.2)	21 (17.6)
Leukopenia	0	4 (10.5)	0	0	4 (3.4)
Cardiac disorders	0	4 (10.5)	10 (20.0)	2 (7.4)	16 (13.4)
Ear and labyrinth disorders	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Eye disorders	2 (50.0)	5 (13.2)	8 (16.0)	3 (11.1)	18 (15.1)
Eye oedema	1 (25.0)	0	0	0	1 (0.8)
Scleral haemorrhage	1 (25.0)	0	0	0	1 (0.8)
Gastrointestinal disorders	4 (100)	37 (97.4)	47 (94.0)	24 (88.9)	112 (94.1)
Diarrhoea	4 (100)	30 (78.9)	41 (82.0)	23 (85.2)	98 (82.4)
Nausea	2 (50.0)	21 (55.3)	22 (44.0)	13 (48.1)	58 (48.7)
Vomiting	0	15 (39.5)	24 (48.0)	8 (29.6)	47 (39.5)
Abdominal pain	0	6 (15.8)	12 (24.0)	6 (22.2)	24 (20.2)
Abdominal pain upper	0	8 (21.1)	8 (16.0)	4 (14.8)	20 (16.8)
Constipation	2 (50.0)	4 (10.5)	6 (12.0)	3 (11.1)	15 (12.6)
Dyspepsia	0	7 (18.4)	4 (8.0)	1 (3.7)	12 (10.1)
Flatulence	0	4 (10.5)	2 (4.0)	2 (7.4)	8 (6.7)
Toothache	1 (25.0)	2 (5.3)	2 (4.0)	0	5 (4.2)
Haemorrhoids	0	1 (2.6)	0	3 (11.1)	4 (3.4)
Gingival pain	1 (25.0)	2 (5.3)	0	0	3 (2.5)
Gastrointestinal sounds abnormal	1 (25.0)	0	1 (2.0)	0	2 (1.7)
General disorders and administration site conditions	3 (75.0)	19 (50.0)	28 (56.0)	10 (37.0)	60 (50.4)
Fatigue	3 (75.0)	8 (21.1)	14 (28.0)	3 (11.1)	28 (23.5)
Pyrexia	1 (25.0)	6 (15.8)	7 (14.0)	4 (14.8)	18 (15.1)
Oedema peripheral	1 (25.0)	1 (2.6)	5 (10.0)	4 (14.8)	11 (9.2)
Asthenia	1 (25.0)	1 (2.6)	2 (4.0)	4 (14.8)	8 (6.7)
Pain	2 (50.0)	1 (2.6)	2 (4.0)	1 (3.7)	6 (5.0)
Chest pain	1 (25.0)	0	3 (6.0)	0	4 (3.4)
Temperature intolerance	1 (25.0)	0	0	0	1 (0.8)
Hepatobiliary disorders	1 (25.0)	0	3 (6.0)	2 (7.4)	6 (5.0)
Hyperbilirubinaemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Immune system disorders	0	5 (13.2)	2 (4.0)	3 (11.1)	10 (8.4)
Infections and infestations	3 (75.0)	15 (39.5)	20 (40.0)	11 (40.7)	49 (41.2)
Nasopharyngitis	1 (25.0)	2 (5.3)	5 (10.0)	4 (14.8)	12 (10.1)

Influenza	0	4 (10.5)	3 (6.0)	3 (11.1)	10 (8.4)
Upper respiratory tract infection	2 (50.0)	2 (5.3)	5 (10.0)	0	9 (7.6)
Lower respiratory tract infection	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Respiratory tract infection viral	0	0	0	3 (11.1)	3 (2.5)
Pharyngitis	1 (25.0)	1 (2.6)	0	0	2 (1.7)
Wound infection	1 (25.0)	0	0	0	1 (0.8)
Injury, poisoning and procedural complications	1 (25.0)	6 (15.8)	8 (16.0)	0	15 (12.6)
Procedural pain	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Investigations	2 (50.0)	15 (39.5)	18 (36.0)	12 (44.4)	47 (39.5)
Alanine aminotransferase increased	1 (25.0)	7 (18.4)	5 (10.0)	6 (22.2)	19 (16.0)
Blood creatinine increased	0	4 (10.5)	4 (8.0)	3 (11.1)	11 (9.2)
Aspartate aminotransferase increased	0	2 (5.3)	3 (6.0)	5 (18.5)	10 (8.4)
Blood alkaline phosphatase increased	0	2 (5.3)	0	3 (11.1)	5 (4.2)
White blood cells urine positive	1 (25.0)	0	0	0	1 (0.8)
Metabolism and nutrition disorders	2 (50.0)	9 (23.7)	18 (36.0)	9 (33.3)	38 (31.9)
Decreased appetite	0	3 (7.9)	6 (12.0)	4 (14.8)	13 (10.9)
Hyperuricaemia	1 (25.0)	1 (2.6)	4 (8.0)	0	6 (5.0)
Hyperkalaemia	0	0	1 (2.0)	3 (11.1)	4 (3.4)
Hypophosphataemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal and connective tissue disorders	3 (75.0)	17 (44.7)	21 (42.0)	9 (33.3)	50 (42.0)
Arthralgia	0	5 (13.2)	9 (18.0)	4 (14.8)	18 (15.1)
Back pain	1 (25.0)	5 (13.2)	4 (8.0)	3 (11.1)	13 (10.9)
Bone pain	0	5 (13.2)	3 (6.0)	1 (3.7)	9 (7.6)
Pain in extremity	0	1 (2.6)	5 (10.0)	3 (11.1)	9 (7.6)
Musculoskeletal pain	0	4 (10.5)	1 (2.0)	1 (3.7)	6 (5.0)
Joint swelling	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal stiffness	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Nervous system disorders	1 (25.0)	12 (31.6)	21 (42.0)	14 (51.9)	48 (40.3)
Headache	1 (25.0)	9 (23.7)	13 (26.0)	8 (29.6)	31 (26.1)
Dizziness	1 (25.0)	5 (13.2)	8 (16.0)	3 (11.1)	17 (14.3)
Dysgeusia	1 (25.0)	0	1 (2.0)	1 (3.7)	3 (2.5)
Paraesthesia	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Neuropathy peripheral	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Sensory disturbance	1 (25.0)	0	0	0	1 (0.8)
Psychiatric disorders	1 (25.0)	2 (5.3)	9 (18.0)	1 (3.7)	13 (10.9)
Insomnia	1 (25.0)	2 (5.3)	4 (8.0)	1 (3.7)	8 (6.7)
Renal and urinary disorders	0	5 (13.2)	4 (8.0)	5 (18.5)	14 (11.8)
Reproductive system and breast disorders	0	2 (5.3)	2 (4.0)	4 (14.8)	8 (6.7)
Respiratory, thoracic and mediastinal disorders	2 (50.0)	13 (34.2)	26 (52.0)	8 (29.6)	49 (41.2)
Cough	1 (25.0)	5 (13.2)	11 (22.0)	4 (14.8)	21 (17.6)
Pleural effusion	0	2 (5.3)	11 (22.0)	1 (3.7)	14 (11.8)
Dyspnoea	0	1 (2.6)	10 (20.0)	1 (3.7)	12 (10.1)
Oropharyngeal pain	1 (25.0)	3 (7.9)	3 (6.0)	2 (7.4)	9 (7.6)
Dyspnoea exertional	1 (25.0)	1 (2.6)	3 (6.0)	0	5 (4.2)

Productive cough	0	0	5 (10.0)	0	5 (4.2)
Skin and subcutaneous tissue disorders	1 (25.0)	22 (57.9)	28 (56.0)	12 (44.4)	63 (52.9)
Rash	1 (25.0)	9 (23.7)	19 (38.0)	3 (11.1)	32 (26.9)
Pruritus	0	10 (26.3)	7 (14.0)	2 (7.4)	19 (16.0)
Dry skin	0	1 (2.6)	2 (4.0)	3 (11.1)	6 (5.0)
Alopecia	1 (25.0)	1 (2.6)	2 (4.0)	0	4 (3.4)
Skin depigmentation	1 (25.0)	0	0	0	1 (0.8)
Vascular disorders	1 (25.0)	1 (2.6)	9 (18.0)	2 (7.4)	13 (10.9)
Hypertension	0	1 (2.6)	6 (12.0)	0	7 (5.9)
Flushing	1 (25.0)	0	0	0	1 (0.8)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

(Source: Pfizer response to clarification questions A5)

Number (%) of Subjects Reporting ≥5% TEAEs Grades 3 or 4 AEs Only (CP3L Safety Population) (Data snapshot 15 Feb 2012)

System Organ Class [a] Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	1 (25.0)	22 (57.9)	38 (76.0)	15 (55.6)	76 (63.9)
Blood and lymphatic system disorders	1 (25.0)	11 (28.9)	16 (32.0)	8 (29.6)	36 (30.3)
Thrombocytopenia	0	7 (18.4)	15 (30.0)	8 (29.6)	30 (25.2)
Neutropenia	1 (25.0)	5 (13.2)	7 (14.0)	4 (14.8)	17 (14.3)
Anaemia	0	2 (5.3)	4 (8.0)	1 (3.7)	7 (5.9)
Cardiac disorders	0	1 (2.6)	7 (14.0)	0	8 (6.7)
Gastrointestinal disorders	0	7 (18.4)	7 (14.0)	2 (7.4)	16 (13.4)
Diarrhoea	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Hepatobiliary disorders	0	0	3 (6.0)	2 (7.4)	5 (4.2)
Infections and infestations	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Investigations	0	2 (5.3)	5 (10.0)	4 (14.8)	11 (9.2)
Alanine aminotransferase increased	0	1 (2.6)	3 (6.0)	4 (14.8)	8 (6.7)
Lipase increased	0	1 (2.6)	1 (2.0)	2 (7.4)	4 (3.4)
Aspartate aminotransferase increased	0	0	1 (2.0)	2 (7.4)	3 (2.5)
Metabolism and nutrition disorders	0	2 (5.3)	1 (2.0)	1 (3.7)	4 (3.4)
Musculoskeletal and connective tissue disorders	0	1 (2.6)	4 (8.0)	2 (7.4)	7 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (6.0)	1 (3.7)	4 (3.4)

Nervous system disorders	0	1 (2.6)	4 (8.0)	0	5 (4.2)
Headache	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6)	5 (10.0)	0	6 (5.0)
Pleural effusion	0	0	3 (6.0)	0	3 (2.5)
Skin and subcutaneous tissue disorders	0	2 (5.3)	6 (12.0)	0	8 (6.7)
Rash	0	0	3 (6.0)	0	3 (2.5)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the
incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject
may report two or more different adverse events within the higher level category.

(Source: Pfizer response to clarification questions A5)

9.17.3 Advanced phase CML population

Summary of adverse events for the advanced phase CML population

Event	AP IM only (n=45)	AP Multi TKI (n-31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Any TEAE	45 (100)	31 (100)	76 (100)	34 (97.1)	29 (100)	63 (98.4)
TEAEs related to study drug	45 (100)	30 (96.8)	75 (98.7)	34 (97.1)	26 (89.7)	60 (93.8)
Grade 3 or 4 TEAEs	36 (80)	30 (96.8)	66 (86.8)	26 (74.3)	23 (79.3)	49 (76.6)
Grade 3 or 4 TEAEs related to study drug	25 (55.6)	22 (71)	47 (61.8)	19 (54.3)	15 (51.7)	34 (53.1)
SAEs	23 (51.1)	18 (58.1)	41 (53.9)	18 (51.4)	17 (58.6)	35 (54.7)
TEAEs leading to discontinuation	10 (22.2)	8 (25.8)	18 (23.7)	1 (2.9)	5 (17.2)	6 (9.4)
TEAEs leading to dose reduction	17 (37.8)	14 (45.2)	31 (40.8)	11 (31.4)	6 (20.7)	17 (26.6)
TEAEs leading to dose delay	23 (51.1)	21 (67.7)	44 (57.9)	17 (48.6)	11 (37.9)	28 (43.8)

(Source: Pfizer response to clarification questions A6)

Rates of most common (≥10%) treatment-emergent adverse events in the advanced phase CML population

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	76 (100)	45(100)	31(100)	63 (98.4)	34 (97.1)	29 (100)
Blood and lymphatic system disorders	56 (73.7)	32 (71.1)	24 (77.4)	35 (54.7)	19 (54.3)	16 (55.2)
Anaemia	32 (42.1)	15 (33.3)	17 (54.8)	18 (28.1)	10 (28.6)	8 (27.6)
Thrombocytopaenia	32 (42.1)	16 (35.6)	16 (51.6)	18 (28.1)	9 (25.7)	9 (31.0)
Neutropaenia	12 (15.8)	4 (8.9)	8 (25.8)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	3 (4.7)	3 (8.6) 0	0
Leukopenia	6 (7.9)	3 (6.7)	3 (9.7)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	6 (7.9)	4 (8.9)	2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Cardiac disorders	14 (18.4)	7 (15.6)	7 (22.6)	8 (12.5)	5 (14.3)	3 (10.3)
Eye disorders	15 (19.7)	7 (15.6)	8 (25.8)	8 (12.5)	6 (17.1)	2 (6.9)
Gastrointestinal disorders	72 (94.7)	42 (93.3)	30 (96.8)	53 (82.8)	28 (80.0)	25 (86.2)
Diarrhoea	65 (85.5)	38 (84.4)	27 (87.1)	42 (65.6)	23 (65.7)	19 (65.5)
Nausea	34 (44.7)	17 (37.8)	17 (54.8)	32 (50.0)	18 (51.4)	14 (48.3)
Vomiting	34 (44.7)	23 (51.1)	11 (35.5)	25 (39.1)	11 (31.4)	14 (48.3)
Abdominal pain	20 (26.3)	16 (35.6)	4 (12.9)	11 (17.2)	9 (25.7)	2 (6.9)
Abdominal pain upper	10 (13.2)	7 (15.6)	3 (9.7)	5 (7.8)	2 (5.7)	3 (10.3)
Constipation	13 (17.1)	8 (17.8)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
General disorders and administration site conditions	47 (61.8)	24 (53.3)	23 (74.2)	41 (64.1)	23 (65.7)	18 (62.1)
Pyrexia	28 (36.8)	16 (35.6)	12 (38.7)	22 (34.4)	16 (45.7)	6 (20.7)
Fatigue	15 (19.7)	3 (6.7)	12 (38.7)	12 (18.8)	5 (14.3)	7 (24.1)
Asthenia	10 (13.2)	6 (13.3)	4 (12.9)	4 (6.3)	4 (11.4)	0
General physical health deterioration	1 (1.3)	0	1 (3.2)	3 (4.7)	0	3 (10.3)
Oedema peripheral	3 (6.7)	4 (12.9)	7 (9.2)	0	4 (13.8)	4 (6.3)
Hepatobiliary disorders	5 (6.6)	3 (6.7)	2 (6.5)	4 (6.3)	4 (11.4)	0
Hyperbilirubinaemia	-	-	-	-	-	-
Infections and infestations	42 (55.3)	23 (51.1)	19 (61.3)	34 (53.1)	19 (54.3)	15 (51.7)
Pneumonia	8 (10.5)	4 (8.9)	4 (12.9)	10 (15.6)	4 (11.4)	6 (20.7)
Sepsis	-	-	-	-	-	-
Upper respiratory tract infection	8 (10.5)	6 (13.3)	2 (6.5)	2 (3.1)	1 (2.9)	1 (3.4)
Investigations	38 (50.0)	20 (44.4)	18 (58.1)	31 (48.4)	18 (51.4)	13 (44.8)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	10 (13.2)	5 (11.1)	5 (16.1)	4 (6.3)	4 (11.4)	0
Neutrophil count decreased	-	-	-	-	-	-
Aspartate aminotransferase increased	11 (14.5)	7 (15.6)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Lipase increased	-	-	-	-	-	-
Metabolism and nutrition disorders	27 (35.5)	17 (37.8)	10 (32.3)	22 (34.4)	11 (31.4)	11 (37.9)
Decreased appetite	6 (7.9)	4 (8.9)	2 (6.5)	12 (18.8)	5 (14.3)	7 (24.1)
Hypokalaemia	2 (2.6)	0	0 2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Hypophosphataemia	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	26 (34.2)	18 (40.0)	8 (25.8)	24 (37.5)	13 (37.1)	11 (37.9)
Arthralgia	10 (13.2)	8 (17.8)	2 (6.5)	7 (10.9)	6 (17.1)	1 (3.4)
Pain in extremity	10 (13.2)	7 (15.6)	3 (9.7)	6 (9.4)	4 (11.4)	2 (6.9)
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	11 (14.5)	6 (13.3)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
Blast crisis in myelogenous leukaemia	-	-	-	-	-	-
Nervous system disorders	24 (31.6)	14 (31.1)	10 (32.3)	26 (40.6)	16 (45.7)	10 (34.5)
Headache	12 (15.8)	9 (20.0)	3 (9.7)	13 (20.3)	9 (25.7)	4 (13.8)
Dizziness	8 (10.5)	4 (8.9)	4 (12.9)	9 (14.1)	6 (17.1)	3 (10.3)
Psychiatric disorders	16 (21.1)	6 (13.3)	10 (32.3)	11 (17.2)	6 (17.1)	5 (17.2)
Renal and urinary disorders	11 (14.5)	5 (11.1)	6 (19.4)	8 (12.5)	5 (14.3)	3 (10.3)
Renal failure acute	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	35 (46.1)	19 (42.2)	16 (51.6)	23 (35.9)	14 (40.0)	9 (31.0)
Dyspnoea	14 (18.4)	8 (17.8)	6 (19.4)	12 (18.8)	7 (20.0)	5 (17.2)
Cough	13 (28.9)	8 (25.8)	21 (27.6)	6 (17.1)	3 (10.3)	9 (14.1)
Oropharyngeal pain	8 (10.5)	4 (8.9)	4 (12.9)	2 (3.1)	1 (2.9)	1 (3.4)
Pleural effusion	9 (11.8)	5 (11.1)	4 (12.9)	4 (6.3)	2 (5.7)	2 (6.9)
Skin and subcutaneous tissue disorders	42 (55.3)	25 (55.6)	17 (54.8)	30 (46.9)	17 (48.6)	13 (44.8)
Rash	25 (32.9)	16 (35.6)	9 (29.0)	20 (31.3)	10 (28.6)	10 (34.5)
Vascular disorders	11 (14.5)	4 (8.9)	7 (22.6)	7 (10.9)	7 (20.0)	0
Hypertension	7 (9.2)	3 (6.7)	4 (12.9)	2 (3.1)	2 (5.7)	0

(Source: Pfizer response to clarification questions A6)

Rates of TEAEs (grade 3/4) occurring in ≥5% of the advanced phase populations

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	66 (86.8)	36 (80.0)	30 (96.8)	49 (76.7)	26 (74.3)	23 (79.3)
Blood and lymphatic system disorders	42 (55.3)	20 (44.4)	22 (71.0)	29 (45.3)	18 (51.4)	11 (37.9)
Anaemia	23 (30.3)	11 (24.4)	12 (38.7)	12 (18.8)	7 (20.0)	5 (17.2)
Thrombocytopaenia	25 (32.9)	11 (24.4)	14 (45.2)	17 (26.6)	9 (25.7)	8 (27.6)
Neutropaenia	11 (14.5)	4 (8.9)	7 (22.6)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Leukopenia	3 (3.9)	1 (2.2)	2 (6.5)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	3 (3.9)	2 (4.4)	1 (3.2)	2 (3.1)	0	2 (6.9)
Cardiac disorders	5 (6.6)	3 (6.7)	2 (6.5)	3 (4.7)	1 (2.9)	2 (6.9)
Eye disorders	0	0	0	3 (4.7)	1 (2.9)	2 (6.9)
Gastrointestinal disorders	14 (18.4)	7 (15.6)	7 (22.6)	14 (21.9)	5 (14.3)	9 (31.0)
Diarrhoea	3 (3.9)	1 (2.2)	2 (6.5)	4 (6.3)	2 (5.7)	2 (6.9)
Nausea	-	-	-	-	-	-
Vomiting	3 (3.9)	1 (2.2)	2 (6.5)	2 (3.1)	0	2 (6.9)
Abdominal pain	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Abdominal pain upper	-	-	-	-	-	-
Constipation	-	-	-	-	-	-
General disorders and administration site conditions	7 (9.2)	1 (2.2)	6 (19.4)	10 (15.6)	4 (11.4)	6 (20.7)
Pyrexia	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Fatigue	3 (3.9)	0	3 (9.7)	2 (3.1)	0	2 (6.9)
Asthenia	-	-	-	-	-	-
General physical health deterioration	0	0	0	2 (3.1)	0	2 (6.9)
Hepatobiliary disorders	2 (2.6)	1 (2.2)	1 (3.2)	3 (4.7)	3 (8.6)	0
Hyperbilirubinaemia	0	0	0	3 (4.7)	3 (8.6)	0
Infections and infestations	12 (15.8)	5 (11.1)	7 (22.6)	14 (21.9)	4 (11.4)	10 (34.5)
Pneumonia	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	1 (2.9)	3 (10.3)
Sepsis	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9) 0	1 (2.9) 0
Upper respiratory tract infection	-	-	-	-	-	-
Investigations	14 (18.4)	8 (17.8)	6 (19.4)	11 (17.2)	5 (14.3)	6 (20.7)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	6 (7.9)	3 (6.7)	3 (9.7)	1 (1.6)	1 (2.9)	0
Neutrophil count decreased	1 (1.3)	1 (2.2)	0	0	0	0
Aspartate aminotransferase increased	4 (5.3)	3 (6.7)	1 (3.2)	0	0	0

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Lipase increased	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Metabolism and nutrition disorders	9 (11.8)	4 (8.9)	5 (16.1)	7 (10.9)	3 (8.6)	4 (13.8)
Decreased appetite	-	-	-	-	-	-
Hypokalaemia	1 (1.3)	0	1 (3.2)	3 (4.7)	1 (2.9)	2 (6.9)
Hypophosphataemia	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9)	0
Musculoskeletal and connective tissue disorders	4 (5.3)	3 (6.7)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Arthralgia	-	-	-	-	-	-
Pain in extremity	-	-	-	-	-	-
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)
Blast crisis in myelogenous leukaemia	2 (2.6)	0	0 2 (6.5)	1 (1.6)	1 (2.9)	0
Nervous system disorders	4 (5.3)	1 (2.2)	3 (9.7)	6 (9.4)	2 (5.7)	4 (13.8)
Headache	2 (2.6)	1 (2.2)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Dizziness	-	-	-	-	-	-
Psychiatric disorders	1 (1.3)	0	1 (3.2)	2 (3.1)	0	2 (6.9)
Renal and urinary disorders	1 (1.3)	0	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Renal failure acute	0	0	0	2 (3.1)	2 (5.7)	0
Respiratory, thoracic and mediastinal disorders	8 (10.5)	3 (6.7)	5 (16.1)	6 (9.4)	4 (11.4)	2 (6.9)
Dyspnoea	6 (7.9)	2 (4.4)	4 (12.9)	2 (3.1)	2 (5.7)	0
Cough	-	-	-	-	-	-
Pleural effusion	4 (5.3)	1 (2.2)	3 (9.7)	2 (3.1)	1 (2.9)	1 (3.4)
Skin and subcutaneous tissue disorders	3 (3.9)	3 (6.7)	0	5 (7.8)	2 (5.7)	3 (10.3)
Rash	3 (3.9)	3 (6.7)	0	2 (3.1)	1 (2.9)	1 (3.4)
Vascular disorders	5 (6.6)	1 (2.2)	4 (12.9)	1 (1.6)	1 (2.9)	0
Hypertension	4 (5.3)	1 (2.2)	3 (9.7)	1 (1.6)	1 (2.9)	0

(Source: Pfizer response to clarification questions A6)

9.17.4 Post-hoc analyses of patients with unmet clinical need

Incidence rates of adverse events by type for the unmet clinical need subpopulation

Event	CP (second-line) (n=15)	CP (third line) (n=21)	Total CP CML (n=36)	AP CML (n=5)	BP CML (n=11)	Total advanced phase CML (n=16)	Total subpopulation of unmet clinical need (n=52)
Any TEAE (N, %)	15 (100)	21 (100)	36 (100)	5 (100)	11 (100)	16 (100)	52 (100)
Grade 3 or 4 TEAEs (N, %)	11 (73.3)	12 (57.1)	23 (63.9)	5 (100)	8 (72.7)	13 (81.3)	36 (69.2)
TEAEs leading to discont. (N, %)	4 (26.7)	5 (23.8)	9 (25.0)	1 (20)	3 (27.3)	4 (25.0)	13 (25)
SAEs (N, %)	6 (40.0)	10 (47.6)	16 (44.4)	4 (80.0)	8 (72.7)	12 (75.0)	28 (53.8)

(Source: Pfizer submission, Table B110, p 365)

9.17.5 Study 3000, number (%) of subjects experiencing drug related treatment-emergent adverse events with an incidence of ≥5%

	Treatment		
System Organ Class Preferred Term	**Bosutinib N=248**	**Imatinib N=251**	**Total N=499**
ANY ADVERSE EVENT	227 (91.5)	218 (86.9)	445 (89.2)
Blood and lymphatic system disorders	94 (37.9)	118 (47.0)	212 (42.5)
Thrombocytopenia	65 (26.2)	67 (26.7)	132 (26.5)
Neutropenia	29 (11.7)	65 (25.9)	94 (18.8)
Anaemia	37 (14.9)	45 (17.9)	82 (16.4)
Leukopenia	21 (8.5)	50 (19.9)	71 (14.2)
Eye disorders	8 (3.2)	34 (13.5)	42 (8.4)
Eyelid oedema	2 (0.8)	18 (7.2)	20 (4.0)
Gastrointestinal disorders	181 (73.0)	106 (42.2)	287 (57.5)
Diarrhoea	163 (65.7)	45 (17.9)	208 (41.7)
Nausea	66 (26.6)	81 (32.3)	147 (29.5)
Vomiting	61 (24.6)	22 (8.8)	83 (16.6)
Abdominal pain upper	24 (9.7)	10 (4.0)	34 (6.8)
Abdominal pain	21 (8.5)	7 (2.8)	28 (5.6)
General disorders and administration site conditions	54 (21.8)	68 (27.1)	122 (24.4)
Fatigue	22 (8.9)	22 (8.8)	44 (8.8)
Oedema peripheral	4 (1.6)	21 (8.4)	25 (5.0)
Investigations	123 (49.6)	75 (29.9)	198 (39.7)
Alanine aminotransferase increased	73 (29.4)	14 (5.6)	87 (17.4)
Aspartate aminotransferase increased	59 (23.8)	12 (4.8)	71 (14.2)
Lipase increased	25 (10.1)	20 (8.0)	45 (9.0)
Blood creatine phosphokinase increased	10 (4.0)	22 (8.8)	32 (6.4)
Blood alkaline phosphatase increased	14 (5.6)	9 (3.6)	23 (4.6)
Gamma-glutamyltransferase increased	14(5.6)	1 (0.4)	15 (3.0)
Metabolism and nutrition disorders	39 (15.7)	43 (17.1)	82 (16.4)
Hypophosphataemia	12 (4.8)	25 (10.0)	37 (7.4)
Decreased appetite	19 (7.7)	3 (1.2)	22 (4.4)
Musculoskeletal and connective tissue disorders	19 (7.7)	80 (31.9)	99 (19.8)
Muscle spasms	1 (0.4)	44 (17.5)	45 (9.0)
Myalgia	6 (2.4)	21 (8.4)	27 (5.4)
Bone pain	2 (0.8)	16 (6.4)	18 (3.6)
Nervous system disorders	34 (13.7)	18 (7.2)	52 (10.4)
Headache	13 (5.2)	6 (2.4)	19 (3.8)
Skin and subcutaneous tissue disorders	80 (32.3)	69 (27.5)	149 (29.9)
Rash	45 (18.1)	28 (11.2)	73 (14.6)
Periorbital oedema	0	34 (13.5)	34 (6.8)
System organ class totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same system organ class. Date of snapshot: 31AUG2010			

(Source: Pfizer response to clarification questions A1)

9.18 Appendix R: Detailed results of probabilistic sensitivity analyses

This section details results of the probabilistic sensitivity analyses which were not felt important enough to include in the main report.

9.18.1 CP model results

Figure 45. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer clarification, Figure 9, p30)

Figure 46. Cost-effectiveness acceptability curve, all strategies (note dotted line is interferon)

(Source: Pfizer clarification, Figure 10, p30)

Figure 47. Pairwise comparison of hydroxycarbamide and bosutinib in PSA (incremental costs and QALYs of bosutinib versus hydroxycarbamide)

(Source: Pfizer clarification, Figure 11, p31)

9.18.2 AP model results

Figure 48. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer submission, Section 7.6.8, p171)

Figure 49. Cost-effectiveness acceptability curve, all strategies

(Source: Pfizer submission, Section 7.6.8, p171)

Figure 50. Pairwise comparison of hydroxycarbamide and bosutinib intervention

(Source: Pfizer submission, Section 7.6.8, p172)

9.18.3 BP model results

Figure 51. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer submission, Section 7.7.8, p181)

Figure 52. Cost-effectiveness acceptability curve, all strategies

(Source: Pfizer submission, Section 7.7.8, p182)

Figure 53. Pairwise comparison of bosutinib versus hydroxycarbamide

(Source: Pfizer submission, Section 7.7.8, p182)

9.19 Appendix S: Shortcomings in Pfizer's analysis with minimal effect on cost-effectiveness

Here, we discuss three aspects of Pfizer's model with which we agree. We do not adjust the model for our base case analysis because, when corrected, the cost-effectiveness of bosutinib changes only incrementally.

9.19.1 Death from non-CML causes

We believe that death due to all-cause mortality (in fact, due to non-CML mortality) for bosutinib patients is not correctly incorporated in the Pfizer model. The Pfizer report states that all-cause mortality is incorporated using the following method (except for bosutinib in CP model):

1. Overall survival is initially estimated by extrapolating from trial data
2. Background mortality already incorporated in the overall survival from the MCyR surrogate method is removed by "subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200)"
3. Age-appropriate background mortality is incorporated by "adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012)"

This contrasts with the method used by PenTAG in TA241[2] in which CML and non-CML mortality were jointly calibrated to OS in Jabbour and colleagues,[44] estimating non-CML mortality from UK Life Tables. We believe this is a more consistent method of estimating CML mortality and hence overall survival, but in reality neither method is ideal as both rely on accounting for the non-CML mortality that would be experienced by an average patient, rather than the average non-CML mortality that would have been experienced by the heterogeneous population described in Jabbour and colleagues.[44] As both methods are subject to the same criticism and the same methodology is applied across all interventions hence not introducing bias, we were content to accept the general methodology, with a few further considerations.

We do not believe that simple addition and subtraction of monthly probabilities of death from survival curves is logical. Instead we believe it is appropriate to estimate hazard rates and cumulative hazard functions, which may be added and subtracted, and then use the net cumulative hazard function to calculate overall survival, as follows:

1. Overall survival is initially estimated using the MCyR surrogate method, and denoted $S_{surrogate}(t)$
2. The cumulative hazard from the MCyR surrogate method is then $\Lambda_{surrogate}(t) = -\ln S_{surrogate}(t)$

3. The cumulative hazard experienced by a patient consistently feeling the force of non-CML mortality as experienced at age 54 is calculated as $\Lambda_{Non-CML|54}(t) = \lambda_{Non-CML|54} \times t$ where $\lambda_{Non-CML|54} = -\ln(1 - q_{54})$ where q_{54} is the probability of dying before age 55 if one is alive at age 54
4. The cumulative hazard experienced by a patient due to non-CML mortality as experienced at the appropriate age is calculated as $\Lambda_{Non-CML}(t_i) = \Lambda_{Non-CML}(t_{i-1}) - \ln\big(1 - q(x_{i-1})\big) \times (t_i - t_{i-1})$ where $q(x_{i-1})$ is the probability of dying before age $x_{i-1} + 1$ if one is alive at age x_{i-1} and x_0 is the starting age (54 years)
5. The net cumulative hazard is calculated as $\Lambda_{OS}(t) = \Lambda_{surrogate}(t) - \Lambda_{Non-CML|54}(t) + \Lambda_{Non-CML}(t)$
6. The overall survival is calculated as $S_{OS}(t) = \exp\{-\Lambda_{OS}(t)\}$

Furthermore, the Pfizer model does not appear to correctly implement the method described in the Pfizer report, as it calculates the monthly probability of death as $(1 + q_x)^{\frac{1}{12}} - 1$ rather than the correct calculation of $1 - (1 - q_x)^{\frac{1}{12}}$. This results in an underestimate of the monthly probability of death, particularly in older patients where q_x is greater. Note that this is in fact irrelevant as we do not consider that a simple correction to this monthly probability calculation would result in a correct and logical overall incorporation of non-CML mortality.

In addition we do not believe that the overall survival should be adjusted according to the mean age of the third-line CP cohort in study 200, since this study does not form the basis of the overall survival estimates, which instead come from Jabbour and colleagues.[44] The mean age of patients is not reported in Jabbour and colleagues, but the median age is reported as 54 years.[44] We also do not believe that simply adjusting according to any average age is ideal as the rate of non-CML mortality is nonlinearly related to age, but in the absence of any further data demonstrating the effect of age on overall survival within Jabbour and colleagues we believe it is a suitable approximation to adjust according to the median age.

Finally we note that in the Pfizer model the age used to adjust overall survival is 56 years rather than 54 years but this has a negligible impact.

We estimate that correct incorporation of non-CML mortality results in a 0.22 year decrease in mean OS for bosutinib from the Pfizer calculation. We felt this was unlikely to result in a significant impact on cost-effectiveness and it would require substantial changes to the model, so we have not pursued further.

9.19.2 Interferon drug administration resource use

Pfizer assume that 25% of interferon patients require assistance with injecting, following the assumption made in Rogers and colleagues (2012),[2] but the model includes only one district nurse visit per cycle for those patients requiring assistance. Rogers and colleagues by contrast assume one district nurse visit per day, which we believe is appropriate. The drug administration cost for interferon per cycle is therefore equal to 25% × £39 × 30.4 = £296.77 (compared to an original cost of £9.75).

Correcting this error results in a change in the Pfizer base case CP model ICER of bosutinib versus interferon from [redacted] per QALY, although interferon continues to be dominated by hydroxycarbamide. ICERs of bosutinib versus hydroxycarbamide and SCT in the CP model are unchanged, as are ICERs in the AP and BP model. As this results in only a small change in the ICER of bosutinib versus interferon (which is not the main comparison in the decision problem as interferon is dominated by hydroxycarbamide which is more reflective of clinical practice) we do not correct this in the base case.

9.19.3 Estimation of OS for bosutinib in CP using MCyR surrogate relationship

As described in Section 5.2.6.1 (p118) Pfizer fit a single curve (denoted curve A in this section) to OS from Jabbour and colleagues (2009)[44] before fitting a weighted combination of curves (denoted curve B in this section) to an adjusted version of curve A (A'). While we are satisfied that curve A is fitted appropriately, we note that Pfizer then use equal weighting across the curve when fitting curve B to curve A', which is particularly inappropriate when the underlying OS data is immature (maximum follow-up 7.7 years) and curve A' is extrapolated for 50 years. We note however that curve B is closely fitted to A' for the first 20 years, and hence although we do not agree with the methodology we do not believe a materially different estimate of cost-effectiveness would be obtained through a more appropriate methodology.

Pfizer assumed that 35/84 = 41.7% of patients in Jabbour and colleagues (2009)[44] achieved or maintained a MCyR, whereas in TA241 it was decided that the appropriate figure was 37/84 = 44.0%.[2] Substituting this value and re-calibrating as described in the Pfizer clarifications we calculated the CP model ICER of bosutinib versus hydroxycarbamide increased marginally from [redacted] per QALY.

Pfizer's model additionally had some logical errors:

- Curve A was adjusted to curve A' by adding and subtracting monthly mortality probabilities from a survival distribution, which is not logical. The more appropriate method is very

similar to the method employed to incorporate CML and non-CML mortality as conducted by Pfizer.

- Monthly probabilities of dying from non-CML causes were incorrectly estimated from annual probabilities taken from life tables. The correct formula is $q_{monthly} = 1 - \left(1 - q_{yearly}\right)^{1/12}$ while Pfizer used $q_{monthly} = \left(1 + q_{yearly}\right)^{1/12} - 1$ which underestimates non-CML mortality.
- Different methods were now used to incorporate non-CML mortality for bosutinib and for the comparators. This inconsistency could introduce bias.

We conducted an exploratory analysis where we corrected all the logical errors, including changing the method to incorporate non-CML mortality for hydroxycarbamide to match the method used for bosutinib. The resulting ICER for bosutinib versus hydroxycarbamide was [redacted] per QALY (up marginally from [redacted] per QALY). We also investigated the joint effect of changing the MCyR rate and correcting the logical errors and obtained an ICER of [redacted] per QALY. We did not feel this was a sufficiently important change in the ICER to warrant changing the base case for the analysis.

9.20 Appendix T: Cumulative survival method for AP and BP models

9.20.1 Cumulative survival method AP

Here, we discuss the Cumulative Survival method applied to treatment starting in AP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

We assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib.

Similarly, in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

We estimate the total life years, costs and QALYs for the (Bosutinib, HU), and (Bosutinib, SCT) treatment arms.

The notation of the time components is given in Table 94 below.

Table 94. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in AP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$
BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$		

Then under the Cumulative Survival method, the component times are calculated as shown in Table 95, where S_{BOS} and d_{BOS} have the analogous meanings as described in Section 6.1.1 (p190).

Table 95. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in AP

	(Bosutinib, HU)	HU	SCT	(Bosutinib, SCT)
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
BP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			

From Pfizer's model, we estimate an upper bound for S_{BOS} as 98.9% by assuming that the only mortality whilst patients are on bosutinib treatment is due to background causes. This estimate is based on Pfizer's base case estimates of time on 3rd-line bosutinib.

d_{BOS} = 94.5% from Pfizer's model, based on Pfizer's base case estimate of time on 3rd-line bosutinib and a discount rate of 3.5% p.a.

Under the cumulative survival method, the component costs are calculated as shown in Table 96.

Table 96. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in AP

	(Bosutinib, HU)	HU	SCT	(Bosutinib, SCT)
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
BP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			

The component QALYs are calculated in exactly the same way.

9.20.2 Cumulative survival method BP

Here, we discuss the Cumulative Survival method applied to treatment starting in BP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

We assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib.

Similarly, in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

We estimate the total life years, costs and QALYs for the (Bosutinib, HU), and (Bosutinib, SCT) treatment arms.

The notation of the time components is given in Table 97 below.

Table 97. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$

Then under the Cumulative Survival method, the component times are calculated as shown in Table 98, where S_{BOS} and d_{BOS} have the analogous meanings as described in Section 6.1.1 (p190).

Table 98. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$

From Pfizer's model, we estimate an upper bound for S_{BOS} as 99.9% by assuming that the only mortality whilst patients are on bosutinib treatment is due to background causes. This estimate is based on Pfizer's base case estimates of time on 3rd-line bosutinib.

d_{BOS} = 97.9% from Pfizer's model, based on Pfizer's base case estimate of time on 3rd-line bosutinib and a discount rate of 3.5% p.a.

Under the cumulative survival method, the component costs are calculated as shown in Table 99.

Table 99. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}} d_{\mathrm{BOS}} \mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}} d_{\mathrm{BOS}} \mathrm{T}_{\mathrm{SCT}}$

The component QALYs are calculated in exactly the same way.

9.21 Appendix U: Correspondence from TA251 concerning medical management

The following text is reproduced from our document "Addendum to PenTAG report for TA251: Prepared and sent by PenTAG, 3rd November 2011".

Novartis correctly state that during chronic phase CML, alongside other monitoring test costs, we originally assumed a monthly frequency of:

0.4 visits with a nurse

0.9 visits with a haematologist/oncologist, and

0.3 bone marrow aspirations.

These figures were taken from the 2009 Oxford Outcomes survey of 6 UK-based CML clinicians (see p179 our report).

Novartis claim that this is an overestimate the frequency of outpatient visits. They claim that it is more reasonable to assume one visit per 3 to 6 months, based on current ELN guidelines. They also claim that we over-estimate the frequency of bone marrow aspirations.

We have presented Novartis' criticisms to our clinical advisor, and he agrees that we have over-estimated these quantities. He believes that it is more likely that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly. Patients on hydroxyurea would be seen about every 6 weeks. Furthermore, patients would rarely be seen by a nurse (without a consultant). Our advisor claims that clinical practice for bone marrow aspiration varies from only a single test, to tests at month 0, 3, 6, 12, 18 and 24 or until CCyR, but not after 24 months.

Given this new information and current European treatment guidelines, we have calculated revised base case cost-effectiveness estimates assuming lower medical management costs during the chronic phase. The modelling for our revised estimates now assumes:

- one visit to a haematologist/oncologist every 3 months for patients on a TKI, i.e. 0.33 visits per month.
- one visit to a haematologist/oncologist every 6 weeks for patients hydroxyurea, i.e. 0.72 visits per month.
- no outpatient nurse visits.
- no bone marrow aspirations (given that some clinicians give no repeat tests and given that for those cases when repeat aspirations are given, costs would cancel to a large extent between treatment arms).

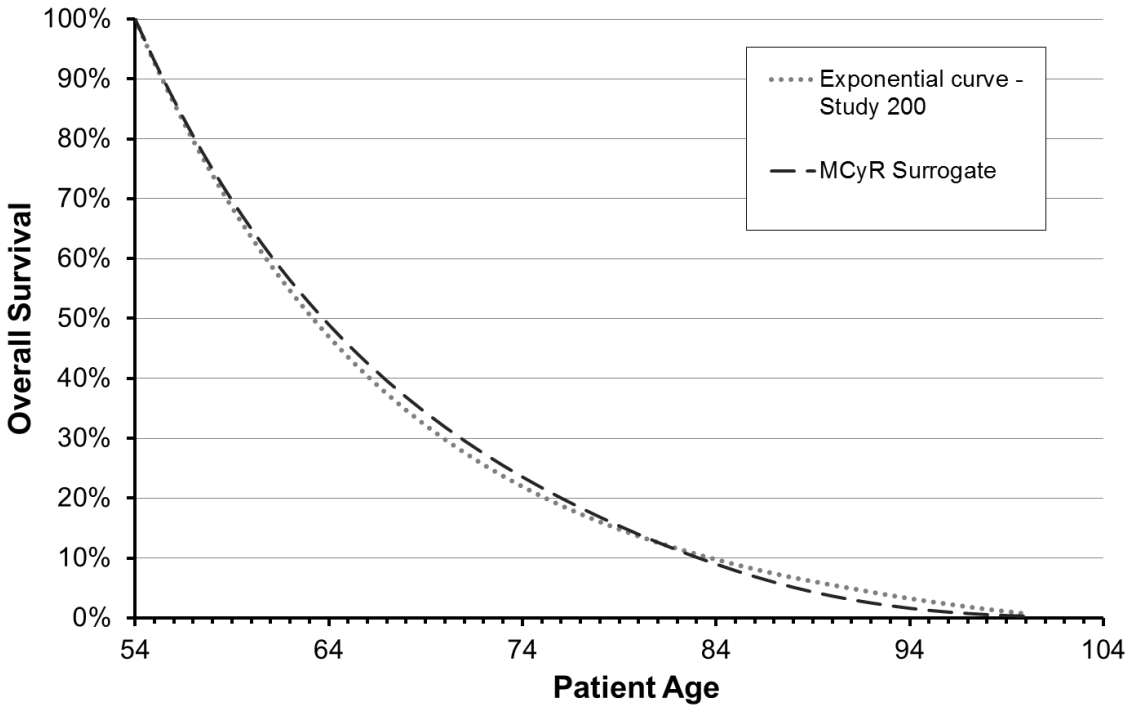
We can safely ignore the initial higher frequency of visits when patients start taking TKIs, as these costs effectively cancel out between treatment arms (because virtually all patients on 1st-line TKIs are still on treatment at 4 months). We leave all other assumptions for the costs of medical management unchanged (see p180 our report), although these contribute only marginally.

These new cost assumptions give a mean medical management cost of £169 per month per patient on TKIs in chronic phase and £317 per patient on HU in chronic phase.

9.22 Appendix V: Comparison of overall survival in CP model calculated by MCyR surrogate, Study 200 Kaplan-Meier and exponential fit

Pfizer state (Pfizer clarification, Figure 7, p28) that the overall survival (OS) obtained by the MCyR surrogate method was validated by comparing it to the exponential curve fitted to Study 200 CP-3L cohort OS, with the curves being very similar:

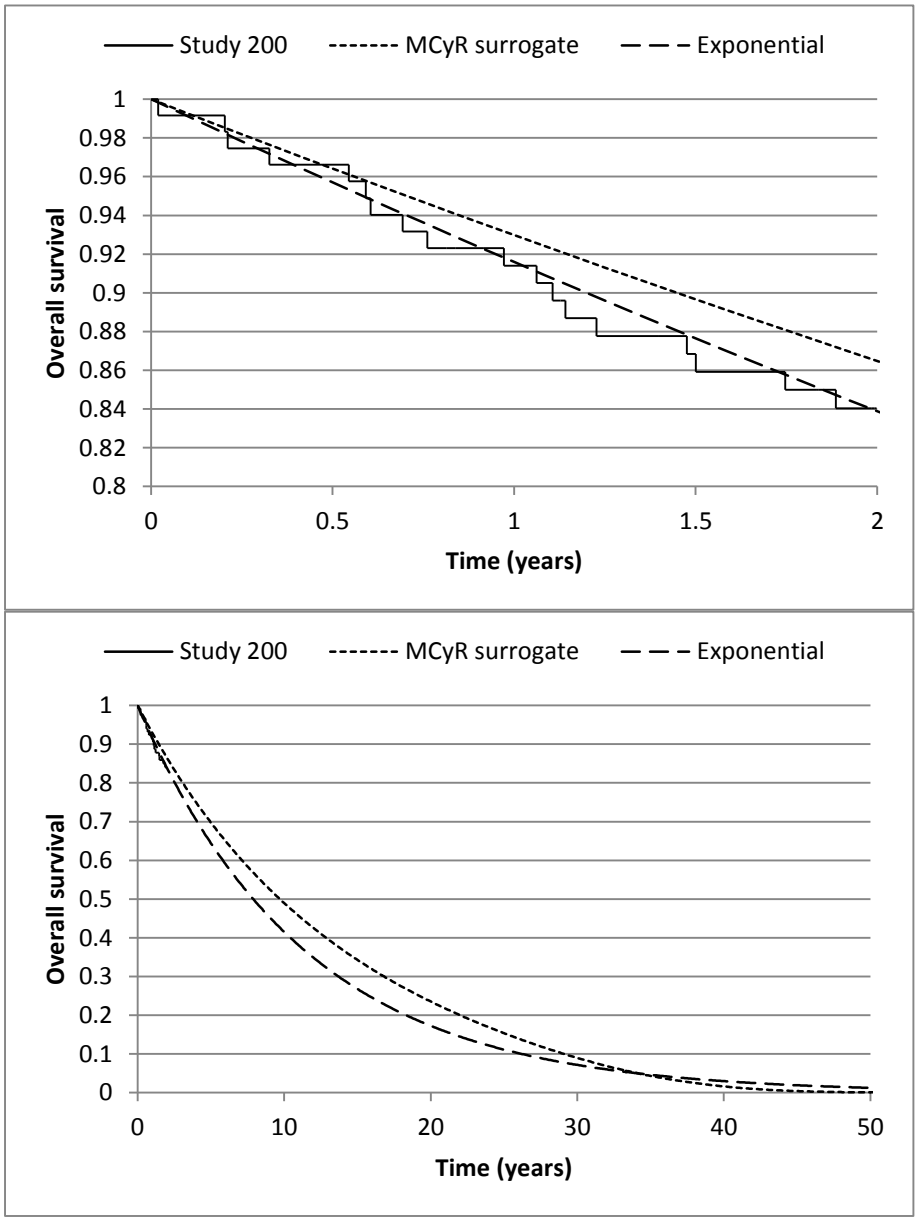
Figure 54. OS in CP model calculated by exponential curve and MCyR surrogate method



(Source: Pfizer clarifications, Figure 7, p28)

We believe this figure is not an accurate reflection of the exponential curve used in Pfizer's model. Figure 55 shows the actual OS in the CP model and demonstrates that the MCyR surrogate method is overestimating the OS.

Figure 55. Actual OS in CP model



Note that we do not accept that the Study 200 OS is good quality data for the purposes of estimating OS for patients on bosutinib in the unmet need population; indeed we identify a number of issues with the data (see Section 5.3.8.1, p165). This is presented only to demonstrate the shortcomings of the MCyR surrogate method (since we believe Study 200 OS is already likely to be biased upwards). As the MCyR surrogate method is a key component of Pfizer's CP base case we believe this is further reason to not accept Pfizer's base case estimate of OS for patients on bosutinib in CP.

9.23 Appendix W: Adjusting Pfizer's model for PenTAG preferred medical management resource use

Table 100. Changes to Pfizer's model to achieve PenTAG preferred medical management resource use

Worksheet	Cell(s)	Change

PF_Bosutinib	AG11	Change from
		`=ae_bosutinib_cost+AB11*c_cpt_bos`
		to
		`=ae_bosutinib_cost+AB11*c_cpt_bos+2*p_clin_onc`

Costs	C117	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$57`
		to
		`=1/3*p_clin_onc+$F$57`

	D117	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$59`
		to
		`=0.72*p_clin_onc+$F$59`

	C118, D118, D119	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$59`
		to
		`=0.72*p_clin_onc+$F$59`

	C119	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55) + Parameters!$N$56 + $F$61 + (1-Parameters!$N$34)*Parameters!$N$33`
		to
		`=0.72*p_clin_onc+$F$61+(1-Parameters!$N$34)*Parameters!$N$33`

	C84, D84	Set to 0

PF_Interferon	BE11:BE610	Change from (row 11)
		`=SUM(Z11:AA11)*SUMPRODUCT( Parameters!$N$37:$N$40, Parameters!$N$52:$N$55) + AB11*SUMPRODUCT(Parameters!$N$42:$N$45, Parameters!$N$52:$N$55) + AC11*SUMPRODUCT(Parameters!$N$47:$N$50, Parameters!$N$52:$N$55)`
		to
		`=SUM(Z11:AA11)*0.72*p_clin_onc + AB11*SUMPRODUCT(Parameters!$N$42:$N$45, Parameters!$N$52:$N$55) + AC11*SUMPRODUCT(Parameters!$N$47:$N$50, Parameters!$N$52:$N$55)`

	BF11:BF610	Change from (row 11)

		`=SUM(Z11:AA11)*Parameters!$N$56 + SUM(AB11:AC11)*Parameters!$N$57`
		to
		`=SUM(AB11:AC11)*Parameters!$N$57`

PF_StemCellTransplant	AE11:AE610	Replace `c_sct_25` with `c_sct_25+(0.54*0.5+0.46*0.08)*p_clin_onc`

Bosutinib for previously treated chronic myeloid leukaemia: a single technology appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School
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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Martin Hoyle	Project manager, led the critique of Pfizer's economic analysis, and contributed to the writing of the clinical and cost-effectiveness chapters.
Tristan Snowsill	Critiqued Pfizer's economic model and contributed to the writing of the cost-effectiveness chapters. Collated the final report.
Marcela Haasova	Critiqued clinical effectiveness evidence and wrote most of the clinical effectiveness chapter.
Chris Cooper	Critiqued Pfizer's searches for clinical and cost-effectiveness evidence.
Claudius Rudin	Advised on possible use of bosutinib in England and Wales and on CML in general.

About the Peninsula Technology Assessment Group (PenTAG)

PenTAG is part of the Institute of Health Service Research at the University of Exeter Medical School. PenTAG was established in 2000 and currently has two major work streams: independent health technology assessments (HTAs) for NICE and the NIHR HTA programme, and evidence synthesis work in relation to the needs of the SW Peninsula Collaboration for Applied Health Research and Care (PenCLAHRC), as well as for other local and national decision-makers.

The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics.

Website: http://sites.pcmd.ac.uk/pentag/

Disclosure of information

This report contains information designated by the manufacturer as 'commercial in confidence' and 'academic in confidence' (data awaiting publication). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

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LIST OF ABBREVIATIONS

AE/SAE/TEAE	Adverse event/ Serious adverse event/ Treatment-emergent adverse event
ALL	Acute lymphoblastic leukaemia
SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BC	Blast crisis
Bcr-Abl	Breakpoint cluster region-Abelson (an oncogene fusion protein consisting of BCR and ABL)
BMS	Bristol-Myers Squibb
BMT	Bone marrow transplant
BNF	British National Formulary
BP	Blast phase
BSC	Best supportive care
C(A)T	Computerised (axial) tomography
CC	Complication/comorbidity (HRG code)
CCyR	Complete cytogenetic response
CENTRAL	The Cochrane Central Register of Controlled Trials
cGvHD	Chronic graft versus host disease
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
DARE	The Database of Abstracts of Reviews of Effects
DET	Data extraction table
ECOG	Eastern Cooperative Oncology Group
EHA	European Haematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-	European Organisation for Research and Treatment of Cancer Quality of Life

C30	Questionnaire-Core 36
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life- 5 Dimensions questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EWB	Emotional well-being
FACT-Leu	Functional Assessment of Cancer Therapy- Leukemia
FDA	US Food and Drug Administration
FISH	Fluorescence *in situ* hybridisation
FLAG-IDA	Fludarabine, cytarabine, idarubicin and G-CSF chemotherapy regimen
FWB	Functional well-being
GBP	Great British Pounds (currency)
G-CSF	Granulocyte-colony stimulating factor
GP	General Practitioner
GVHD	Graft versus host disease
HCHS	Hospital and community health services
HDI	High-dose imatinib
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HTA	Health Technology Assessment
HTN	Hypertension
HU	Hydroxyurea/hydroxycarbamide
ICER	Incremental cost-effectiveness ratio
ICLLM	International Congress on Leukemia Lymphoma Myeloma
ICU	Intensive-care unit
IFN	Interferon alpha
IFR	Individual funding requests
IM-I	Imatinib-intolerant
IM-R	Imatinib-resistant
INHB	Incremental net health benefit
INR	International Normalised Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LEUS	Leukaemia subscale
MCyR	Major cytogenetic response
mg	Milligrams
MHR	Major haematological response
MiCyR	Minor cytogenetic response
MMR	Major molecular response

MUD	Matched unrelated donor
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	No evidence of leukaemia
NHB	Net health benefit
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation Database
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Clinical Excellence / National Institute for Health and Care Excellence
NR	Not reported
OHR	Overall haematological response
ONS	Office for National Statistics
OS	Overall survival
PAOD	Peripheral arterial occlusive disease
PAS	Patient Access Scheme
PB	Peripheral Blood
PBSCT	Peripheral blood stem cell transplant
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
Ph^+	Philadelphia chromosome-positive
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PWB	Physical well-being
QALY	Quality-adjusted life year
QTc	Corrected QT interval
RCP	Return to chronic phase
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
SmPC/SPC	Summary of Product Characteristics
STC	Stem cell transplant
SWB	Social well-being
TA[number]	Technology appraisal [number]
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor

UK	United Kingdom
ULN	Upper limit of normal
USA/US	United States of America
WBC	White blood cell
WHO	World Health Organisation
WTP	Willingness to pay

(Adapted from Pfizer submission, pp8–12)

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency.

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML)
- Hydroxycarbamide
- Interferon alpha
- Best supportive care

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 1.5.2, p30).

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence of bosutinib (Bosulif®) in treatment of adult patients with Ph+ CML was reviewed. The entire clinical evidence for bosutinib comes from a single arm, phase I/II multi-centre trial, Study 200. Because no RCT evidence was identified, separate clinical effectiveness evidence was submitted for the Scope defined comparators. Thirteen non-randomised comparator studies were included.

1.2.1 Bosutinib

Study 200 (Phase II) examined the efficacy and safety of bosutinib 500mg daily in 546 Ph+ CML patients with previous imatinib failure. Patients in all three phases of Ph+ CML were recruited; second line CP (N=288), third line CP (N=118), AP (N=76) and BP (N=64). In addition, based on

EMA recommendation, a subgroup of patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (population of unmet clinical need) was identified and analysed post hoc. Baseline characteristics across all phases of the disease and lines of treatment are summarised in Table 1.

Table 1. Study 200 baseline patient characteristics

Population	**Age (years) [Median (range)]**	**Male [N (%)]**	**CML duration (years) [Median (range)]**	**IM duration (years) [Median (range)]**	**ECOG performance status N (%)**		
					0	*1*	*2*
CP2L (n=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.11–22.06)	NR	41 (54%)	33 (43%)	2 (3%)
BP (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.35–14.46)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need (N=52)[b]	58 (19-81)	31 (605)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NR = not reported

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

In the complete population of Study 200, bosutinib was associated with good cytogenetic and haematological response rates and overall survival (Table 2). However, the OS data from Study 200 for CP patients is very immature. Cytogenetic and haematological responses were also observed among participants with mutations that would confer the use of nilotinib or dasatinib inappropriate (Table 3). Apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical need population. For example, MCyR was 60%, 42.9%, 60% and 18.2 % for second and third line CP and AP and BP unmet clinical need population respectively. However these response rates are based on very small sample sizes (N=3–21) and are therefore uncertain.

Table 2. Study 200 cytogenetic and haematological response rates for full Study 200 population

	Evaluable population			
	MCyR March 2011	*CCyR March 2011*	*CHR March 2011*	*K-M estimates of OS at 2 years*
CP2L	53.4%	41.4%	84.7%	90.6%[a]
CP3L	38.9%	30.6%	73.3%	84.0%[a]
AP	34.8%	24.6%	34.8%	65.6%[b]
BP	29.6%	20.4%	15%	35.4%[c]

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a 24 month minimum follow-up, median OS had not yet been reached

b 12 month minimum follow-up, median OS had not yet been reached

c 18 month minimum follow-up, median OS for BP patients was 11.1 months

Table 3. Study 200 response rates by baseline mutation

Mutation	**CP2L CHR [n/N %]**	**CP2L MCyR [n/N %]**	**CP3L CHR [n/N %]**	**CP3L MCyR [n/N %]**	**AP & BP CHR [n/N %]**	**AP & BP MCyR [n/N %]**
Y253	2/2 100%	2/2 100%	5/6 83%	4/6 67%	1/7 14.3%	2/7 28.6%
E255	0/2 0%	2/3 67%	NA	NA	0/4 0%	1/3 33.3%
F317	4/4 100%	3/4 75%	4/8 50%	1/7 14%	0/9 0%	0/6 0%
F359	8/9 89%	4/9 44%	0/2 0%	1/2 50%	0/2 0%	1/2 50%

Notes: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, n = numbers of participants with response, N = number of participants with mutation, NA = not applicable

Bosutinib was found to have an acceptable safety profile across all phases of the disease and lines of treatment. Low rates of transformation to the next phase of CML were observed on bosutinib treatment for both chronic and advanced phase populations (Table 4). Adverse events were mainly restricted to gastrointestinal toxicities (Table 4) and in the majority of cases these toxicities were mild in severity. The most common haematological events across all phases of the disease and lines of treatments in both the chronic and advanced phases of the disease were thrombocytopaenia, neutropaenia and anaemia. Severe cases of anaemia seemed to be more pronounced at the more advanced stages of the disease (Table 4). The profile of AE associated with bosutinib appears to be more similar to those associated with nilotinib than with dasatinib. In comparison, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections,

haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI.

Table 4. Study 200 safety

	CP2L	CP3L	AP	BP
Rates of disease transformation to the next phase of CML	3.8%	4%	6.4%	NA
Treatment discontinuation	58% (36 months minimum follow-up)	76% (24 months minimum follow-up)	NR	NR
Treatment discontinuation due to AE	23%	22%	23.7%	9.4%
Diarrhoea	85.3%	82.4%	85.5%	65.6%
Nausea	45.5%	48.7%	44.7%	50%
Vomiting	36.7%	39.5%	44.7%	39.1%
Rash	36%	26.9%	32.9%	31.3%
Thrombocytopenia Grade 3/4	24%	25.4%	32.9%	26.6%
Neutropenia Grade 3/4	18%	14.4%	14.5%	20.3%
Anaemia Grade 3/4	13%	5.1%	30.3%	18.8%

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable, NR = not reported

EQ-5D data were collected in Study 200. The mean EQ-5D utilities, averaged mostly over the first two years of treatment, were [redacted] in the CP 2nd-line, 3rd-line, AP and BP populations respectively.

1.2.2 Comparator treatments

No studies reporting on interferon alpha in a refractory setting were identified. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] However only 7 studies[3, 4, 6, 7, 10, 12, 13] were considered in Pfizer's submission as five SCT studies did not stratify results by disease phase.

In summary, the clinical effectiveness evidence for the comparator treatments is very poor. Hydroxycarbamide was considered to be a proxy for best supportive care. Participants in the comparator studies appear to be younger, and most of the comparator studies are small and the outcomes reported vary. Pfizer describe the HU comparator studies as "not strictly eligible" (p89 Pfizer Submission) for inclusion and only three included SCT studies[7, 10, 13] are considered to be a good quality evidence according to the Chambers (2009)[16] criteria (Pfizer submission, p216). This

further highlights the difficulty inherent to such naïve comparisons and impedes any comparisons of Study 200 with comparator studies.

The CP cost-effectiveness model used data from Kantarjian (2007)[3] for the clinical effectiveness of HU and Jabbour (2011)[10] for the clinical effectiveness of SCT. Of particular importance for the model are:

- OS after SCT in CP of 72% at year 2 in Jabbour (2011)[10]
- OS for HU in CP of 77% at year 2 and 70% at year 3 in Kantarjian (2007)[3]

No safety data were reported for HU, and the grade 3–4 graft versus host disease reported in SCT studies varied across the lines of treatment as well as the studies from 6.25% to 40%.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

First, the main weakness of the clinical effectiveness evidence is the fact that no RCT evidence was identified. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML. Similarly, the evidence for comparator treatments comes from 13 non-randomised comparator studies.

Second, the bosutinib licence is intended for treatment of adult patients with CP, AP and BP Ph+ CML patients previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. However only 52 of the 546 patients in Study 200 fulfilled the criteria for this unmet need population.

Third, Pfizer do not state the nature of treatments given after bosutinib failure. This means that the relevance of the OS data from Study 200 is uncertain, because many patients may have proceeded to take a different TKI on bosutinib failure. Also, the OS data in CP is very immature, which means that it is difficult to estimate mean OS, a key driver of the cost-effectiveness of bosutinib.

Fourth, we cannot stress enough, that the naïve comparison of the single arm Study 200 with non-randomised comparator studies is predisposed to bias. The evidence for the two comparator treatments, HU and SCT, is taken from small studies with populations that mostly did not meet the unmet need criteria.

Fifth, Pfizer present no evidence for the clinical effectiveness of IFN, which is one of the comparator treatments in the CP economic model.

1.4 Summary of cost-effectiveness evidence submitted by the manufacturer

Pfizer conducted a systematic review for cost-effectiveness evidence relating to the decision problem. This did not identify any relevant studies for bosutinib.

Pfizer therefore developed a *de novo* economic model to answer the decision problem. The model developed was an "area-under-the-curve" cohort model where patients could be on or off the principal treatment in the treatment arm and patients could undergo transformation to later disease phases (accelerated and blast crisis phase). Patients could start in either the chronic phase, accelerated phase or blast crisis phase and these are denoted the CP, AP and BP models.

Pfizer consider the following four treatment sequences in the CP model:

- Bosutinib followed by hydroxycarbamide, denoted (Bosutinib, HU),
- Hydroxycarbamide, denoted HU,
- Stem cell transplant, denoted SCT,
- Interferon followed by hydroxycarbamide, denoted (IFN, HU).

For the AP and BP models, they consider the same treatment sequences but without (IFN, HU).

Overall survival was estimated for (Bosutinib, HU) in the CP model using a MCyR surrogate method, which has been used previously by PenTAG in TA241. They did not however use this method to estimate overall survival for comparator treatments, instead extrapolating from trials and using clinical expert opinion. Overall survival for (Bosutinib, HU) in the AP and BP models was estimated by extrapolating from Study 200.

Time on bosutinib treatment was estimated by extrapolating from Study 200. Time on interferon treatment was extrapolated from clinical expert opinion. Patients did not discontinue hydroxycarbamide treatment and patients who received a stem cell transplant were assumed to receive no further drug treatment.

Resource uses and costs were generally based on previous assessments by PenTAG, TA241 and TA251.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 and TA241. Their only departure from our previous assumptions is their estimate of the utility after stem cell transplant in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Importantly, for the estimated utility under bosutinib treatment, they prefer the utilities that we have used previously for utilities for TKIs to those from their Study 200.

1.4.1 CP model results

Pfizer's analysis showed that (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY), and more effective and less costly than SCT, i.e., (Bosutinib, HU) dominates. Pfizer found that (IFN, HU) was less effective and more costly than HU (HU dominates). The ICER of (Bosutinib, HU) versus (IFN, HU) was [redacted] per QALY.

Table 5. Pfizer CP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	(IFN, HU)	SCT
Life years	12.75	3.52	3.62	6.60
QALYs	7.26	2.43	2.42	3.70
Costs	[redacted]	£29,473	£38,268	£171,539

QALYs and costs discounted at 3.5% per annum

1.4.2 AP model results

Pfizer's AP base case results showed that similar to the CP model (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY), and that (Bosutinib, HU) dominates SCT.

Table 6. Pfizer AP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	4.48	1.37	3.02
QALYs	2.76	0.90	1.96
Costs	[redacted]	£26,078	£178,093

QALYs and costs discounted at 3.5% per annum

1.4.3 BP model results

Pfizer's BP base case results showed that (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY). The results also showed that (Bosutinib, HU) was less effective and less costly than SCT (ICER [redacted] per QALY).

Table 7. Pfizer BP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	1.77	0.54	2.64
QALYs	0.88	0.28	1.28
Costs	[redacted]	£14,170	£200,526

QALYs and costs discounted at 3.5% per annum

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

In this section, we highlight our key areas of disagreement with Pfizer's analysis. As a result of our critique of their model, we have developed PenTAG base case ICERs (Section 1.7, p35) for each of the CP, AP and BP models. In order to develop our base case, we have adjusted the following items in Pfizer's CP model:

- The method of estimation of OS for all comparators using our "cumulative survival method",
- Mean overall survival on HU,
- Mean overall survival after SCT,
- Resource use in CP CML.

We have changed just the first item in Pfizer's AP and BP models.

1.5.1 Model wiring errors

We discovered an important wiring error in the version of the model that Pfizer originally sent us on 14th March 2013. Pfizer sent as a corrected version of their model on 19th April 2013. Their base case ICER for bosutinib versus HU in CP then decreased from [redacted] per QALY.

In order to check the wiring of Pfizer's cost-effectiveness model, we built a model that is completely independent of their model. We feel confident that there are no major wiring errors in Pfizer's corrected model because the results from our independent model are very similar to those of Pfizer's model.

1.5.2 Comparator treatment sequences

Pfizer model the four treatment sequences in CP in Section 1.4, p28. In addition, we believe it is important to model the sequence (Bosutinib, SCT) for patients eligible for SCT. In summary, we assume the following comparator treatment sequences for CP:

- (Bosutinib, HU),
- (Bosutinib, SCT) (only for those eligible for SCT),
- HU,
- SCT (only for those eligible for SCT),
- (IFN, HU).

For the AP and BP models, we assume the same comparators, but without (IFN, HU).

We believe that the most important comparison in all model phases is (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Furthermore, we understand that a minority of patients (<30%) will be eligible for SCT and hence (Bosutinib, HU) versus HU is the most important treatment comparison in all disease phases.

1.5.3 Method of overall survival (OS) estimation

As stated in Section 1.4, p28, in the CP model, Pfizer use very different methods to estimate OS across treatments in the CP model. We believe that this lack of consistency, the lack of randomised evidence, and problems specific to the estimation of OS for bosutinib using the MCyR surrogate relationship leads to the following important prediction that lacks face validity. The mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) (shown in Figure 1 below). We believe, and clinical expert advice confirms, that this is unreasonable. Furthermore, this assumption dramatically biases the cost-effectiveness in favour of (Bosutinib, HU) versus HU because the price of HU is negligible.

Figure 1.

[redacted]

Although OS for all treatments is consistently estimated by extrapolating trial data in the AP and BP model, we believe there are still serious problems with Pfizer's method of estimating OS for all treatments in AP and BP. This similarly leads to the implausible prediction that, in both the AP and BP models, the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm.

Instead, we suggest that a far more parsimonious method is required to estimate OS across comparators. Indeed, we suggest such a method, which we describe as the Cumulative Survival method. We believe that it is far preferable for estimating OS for all comparator treatments for all

model phases. We believe that it should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The key assumption of the Cumulative Survival method is that in the (Bosutinib, HU) and (IFN, HU) arms, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. In Figure 1, the heights of the HU sections then become approximately equal. Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

The revised cost-effectiveness results are then:

- In the CP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases substantially, from [redacted] to [redacted] per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY.
- In the AP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY.
- In the BP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY. In their base case, Pfizer estimate an ICER of [redacted] for (Bosutinib, HU) versus SCT, with (Bosutinib, HU) cheaper and less effective than SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY, i.e. (Bosutinib, SCT) gives poor value versus SCT.

Of all the changes we make to Pfizer's model, this has the largest impact on the estimated cost-effectiveness of bosutinib.

1.5.4 OS for HU in CP

Relevant data for OS on HU for patients in CP is sparse. Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] We used this study for this purpose in TA251. Pfizer claim that the agreed estimate of mean OS for HU in CP was 3.5 years in TA251, and they therefore use this value in their base case. However, we disagree. Instead,

we calculated a mean OS of 7.0 years in TA251.[17(p164)] Furthermore, the 3.5 years estimated by Pfizer is clearly incompatible with the Kaplan-Meier OS curve from this study.

The quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is clearly poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available for this purpose.

Pfizer's base case ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY, and the cost-effectiveness of (Bosutinib, HU) versus SCT is unchanged.

1.5.5 OS after SCT in CP

Relevant data for OS after SCT for patients in CP is also sparse. Pfizer's base case estimate of OS after SCT for patients in CP was based on data from the study Jabbour and colleagues (2011).[10] Whilst we agree that this study is relevant, the sample size is extremely small, with only 16 CP patients contributing to the estimates of OS. Instead, we use data from the study by Oehler and colleagues (2007),[12] in our base case, as it is relevant, has a much larger sample of 72 patients and reports OS that is more consistent with the OS from two other relevant studies. Our estimated OS of 11.6 years is far greater than Pfizer's estimate of 6.6 years.

Pfizer's base ICER for (Bosutinib, HU) versus HU then remains unchanged, and (Bosutinib, HU) still dominates SCT, but the cost-effectiveness of (Bosutinib, HU) deteriorates versus SCT.

1.5.6 Medical management costs in CP

Pfizer's assumptions for medical management, monitoring and testing are based on those that we originally used in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey. However, Pfizer seem unaware that after the first NICE committee meeting for TA251, our assumptions were challenged by Novartis, the manufacturer of nilotinib. In response, we amended some of our assumptions for resource use in CP CML in TA251, and these were accepted by the NICE committee.

These changes plus changes to resource use assumptions for patients after SCT are reflected in our base case assumptions. When we amend Pfizer's model, their ICER for (Bosutinib, HU) versus HU decreases from [redacted] to [redacted] per QALY and (Bosutinib, HU) continues to dominate SCT.

1.5.7 Line of treatment

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used 2nd-line. However, we believe that bosutinib will be

used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis also assumes 3rd-line use of bosutinib, and we consider use of bosutinib in 2nd-line in an important scenario analysis.

Pfizer estimate the mean time on 3rd-line bosutinib in CP from Study 200 as [redacted]. Based on the Kaplan-Meier data from Study 200 we requested from Pfizer, we estimate the mean time on 2nd-line bosutinib as being far longer, at [redacted].

Changing Pfizer's model for this estimate and for the 2nd-line MCyR from Study 200, Pfizer's base case ICER for (Bosutinib, HU) versus HU for CP increases substantially, from [redacted] to [redacted] per QALY and (Bosutinib, HU) changes from dominating SCT to being more costly and more effective than SCT (ICER [redacted] per QALY).

1.5.8 Utilities

In short, we accept Pfizer's utilities. However, we believe that there are strong arguments that we should instead use the utilities from Study 200 for bosutinib treatment, and our estimate of 0.80 after SCT in CP in preference to their estimate of 0.71.

In the first case, Pfizer's ICER for (Bosutinib, HU) versus HU in CP increases marginally, from [redacted] to [redacted] per QALY.

In the second case, based on Pfizer's analysis, (Bosutinib, HU) still dominates SCT in CP, but to a lesser extent.

1.5.9 End of Life criteria

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML. By contrast, we believe bosutinib does not meet the criteria in any phase of CML. We believe that bosutinib does not quality in AP and BP due to lack of robustness of the estimates of extension to life.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- Pfizer's analysis was clearly described in their report.
- We found only one important wiring error in Pfizer's model.
- The structure of Pfizer's model is mostly consistent with the natural history of CML.
- With the exception of the Cumulative Survival method, Pfizer clearly studied TA241 and TA251 in detail and adapted their model accordingly.
- The time on bosutinib treatment from Study 200 is mature.

- Extrapolations for time on bosutinib treatment appear reasonable.
- The modelled unit costs seem appropriate.
- The modelled utilities are plausible.

1.6.2 Weaknesses

- The clinical effectiveness evidence is taken from a single non-randomised trial (Study 200).
- Only a small subset of the patient population in Study 200 reflects the population indicated for bosutinib.
- Although some effectiveness results are presented for the patients indicated for bosutinib, some key effectiveness results, such as time on bosutinib treatment, are not.
- OS for patients on bosutinib in CP is very immature.
- In Pfizer's model, all patients were assumed to receive hydroxycarbamide following bosutinib failure. Instead, we believe that some patients would receive SCT after bosutinib.
- Pfizer's important prediction that the mean time in the CP model on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) lacks face validity.
- We believe that Pfizer's estimate of mean OS on HU in CP is logically flawed, as described in Section 1.5.4, p32.
- We believe that Pfizer's estimate of mean OS after SCT in CP is biased, as described in Section 1.5.5, p33.

1.6.3 Areas of uncertainty

There is substantial uncertainty in almost all the key parameters of Pfizer's model. Much of this has already been discussed above, but some of the key parameters which are uncertain include:

- The line of treatment that clinicians would use bosutinib if it were recommended by NICE,
- Mean OS on bosutinib in all phases, specifically for patients unsuited to TKIs,
- Mean time on bosutinib treatment in all phases, specifically for patients unsuited to TKIs,
- Mean OS on HU in all phases of CML,
- Mean OS after SCT in all phases of CML,
- Utilities for patients after SCT.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Summaries of the derivation of our base case ICERs and sensitivity analyses are given in the following tables below:

- Table 8 and Table 9 (CP)

- Table 10 (AP)
- Table 11 (BP)

The key treatment comparisons are highlighted in bold: (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Our base case ICERs for these key comparisons are as follows:

- CP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY
- AP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY
- BP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY

Table 8. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) versus**			**(Bosutinib, SCT) versus**		
	Comparator	*HU*	*SCT*	*IFN*	*HU*	*SCT*	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	n/c	n/c	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	n/c	n/a		
1+2[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+3[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+4[b]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+3+4		[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from Pfizer base case

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT

b Interferon is more costly and more effective than hydroxycarbamide
c Interferon is less costly and less effective than hydroxycarbamide

Table 9. Important scenario analyses applied to PenTAG base case for CP model

Intervention	(Bosutinib, HU) versus			(Bosutinib, SCT) versus		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	[redacted]	[redacted]	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	[redacted]	Dominant	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	[redacted]	[redacted]	[redacted]
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
SCT utility set to TA251 utility	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]

n/c – Not changed from PenTAG base case
Shading as in Table 8
a (Bosutinib, HU) is less costly and less effective than SCT

Table 10. Derivation of PenTAG base case AP CML

	Intervention	(Bosutinib, HU) versus		(Bosutinib, SCT) versus	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

Shading as in Table 8

Table 11. Derivation of PenTAG base case BP CML

	Intervention	(Bosutinib, HU) versus		(Bosutinib, SCT) versus	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

Shading as in Table 8
a Bosutinib is less costly and less effective than SCT

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

Leukaemia is a form of cancer affecting blood. Chronic myeloid leukaemia (CML) is characterised by excessive proliferation of white blood cells (mainly granulocytes) in the bone marrow, and an initial slow disease progression.[2] The Haematological Malignancy Research Network (HMRN) estimates that 560 cases of CML are newly diagnosed in the UK each year; an annual age-standardised rate of 1.2 per 100,000 for men and 0.7 per 100,000 for women (based on HMRN 2004-11 and 2001 UK census data). Natural history and epidemiology of CML, technologies and clinical pathways available, as well as the patients' life expectancy were described in Sections 2.1–2.6 of the manufacturer's submission.

2.1.1 Natural history of CML

The introduction of TKIs in the treatment of CML has changed the management and outcome of this disease dramatically. Although a true cure for CML is not generally achieved, CML was transformed from an immediately life-threatening cancer, with a 10–20% mortality rate per year, to a disease, managed with oral medications, and with 1–2% mortality per year.[18]

CML is characterised by the presence of the BCR-ABL fusion gene as the result of a reciprocal chromosome translocation between chromosomes 9 and 22; t(9q34;22q11). This acquired (non-inherited) translocation results in a truncated derivative chromosome 22 known as the Philadelphia chromosome. Approximately 90–95% of the CML population are Philadelphia chromosome positive (Ph+). A further 5% do not exhibit the characteristic Philadelphia chromosome, but have cryptic chromosomal rearrangements resulting in the BCR-ABL fusion gene. The resulting Bcr-Abl fusion protein is a constitutively active tyrosine kinase, resistant to apoptosis (programmed cell death). It phosphorylates numerous substrates, disrupting the regulation of intracellular signal transduction pathways, promoting proliferation and genetic instability.

CML has three phases: chronic (CP), accelerated (AP) and blast (BP), each corresponding to increasing leukaemic blast counts in the blood and bone marrow and clinical severity ([Pfizer submission] Table 3). Blast is a term which describes an immature blood cell of any type. Normally, a blast will develop into a mature blood cell, but in CML these cells are abnormal and do not fully develop, becoming known as leukaemic blasts.

Approximately 90% of patients are diagnosed while in CP, 9% in AP and 1% in the BP. If left untreated, the average time a patient would remain in CP, AP and BP is 3–5 years, 6–24 months and 6 months, respectively.

(Source: Pfizer submission, p23)

2.1.2 Epidemiology

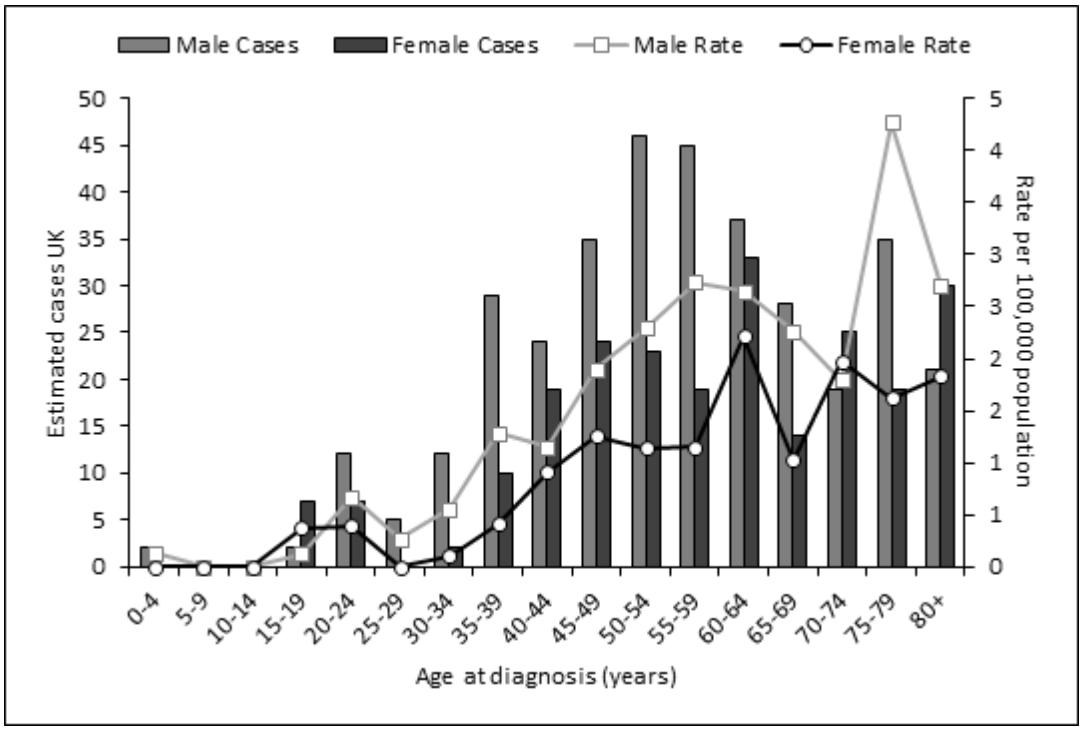
CML occurs in all age groups, but is most common in older adults and the median age at diagnosis is 59.1 years. A French study has shown that the prevalence of CML is increasing. In the pre-imatinib era, prevalence increased 4.1% annually (from 1998 to 2002), however, since the introduction of imatinib a mean annual increase of 9.3% has been observed (from 2003 to 2007). Apart from the impact of imatinib, better diagnosis and an aging population may play a part in increasing prevalence.

In 2003, the prevalence of CML in England and Wales was estimated at 2,660. Therefore, assuming a mean annual increase in cases of 9.3% since then, current prevalence of CML in England and Wales is estimated at 5,922.

(Source: Pfizer submission, p24)

Figure 2 shows the HMRN gender and age specific incidence estimates for CML.

Figure 2. Estimated age-specific incidence of CML[19]



Pfizer's estimates of the annual incidence of patients in the unmet need population at each phase of CML are given in Appendix A. In summary, they assume that bosutinib will be used mostly 4th-line, after 3 previous lines of TKIs: 12 patients p.a. 2nd-line, 19 p.a. 3rd-line and 49 p.a. 4th-line.

2.1.3 Prognosis

> If left untreated CML will typically progress from the CP to the AP in 3-5 years, and then to BP within 6-24 months. Median survival in the BP, without treatment, is around 6 months. As such, the typical life expectancy for a CML patient diagnosed in CP is around 4-7 years without treatment.
>
> The majority (>90%) of patients are diagnosed with CML in CP. Imatinib currently represents the established first-line treatment for these CP CML patients in clinical practice, having replaced interferon alpha upon its introduction. This new treatment paradigm has led to a dramatic improvement in the prognosis for patients diagnosed with CP CML. The estimated median survival with imatinib exceeds 25 years with median age of diagnosis of almost 60 years.
>
> Patients who respond well to standard-dose imatinib treatment (approximately 55% of patients) will often continue to receive this treatment for life and have a normal life expectancy.

(Source: Pfizer submission, p24)

We agree with Pfizer's statement above. However, our clinical advisor suggests that whilst imatinib used to be the 1st-line treatment of choice, nilotinib is now preferred given the recent NICE TA251 guidance. Treatments and clinical pathways are discussed in detail in Section 2.2.1, p43.

Two prognostic staging scores, developed prior TKI treatments, are available: the Sokal[20] and the Hasford[21] scores. Risk factors are used to determine if a patient is at a low, intermediate or high risk of death. In addition, The European Treatment and Outcome Study (EUTOS) prognostic scoring system was developed after the first TKI was introduced.[22] Although the Sokal and Hasford scores were briefly mentioned in the submission (Pfizer submission, p24), no risk factors were reported for Study 200 participants. While risk factors may allow comparisons across studies, our clinical advisor suggests they are not used to make treatment decisions.

2.1.4 Quality of life

We agree with Pfizer's description of HRQL for CML patients:

> Patients in the CP may experience mild and non-specific symptoms such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss. Approximately 40% of CP patients are asymptomatic and diagnosed as a result of a routine blood test. Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising,

bleeding and infections. In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.

Health-Related Quality of Life (HRQL) for CML patients can vary greatly, depending on the treatment regime used. The introduction of effective therapies such as those of the TKI class has led to improvements in the HRQL of CML patients. In contrast, there is some evidence that CML patients treated long-term with interferon alpha may experience reduced HRQL.

(Source: Pfizer submission, p23)

2.1.5 Rationale for bosutinib

Treatment options are limited for patients who have previously tried all three currently available TKIs (i.e. fourth-line patients) or second- and third-line patients for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. There is a clear unmet need for an effective treatment for these patients, the majority of who will currently be managed with hydroxycarbamide, which represents best supportive care (BSC).

(Source: Pfizer submission, p25)

Mutations in the BCR-ABL kinase domain often lead to imatinib resistance, particularly secondary resistance, and are often responsible for treatment failure:

The proposed indication for bosutinib is as a treatment for patients who have been previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are inappropriate. In some cases, a patient may be inappropriate for one of these TKIs as a result of the presence of Bcr-Abl mutations that confer resistance to currently available TKIs. Bosutinib has demonstrated clinical activity in CML patients with mutations that confer resistance to currently available TKIs. In a study of CP CML patients, treatment with bosutinib in the third-line setting resulted in complete haematological responses and major cytogenetic responses across a broad range of Bcr-Abl mutants, including those conferring clinical resistance to nilotinib (Y253H, E255K/V, F359C/I/V) and dasatinib (F317L). Efficacy of bosutinib in CML patients with a broad range of Bcr-Abl mutations have also been demonstrated for bosutinib in a second-line setting. Bosutinib is therefore innovative in its potential to treat a patient group, with unmet needs, which is identifiable by its genetic characteristics: Bcr-Abl kinase mutations conferring resistance to current TKIs.

(Source: Pfizer submission, p33)

Unfortunately Bosutinib was found to be ineffective in patients with the T315I gatekeeper mutation.[23]

2.2 Critique of manufacturer's overview of current service provision

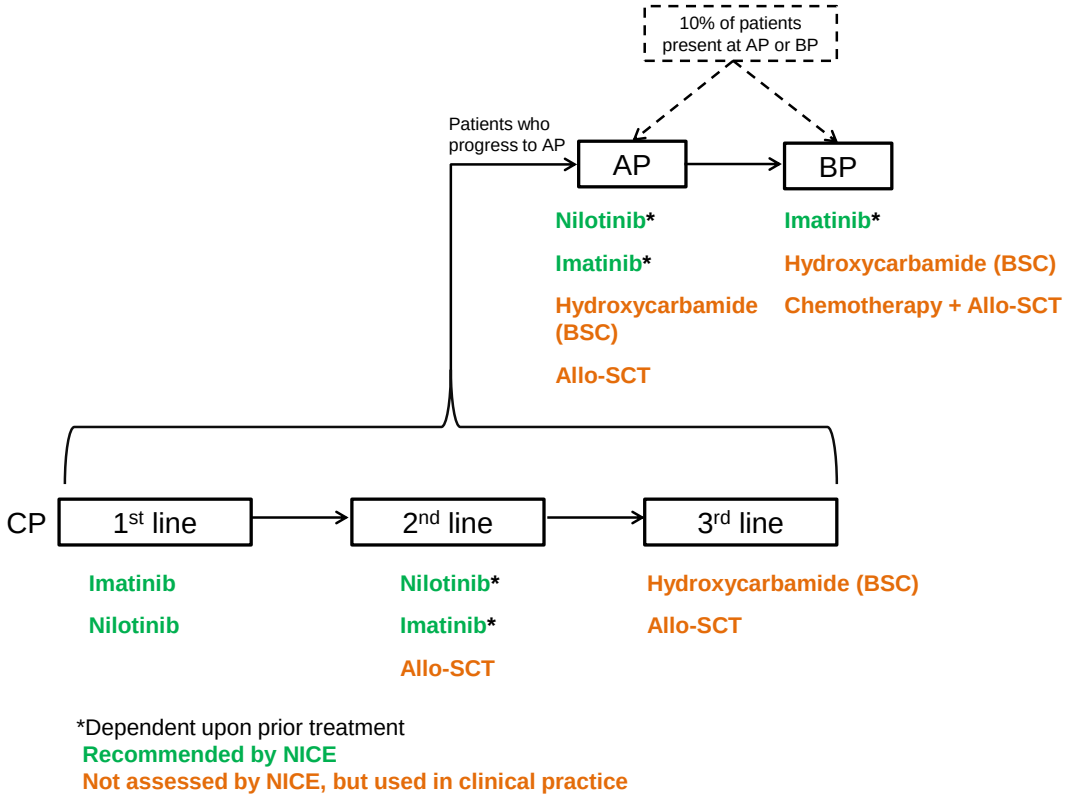
2.2.1 Current treatments for CML

We agree with Pfizer's assertion (Pfizer submission, p27) that the previous NICE technology appraisals that are relevant to the current appraisal are:

- TA251, 2012, 'Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)'.
- TA241, 2012, 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review TA70) and dasatinib and nilotinib for people with chronic myeloid leukaemia for whom treatment with imatinib has failed because of intolerance'.
- TA70, 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia. This guidance has now been partially updated by TA241 and TA251.

We further agree with Pfizer's summary of NICE recommended treatments for Ph+ CML, as shown in Figure 3 and in the text below (p28 Pfizer submission, p28).

Figure 3. NICE recommended clinical pathway of care



(Source: Pfizer submission, Figure A2)

NICE recommendations for 1st-line treatment are as follows (Figure 3):

- Nilotinib and standard-dose imatinib in CP CML (TA251).
- Dasatinib is not recommended for 1St-line use in CP, despite having an EMA marketing authorisation (TA251).
- Imatinib for CML that initially presents in AP or BP or that initially presents in CP and then progresses to AP or BP if imatinib has not been used previously.

NICE recommendations for 2nd-line treatment are as follows (Figure 3):

- Nilotinib for the treatment of CP or AP that is resistant or intolerant to standard dose imatinib (TA241).
- Dasatinib is not recommended for 2nd-line use for any phase of CML, despite having an EMA marketing authorisation (TA241).
- High-dose imatinib is not recommended for 2nd-line use for any phase of CML (TA241).
- NICE recommendations allow for the use of standard-dose imatinib 2nd-line after treatment with 1st-line nilotinib.
- NICE does not make any recommendations for treatment of patients in BP that is resistant or intolerant to standard-dose imatinib.

The following claim from Pfizer (Pfizer submission, p29) seems reasonable:

> There remains significant unmet need in the treatment of CP, AP and BP CML. Development of resistance, progression of disease despite treatment and intolerance to the currently recommended TKIs (imatinib, nilotinib and dasatinib) pose a significant challenge in the treatment of these patients and may cause withdrawal of therapy and can adversely affect compliance and outcomes. Furthermore, the presence of specific mutations or co-morbidities may render current therapies inappropriate. Hydroxycarbamide represents the main option in this patient population and therefore equates to best supportive care (BSC) for these patients. Given the limited efficacy of hydroxycarbamide (BSC), these patients represent a population of significant unmet need, for whom bosutinib offers an effective alternative.

We also agree with Pfizer's statements concerning the use of allogeneic stem cell transplantation (SCT) as follows (Pfizer submission, pp30–31):

> SCT is a treatment option for patients in CP, AP and BP and may be used in patients who have failed (due to lack of efficacy or tolerability) on currently available TKIs or for whom TKIs are inappropriate. In BP, SCT is typically preceded by treatment with acute leukaemia-style chemotherapy to try and establish haematological control. Bosutinib may therefore be considered as an alternative to SCT in CP, AP and BP patients, however as noted in Section 2.3 [Pfizer submission],

SCT is restricted by the number of matched donors available and is associated with high levels of morbidity and mortality.

The probability of success of this procedure is influenced by many factors, including (but not limited to): patient age, timing of the transplant, availability of a matched donor and level of progression of the disease. Therefore, SCT does not occupy a single, well-defined space in the CML pathway of care and could be applied at various stages of this pathway depending upon a complement of patient-related factors and the preference of the responsible physicians. This tends to be reflected in the evidence base for SCT, whereby the population is frequently heterogeneous including patients at different lines of treatment and even phases of CML. Additionally, its use in patients who are not suitable for or who have failed on all currently available TKIs is not known.

2.2.2 Bosutinib use in 2nd-, 3rd- and 4th-line treatment

Here we discuss the likely relative use of bosutinib across 2nd-, 3rd- and 4th-line lines of treatment. This is important because this dictates the most relevant clinical data to use in the economic model.

Pfizer assume that bosutinib will be used mostly 4th-line, after 3 previous lines of TKIs. In particular, they assume 12 patients p.a. 2nd-line, 19 p.a. 3rd-line and 49 p.a. 4th-line (Appendix A). For their economic model, Pfizer use clinical data from 3rd-line bosutinib as justified below:

With regards to the use of bosutinib in CP in practice, very few second-line patients are likely to be unsuitable for imatinib, nilotinib and dasatinib. As such, the third-line cohort from Study 200 is the focus for this submission as this is more likely to be representative of the patients expected in clinical practice, the majority of whom will likely be at least third-line. Data from the second-line CP CML patient population are only presented in Appendix 10.15 [Pfizer submission] for completeness.

(Source: Pfizer submission, p46)

Pfizer indicate that if 4th-line data were available from Study 200, they would have used this in their model (Pfizer submission, Section 7.2.1, p108).

Pfizer assume that most patients will receive imatinib 1st-line, and that dasatinib will be available in England & Wales, despite not being recommended by NICE in TA241 and TA251. They justify this by its current use under the Cancer Drugs Fund or individual funding requests (IFR).

By contrast, we believe that, if recommended by NICE, bosutinib will be used most often either as 2nd- or 3rd-line treatment, but rarely 4th-line.

Both imatinib and nilotinib, but not dasatinib, are recommended by NICE as 1st- and 2nd-line treatments in CP. Since NICE's TA251 recommendations, we understand that nilotinib has replaced imatinib as the 1st-line TKI of choice because it is similar in action to, but more potent than imatinib. Further, we understand that clinicians would be unlikely to use imatinib after nilotinib failure for the same reason. Dr Byrne, representing the Royal College of Pathologists and the BSH, appears to agree, stating (in a statement to NICE for this appraisal):

> Since an increasing number of patients are now receiving Nilotinib as a 1st-line treatment, this limits its usefulness as a 2nd-line agent in these patients. Furthermore as Nilotinib is generally accepted as a more potent bcr-abl inhibitor than Imatinib, with activity in many but not all the known mutations, there is little point in switching patients who have failed Nilotinib to Imatinib. However, Imatinib may be useful as a 2nd-line agent for patients experiencing toxicity on Nilotinib.

In contrast to Pfizer, we assume that dasatinib will be used only rarely from 2014 because we understand that the Cancer Drugs Fund is due either to end completely or to be scaled down in 2014, and because NICE have not recommended it for 1st- or 2nd-line use.

We imagine that if bosutinib were recommended by NICE in this appraisal, it will be used most heavily 2nd-line, after nilotinib, given that clinicians would be disinclined to use imatinib 2nd-line as it is less potent than nilotinib and given that dasatinib would not be available. However, it is possible that, at least initially, clinicians may prefer to delay use of bosutinib because they will be unfamiliar with it and because of the rather high treatment discontinuation rates. In this case, the preferred treatment sequence may be nilotinib then imatinib then bosutinib, i.e. bosutinib 3rd-line.

Bosutinib has a licence for patients who are unsuitable for imatinib, nilotinib and dasatinib. If it did not have this restriction, we imagine that it would be the 2nd-line treatment of choice after nilotinib. In particular, it is possible that most of the predicted 234 p.a. patients who Pfizer predict to fail on a 1st-line TKI would be treated with bosutinib 2nd-line. However, most patients who fail on 1st-line nilotinib will be suited to either imatinib or dasatinib. Given the restriction of the licence for bosutinib, these patients would then not be eligible for bosutinib, and they would instead likely receive 2nd-line imatinib, HU or SCT.

[redacted]. However, for the reasons given above, we imagine these sequences of treatment will be less likely to be relevant from 2014, given

that now most patients receive 1st-line nilotinib and we predict that dasatinib will rarely be used from 2014.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency (see Section 3.2 below).

The clinical evidence for bosutinib is taken entirely from Study 200, a single arm trial. The fitness of patients in this trial, as measured by ECOG, is representative of patients in clinical practice in England & Wales. However, the main weakness in the relevance of this evidence to the patient population in question is that most patients in this trial were suited to imatinib, nilotinib or dasatinib. Indeed, only 52 out of a total of 546 patients in Study 200 were not suited to all TKIs.

Other, probably more minor, weakness of Study 200 are that: (a) approx. 40% of patients had previously taken IFN, but IFN is now virtually never given for CML in the UK and (b) all patients had previously been treated with imatinib, but we understand that since TA251, 1st-line treatment for CML is now usually nilotinib.

3.2 Intervention

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

Pfizer state (Pfizer submission, p18):

> European Medicines Agency (EMA) filing originally occurred on 29th July 2011 for the indication stated below. This application was initially based on data from a pivotal phase III study, 3160A4-3000-WW (Study 3000). This was a randomised, open-label study comparison with imatinib. At this time the proposed indication applied for was:
>
> Bosutinib is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph^+ CML) in chronic phase (CP).

In this RCT, bosutinib failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib. Furthermore, toxicity with bosutinib was more pronounced than with imatinib. (EMA assessment report for bosutinib, Jan 2013).

Pfizer continue (p18 submission):

> Following ongoing discussions with the EMA, Pfizer agreed to revise the indication for bosutinib to:
>
> Bosutinib is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
>
> On the 17th January 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for bosutinib in this indication.
>
> In addition, the COMP adopted a positive opinion on the maintenance of orphan designation for bosutinib in EU in this indication on February 13th 2013

The final EPAR is now available on the EMA website.

3.3 Comparators

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML),
- Hydroxycarbamide,
- Interferon alpha,
- Best supportive care.

The comparators in the submission are as in the Scope, but without "best supportive care". Pfizer justify this by saying that hydroxycarbamide is accepted as best supportive care (Pfizer submission, p31), and we agree.

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 2.2.2, p45).

3.4 Outcomes

The outcomes in the Final Scope are as follows:

- overall survival,
- event-free survival,
- progression-free survival,
- time to progression,
- response rates: cytogenetic, haematological and molecular, including time to response and duration of response
- time to treatment failure
- adverse effects of treatment
- health-related quality of life

Pfizer consider all these outcomes in their submission. In addition, they consider rates of transformation from CP to AP/BP CML.

One important limitation of Pfizer's economic analysis is that, given that overall survival (OS) is immature for CP patients in Study 200, they estimate OS using a surrogate relationship based on the rate of major cytogenetic response.

The EQ-5D was used in Study 200, which is NICE's preferred instrument for measured health-related quality of life.

3.5 Other relevant factors

Pfizer present a discussion on matters of equity (Pfizer submission, p33) in which they state:

> There are no specific equality issues relating to bosutinib itself, however, the inclusion of bosutinib as an additional treatment option in the clinical pathway of care may help to address some of the equality issues associated with SCT, […]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

We validated the search strategy, critically appraised the systematic reviews described in Pfizer submission and critically appraised both the single arm phase I/II trial Study 200, the base of clinical effectiveness for bosutinib, as well as the studies with comparator data evidence. The power calculations for Study 200 were also re-run. The work has been undertaken between 11 March and 15 May 2013.

4.1.1 Searches

Pfizer provided detailed information on the search strategy. The complete search strategy (as included in Pfizer submission) is presented in Appendix B. In summary, the following search approach was used in Pfizer submission:

The following electronic databases were searched:

Medline (R) In-Process & Other Non-Indexed Citations
(searched from 1946 to January 21st 2013)
Ovid MEDLINE (R) 1946 to present (via OVID; searched from 1946 to January 21st 2013)
EMBASE, 1980 to present (via OVID; searched from 1974 to January 18th 2013)
The Cochrane Library (via OVID), searching the following databases:
The Cochrane Central Register of Controlled Trials (CENTRAL; searched to December 2012)
The Cochrane Database of Systematic Reviews (Cochrane Reviews; searches from 2005 to December 2012)
The Database of Abstracts of Reviews of Effects (DARE; searched 4th Quarter 2012)
The Health Technology Assessment Database (HTA; searched 4th Quarter 2012)
NHS Economic Evaluation Database (searched 4th Quarter 2012)

The following conference proceedings were searched (2010-2012):

American Society of Haematology (ASH)
American Society of Clinical Oncology (ASCO)
European Haematology Association (EHA)

(Source: Pfizer submission, adapted from Appendix 2, p201)

The searches were run in January 2013. The search strategy for the electronic databases took terms for CML and combined this with terms for imatinib (though this was restricted to incidences of intolerance, failure or resistance), hydroxycarbamide, stem cell transplantation, interferon, and bosutinib. A limit to systematic reviews and trials was used for this search. No separate searches were conducted for adverse event (AE). This could have compromised AE information.

In summary, the literature searching and search methods were found appropriate to the research question.

4.1.2 Inclusion criteria

Because of the lack of RCT evidence, the submission included separate clinical evidence for bosutinib and bosutinib comparators. The following study designs were included:

No RCTs were identified in the systematic review that specifically matched the licensed population for bosutinib. The data on which the license has been derived comes from a single-arm study, Study 200. The Study 200 Clinical Study Report (CSR), provides data across four cohorts of patients recruited separately into the study. In addition, a number of publications and conference abstracts/posters based on Study 200 are also available and are presented in this submission.

(Source: Pfizer submission, p44)

Comparators

No studies specifically evaluating comparator treatments in patients for whom imatinib, nilotinib and dasatinib are unsuitable were found. However, the systematic review identified 13 comparator studies that, like bosutinib, considered the use of the comparators in the broad second-line or later populations, in CP, AP and BP.

(Source: Pfizer submission, p48)

Inclusion and exclusion criteria as described in Table 12 are appropriate.

Table 12. Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years) with CP, AP and/or BP CML who have failed imatinib treatment	
Interventions/Comparators	• Bosutinib • Interferon alpha • Hydroxycarbamide (hydroxyurea) • SCT	
Outcomes	Efficacy: • Treatment response rates (including molecular, cytogenetic and haematological responses) • Time to- and duration of response • Overall survival • Event-free survival • Progression-free survival • Time to treatment failure • Health-related quality of life Safety/Tolerability: • Adverse events (all grades) • Incidence of serious adverse events	
Study design	• Prospective randomised controlled trials (RCTs) • Observational studies	Single case studies
Language	English abstracts of foreign language publications	Non-English publications

(Source: Pfizer submission, Table B1, p43)

4.1.3 Critique of data extraction

The submission explains the processes used in study selection and data extraction which is in line with the standard review process. The screening of the literature was performed by one reviewer and inclusion and exclusion criteria were verified by a second reviewer. Any disputes were resolved by a third party. The following data extraction strategy was used:

Results from database searches were downloaded into a bespoke Access® database, which was used to manage citation screening. Following full-text review and identification of studies to be included, data was extracted into a Data Extraction Table (DET). The DET included, but was not limited to, the following column headings:

- Country
- Study design
- Number of patients
- Key inclusion and exclusion criteria including subgroups
- Baseline characteristics
- Outcomes reported as summarised on page 6
- Likelihood of bias (quality components)

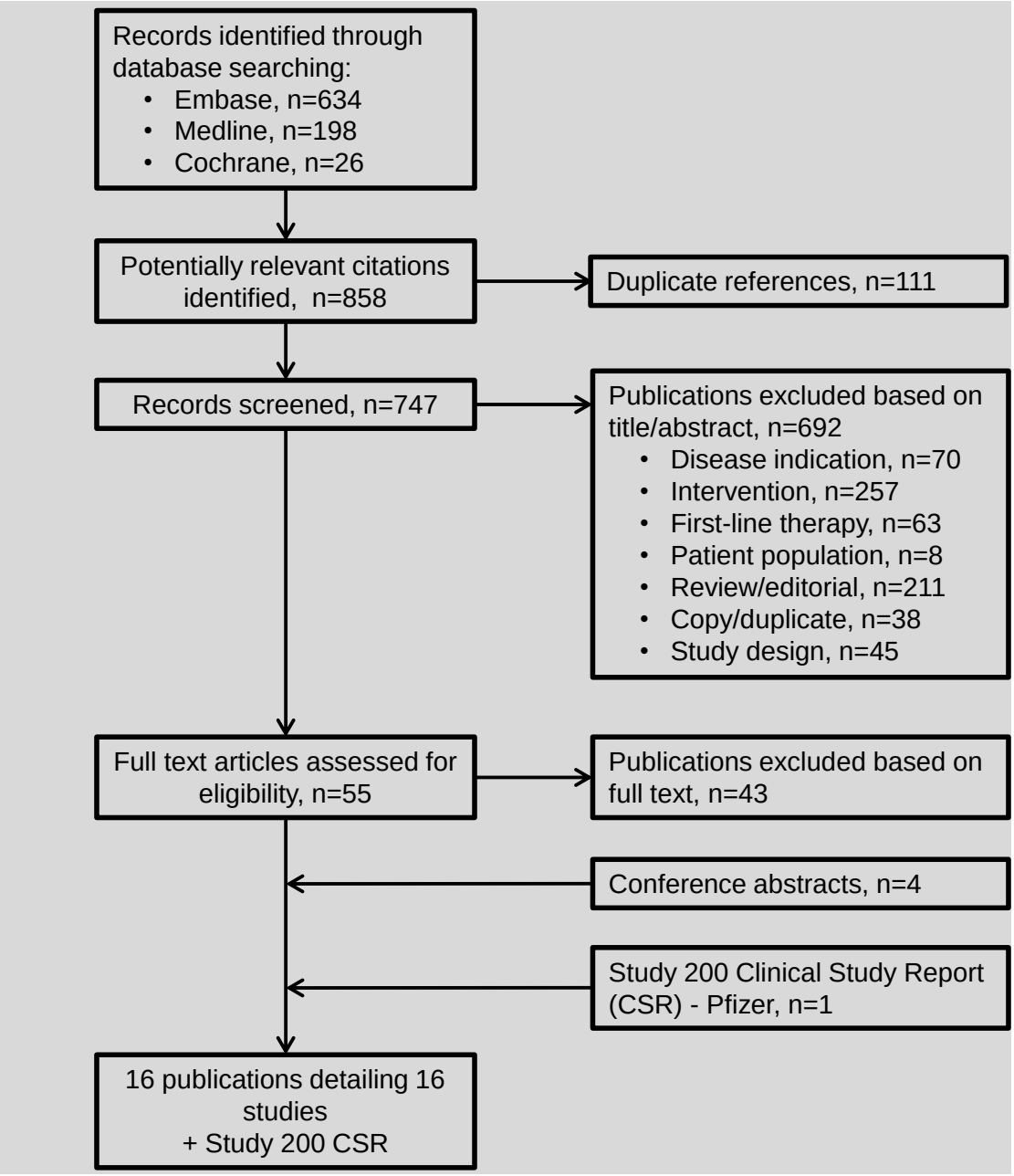
This data extraction was performed by one reviewer and verified by a second party.

(Source: Pfizer submission, Appendix 10.2.7, p212)

Overall, 16 studies were identified (Figure 4, p55), of these 13[3-15] reported on comparator treatments, and three[24-26] reported on bosutinib. All bosutinib studies are related to phase I/II Study 200 (NCT00261846; 3160A4-200). Further information on Study 200 was extracted from the Pfizer CSR,[27] and two conference posters based on Study 200 were identified.[1, 28] In addition, a similar on-going phase I/II study trial (NCT00811070; 3160A4-2203) evaluating bosutinib in Japanese subjects is expected to be completed in September 2014. Both Study 200 and the trial evaluating bosutinib in Japanese subjects, are Pfizer funded studies.

[redacted] Pfizer did not supply us with any information about the results from the Japanese trial. However, we found that some information on this phase I/II trial was reported in the EMA assessment report for Bosulif.[29] Given that Study 200 is a large multi-centre trial (conducted in North America, the European Union, Eastern Europe, Africa and Asia), and includes patients in all stages of CML, we believe that the lack of the results from the Japanese population (N=53) is not a significant weakness of the submission. In addition, one more study based on Study 200 and not identified in the submission, a study reporting baseline HRQL,[30] was identified.

Figure 4. Flow diagram of included studies



(Source: Pfizer submission, Figure B1, p44)

4.1.4 Quality assessment

We will now discuss Study 200, the clinical evidence for the comparator treatments is discussed in 4.3 (p95). Pfizer's quality assessment of Study 200 was performed according to the Chambers (2009) criteria for case series studies.[16] Further information on the quality assessment criteria can be found in Appendix C.

The most challenging aspect of the Study 200 quality assessment critique is its non-randomised single arm design. The design of single-arm studies makes it difficult to assess and generalise results. Results from non-randomised studies may differ from RCT evidence and case series design is considered to be the weakest source of clinical effectiveness evidence in the hierarchy of study designs. Interestingly, case series evidence was considered in 14 out of 47 Heath Technology Assessment reports.[31] While RCTs are designed to maximise internal validity, it can be argued that large, prospective and comprehensive case series may achieve high external validity. Study 200 was a multicentre trial and recruited people consecutively, which could reduce the risk of bias. There is no agreed 'gold standard' appraisal tool for the assessment of non-randomised studies.[32] The Cochrane handbook suggests that reviewers should select and modify or develop a tool that is most appropriate to their topic and the study design.[33] Similarly, the Centre for Reviews and Dissemination (CRD)[34] recommends considering the appropriateness of study design to the research objective, risk of bias, other issues related to study quality, choice of outcome measure, statistical issues, quality of reporting, quality of the intervention and generalizability in a quality assessment of any study. Therefore we will comment on both internal and external validity of Study 200 in addition to the Chambers (2009) criteria.[16] Details of the manufacturer's critical appraisal of Study 200 alongside our critique can be seen in Table 13.

Table 13. Quality assessment of Study 200 using Chambers (2009)[16] criteria

Study	1. Eligibility criteria adequately reported?	2. Study population representative of a normal population?	3. An appropriate measure of variability reported?	4. Loss to follow-up reported or explained?	5. At least 90% included at baseline followed-up?	6. Were patients recruited prospectively?	7. Were patients recruited consecutively?	8. Did the study report relevant prognostic factors?	Quality score
Bosutinib, advanced disease study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 2nd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 3rd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
PenTAG comment	Yes	Yes	Yes	Partially, see section below for more details.	Yes	Yes.	Yes, based on information in this table.	Partially, no risk factors reported.	Good, assuming "partially" is "yes".

4.1.4.1 Internal validity

Selection bias

Full details of Study 200 recruitment procedures are not given. It is not clear whether all eligible patients were invited, or if investigators' discretion affected those included. However, Pfizer states that participants were recruited consecutively in the quality assessment of Study 200 (Pfizer submission, p246) and details for recruited participants are given. Analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. Table 14 shows the difference between recruited and evaluable populations for CML disease phases at different snapshots.

The eligibility criteria allowed investigators to exclude participants if they were considered unable to take daily oral medication reliably. While this is reasonable, it may have allowed some potential for investigators to influence which participants were included.

Table 14. Recruited and evaluable population in Study 200

Population	**CP2L (N=288)**		**CP3L (N=118)**		**AP(N=76)**	**BP(N=64)**
Outcome	March 2011 snapshot evaluable population	February 2012 snapshot evaluable population	March 2011 snapshot evaluable population	February 2012 snapshot evaluable population	March 2011 snapshot evaluable population	March 2011 snapshot evaluable population
Cytogenetic	266	264	108	110	69	54
Haematological	288	285	116	115	69	60
Molecular	200	NR	105[a]	NR	NR	NR

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, N = number of participants, NR = not reported

a Excluded 13 subjects from China, India, Russia and South Africa, where molecular assessment was not performed due to logistical constraints

Performance bias

The dosage of bosutinib in Study 200 was 500mg once daily. Escalation to 600mg in case of haematological or cytological resistance, or reduction to 400 mg and 300mg once daily in case of AE was possible and the protocol for drug dosage was described. Eighty five subjects (15.2%) who started treatment at ≤ 500 mg (n=558) received dose escalations to 600 mg. Detailed information on treatment interruption was requested by PenTAG (Table 15). However, only some information is given for bosutinib dose reduction.

Table 15. Mean days of treatment interruption in Study 200

	CP2L (N=288)	CP3L (N=118)	AP (N=76)	BP (N=64)
Patients with an interruption [N (%)]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days interrupted [Mean (SD)]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Pfizer clarifications, question B5)

Patients were allowed to receive hydroxycarbamide and anagrelide while taking part in Study 200. In addition, patients after SCT or with previous interferon alpha therapy were eligible to take a part. It is not clear if anagrelide or previous SCT and interferon alpha treatment may have an effect on the expected outcomes in Study 200. In fact, 52% of 3rd-line CP patients and 32% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy. Since other than as a bridge to SCT, interferon alpha therapy is hardly used in England and Wales, it increases the uncertainty of Study 200 relevance to the expected clinical population.

Only some data were available on patient compliance with the treatment regiments. One participant (1%) was excluded based on protocol violation in the third line CP CML population.

Detection and reporting bias

No blinding was reported; investigators, care providers and patients were aware that bosutinib was the test drug. This could influence outcomes reporting, especially AE and HRQL, reflecting an understandable enthusiasm for a new drug therapy. However, since the main outcomes are measured objectively, they are less likely to be affected.

Attrition bias

Only 2 patients (0.7%) were lost to follow up in the March 2011 snapshot of second line CP CML patients. Similarly, 2 patients (2%) were lost to follow up in the March 2011 snapshot of third line CP CML patients. At the same snapshot, 3 participants requested treatment discontinuation in third line CP CML. No data are available on the numbers of patients lost to follow up in advanced phase CML.

4.1.4.2 External validity

Patients' characteristics

The full baseline characteristics are discussed in Section 4.2.5 (p69); here we discuss potential threats to external validity. Firstly, Study 200 was not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate (population of unmet clinical need appropriate for

this appraisal). The submission assumes that Study 200 is representative of the population expected in clinical practice. Although based on EMA recommendation, post-hoc analyses of the population of unmet clinical need are available; only 52 patients from Study 200 were eligible. In addition, the submission assumes that mostly third and fourth line patients would be eligible, thus the cost-effectiveness model is based on third-line CP, and combined second-line and multiple TKI AP and BP Study 200 sub-populations. However, we believe that based on current practice, if recommended, bosutinib would be mostly used in second and third line setting (see Section 2.2.2, p45).

Secondly, all patients in Study 200 had previously taken imatinib. Pfizer report the median duration of previous imatinib in the 2nd-line bosutinib chronic phase population as 2.6 years for imatinib-resistant people and as 1.5 years for imatinib-intolerant people (Pfizer submission, p350). Similarly, they report the median duration of previous imatinib in the 3rd-line CP population as 2.7 years (Pfizer submission, p54). However, these durations are much lower than the median of 8 years on 1st-line imatinib in the IRIS trial.[17] We are unable to account for this large discrepancy. We believe that if patients in Study 200 were truly representative of people who fail on imatinib, their median duration of imatinib should be approximately 8 years.

In addition, in third line CP CML, 37 patients were resistant to dasatinib, 50 were intolerant to dasatinib, 27 were resistant to nilotinib and only 1 was intolerant to nilotinib. The patients' characteristics for the third line CP subgroups were similar (Section 4.2.5, p69) to those of all patients in Study 200 (Table 16). We cannot explain why there was only 1 third line patient intolerant to nilotinib. While we cannot comment on treatment effects for nilotinib resistant patients in third line CP CML, the lack of participants in the nilotinib resistant sub-group may have been due to a small sample size.

Table 16. Baseline characteristics for Study 200

	CP2L (N=288)	**CP3L (N=118)**	**AP (N=76)**	**BP (N=64)**	**Unmet clinical need (N=52)**
Age (years) [Median (range)]	53 (18–91)	56 (20–79)	50.5 (18–83)	48.5 (19–82)	58 (19–81)
Male [N (%)]	154 (53%)	53 (45%)	42 (55%)	41 (64%)	31 (60)
Duration of CML disease (years) [Median (range)]	3.6 (0.1–15.1)	6.7 (0.6–18.3)	5.06 (1.11–22.06)	3.08 (0.35–14.46)	NR

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, N = number of participants, NR = not reported

Unsuitability was determined based on Bcr-Abl kinase domain mutations that would be reasonably expected to confer resistance to dasatinib (F317, E255) or nilotinib (E255, Y253, F359) and expected to have sensitivity to bosutinib, or the presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatinib therapy (for more details see Appendix G). Although Pfizer does not propose bosutinib use in patients with T315I mutation, no exclusion criteria for bosutinib use in CML patients was included in the submission.

Mutations T315I and V299L appear to be resistant to bosutinib,[23] Pfizer acknowledged this (Pfizer submission, p14). Indeed, patients with a documented history of prior T315I Bcr-Abl mutation were excluded from Study 200 as of 10 June 2008 due to a lack of efficacy in this group. This change in eligibility criteria resulted in inclusion of some participants with T315I mutation in Study 200. In addition, some participants with V299L may have been included. In fact, 2 participants with V299L were identified in third line CP CML population. Table 17 summarises the efficacy based on the different mutations. Although the numbers of recruited patients with a baseline T315I mutation were small (Appendix H), it may have caused more stringent efficacy estimates.

Table 17. Efficacy in full Study 200 evaluable populations versus those with a baseline T315I and V299L mutations

	Evaluable population		**T315I subpopulation**		**V299L subpopulation**	
	CHR	*MCyR*	*CHR*	*MCyR*	*CHR*	*MCyR*
CP2L	85.0%	53.4%	22.2%	22.2%	50%	0%
CP3L	73.3%	38.9%	28.6%	0%	NA	NA
Advanced phase	25.6%	32.5%	0%	7.7%	NA	NA

Abbreviations: CHR = Complete Haematological Response, MCyR = Major Cytogenetic Response, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable (no patients with V299L mutation identified)
(Source: Pfizer clarifications, question A2; Pfizer submission, Table B19, p71)

Co-morbidity

Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 were excluded from CP CML population and patients with a score of 3 were excluded from advanced phase leukaemia population. Thus 74% and 77% patients were ECOG 0 and 26% and 23% were ECOG 1 in third and second line CP CML respectively. Similarly, in accelerated phase, 54% were ECOG 0, 43% ECOG 1, 3% ECOG 2, and in blast phase, 34% were ECOG 0, 44% ECOG 1, 22% ECOG 2. Our clinical expert believes that these values are similar to those expected in clinical population. Patients

with liver, kidney and severe cardiac disease were excluded; for details on co-morbidities exclusion criteria see Appendix D.

Duration of response

The length of follow up for patients in Study 200 varied. Patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, whereas all patients still on bosutinib were followed up whilst on bosutinib. Thus the OS may be over-estimated because of selective censoring of patients, and this is acknowledged by Pfizer (Pfizer submission, p119).

Statistical analyses

For all populations (disease phases), analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. Intention-to-treat analyses were not reported; this may have resulted in more generous response estimates. PFS and OS were calculated based on all enrolled patients who received at least one dose of bosutinib. All patients who received at least 1 dose of bosutinib (the all-treated population) were also included in the analysis of safety. In addition, no adjustments for multiple comparisons were made for secondary or exploratory analyses (Pfizer response to clarification question A4).

4.2 Critique of clinical evidence for bosutinib

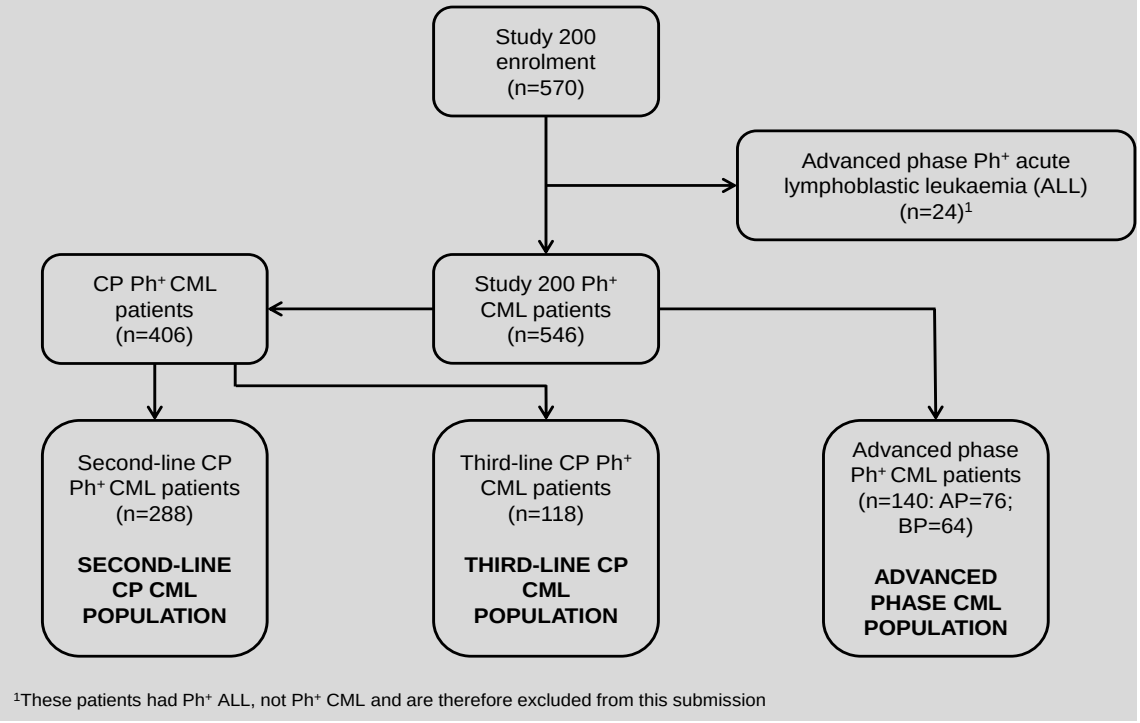
The search results presented by the manufacturer did not identify any randomised controlled trials directly comparing bosutinib with an appropriate comparator. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML:

- **Phase I** of this study defined the maximum tolerated dose of bosutinib in 18 Chronic Phase (CP) CML patients refractory to imatinib
- **Phase II** (n=570, including 18 patients enrolled in Phase I) investigates the efficacy and safety of bosutinib 500mg daily in four clinical sub-populations:
    - Second-line CP CML: Patients in CP CML with imatinib resistance or intolerance (n=288)
    - Third-line CP CML: Patients with imatinib resistance/intolerance followed by dasatinib resistance/intolerance or nilotinib resistance/intolerance or both dasatinib and nilotinib resistance/intolerance (n=118). This population also includes 3 patients who had prior exposure to imatinib, dasatinib and nilotinib, thus received bosutinib in fourth-line setting.

- Advanced phase CML: Patients with imatinib resistance/intolerance or resistance/intolerance to imatinib, dasatinib and/or nilotinib (n=140). This population includes patients receiving bosutinib second line or later:
  - Second line AP CML (n=45)
  - Multi TKI AP CML (n=31)
  - Second line BP CML (n=35)
  - Multi TKI BP CML (n=29)
- Acute lymphoblastic leukaemia: Patients with imatinib resistance or intolerance (n=24)

Figure 5 represents participants' flow in Study 200.

Figure 5. Study 200 participant flow diagram



(Source: Pfizer submission, Figure B2, p50)

Pfizer submission acknowledges that Study 200 was not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate (population of unmet clinical need). However, Study 200 is the only study that evaluates bosutinib in patients who have tried one or more prior TKI therapy (i.e. received bosutinib at second-line or later). The Committee for Medicinal Products for Human Use (CHMP) accepted Study 200 to be representative of the population of unmet clinical need. In addition, based on EMA (European Medicines Agency) recommendations, post-hoc analyses of patients with unmet clinical need from Study 200 were performed.

We agree that after excluding Phase I and the sub-population of acute lymphoblastic leukaemia (Phase II), the results from Study 200 are relevant to the research question. For participant flow of the sub-populations please see Appendix F. A total of 52 patients were eligible for inclusion in the post-hoc analysis of unmet clinical need population based on the presence of a mutation, a medical condition, or prior toxicities that may predispose patients to be unsuitable to nilotinib or dasatinib therapy (Appendix F).

Even though there is only one study assessed in the clinical effectiveness review, multiple references and various data snapshots of Study 200 are available (Table 18).

Table 18. Data sources for Study 200 populations

Third-line CP CML population	Second-line CP CML population	Advanced phase population (AP and BP)
Data snapshot 28 Mar 2011 (minimum/median follow-up: 12/28.5 months): • Khoury (2012)[25] • CSR[27] Data snapshot 15 Feb 2012 (minimum/median follow-up: 24/31.4 months): • Khoury (2012)[28]	Data snapshot 3rd June 2010 (24.2 months median follow-up): • Cortes (2011)[24] Data snapshot 28th March 2011 (24 month minimum follow-up): • CSR[27] Data snapshot 15th May 2012 (36 month minimum follow-up update): • Cortes (2012)[1] HRQL data • Trask (2012)[26]	Data snapshot 28 Mar 2011 (minimum follow-up: 12 months for AP; 18 months for BP): • CSR[27]
Baseline HRQL data • Trask (2013)[30]		

4.2.1 Eligibility criteria

Study 200 evaluates bosutinib in patients who have tried one or more prior TKI therapy. Appendix D lists the Study 200 eligibility criteria. The difference between the Study 200 population and the population defined in Pfizer submission (population of unmet clinical need) was already noted. In addition, criteria that we felt may have an effect on the generalizability of the Study 200 results to the population expected in clinical practice were discussed in Section 4.1.4.2 (p59).

The similarity and differences between the Study 200 and population of the unmet clinical need subpopulation (Appendix G) are discussed in Section 4.2.6 (p72).

4.2.2 Outcomes

Table 19 (p66) summarises primary and secondary outcomes for the three clinical sub-populations considered. Study 200 outcomes definitions are presented in Appendix E. The primary outcome for second and third line CP CML population was the rate of major cytogenetic response (MCyR) by 24 weeks, while the rate of overall haematological response (OHR) by 48 weeks was the primary outcome for the advanced phase populations. Cytogenetic responses (MCyR, CyR), haematological responses (mainly CHR), survival (mainly OS), HRQL and safety outcome (AE) at the March 2011 snapshot and at longer follow up are discussed. No data are available on patients' treatment after bosutinib failure, which adds to the uncertainty in the relevance of the OS data from Study 200.

Table 19. Summary of the methodology applied to Study 200 populations

	Second-line CP CML population (n=288)	Third-line CP CML population (n=118)	Advanced phase CML population (n=140; AP=76, BP=64)
Location	Multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. The 5 countries enrolling the most patients were the United States (147), Russia (66), Italy (53), China (43) and Germany (39).		
Design	Patients were treated with bosutinib 500mg once-daily until disease progression, unacceptable toxicity or withdrawal of consent. Dose escalation to bosutinib 600 mg once daily was permitted in cases of lack of efficacy (CHR not reached by week 8 or CCyR not reached by week 12) and dosage could be reduced in increments of 100 mg, as necessary in accordance with observed toxicities, down to a minimum of 300 mg/day. The dosing regimen used in Study 200 is reflective of the SPC recommendations, discussed in Table 1 [Pfizer submission]. Study 200 was a single-arm trial with no randomisation or blinding procedures. The only intervention was bosutinib 500mg once daily. There were no comparators.		
Duration of study	Study 200 began in January 2006 and is currently still on-going. Patients remain in the trial until death or lost to follow-up.		
Primary outcomes	Rate of MCyR by 24 weeks		Rate of attainment or maintenance of OHR by Week 48
Secondary outcomes	• Further response rates for efficacy endpoints: CCyR, CHR, MMR and CMR • Median duration of MCyR and CHR • Median time to MCyR and CHR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • Transformation Rate • HRQL: FACT-Leu & EQ-5D Safety outcomes were also considered: • Incidence rate of any AEs	• Further response rates for efficacy endpoints: CCyR, MiCyR, CHR, CMR and MMR • Median duration of MCyR, CCyR and CHR • Median time to MCyR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • HRQL: FACT-Leu & EQ-5D Safety outcomes were also considered • Incidence rate of any AEs • Incidence rate of Grade 3/4 AEs • Rate of patient deaths	• Duration of OHR, CHR and MCyR • Median time to confirmed (attained or maintained) OHR and CHR • Cumulative haematological response (for OHR, MHR and CHR) • Cumulative MCyR • BP transformation rate • PFS at 1 year and 2 years • OS at 1 year and 2 years • Time to treatment failure • HRQL: FACT-Leu & EQ-5D

4.2.3 Sample size calculation

The manufacturer used Simon two-stage design for sample size calculation which is often used for phase II cancer clinical trials.[35] The first stage requires a small sample size and sets a benchmark number of successes above which the trial enters the second stage.[36] The power calculations were determined separately for different patient populations, dependent upon their experience with prior TKI therapy and disease progression. The sample size calculation was based on primary outcomes; the rate of MCyR by 24 weeks for second and third line CP CML population and the rate of OHR by 48 weeks for the advanced phase populations (Appendix I). The MCyR rates for third line CP CML populations were based on clinical estimates, and the MCyR rates for second line CP CML as well as the OHR rates for AP and BP populations were based on published dasatinib and nilotinib data. We requested further information on the source of the OHR and MCyR rates used in the sample size calculation:

Due to the paucity of data available in the third line CP CML population when the study was designed, we were unable to provide sample size estimates based on specific clinical trial data. Although the original expectations for the treatment effect for this heavily pre-treated population were based on 2L clinical experience, the response rates observed were considered clinically meaningful within this heavily pre-treated cohort.

The published dasatinib data upon which the accelerated phase sample size calculation was based was taken from the three references below, whilst the blast phase sub-group estimates were based on the first two publications.

1. Talpaz M, Apperley JF, Kim DW, et al. Dasatinib (D) in patients with accelerated phase chronic myeloid leukemia (AP-CML) who are resistant or intolerant to imatinib: Results of the CA180005 'START-A' study. J Clin Oncol. 2006;24: 6526

2. Cortes JE, Kim DW, Rosti G, et al. Dasatinib (D) in patients (pts) with chronic myelogenous leukemia (CML) in myeloid blast crisis (MBC) who are imatinib-resistant (IM-R) or IM intolerant (IM-I): Results of the CA180006 'START-B' study. J Clin Oncol. 2006;24:6529

3. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or –intolerant accelerated-phase chronic myelogenous leukemia. Blood. 2008;111:1834 -1839

(Source: Pfizer clarifications, response to question A4)

It is not clear how Pfizer arrived at the rates of MCyR and OHR used in the sample size calculation. However based on the results of a systematic review of clinical effectiveness of dasatinib and nilotinib,[2] the estimates used in the submission appear to be within the range of reported results.

Interestingly, while no sample size calculation for imatinib and nilotinib intolerant third line CP CML patients was included in the submission, the response to clarification questions states that no statistical analyses of these patients were planned (Appendix J). Also no post-hoc sample size calculation for the unmet clinical need population was provided.

Study 200 recruitment was closed without reaching planned sample sizes for AP and BP CML patients due to slow accrual. Patients in second and third line CP CML were over-recruited because of a change in the evaluable population definition.

4.2.4 Statistical analysis

As already mentioned in Section 4.1.4, analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. Table 14 (p58) showed the difference between recruited and evaluable populations for CML disease phases at different snapshots. OS and AE were calculated for all patients who received at least 1 dose of bosutinib (the all-treated population). No intention-to-treat analyses or adjustments for multiple comparisons were reported.

Importantly, the analyses defined in the protocol have changed. The protocol pre-defined analyses considered patients with baseline MCyR or CCyR as non-responders. The new analyses consider patients who maintained or achieved a cytogenetic or haematological response as responders. Using the two approaches, 32%, or 38.9% of third-line CP CML patients, achieved, or attained and achieved MCyR at 12 months minimum follow up respectively. The results of the post-hoc analyses, with higher response rates, when both achieved and maintained response are considered to be a response, were reported in Pfizer submission, and are used in the cost-effectiveness model.

Of note is that the definition of evaluable patients has changed, from all treated patients with a valid baseline and post-baseline measurement or early death or progression, to all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. The first definition was found to produce a biased analysis, as subjects who discontinued early due to adverse events are ‘unevaluable’.

The outcomes used in the cost effectiveness model: MCyR, OHR, overall survival (OS), treatment discontinuation, HRQL and adverse events (AE) rates, are discussed in Section 4.2.6 (p72). The

results are described separately for the Study 200 sub-populations, and the post hoc analyses of patients that may have an unmet clinical need according to the proposed EMA indication.

4.2.5 Baseline characteristics

Study 200 baseline characteristics are summarised in Table 20 (p70). The full characteristics as supplied by Pfizer are included in Appendix K. We discussed some of the participants' characteristics in Section 4.1.4. ECOG performance status of Study 200 appears to be similar to the one expected in clinical population. The median age seems to be close to 50 years for all subpopulations, with the exception of second line BP patients. The post imatinib BP population (n=35) median age is 37 years (range 19–79), which is particularly low probably due to a small sample size. The proportion of male patients differs from 38% to 69% across the Study 200 subpopulations.

Baseline mutation status was recorded for 210 second-line CP, 117 third-line CP and 86 advanced phase CML patients. Based on May 2011 snapshot evaluable population, 78 (37%) second-line CP participants had ≥1 of 42 unique Bcr-Abl kinase domain mutations, of these 9 (4%) with the T315I mutation. Similarly, 65 (55.6%) third-line CP participants had Bcr-Abl kinase domain mutations, of these 15 (12.8%) with the T315I mutation. Forty (47%) advanced phase participants had ≥1 of 19 unique Bcr-Abl kinase domain mutations, including 7 (8%) with the T315I mutation. Information on cytogenetic and haematological response by baseline mutation status is included in Appendix L.

An important comparison is between the complete Study 200 population with the population of unmet clinical need (Appendix G). The results of the Study 200 populations and the population of the unmet clinical need sub population are discussed in Section 4.2.6 (p72).

Table 20. Study 200, baseline characteristics

Population		Age (years) [Median (range)]	Male [N (%)]	CML duration (years) [Median (range)]	IM duration (years) [Median (range)]	ECOG Performance Status [N (%)]		
						0	*1*	*2*
CP2L (N=288)	IM-R CP2L (N=200)	51.0 (18–86)	116 (58%)	4.0 (0.1–15.1)	2.6 (0.4–8.8)	151[a] (77%)	44[a] (23%)	0[a] (0%)
	IM-I CP2L (N=88)	54.5 (23–91)	38 (43%)	2.8 (0.1–13.6)	1.5 (<0.1–8.3)	68[a] (76%)	21[a] (23%)	1[a] (1%)
	Total CP2L (N=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	IM + DAS resistant CP3L (N=37)	54.0 (23–69)	14 (38%)	7.5 (1.2–17.6)	2.6 (0.02–6.4)	28 (76%)	9 (24%)	NA
	IM + DAS intolerant CP3L (N=50)	58.0 (25–79)	23 (46%)	5.6 (0.6–18.3)	3.3 (0.1–6.6)	31 (62%)	18 (36%)	NA
	IM + NI resistant CP3L (N=27)	52.0 (20–79)	14 (52%)	5.9 (1.2–16.3)	2.5 (0.7–5.9)	25 (93%)	2 (7%)	NA
	IM + DAS ± NI CP3L (N=4)	54.5 (31–62)	2 (50%)	11.7 (2.2–11.9)	3.0 (1.4–6.4)	2 (50%)	2 (50%)	NA
	Total CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	AP IM only (N=45)	47.0 (18–73)	24 (53%)	3.85 (1.1–22.1)	NR	26 (58%)	18 (40%)	1 (3%)
	AP Multi TKI (N=31)	56.0 (21–83)	18 (58%)	8.25 (1.5–19.2)	NR	15 (48%)	15 (48%)	1 (3%)
	AP Total (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.1–22.1)	NR	16 (46%)	10 (29%)	9 (26%)
BP (N=64)	BP IM only (N=35)	37.0 (19–75)	24 (69%)	1.75 (0.4–5.6)	NR	16 (46%)	10 (29%)	9 (26%)
	BP Multi TKI	53.0 (22–82)	17 (59%)	5.75 (1.1–14.6)	NR	6 (21%)	18 (62%)	5 (17%)

	(N=29)							
	BP Total (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.4–14.5)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need[b](N=52)	CP2L (N=15)	65 (24-81)	10 (67%)	NR	NR	6 (40%)	9 (60%)	0
	CP3L (N=21)	58 (30-79)	11 (52%)	NR	NR	13 (62%)	8 (38%)	0
	AP (N=5)	66 (48-73)	6 (60%)	NR	NR	1 (20%)	4 (80%)	0
	BP (N=11)	51 (19-80)	7 (64%)	NR	NR	2 (18%)	6 (55%)	3 (27%)
	Total (N=52)	58 (19-81)	31 (60%)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

4.2.6 Results

4.2.6.1 Cytogenetic response

As mentioned in Section 4.2.4 (p68), the protocol pre-defined analyses considering patients with baseline MCyR or CCyR as non-responders were not used. The post-hoc analyses (when both achieved and maintained MCyR or CCyR are considered to be a response) were used. The MCyR in the third line CP population was used in the cost-effectiveness model to estimate OS for bosutinib in CP CML. Because of the number of snapshots available and the multiple results reported, we collated the various results and calculated 95% Clopper-Pearson confidence intervals using Stata v.12[37] (Table 21). The cytogenetic response tables supplied in the submission are included in Appendix M. The rate of MCyR and CCyR increases only slightly as the duration of minimum follow-up increases, and the rate decreases with disease progression (Table 21). The imatinib resistant population seems to achieve similar rates as imatinib intolerant second line CP CML population (Appendix M), while dasatinib and nilotinib resistant patients seem to have slightly lower response rates than dasatinib intolerant third line CP CML patients (Appendix M).

It is interesting to compare the different sup-populations with the unmet clinical need sub-groups. It seems that apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical population. This would act to give a conservative estimate of the cost-effectiveness of bosutinib use in CP, given that Pfizer estimate OS for bosutinib in CP based on MCyR. However due to the very small numbers of participant in the unmet clinical need populations, any assumptions based on the unmet clinical need result have a high degree of uncertainty.

Table 21. Cytogenetic responses for all subpopulations at different snapshots

Population		Responding/N	MCyR% (95%CI)	Responding/N	CCyR% (95%CI)
CP2L	CP2L June 2010[24]	140/266[a]	52.6%[a] (46.4, 58.8)	110/266[a]	41.4%[a] (35.4, 47.5)
	CP2L March 2011[27]	142/266	53.4% (47.2, 59.5)	114/266	42.9 (36.8, 49.0)
	CP2L February 2012[27][b]	168/286	58.7% (52.8, 64.5)	141/286	49.3% (43.4, 55.3)
	CP2L May 2012[1]	155/264	58.7% (52.5, 64.7)	130/264	49.3% (43.1, 55.4)
	CP2L unmet clinical need population[27]	9/15	60% (32.3, 83.7)	8/15	53.3% (26.6, 78.7)
CP3L	CP3L March 2011[25, 27]	42/108	38.9%[c] (29.7, 48.7)	33/108	30.6%[d] (22.1, 40.2)
	CP3L February 2012[27, 28]	45/110	40.9%[e] (31.6, 50.7)	35/110	31.8%[f] (23.3, 41.4)
	CP3L unmet clinical need population[27]	9/21	42.9%[g] (21.8, 66.0)	7/21	33.3% (14.6, 57.0)
AP	AP March 2011[27]	24/69	34.8% (23.7, 47.2)	17/69	24.6% (15.1, 36.5)
	AP February 2012[27][b]	30/77	39.0% (28.0, 50.8)	23/77	29.9% (20.0, 41.4)
	AP unmet clinical need population[27]	3/5	60.0% (14.7, 94.7)	3/5	60.0% (14.7, 94.7)
BP	BP March 2011[27]	16/54	29.6% (18.0, 43.6)	11/54	20.4% (10.6, 33.5)
	BP February 2012[27][b]	21/64	32.8% (21.6, 45.7)	16/64	25% (15.0, 37.4)
	BP unmet clinical need population[27]	2/11	18.2%[h] (2.3, 51.8)	2/11	18.2% (2.3, 51.8)

Abbreviations: AP = accelerated phase, BP= blast phase, CP2L= second line chronic phase, CP3L= third line chronic phase

a Only patients attaining cytogenetic response counted as responders, not directly comparable with the rest of the table (protocol pre-specified analyses)

b Information extracted from the cost-effectiveness model supplied with the submission

c Results for the protocol pre-specified analysis for MCyR were 32.4% (23.7, 42.1)

d Results for the protocol pre-specified analysis for CCyR were 24.1% (16.4, 33.3)

e Different results found in Pfizer's economic model: 41.2% (32.1, 50.6)

f Different results found in Pfizer's economic model: 32.8% (24.4, 42.0)

g Different results found in Pfizer's economic model: 47.6% (25.7, 70.2)

h Different results found in Pfizer's economic model: 36.4% (10.9, 69.2)

4.2.6.2 Haematological response

Similarly to cytogenetic responses, not the protocol pre-defined analyses considering patients with baseline CHR as non-responders, but new analyses when both, achieved and maintained response, are considered to be a response, are discussed. Because of the number of snapshots available and the multiple results reported, we collated the various results and calculated 95% Clopper-Pearson confidence intervals using Stata v.12[37] (Table 22). The haematological response tables supplied in the submission are included in Appendix N. While the rate of CHR does not seem to change with increased duration of minimum follow-up, the rates decrease with disease progression. Again, it seems that the results of the post-hoc unmet clinical need population show slightly higher response rates. However, due to the very small numbers of participant in the unmet clinical need populations, any assumptions based on the unmet clinical need result have a high degree of uncertainty.

Table 22. Haematological responses for all sub-populations at different snapshots

Population		Responding/N	CHR% (95%CI)
CP2L	CP2L June 2010[24]	247/287	86.1% (81.5, 89.9)
	CP2L March 2011[27]	244/288	84.7% (80.0, 88.7)
	CP2L February 2012[27][a]	245/286	85.7% (81.1, 89.5)
	CP2L May 2012[1]	244/285	85.6%[b] (81.0, 89.5)
	CP2L unmet clinical need population[27][a]	12/15	80% (51.9, 95.7)
CP3L	CP3L March 2011[25, 27]	85/116	73.3% (64.3, 81.1)
	CP3L February 2012[27]	87/119	73.1% (64.2, 80.8)
	CP3L February 2012[27, 28]	84/115	73.0% (64.0, 80.9)
	CP3L unmet clinical need population[27]	18/21	85.7%[c] (63.7, 97.0)
AP	AP March 2011[27]	24/69	34.8% (23.7-47.2)
	AP unmet clinical need population[27]	4/5	80% (28.4, 99.5)
BP	BP March 2011[27]	9/60	15% (7.1, 26.6)
	BP unmet clinical need population[27]	3/11	27.3% (6.0, 61.0)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a Information extracted from Pfizer's economic model

b Reported in submission as 85%

c Different results found in Pfizer's economic model: 81.0% (58.1, 94.6)

4.2.6.3 Overall survival

Overall survival (OS) results were based on all enrolled patients who received at least one dose of bosutinib. Table 23, Table 24 and Table 25 detail the Kaplan-Meier (K-M) estimates of Study 200 subpopulations based on different snapshots. As expected, the estimated OS is shorter for more advanced disease phases. The OS tables supplied in the submission are included in Appendix O. In addition, as mentioned earlier, patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, while patients on bosutinib were followed up whilst on bosutinib. Thus the OS may be overestimated beyond 2 years because of selective censoring of patients.

Table 23. Kaplan-Meier estimate of overall survival in CP2L subpopulation at different snapshots

CP2L	**OS at 1 year (95%CI)**			**OS at 2 years (95%CI)**		
	Total N	**IM resistant N**	**IM intolerant N**	**Total N**	**IM resistant N**	**IM intolerant N**
June 2010[24]	97% 288	NR	NR	92% 288	92% 200	98% 88
March 2011[27[a]]	96.8% (94.0, 98.3) 288	95.9% (92.0, 97.9) 200	87.6% (82.1, 91.5) 88	90.6% (86.5, 93.5) 288	98.8% (92.0, 99.8) 200	97.6% (90.9, 99.4) 88
May 2012[1]	NR	NR	NR	NR 286	88% (83, 92) 195	98% (91, 99) 91
Unmet clinical need[27]	NR	NR	NR	NR	NR	NR

Abbreviations: CP2L = second line chronic phase, OS = overall survival, CI = confidence interval, IM = imatinib, N = number of participants, NR = not reported

a Source: Pfizer clarifications

Table 24. Kaplan-Meier estimate of overall survival in CP3L subpopulation at different snapshots

CP3L	OS at 1 year (95%CI)				OS at 2 years (95%CI)			
	Total N	IM + DAS resistant N	IM + DAS intolerant N	IM + NI resistant N	Total N	IM + DAS resistant N	IM + DAS intolerant N	IM + NI intolerant N
March 2011[25, 27]	91.2% (84.3, 95.2) 118	82.8% (65.6, 91.9) 37	93.9% (82.3, 98.0) 50	96.3% (76.5, 99.5) 27	82.9% (74.1, 88.9) 118	75.2% (56.1, 86.9) 37	85.4% (71.7, 92.8) 50	91.7% (70.5, 97.5) 27
February 2012[27, 28]	91.4% (84.6, 95.3) 119	83.6% (67.0, 92.3) 38	93.9% (82.3, 98.0) 50	96.3% (76.5, 99.5) 27	84.0% (75.8, 89.6) 119	77.4% (59.7, 88.0) 38	85.4% (71.7, 92.8) 50	92.4% (73.0, 98.1) 27
Unmet clinical need[27]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CP3L = third line chronic phase, OS = overall survival, CI = confidence interval, IM = imatinib, DAS = dasatinib, NI = nilotinib, N = number of participants, NR = not reported

Table 25. Kaplan-Meier estimate of overall survival in AP and BP subpopulations at different snapshots

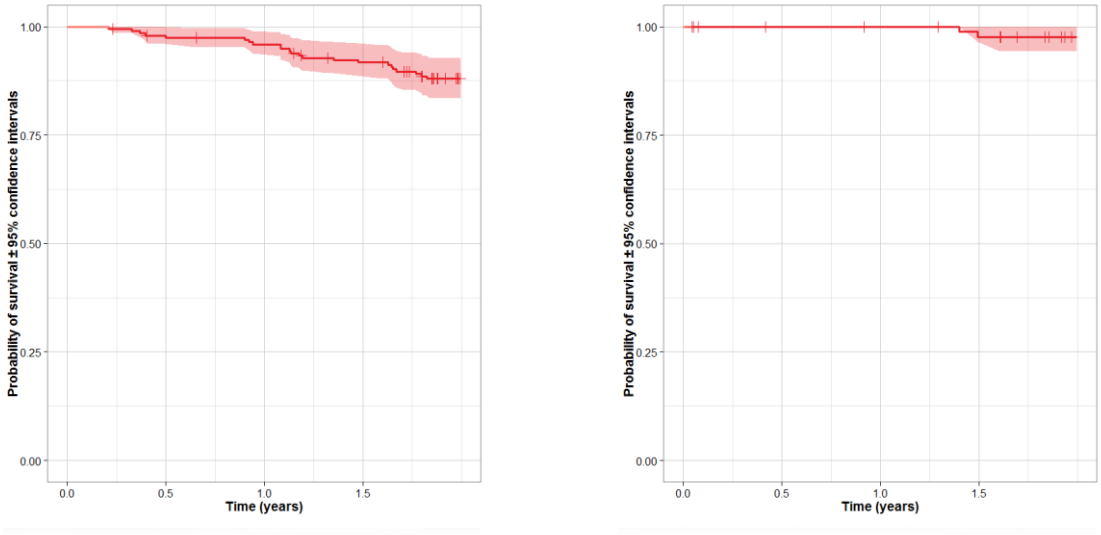
AP and BP	OS at 1 year (95%CI)			OS at 2 years (95%CI)		
	Total N	IM N	Multi TKI N	Total N	IM N	Multi TKI N
AP March 2011[27]	76.0% (64.7, 84.2) 76	NA	NA	65.6% (53.4, 75.4) 76	NA	NA
AP unmet clinical need[27]	NR	NR	NR	NR	NR	NR
BP March 2011[27]	43.8% (31.3, 55.6) 64	NA	NA	35.4% (23.8, 47.3) 64	NA	NA
BP unmet clinical need[27]	NR	NR	NR	NR	NR	NR

Abbreviations: AP = accelerated phase, BP = blast phase, OS = overall survival, CI = confidence interval, IM = imatinib, TKI = tyrosine kinase inhibitor, N = number of participants, NR = not reported

The imatinib-intolerant population seems to achieve better OS than the imatinib-resistant second line CP CML population. The nilotinib-resistant population seems to have the highest, while dasatinib-resistant populations seem to have the lowest OS estimates in third line CP CML population. Figure

6, Figure 7 and Figure 8 show the K-M estimates of OS for all three subpopulations (as included in Pfizer submission and Pfizer response to clarification questions).

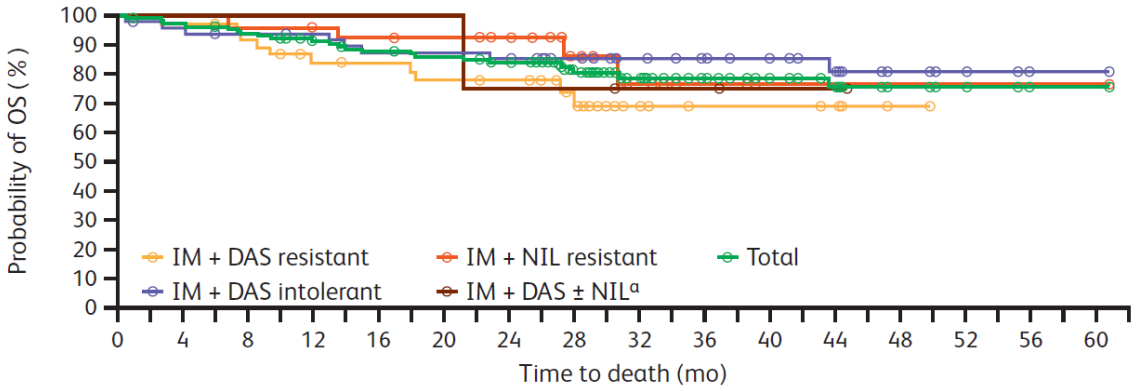
Figure 6. Kaplan-Meier estimates of overall survival for the 2nd-line CP all-treated population



Imatinib-resistant Imatinib-intolerant

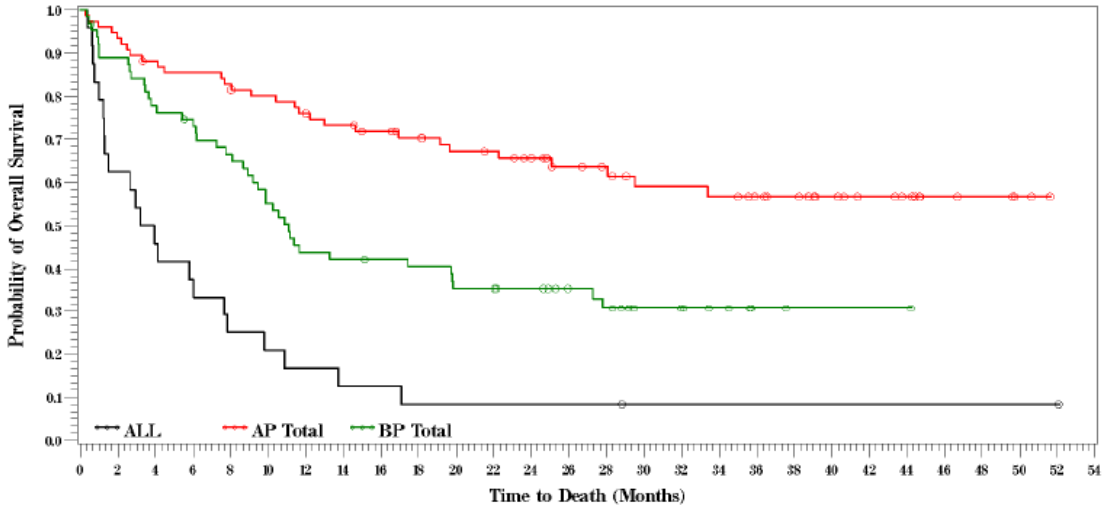
(Source: Pfizer response to clarification question B3)

Figure 7. Kaplan-Meier estimate of overall survival for the 3rd-line CP all-treated population (15 Feb 2012 snapshot)



(Source: Pfizer submission, Figure B12, p70)

Figure 8. Overall survival for the advanced phase CML population (28 Mar 2011 snapshot)



(Source: Pfizer submission, Figure B12, p79)

4.2.6.4 Treatment discontinuation and adverse events

All toxicities, up to 30 days after the last dose of bosutinib, were assessed according the National Cancer Institute Common Terminology for Adverse Events Version 3.0. We have already mentioned that no separate searches were conducted to search for adverse events evidence. However safety data are also available from a Phase III Study 3000 (NCT00574873; 3160A4-3000), a two-arm, randomized, open-label trial designed to evaluate the efficacy and safety of bosutinib compared to imatinib in subjects newly diagnosed with chronic phase CML (bosutinib n=248 and imatinib N=251). In addition, the Summary of Product Characteristics (SPC) for bosutinib combined evaluation of AE from the following three studies: Study 300 (248 patients treated with bosutinib), Study 200 (n=570, including 24 patients with acute CML) and 53 patients in the Japanese phase I/II trial (a dose-escalation study in CP CML patients followed with an evaluation study of safety and efficacy of the maximum tolerated dose in CML patients); all patients received at least 1 dose of single agent bosutinib. A summary of the three efficacy and safety studies is in Appendix P.

The treatment discontinuation and adverse events tables as supplied in the submission and response to clarification questions (including results from Study 3000) are presented in Appendix Q. Table 26 summarises reasons for treatment discontinuation in Study 200, the results reported are medians, not Kaplan-Meier estimates. While Table 27 and Table 28 summarise AE reported in Study 200 for different subpopulations. Finally Table 29 shows the combined AE from the three efficacy studies as reported in SPC. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (CP3L subgroup, n=4).

Adverse events were mainly restricted to gastrointestinal toxicities in both the chronic and advanced phases of the disease and in the majority of cases these toxicities were mild in severity. Overall, grade 3–4 non-haematological AE appear rare; diarrhoea was reported in patients in all lines of treatment: imatinib resistant CP2L 9%, imatinib intolerant CP2L 11%, CP3L 8.5%, AP 3.9% and BP 6.3%. Similarly rash was reported in imatinib resistant CP2L 8%, imatinib intolerant CP2L 12%, CP3L 4.2%, AP 3.9% and BP patients 3.1%. In addition, vomiting was reported in imatinib resistant CP2L 2%, imatinib intolerant CP2L 9%, AP 3.9% and BP 3.1%, but not among CP3L patients. In the advanced phases, fatigue (3.9 % and 3.1 % for AP and BP respectively), pleural effusion (5.3 % and 3.1 % for AP and BP respectively), and dyspnoea (7.9 % and 2.3 % for AP and BP respectively) were also reported. Fatigue was also reported in CP 2L; imatinib resistant CP2L 1%, imatinib intolerant CP2L 2%. The most common haematological events were thrombocytopaenia, neutropaenia and anaemia. In comparison with other TKIs, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] While the most commonly reported nilotinib AEs were thrombopenia, neutropenia , anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase, and bilirubin. In addition, the FDA has stipulated that nilotinib carry a 'black box' warning for possible heart problems that may lead to an irregular heart beat and possibly sudden death.[2]

Table 26. Treatment discontinuation in Study 200

Reason for discontinued treatment	Second line CP[a]			Third line CP[b]					Advanced CML[c]		Unmet clinical need population[d]
	15 May 2012 snapshot			15 February 2012 snapshot					28 March 2011 snapshot		28 March 2011 snapshot
	IM-R (n=200)	IM-I (n=88)	Total (n=288)	IM + DAS resistant (n=38)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NIL[a] (n=4)	Total (n=119)	AP CML (n=76)	BP CML (n=64)	Total (n=52)
Discontinued treatment, n (%)	109 (56)	57 (63)	166 (58)	32 (84)	37 (74)	18 (67)	3 (75)	90 (76)	61 (80)	61 (95)	NR
AE	35 (18)	6 (7)	66 (23)	6 (16)	17 (34)	3 (11)	0	26 (22)	18 (23.7)	6 (9.4)	13 (25)
Lack of efficacy	19 (10)	5 (6)	24 (8)	12 (32)	7 (14)	5 (19)	1 (25)	25 (21)	NR	NR	NR
Disease progression	35 (18)	6 (7)	41 (14)	7 (18)	4 (8)	7 (26)	2 (50)	20 (17)	NR	NR	NR
Patient request	11 (6)	6 (7)	17 (6)	2 (5)	3 (6)	1 (4)	0	6 (5)	NR	NR	NR
Death	6 (3)	0	6 (2)	2 (5)	2 (4)	0	0	4 (3)	NR	NR	NR
Investigator Request	2 (1)	0	2 (1)	0	0	2 (7)	0	2 (2)	NR	NR	NR
Lost to follow-up	2 (1)	0	2 (1)	2 (5)	0	0	0	2 (2)	NR	NR	NR
Protocol violation	NR	NR	NR	0	1 (2)	0	0	1 (1)	NR	NR	NR
Other	4 (2)	4 (4)	8 (3)	1 (3)	3 (6)	0	0	4 (3)	NR	NR	NR

Abbreviations: CP = chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

a Pfizer response to clarification questions A1

b Pfizer submission, Table B19, p73

c Pfizer response to clarification questions A6 and Pfizer submission Table B21, p74

d Pfizer submission Table B110, p366

Table 27. Non-haematological bosutinib AEs for all sub-populations at different snapshots

Population		Diarrhoea % (n/N)	Nausea % (n/N)	Vomiting % (n/N)	Rash % (n/N)	Dose reduction due to AE % (n/N)	Treatment discontinuation due to AE % (n/N) [% of participants with treatment discontinuation (n/N)]
CP2L	CP2L Total	85.3%* (244/286)	45.5%* (130/286)	36.7%* (105/286)	36%* (103/286)	47%[g] (135/288)	23%[a] (66/286) [58% (168/286)]
	CP2L IM-R	85%* (165/195)	43%* (83/195)	36%* (70/195)	32%* (63/195)	43%[g] (86/200)	15%[a] (30/195) [56% (109/195)]
	CP2L IM-I	87%* (79/91)	52%* (47/91)	39%* (35/91)	44%* (40/91)	56%[g] (49/88)	40%[a] (36/91) [63% (578/91)]
CP3L	CP3L total	82.4%[b] (98/119)	48.7%[b] (58/119)	39.5%[b] (47/119)	26.9%[b] (32/119)	63%[f]	22%[e] (26/119) [76% (90/119)]
	CP3L IM+NI resistant	85.2%[b] (23/27)	48.1%[b] (13/27)	29.6%[b] (8/27)	11.1%[b] (3/27)	NR	11%[e] (3/27) [67% (18/27)]
	CP3L IM+DAS resistant	78.9%[b] (30/38)	55.3%[b] (21/38)	39.5%[b] (15/38)	23.7%[b] (9/38)	NR	16%[e] (6/38) [84% (32/38)]
	CP3L IM+DAS intolerant	82%[b] (41/50)	44%[b] (22/50)	48%[b] (24/50)	38%[b] (19/50)	NR	34%[e] (17/50) [74% (37/50)]

AP	AP total	85.5%[c] (65/76)	44.7%[c] (34/76)	44.7%[c] (34/76)	32.9%[c] (25/76)	40.8%[c] (31/76)	23.7%[c] (18/76)
	AP IM	84.4%[c] (38/45)	37.8%[c] (17/45)	51.1%[c] (23/45)	35.6%[c] (16/45)	37.8%[c] (17/45)	25.8%[c] (10/45)
	AP Multi TKI	87.1%[c] (27/31)	54.8%[c] (17/31)	35.5%[c] (11/31)	29%[c] (9/31)	45.2%[c] (14/31)	29%[c] (8/31)
BP	BP total	65.6%[c] (42/64)	50%[c] (32/64)	39.1%[c] (25/64)	31.3%[c] (20/64)	26.6%[c] (17/64)	9.4%[c] (6/64)
	BP IM	65.7%[c] (23/35)	51.4%[c] (18/35)	31.4%[c] (11/35)	28.6%[c] (10/35)	31.4%[c] (11/35)	2.9%[c] (1/35)
	BP Multi TKI	65.5%[c] (19/29)	48.3%[c] (14/29)	48.3%[c] (14/29)	34.5%[c] (10/29)	20.7%[c] (6/29)	17.2%[c] (5/29)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

* Subjects reporting ≥20% treatment-emergent adverse events (Pfizer submission table B108, p359)

a May 2012 snapshot (Pfizer response to clarification questions A7)

b Subjects reporting ≥10% treatment-emergent adverse events, Feb 2012 snapshot (Pfizer response to clarification questions A5)

c Subjects reporting ≥10% treatment-emergent adverse events (Pfizer response to clarification questions A6)

d Patients with an interruption (Pfizer response to clarification question B5)

e Treatment discontinuation, February 2012 snapshot (Pfizer submission, Table B19, p73)

Table 28. Haematological bosutinib adverse effects for all subpopulations at different snapshots

Population		Thrombocytopenia	Neutropenia	Anaemia	Thrombocytopenia Grade 3/4	Neutropenia Grade 3/4	Anaemia Grade 3/4
CP2L	CP2L Total	66%[a] (191/288)	40%[a] (116/288)	90%[a] (258/288)	24%[a] (68/288)	18%[a] (53/288)	13%[a] (36/288)
	CP2L IM-R	68%[a] (60/88)	48%[a] (42/88)	86%[a] (76/88)	33%[a] (29/88)	28%[a] (25/88)	18%[a] (16/88)
	CP2L IM-I	66%[a] (131/200)	37%[a] (74/200)	91%[a] (182/200)	20%[a] (39/200)	14%[a] (28/200)	10%[a] (20/200)
CP3L	CP3L Total	34.7%[b] (41/118)	17.8%[b] (21/118)	15.3%[b] (18/118)	25.4%[b] (30/118)	14.4%[b] (17/118)	5.1%[b] (6/118)
	CP3L IM+NI resistant CP3L IM+DAS resistant CP3L IM+DAS intolerant	NR					
AP	AP Total	42.1%[c] (32/76)	15.8%[c] (12/76)	42.1%[c] (32/76)	32.9%[c] (25/76)	14.5%[c] (11/76)	30.3%[c] (23/76)
	AP IM / Multi TKI	NR					
BP	BP total	28.1%[c] (18/64)	20.3%[c] (13/64)	28.1%[c] (18/64)	26.6%[c] (17/64)	20.3%[c] (13/64)	18.8%[c] (12/64)
	BP IM / Multi TKI	NR					

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor, NR = not reported, subjects reporting ≥10% treatment-emergent adverse events, and subjects reporting ≥5% treatment-emergent adverse events

a Cortes (2011)

b March snapshot (Pfizer submission, Table B27, p81)

c March snapshot (Pfizer submission, Table B29, p81)

Table 29. Adverse reactions for bosutinib from SPC

System Organ Class	Frequency	Adverse reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations	Very common	Respiratory tract infection[a]	99 (11.4)	4 (0.5)	0
	Common	Pneumonia[b]	45 (5.2)	21 (2.4)	5 (0.6)
		Influenza	47 (5.4)	2 (0.2)	0
		Bronchitis	27 (3.1)	1 (0.1)	0
		Nasopharyngitis	81 (9.3)	0	0
Blood and lymphatic system disorders	Very common	Thrombocytopenia	335 (38.5)	127 (14.6)	94 (10.8)
		Neutropenia	141 (16.2)	67 (7.7)	33 (3.8)
		Anaemia	238 (27.4)	82 (9.4)	25 (2.9)
		Leukopenia	94 (10.8)	31 (3.6)	8 (0.9)
	Common	Febrile Neutropenia	13 (1.5)	8 (0.9)	3 (0.3)
	Uncommon	Granulocytopenia	2 (0.2)	0	2 (0.2)
Immune system disorders	Common	Drug hypersensitivity	12 (1.4)	7 (0.8)	0
	Uncommon	Anaphylactic shock	2 (0.2)	0	2 (0.2)
Metabolism and nutrition disorders	Very Common	Decreased appetite	109 (12.5)	4 (0.5)	0
	Common	Dehydration	20 (2.3)	2 (0.2)	0
		Hyperkalaemia	23 (2.6)	2 (0.2)	1 (0.1)
		Hypophosphataemia	54 (6.2)	18 (2.1)	0
Nervous system disorders	Very common	Headache	148 (17.0)	9 (1.0)	3 (0.3)
	Common	Dizziness	74 (8.5)	2 (0.2)	0
		Dysgeusia	18 (2.1)	0	0
Ear and labyrinth disorders	Uncommon	Tinnitus	8 (0.9)	0	0
Cardiac disorders	Common	Pericardial effusion	16 (1.8)	2 (0.2)	1 (0.1)
		Electrocardiogram QT prolonged[c]	10 (1.1)	1 (0.1)	0
	Uncommon	Pericarditis	1 (0.1)	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	125 (14.4)	0	0
	Common	Dyspnoea	82 (9.4)	15 (1.7)	3 (0.3)
		Pleural effusion	52 (6.0)	14 (1.6)	1 (0.1)
	Uncommon	Respiratory failure	5 (0.6)	1 (0.1)	1 (0.1)
		Acute pulmonary oedema	3 (0.3)	1 (0.1)	1 (0.1)
		Pulmonary hypertension	4 (0.5)	1 (0.1)	0

Gastrointestinal disorders	Very common	Diarrhoea	683 (78.5)	78 (9.0)	1 (0.1)
		Vomiting	323 (37.1)	25 (2.9)	0
		Nausea	366 (42.1)	10 (1.1)	0
		Abdominal pain[d]	291 (33.4)	15 (1.7)	0
	Common	Gastritis	25 (2.9)	3 (0.3)	1 (0.1)
	Uncommon	Acute pancreatitis	3 (0.3)	2 (0.2)	1 (0.1)
		Gastrointestinal haemorrhage[e]	6 (0.7)	5 (0.6)	0
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	194 (22.3)	79 (9.1)	10 (1.1)
		Aspartate aminotransferase increased	160 (18.4)	41 (4.7)	3 (0.3)
	Common	Hepatotoxicity[f]	15 (1.7)	5 (0.6)	1 (0.1)
		Hepatic function abnormal	27 (3.1)	8 (0.9)	3 (0.3)
		Blood bilirubin increased	33 (3.8)	8 (0.9)	0
		Gamma-glutamyltransferase increased	29 (3.3)	7 (0.8)	0
	Uncommon	Liver Injury	2 (0.2)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	Very common	Rash[g]	282 (32.4)	51 (5.9)	2 (0.2)
	Common	Urticaria	26 (3.0)	2 (0.2)	1 (0.1)
		Acne	25 (2.9)	0	0
		Pruritus	71 (8.2)	3 (0.3)	0
	Uncommon	Erythema multiforme	1 (0.1)	0	1 (0.1)
		Exfoliative rash	6 (0.7)	1 (0.1)	0
		Drug eruption	5 (0.6)	1 (0.1)	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	96 (11.0)	3 (0.3)	0
	Common	Myalgia	49 (5.6)	3 (0.3)	0
		Back pain	72 (8.3)	7 (0.8)	1 (0.1)
Renal and urinary disorders	Common	Renal failure	13 (1.5)	2 (0.2)	1 (0.1)
	Uncommon	Renal failure acute	7 (0.8)	3 (0.3)	1 (0.1)
		Renal impairment	8 (0.9)	1 (0.1)	0
General disorders and administration site conditions	Very common	Pyrexia	204 (23.4)	6 (0.7)	1 (0.1)
		Oedema[h]	100 (11.5)	1 (0.1)	0
		Fatigue[i]	169 (19.4)	14 (1.6)	1 (0.1)
	Common	Chest pain[j]	61 (7.0)	4 (0.5)	1 (0.1)
		Pain	41 (4.7)	5 (0.6)	0

		Asthenia	86 (9.9)	7 (0.8)	2.(0.2)
Investigations	Common	Lipase increased	76 (8.7)	41 (4.7)	4 (0.5)
		Blood creatinine increased	42 (4.8)	2 (0.2)	0
		Blood amylase increased	31 (3.6)	7 (0.8)	0
		Blood creatine phosphokinase increased	28 (3.2)	3 (0.3)	2 (0.2)

The following terms have been combined:

a Respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral
b Pneumonia, bronchopneumonia, primary atypical pneumonia, lobar pneumonia
c Electrocardiogram QT prolonged, long QT syndrome
d Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain
e Gastrointestinal haemorrhage, gastric haemorrhage, upper gastrointestinal haemorrhage
f Hepatotoxicity, toxic hepatitis, cytolytic hepatitis
g Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash
h Oedema, face oedema, localized oedema, peripheral oedema
i Fatigue, malaise
j Chest pain, chest discomfort

(Source: Pfizer response to clarification question A1)

Cross-intolerance and cross-resistance

The reported cross-intolerance between bosutinib and dasatinib showed that 8% patients discontinued treatment with bosutinib as a result of same AE:

> This study included a retrospective evaluation of cross-intolerance between dasatinib and bosutinib. This retrospective evaluation provides an indication of how likely it is that the reason(s) for inappropriateness of dasatinib may also render bosutinib inappropriate, where the reason(s) are based on intolerance due to adverse events. This is therefore highly relevant to the scope of this submission, since the indication for bosutinib includes patients for whom dasatinib is not appropriate.
>
> Of 50 patients with dasatinib intolerance, 11 (22%) were found to experience the same adverse event as a grade 3/4 event when treated with bosutinib. Of 50 patients, 4 (8%) discontinued treatment with bosutinib as a result of the same AE.

(Source: Pfizer submission, p83)

No data on bosutinib and nilotinib cross-intolerance are available (only 1 third line patient intolerant to nilotinib was recruited in Study 200). However, the EMA highlighted a high degree of cross-resistance between bosutinib and dasatinib or nilotinib.[29] The reported MCyR for CP 3L dasatinib

intolerant subgroup was 47.7%, in comparison dasatinib resistant and nilotinib resistant patients achieved 33.3% and 38.5% respectively. Advanced phase patients treated with bosutinib at second line reported better MCyR than patients receiving bosutinib at third line or later. In fact, AP patients achieved 47.6% and 14.8% MCyR at second line and multi TKI respectively, while BP patients achieved 44.8% and 12.6% MCyR at second line and multi TKI respectively (March 2011 snapshot). We can argue, that at least some of the difference between the results could be explained by cross-resistance between second generation TKIs. The results of the retrospective evaluation of dasatinib cross-intolerance are presented in Table 30.

Table 30. Cross-intolerance between dasatinib and bosutinib for third-line CP CML population

AE, n (%)[a]	Dasatinib intolerant	Grade 3/4 event	Discontinued bosutinib because of event
Any AE	50	11 (22)	4 (8)
Haematological events	20	8 (40)	2 (10)
Thrombocytopaenia	8	6 (75)	1 (13)
Pancytopenia	5	0	0
Neutropaenia	4	4 (100)	1 (25)
Haematoxicity	3	0	0
Cardiovascular events	3	0	1 (33)
Gastrointestinal events	6	0	0
Diarrhoea	3	0	0
Musculoskeletal events	4	0	0
Respiratory events	23	3 (13)	1 (4)
Pleural effusion	19	2 (11)	0
Dyspnoea	3	1 (33)	1 (33)
Skin disorders	5	0	0

a Includes all AEs with ≥3 patients categorized as intolerant on prior dasatinib
(Source: Pfizer submission, Table B28, p83)

4.2.6.5 Quality of life

Tyrosine kinase inhibitors have revolutionised the treatment of CML and led to improvements in HRQL:

CML is a chronic disease and unless a patient is able to receive a SCT, patients remain on medication for many years. The estimated median survival with imatinib exceeds 25 years in patients with a median age of diagnosis of almost 60 years. Quality of life is not significantly impaired in the chronic phase of CML compared to those of a similar age without CML, indeed approximately 40% of CP

patients are asymptomatic and diagnosed as a result of a routine blood test. For those that do experience symptoms in the chronic phase they tend to be mild and non-specific, such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss.

Although quality of life is not assumed to be very different for CML patients on and off treatment, low grade chronic AEs can be debilitating, particularly if experienced over long periods of time, such as fatigue, oedema, muscle aches, rash or diarrhoea. Some more serious AEs may have a more significant impact on quality of life and may require intervention, for example a pleural effusion requiring steroids, pleural taps or pleural drains, PAOD requiring surgical bypass or balloon angioplasty or pulmonary HTN requiring cardiac catheterisation and medication.

Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising, bleeding and infections.18 In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease. For patients, symptoms such as breathlessness, tiredness, bleeding and infections can seriously affect patients' quality of life.

Please describe how a patient's HRQL is likely to change over the course of the condition.

Quality of life is expected to worsen as the disease progresses from chronic phase to accelerated phase and again to blast crisis phase.

In the chronic phase of the disease, previous studies have found that quality of life is not seriously impaired compared to those of a similar age without CML. In the advanced phases, HRQL is expected to be significantly worse.

(Source: Pfizer submission, p130)

A disease specific, The Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale, and a general, European Quality of Life- 5 Dimensions questionnaire (EQ-5D), were reported in Study 200. Since EQ-5D is NICE's preferred instrument, the submission commented on these results only. The EQ-5D was valued using the UK tariff.

The mean EQ-5D for CP patients across the trial was [redacted] and [redacted] (estimated by us from data on p357-8 Pfizer submission) for second and third- line for patients respectively. The mean utility values at screening were [redacted] and [redacted] for second and third-line respectively. Similarly, the mean EQ-5D for advanced phase patients across the trial was [redacted] and [redacted] for AP and BP for patients respectively. The mean utility values at screening were [redacted] and [redacted] for AP and BP respectively. In comparison, the average utility used in TA251 and TA241 for first and second- line CP patients

(based on IRIS study) was 0.85 (SE 0.004) at diagnosis (Pfizer submission, p135). Interestingly, the mean EQ-5D values did not differ much across the disease phases.

Pfizer reports improvements in HRQL in all disease phases at the March 2011 snapshot:

> Improvements in overall health status as assessed by the EQ-5D were observed for second-line CP patients over the course of treatment, as of 28 Mar 2011 snapshot.
>
> Imatinib-resistant subjects experienced a significant improvement in overall health status from baseline starting at Week 8 ($p<0.05$) and continuing at each subsequent assessment until Week 48 (all $p<0.001$). Imatinib-intolerant subjects experienced significant improvement from baseline by Week 24 ($p<0.001$) that continued until Week 48 ($p<0.001$).

(Source: Pfizer submission, p 357)

> *3L CP:*
>
> Improvements or maintenance of baseline levels of overall health status as assessed by the EQ-5D was observed for dasatinib-intolerant, dasatinib-resistant and nilotinib-resistant patients over the course of treatment, as of the 28 March 2011 snapshot. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (n=4).

(Source: Pfizer submission, p 72)

> Improvements in overall health status as assessed by the EQ-5D were observed for the AP CML and BP CML subjects over the course of treatment, as of the 28 Mar 2011 snapshot.
>
> The mean and median EQ-5D scores, and the number of patients with an EQ-5D score at each observation, are presented along with cost-effectiveness data in Section 7.4.3 [Pfizer submission].

(Source: Pfizer submission, p 79)

However as can be seen in the following tables (Table 31, Table 32, Table 33 and Table 34), the numbers of patients reporting at each week varied significantly.

Table 31. Summary of EQ-5D results by visit for second-line CP patients, n=288 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					

(Source: Pfizer submission, Table B107, p357)

Table 32. Summary of EQ-5D results by visit for third-line CP CML patients, n=118 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					

(Source: Pfizer submission, Table B39, p131)

Table 33. Summary of EQ-5D results by visit for AP patients, n=76 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]		

(Source: Pfizer submission, Table B40, p131)

Table 34. Summary of EQ-5D results by visit for BP patients, n=64 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
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[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

(Source: Pfizer submission, Table B42, p132)

4.3 Critique of the clinical evidence for comparator treatments

As previously mentioned – because of the lack of RCT evidence – the submission included separate studies to inform clinical effectiveness for bosutinib and bosutinib comparators. The following comparators were considered in the literature searches:

- Hydroxycarbamide (HU; as a proxy for best supportive care)
- Allogeneic stem cell transplantation (SCT)
- Interferon alpha

The submission identified 13 non-RCT comparator studies (Table 35). Again we cannot emphasize enough, that the naïve comparison of single arm Study 200 with non-randomised comparator studies is strongly susceptible to bias. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] The submission did not identify any studies reporting on interferon alpha in a refractory setting (post-TKI or post-other treatments). The submission further excluded 5 SCT studies from the review as they did not stratify results according to CML disease phase.[5, 8, 9, 11, 15] Studies that reported combined results for AP and BP CML patients were included in the Pfizer submission.[6, 10, 13]

Table 35. Summary of studies of hydroxycarbamide and stem cell transplant

Study	Patients (Disease phase at transplantation)	Survival	Response	Safety	Pfizer analysis	PenTAG comments
Benedicte (2010)[5]* Median follow-up: 27 months (range 1.2-50.2).	N=31 (median age 39.8 years), (CP 21 (including second CP), AP 10) Received SCT at: • 3rd-line (imatinib and dasatinib or nilotinib) • 4th-line (imatinib, dasatinib and nilotinib)	**OS:** CP and AP combined • 1 year: 79.2% (95% CI 64.3-94.1) Estimated: • 2 years: 55.5% (95% CI 35.0-75.9)	NR	**GVHD** CP and AP combined Grade 2–4: 37.9% Grade 3–4: 20.6% Chronic: 60%	Excluded: Mixed phases.	Only abstract with limited information available. Combined results for CP and AP CML patients.
Bornhäuser (2006)[6] Median follow-up: 18 months (range 2–62).	N=61 (CP 47 (including second CP), AP 8, BP 6), (mean age=45, 57% male) Received SCT at: • 2nd-line (imatinib)	**OS** CP, AP and BP combined (N=61) • 18 months: 37% **Disease Free Survival at 18 months:** CP (N=47) = 34.6% AP and BP combined (N=14) = 29.4% CP, AP and BP combined (N=61) = 33.0%	CP, AP and BP combined Molecular response recorded in 25 from 26 participants alive at last follow up: molecular remission achieved in 19 participants.	**GVHD** CP AP and BP combined Grade 2–4: 66% Grade 3–4: 38% Chronic: 29%	Included: Second-line (post-imatinib failure)	Although 32 (50%) patients were at high risk for transplant-related deaths Gratwohl score of 5-7, 47(77%) patients were in chronic phase at the time of transplantation.
Holroyd (2010)[7]* Median follow-up: NR.	N=43, (CP 17 (including second CP), AP 24, BP 2), (median age 40.8 years) Received SCT at: • 2nd-line: 35	**OS** Estimated: CP (N=17) • 1 year: 49.4%	11 patients relapsed post SCT.	**GVHD** CP, AP and BP combined Grade 2–4: 24%	Included: Multiple lines.	Only abstract with limited information available. Small numbers of participants in all disease cohorts.

	participants (34 imatinib and 1 dasatinib) • 3rd-line: 6 participants (imatininb and dasatinib) • 4th-line: 2 participants (imatinib, dasatinib and nilotinib) Some patients received chemotherapy.	• 3 years: 29.6% <u>AP (N=24)</u> • 1 year: 54.2% • 3 years: 50% <u>BP (N=2)</u> • 1 year: 0% • 3 years: 0% The impact of maximal disease stage, AP(n=23) vs. BP (n=20): • 3 years: 61% and 33% respectively.		Chronic: 54%		
Ibrahim (2011)[4] Median follow-up: 50.4 months (range 2-202)	N=293 (57.3 % male) Subpopulation of interferon alpha versus chemotherapy RCT for CP CML[38]. 247 patients failed to response to interferon alpha. Of these, 117 CP patients received HU after: • interferon alpha treatment failure.	**OS** Estimated: <u>CP(N=246)</u> • 7 years: 34.4 %	NR	NR	Included: Second-line (post-IFN failure)	Results given for all 246 patients who failed to response to interferon alpha; of these only 117 received HU, 122 remained on interferon alpha till disease progression and 7 received bosutinib.
Jabbour (2006)[9] Median follow-up: 19 months (range 13-24).	N=10 (CP 3, AP 4, BP 2, acute 1), (median age 44 years, 80% male) Received SCT at: • 2nd-line: 10 participants (imatinib)	**OS** <u>CP, AP and BP combined</u> • 1 year: 70%	<u>CP, AP and BP combined</u> 2 patients relapsed post SCT. CMR=66.7% MMR=77.8%	**GVHD** <u>CP, AP and BP combined</u> Acute: 44% Chronic: 60%	Excluded: Mixed phases.	Very small study (N=10). Results are reported for all participants, including the one acute CML patient.

Jabbour (2007)[8]	N=12 (CP 7 (including second CP), AP 1, BP 4), (median age 41 years, 58% male) Received SCT at: • 2nd-line: 9 participants (dasatinib (2) and nilotinib (7)) • 3rd-line: 3 participants (dasatinib and nilotinib)	**OS** CP, AP and BP combined • Median follow up of 6 months (2, 11): 58%	CP, AP and BP combined Median follow-up: 10 months: Molecular response in 58% participants.	**GVHD** CP, AP and BP combined Acute: 58.3% Chronic: 50%	Excluded: Mixed phases.	Very small study (N=12).
Jabbour (2011)[10] Median follow-up: 22 months (range 5–53).	N= 47 (CP 26 (10 second CP), AP 12, BP 9), (median age 44 years; 57% male) Received SCT • 2nd-line: 18 (38%) patients received imatinib only • 3rd-line: 29 (62%) patients received imatinib and nilotinib (13), dasatinib (13) or bosutinib (30) • 4th-line: 5 (11%) patients received imatinib and two more TKIs	**OS** CP(N=16) • 2 years: 72% (95% CI 49–96) Advanced (N=31; include 10 second CP patients) • 2 years: 59% (95% CI 41–77) ALL combined (N=47) • 2 years: 63% (95% CI 49–78)	**CMR** CP (N=16) 87.5% Advanced (including second CP) (N=31) 54.8% All combined (N=47) 66% **CCyR** CP (N=16) 6.25% Advanced (including second CP) (N=31) 32.3% CP, AP and BP combined (N=47)	**GVHD** CP, AP and BP combined (N=47) Grade 2–4: 42% Grade 3–4: 17% Chronic: 46%	Included: Multiple lines. Pfizer Base case:	Small study, only 16 patients in CP and advanced phase cohort (N=31) included 10 second CP patients. Submission (p384) shows OS is very immature, therefore poor data source.

			23%			
Kantarjian (2007)[3]	N=574 (CP 321, AP 161, BP 92) participants who discontinued imatinib therapy. Results reported for 104 CP CML participants post-imatinib failure who received: • SCT (n=8) • TKI (n=35) • Other treatment, (n=61), of these 12 participants received HU. Outcome for 127 participants is missing	**OS** Estimated: <u>CP SCT cohort (N=8)</u> • 2 years: 60.0 % • 3 years: 45.0 % <u>CP other treatment cohort (N=61)</u> • 2 years: 77.0 % • 3 years: 70.0 % **Mortality** <u>CP SCT cohort (N=8)</u> CP: 4/10 (40%) AP: 1/5 (20%) BP: 5/8 (63%) <u>Other treatment cohort (N=61):</u> CP: 24/68 (35%) AP: 53/64 (83%) BP: 85/95 (90%)	NR	NR	Included: Second-line (post-imatinib failure)	Data for large number of patients are missing (N=127). A very small SCT cohort (N=8), and in the HU cohort (N=61) only 12 patients received HU.
Markiewicz (2011)[11]*	N= 48 (NR), (median age 33 years) Received SCT at: • 2nd-line: 39 Imatinib (37), dasatinib (2) • 3rd-line: 6 Imatinib and dasatinib or nilotinib	**OS:** Estimated •5 years: 79%	NR	**GVHD** <u>Disease progression NR</u> Grade 3–4: 6.25% Chronic, limited: 35.4% Chronic, extensive: 18.75%	Excluded: Mixed phases.	Only abstract with limited information available. Disease stage not reported.

	• 4th-line: 3 patients, imatinib and dasatinib and nilotinib					
Oehler (2007)[12]	N= 145 (CP 72, AP (or second CP) 60, BP 13), (median age= 40.1; 64% male) Received SCT at: • 2nd-line: after imatinib (not after imatinib failure, 23 patients had previous INF)	**OS:** Estimated: <u>CP(N=72)</u> • 3 years: 78.0 % <u>AP and second CP(N=60)</u> • 3 years: 48.0 % **Mortality** <u>BP</u> 6/12 (follow up 542-1593 days) **Mortality** **by response to imatinib:** <u>69 CP patients with available data:</u> *Suboptimal/loss of response to prior imatinib:* 26% (8/31), i.e. OS = 74% *Good response to prior imatinib:* 5% (2/38), i.e. i.e. OS = 95% <u>Advanced phases</u> *Disease progressed from CP whilst on imatinib:* 45% (19/42), i.e. OS = 55%	NR	Results only reported as HR and OR compared with a historical cohort of patient who underwent SCT without previous imatinib treatment	Included: Second-line (post-imatinib failure)	**OS** of the CP cohort (N=72) was not reported in the submission; however mortality by response to imatinib were recorded. Large trial in comparison with the rest of comparator studies.

		Patients in advanced phases with no prior response to imatinib: 35% (6/17), i.e. OS = 65%				
Saussele (2010)[13] Median follow-up: 26 months (range 1-50) for CP, and 24 months (range 0-50) for advanced phase.	N= 65 (CP 37 , AP 3, BP 25; 11 of advanced patients achieved second and 1 patient achieved third CP before SCT), (mean age=38; 57% male in CP and 79% in AP & BP). Received SCT at: CP: • 2nd-line: 32 patients • 3rd-line or 4th-line: 5 patients AP and BP: • 2nd-line: 22 patients • 3rd-line or 4th-line: 6 patients • 22 patients treated with chemotherapy	**OS:** Estimated: CP (N=37) • 3 years: 94.1% (95% CI 83.8–99.4%) AP and BP combined (N=28) • 3 years: 58.8% (95% CI 38.6-77.5%)	**CMR** CP(N=37) 89% AP and BP combined (N=28) 93%	**GVHD** CP(N=37) Grade 3–4: 19% Chronic: 36% AP and BP combined (N=28) Grade 3–4: 35% Chronic: 21%	Included: Multiple lines.	Results for CP reported (N=37).
Schleuning (2010)[14]* Median follow-up: 19 months.	N=56 (first CP 21, second or higher CP 20, AP or BP 15) Had nilotinib and/or dasatinib (had not received first-line imatinib) prior to SCT.	**OS** Estimated: First CP(N=21) • 2 years: 85%. AP,CP, BP combined (N=56) Estimated non relapse mortality at 2 years: 33%	NR	NR	Included: Multiple lines.	Only abstract with limited information available. Small numbers of patients in first CP phase (N=21).

		and relapse incidence 15%.				
Weisser (2007)[15]	N=30 (second or higher CP; 10 and 20 patients had history of BP and AP respectively) (median age =51, 60% male) Received SCT at: • 2nd-line: after imatinib (imatinib given after IFN failure)	**OS** Estimated: <u>Second or higher CP</u> • 3 years: <35% BCR-ABL positive nuclei (N=13, 11 censored, median survival not reached): 81%; ≥35% BCR-ABL positive nuclei (N=17, 6 censored, median survival 101 days): 28%[a] **Mortality** at 1 year: 30%	<u>Second or higher CP</u> Cytogenetical relapse in 20%	**GVHD** <u>Second or higher CP(N=30)</u> Grade 3–4: 40%	Excluded: Mixed phases.	Although all patients are in the same phase, (second or higher CP), OS data are reported separately for patients with <35% and ≥35% BCR-ABL positive nuclei in bone marrow. Small study.

Abbreviations: AP = accelerated phase, BP = blast phase, CMR = Complete molecular response, CP = chronic phase, GVHD = Graft versus host disease, N = number of participants, NR = not reported, OS = overall survival

* Abstract presented at the Annual Meeting of ASH (2010-2011); no full publication is available for these sources, hence the data presented is limited to that present in the abstract

a Results estimated from figures

4.3.1 Hydroxycarbamide

Only two studies, Ibrahim (2011) and Kantarjian (2007) reported using HU in a refractory setting (Table 35).[3, 4] Ibrahim (2011)[4] used data from an interferon-failure sub-population in The UK Medical Research Council CML-III randomised trial of interferon alpha versus chemotherapy in CP CML patients.[38] In the Allan (1995) RCT,[38] 293 patients received interferon alpha and 294 patients received chemotherapy (with busulphan or hydroxyurea) treatment. In addition, all patients received a course of chemotherapy for tumour reduction as an induction treatment, and some patients also received chemotherapy while on interferon alpha. There were 278 Philadelphia positive CP CML patients in both the interferon alpha, and the no interferon alpha arm. The actual survival rates at 5 years for Philadelphia positive CP CML patients were, 36% (SD 3.8), and 54% (SD 3.7) for no interferon alpha and interferon alpha arms respectively. Ibrahim (2011)[4] reported data on 246 patients who failed interferon therapy (in the interferon alpha arm). However, of these, only 117 actually received HU; 122 remained on interferon alpha till disease progression and 7 received busulfan. The estimated 7 years overall survival for the interferon-failure sub-population was 34.4%. It may be that these results include a small proportion of Philadelphia negative CP CML patients. Pfizer did not consider this population in the submission because patients did not receive any TKI prior to HU treatment.

Kantarjian (2007)[3] is a retrospective study of 420 CML patients, who received first line imatinib treatment. One hundred and four patients were identified with imatinib failure in CP CML. The post-imatinib failure treatment was either SCT (8 patients), dasatinib/nilotinib (35 patients) or other treatment (61 patients). Out of the 61 patients receiving other treatment, only 12 received HU; remaining treatments included tipifarnib, lonafarnib, cytarabine, homohorringtonine, decitabine, homoharringtonine, interferon alpha and others. The estimated 2 and 3 years OS for CP CML patients receiving "other" treatment was 77% and 70% respectively. Based on Hoyle (2011) report,[17] the submission used the estimated OS from the "other" treatment group in their model. Hoyle (2011)[17] assumed that survival when taking HU is the same as that of the "other" treatment arm for imatinib resistant patients. However, they also acknowledged that based on this assumption, the OS estimates for HU following TKI failure are uncertain.

4.3.2 Allogeneic stem cell transplantation

Eight studies[3, 6, 8-10, 12, 13, 15] and four conference abstracts[5, 7, 11, 14] reported on SCT in a refractory setting. Table 35 summarises results of all comparator studies.

4.3.3 Interferon alpha

Considering the highly unlikely usage of interferon (other than as a bridge to SCT, interferon alpha therapy is hardly used in England and Wales) and of the lack of suitable data, we did not consider clinical data on interferon alpha further here.

4.3.4 Quality assessment

Similarly to the quality appraisal of Study 200, comparator studies were assessed according to the Chambers (2009) criteria.[16] We have already emphasised the weakness of using a single arm study design as the only source for clinical evidence. We have also highlighted the further difficulties arising from comparing results from different single arms studies. Finding suitable comparator studies is very challenging, not least in terms of potential differences in the populations studied, the variable completeness of follow-up, publication bias, and lack of blinding throughout the literature.

Thirteen comparator studies[3-15] were identified. However, four of these are available only as conference abstracts,[5, 7, 11, 14] thus only limited information on quality assessment is available. Earlier in this section we commented on some of the weaknesses (Table 35) of the comparator studies, thus only our assessment of the Chambers (2009) criteria[16] is included in Table 36.

Table 36. Quality assessment of comparator non-RCTs identified by the systematic review

Study	Comparator	Eligibility criteria adequately reported?	Study population representative of a normal population?	An appropriate measure of variability reported?	Loss to follow-up reported or explained?	At least 90% included at baseline followed-up?	Were patients recruited prospectively?	Were patients recruited consecutively?	Did the study report relevant prognostic factors?	Pfizer Quality score	PenTAG comment
Benedicte (2010)[5]	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Bornhäuser (2006)[6]	SCT	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Poor	OK
Holroyd (2010)[7]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Ibrahim (2011)[4]	HU	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Jabbour (2006)[9]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Jabbour (2007)[8]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Jabbour (2011)[10]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Kantarjian (2007)[3]	SCT, HU	Yes	Yes	Yes	Yes	No[b]	No	Yes	Yes	Poor	OK
Markiewicz (2011)[11]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Oehler (2007)[12]	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Saussele (2010)[13]	SCT	Yes	Yes	Yes	Yes	Yes[c]	Yes	Yes	Yes	Good	OK
Schleuning	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK

(2010)[14]											
Weisser (2007)[15]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK

a >50% of patients (n=32) were at high risk for transplant-related deaths (Gratwold scores of 5–7)

b Of the 574 patients analysed, the outcome of 127 could not be retrieved in detail in relation to subsequent therapies or survival. The next analysis concentrated only on patients in whom imatinib therapy was discontinued for either clear cut resistance or recurrence (n=374) or for imatinib. toxicities (n=46)

c Follow-up was reported in the 84 patients who underwent transplantation

(Source: Pfizer submission, adapted from Table B83, p216)

4.4 Conclusions of the clinical effectiveness section

Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI. Bosutinib was also found to have an acceptable safety profile across all phases of the disease. Adverse events were restricted primarily to gastrointestinal toxicities (Table 4, p26).

The main two weaknesses of the clinical effectiveness evidence are, that Study 200 is a non-randomised single arm trial, and that while the licence is intended for treatment of adult patients with Ph^+ CML previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, the clinical evidence for bosutinib is taken entirely from Study 200, in which the great majority of patients were suited to either imatinib, nilotinib or dasatinib. Secondly, the clinical effectiveness evidence for the comparator treatments is very poor. Any comparison between Study 200 and comparator studies is highly prone to bias. In addition, OS data from Study 200 for CP patients is very immature.

Other, minor weaknesses of Study 200 are that approximately 40% of patients had previously taken IFN, while IFN is a very rare CML treatment in England and Wales, the fact that all patients had previously been treated with imatinib while the current first line treatment is nilotinib, the discrepancy between the duration of imatinib treatment reported in Study 200 and in IRIS trial, and the fact that only one participant with nilotinib intolerance was recruited in third line CP CML subpopulation.

On the other hand, the strength of the submitted evidence is that Study 200 is a large, multi-centre, consecutively recruited trial, with patients representative of population expected the in clinical practice in England and Wales (based on ECOG scores).

5 COST-EFFECTIVENESS

5.1 Manufacturer's review of cost-effectiveness evidence

5.1.1 Objective

The objective of the manufacturer's cost-effectiveness review was to identify cost-effectiveness studies in CML patients previously treated by one or more TKIs. It was assumed this population would include and be representative of the indicated population (patients for whom imatinib, nilotinib and dasatinib would be inappropriate).

We believe the objective of the cost-effectiveness review was appropriate for identifying existing answers to the decision problem, but note that by excluding studies of first-line TKIs possible sources of economic evidence to inform the *de novo* analysis could be missed.

5.1.2 Search strategy

Pfizer conducted two sets of searches to locate cost-effectiveness studies for this submission.

The first search (Pfizer submission, Section 10.10, p218) took terms for CML or Philadelphia Chromosome combined with methodological limits to economics/cost studies (see Pfizer submission, Section 10.10.4, p218 for full search strategy). These searches were run 2nd October 2012 and were performed in the databases listed in Table 37.

Table 37. Electronic databases searched by Pfizer for cost-effectiveness review (run from database inception; Source: Pfizer submission, Section 10.10, p218)

Database	Searched via
Ovid MEDLINE®	Ovid
EMBASE	Ovid
MEDLINE® In-Progress	Ovid
EconLit	Ovid
NHS EED	Cochrane Library and Centre for Reviews and Dissemination
Cochrane Library	Ovid

Pfizer state that search results were limited to Dasatinib, Nilotinib, Imatinib, Bosutinib, Stem-Cell, Hydroxycarbamide, Interferon, or Standard Care (Pfizer submission, Section 10.10.4, p220). It is not clear from the submission how this was achieved.

Pfizer additionally searched proceedings of selected conferences (Table 38) in February 2013 and NICE HTAs. Pfizer report that horizon scans were performed using the Google search engine (Pfizer submission, Section 10.10.5, p221).

Table 38. Conferences searched by Pfizer (Source: Pfizer submission, Section 10.10.5, p221)

Conference
International Society for Pharmacoeconomics and Outcomes (ISPOR)
International Congress on Leukemia Lymphoma Myeloma (ICLLM)
ESMA[a]
American Society of Clinical Oncology (ASCO)
American Society of Hematology (ASH)

a We were unable to identify this conference, but we believe, as does our clinical expert, Dr Rudin, that it probably refers to ESMO (European Society of Medical Oncology)

5.1.2.1 Update searches

In clarification, Pfizer confirmed they had updated the submission searches from 2nd October 2012 to April 2013. We are happy to accept these update searches in place of the horizon scanning.

5.1.2.2 ERG comment on search strategy

The searches performed were appropriate to the task.

5.1.3 Inclusion and exclusion criteria used in the study selection

Inclusion and exclusion criteria in the cost-effectiveness review are shown in Table 39. By excluding studies of first-line TKIs and excluding cost- (without assessment of effectiveness) it is possible that studies capable of informing the *de novo* model would be missed, but we note in Section 5.2.9.1 (p127) that an additional search was conducted in which the study type criteria were dropped. We believe the inclusion and exclusion criteria were appropriate to the objective of the cost-effectiveness review.

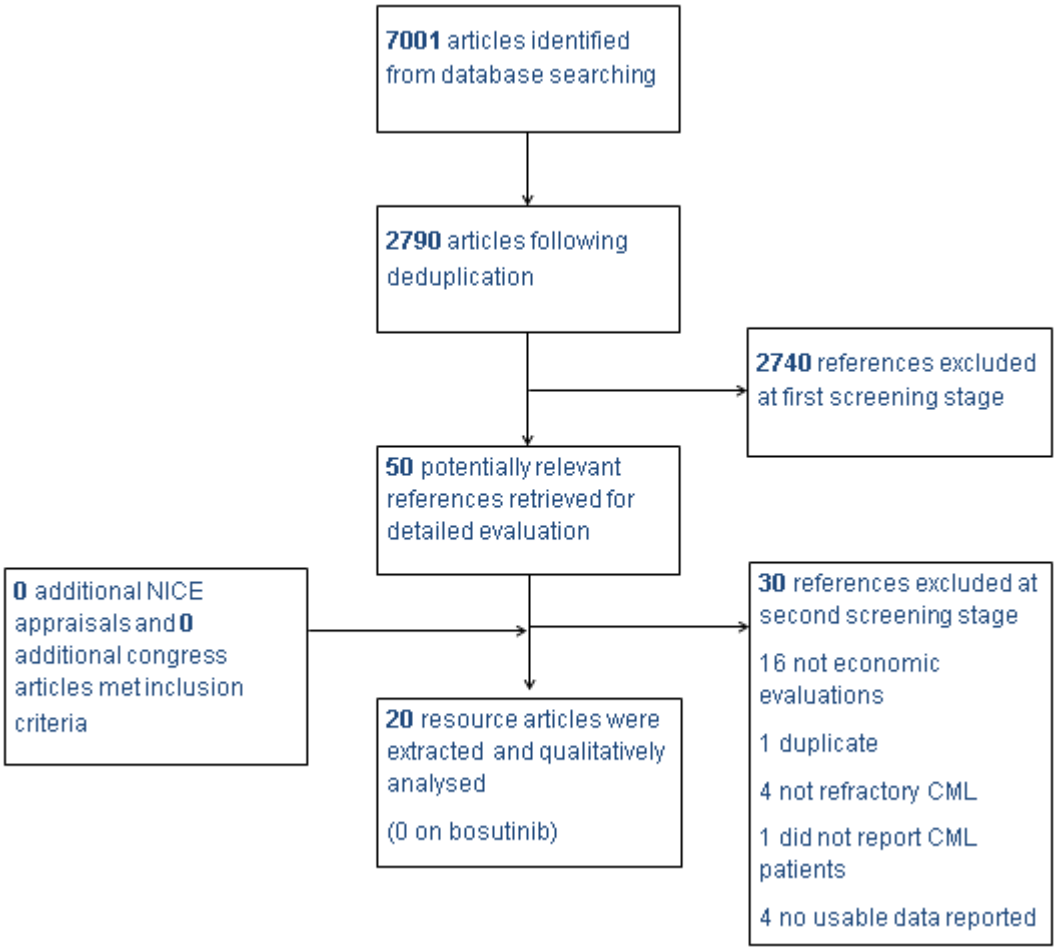
Table 39. Inclusion and exclusion criteria for systematic review of economic evidence

Category	Include	Exclude
Population	Adult patients with refractory CP, AP or BP Ph^+ CML (treated with at least one prior TKI)	Studies that did not report adult patients Studies that did not report patients with refractory Ph^+ CML
Intervention	Include but not limited to bosutinib, dasatinib, nilotinib and imatinib	
Comparators	Hydroxycarbamide, interferon, SCT, best supportive care, dasatinib, nilotinib, imatinib	
Outcomes	Incremental costs and QALYs Any other measure of effectiveness reported together with costs	
Study type	Full economic evaluation (including cost-consequence, cost-minimisation, cost-effectiveness, cost-utility, cost-benefit) comparing two or more interventions	
Publication type		Letters, editorials, reviews of economic articles (although reference lists of these would be hand searched)
Other	Reported in sufficient detail to assess methodological quality and extract data and results	

5.1.4 Results

Figure 9 shows the study flow diagram for the cost-effectiveness review. Searching identified 7,001 articles, which corresponded to 2,790 articles following de-duplication. Fifty articles were retrieved for detailed evaluation, of which 20 were included and 30 were excluded from the final set of studies for extraction and quality assessment. Details of the excluded studies were not given, and the reasons for exclusion are given for at most 26 of the 30 articles. We would have preferred to have access to the set of articles excluded after full paper retrieval but this was not provided by Pfizer.

Figure 9. Study flow diagram for systematic review of economic evidence



(Source: Pfizer submission, Section 7.1.1, p107)

The key included studies were Hoyle and colleagues (2011),[39] Rogers and colleagues (2012)[2] and Loveman and colleagues (2012),[40] which are all publications based on TA241 (Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance). These studies are most relevant to the decision problem as they study refractory CML in adults in the UK treated by TKIs. These studies also included details of submissions by Novartis and Bristol-Myers Squibb on the cost-effectiveness of nilotinib and dasatinib.

No studies were identified which investigated the cost-effectiveness of bosutinib in refractory CML.

5.1.5 Conclusions and ERG critique

Pfizer did not identify any economic evaluations of bosutinib in refractory CML. As such no conclusions were drawn from the systematic review regarding the decision problem. An additional

review was conducted by Pfizer (see Section 5.2.9.1, p127) to identify inputs for the *de novo* model, which relaxed inclusion criteria.

We believe the review of cost-effectiveness evidence was appropriate and accept that there are no economic evaluations of bosutinib in refractory CML.

5.2 Summary of the manufacturer's submitted evaluation

5.2.1 History of submission

Table 40 details the history of the Pfizer model submission. This report references the latest version of the model and report (received 22/04/2013).

Table 40. History of Pfizer model submission

Date	Detail
14/03/2013	PenTAG receive Pfizer model from NICE
19/04/2013–22/04/2013	PenTAG receive updated Pfizer model and supplementary report with corrections to errors highlighted by PenTAG in questions for clarification[a]

a PenTAG identified that the hazard ratio for OS in bosutinib CP patients was not implemented correctly. When Pfizer corrected the error the CP model base case ICER for bosutinib decreased from [redacted] per QALY to [redacted] per QALY.

5.2.2 Model structure

The submission includes three cohort models (for patients starting in CP, AP and BP). In each model bosutinib is compared with hydroxycarbamide, interferon (CP model only) and SCT. The models are described as "semi-Markov models" but there are no transition probabilities as would be expected from a Markov model.[41, 42] The membership of each state is calculated in a manner similar to that which would be expected in an area-under-the-curve model.

Cycles in the models last one month and a half-cycle correction was not applied.

Bosutinib patients receive bosutinib until they discontinue treatment due to intolerance or resistance, progress to a later disease stage (AP or BP for those in CP, BP for those in AP, not applicable for those in BP), or die. Bosutinib patients receive hydroxycarbamide following bosutinib discontinuation until death (even in the case of further disease progression).

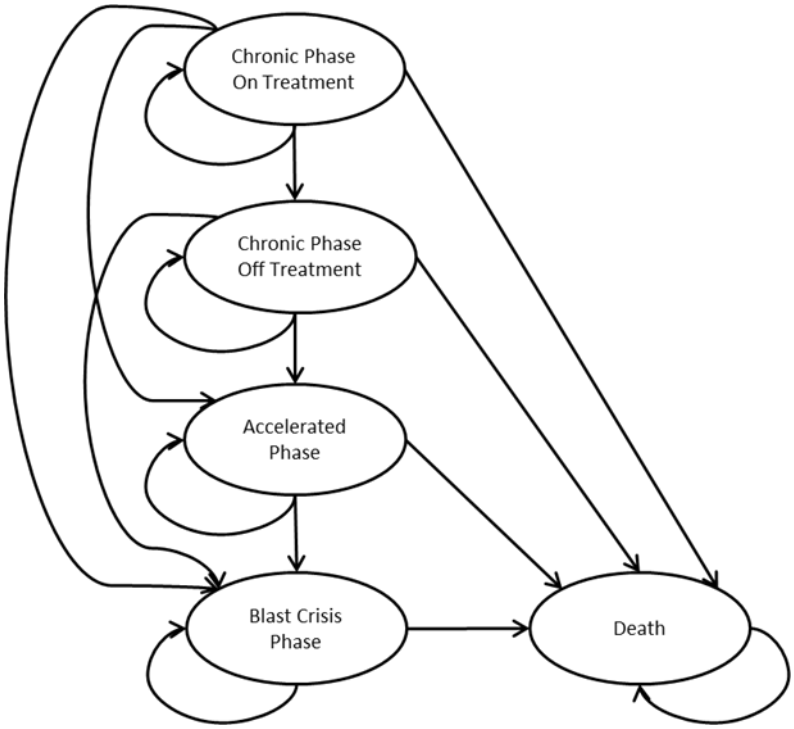
Hydroxycarbamide patients receive hydroxycarbamide regardless of disease progression until death.

Interferon patients receive interferon until they discontinue treatment (similarly to bosutinib patients), progress to a later disease stage (AP or BP), or die. Interferon patients receive hydroxycarbamide following bosutinib discontinuation until death (even in the case of further disease progression).

SCT patients receive SCT and are thereafter regarded as cured in the base case analysis and so do not progress to later disease stages and do not receive drug treatment after SCT.

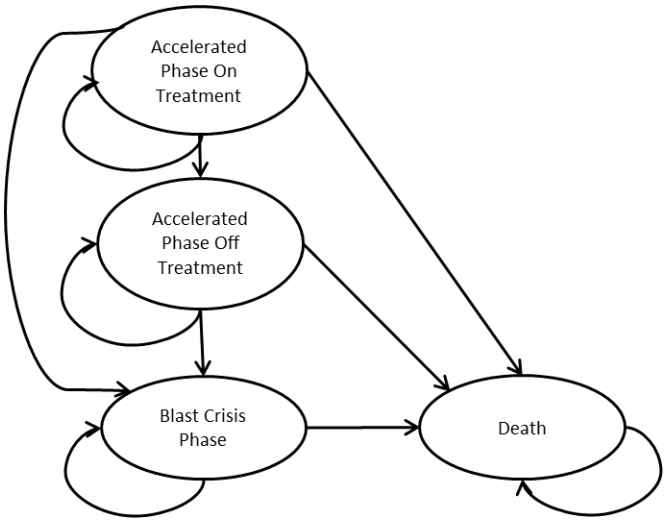
The models are structured similarly, with time on and off treatment in the initial phase, later disease phases (if applicable) and death. Figure 10 shows the CP model structure, Figure 11 shows the AP model structure and Figure 12 shows the BP model structure.

Figure 10. Chronic phase (CP) model structure



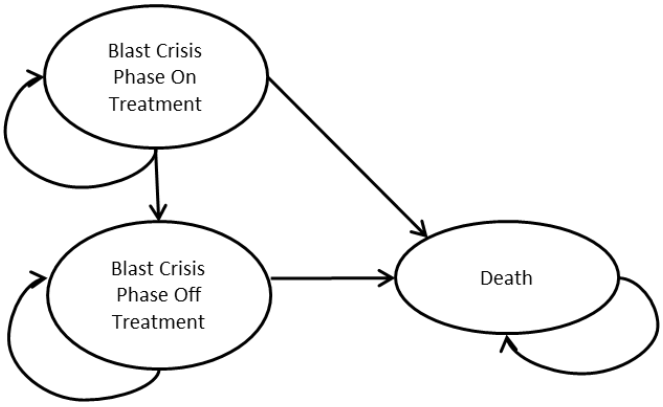
(Source: Pfizer submission, Section 7.2.2, p109)

Figure 11. Accelerated phase (AP) model structure



(Source: Pfizer submission, Section 7.2.2, p110)

Figure 12. Blast phase (BP) model structure



(Source: Pfizer submission, Section 7.2.2, p110)

5.2.2.1 State membership in the CP model

The proportion of the cohort in each state in the CP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)
2. The proportion in the Blast Crisis Phase state is set so that patients spend 6 months in the blast crisis phase
3. The proportion in the Accelerated Phase state is set so that patients spend 10 months in the accelerated phase

4. The proportion in the Chronic Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive or the proportion in the Blast Crisis Phase and Accelerated Phase states
5. The remainder of the population is in the Chronic Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Chronic Phase Off Treatment state is always zero.

Patients receiving a stem cell transplant are assumed to be cured and hence do not progress to the accelerated and blast crisis phases. Therefore the proportions in the Blast Crisis Phase, Accelerated Phase and Chronic Phase Off Treatment states are zero and the proportion in the Chronic Phase On Treatment state is set equal to the relevant overall survival curve.

5.2.2.2 State membership in the AP model

The proportion of the cohort in each state in the AP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)
2. The proportion in the Blast Crisis Phase state is set so that patients spend 6 months in the blast crisis phase
3. The proportion in the Accelerated Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive or the proportion in the Blast Crisis Phase state
4. The remainder of the population is in the Accelerated Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Accelerated Phase Off Treatment state is always zero.

Patients receiving a stem cell transplant are assumed to be cured and hence do not progress to the blast crisis phase. Therefore the proportions in the Blast Crisis Phase and Accelerated Phase Off Treatment states are zero and the proportion in the Accelerated Phase On Treatment state is set equal to the relevant overall survival curve.

5.2.2.3 State membership in the BP model

The proportion of the cohort in each state in the BP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)

2. The proportion in the Blast Crisis Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive
3. The remainder of the population is in the Blast Crisis Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Blast Crisis Phase Off Treatment state is always zero. Patients receiving a stem cell transplant are assumed to be cured; therefore the proportion in the Blast Crisis Phase Off Treatment state is always zero.

5.2.3 Population

Bosutinib is indicated for patients with Ph^+ CML in the chronic, accelerated or blast phase who have failed one or more TKIs and for whom imatinib, nilotinib and dasatinib are considered inappropriate.

Pfizer estimate that each year, 80 of the 631 annual CML cases in England and Wales will be eligible to receive bosutinib, and of these 12 (15%) will be eligible to receive it second-line (following imatinib failure), 19 (24%) will be eligible to receive it third-line (following failure of imatinib and nilotinib), and 49 (61%) will be eligible to receive it fourth-line (Pfizer submission, Section 8.1, pp188-189).

Pfizer suggest that the third-line chronic phase cohort in Study 200 is most representative of the intended population, and hence this forms the basis of the population in the CP model and for many other parameters in the CP model.

All patients in the CP model were assumed to start treatment at age 54 years, which was the mean baseline age in the third-line CP cohort of Study 200 (Pfizer submission, Section 7.3.2, p124). All patients in the AP and BP models were assumed to start treatment aged 50 and 47 years respectively, which were the mean baseline ages in the AP and BP cohorts of Study 200 (Pfizer submission, Section 7.3.2, p124).

Pfizer assumed equal proportions of males and females in the patient population.

No assumptions were made in the model about previous treatments, although Study 200 evaluated patients who received imatinib first-line, followed by nilotinib and/or dasatinib. Some patients in Study 200 had previous interferon use (52% of third-line CP cohort, 50% of AP cohort and 30% of BP cohort) and some patients had previously received stem cell transplants (8% of third-line CP cohort, 9% of AP cohort and 6% of BP cohort).

There were no subgroups in any of the models.

5.2.4 Intervention and comparators

The intervention is bosutinib given until any of the following occur:

- progression to later phase CML,
- patient has/develops resistance to bosutinib,
- patient no longer tolerates bosutinib, or
- patient dies.

Following bosutinib discontinuation patients receive hydroxycarbamide until death.

The comparator treatments are:

- Hydroxycarbamide (patients receive until death)
- Interferon alpha (patients may discontinue treatment and then receive hydroxycarbamide until death)
- Allogeneic stem cell transplant (one-off treatment followed by medical management)

Interferon alpha is only considered as a comparator in the CP model because effectiveness estimates were not available for interferon alpha in the advanced and blast phases.

5.2.5 Perspective, time horizon and discounting

The Pfizer submission adopts the perspective of the NHS. Costs of drug acquisition, drug administration, medical management, adverse events and death are included. Impacts on costs outside the NHS budget (e.g., Personal Social Services) were not included as they were not expected to be affected significantly. Wider societal costs are not included. Health benefits are only included from the patient population being treated. Wider societal benefits are not included.

The time horizon is 50 years. As the patients start aged 47–54 years, this means the time horizon is to age 97–104 years.

Costs and QALYs are discounted at 3.5% per annum.[43] Life years are not discounted.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Overall survival

Overall survival (OS) is one of the most clinically relevant measures of treatment effectiveness and is also a key driver of cost-effectiveness.

Pfizer used results from Study 200 to inform the OS of bosutinib and estimated OS of hydroxycarbamide, interferon and SCT from published literature. Table 41 shows the methods which were used to calculate OS in the CP, AP and BP models, both in the base case and in a number of scenario analyses.

Overall survival of bosutinib is extrapolated in all three models, but most significantly in the CP model. Due to study protocol the OS after two years is biased (since patients are only followed up for two years after treatment discontinuation) and hence OS is only available from Study 200 up to two years. In the CP-3L cohort OS at two years (calculated by the Kaplan-Meier method) was 84%, so significant extrapolation takes place in the model. In the AP cohort OS at two years was 65.6%, again requiring significant extrapolation. In the BP cohort OS at two years was 35.4%, with median OS of 11.1 months, so some extrapolation was still necessary, but not to the same extent as for the CP and AP models.

Table 41. Methods used to calculate overall survival (OS) in Pfizer submission base case and scenario analyses

Model	Treatment	Base case OS	Scenario analysis OS
CP	Bosutinib	MCyR surrogate relationship based on Jabbour and colleagues (2009)[44] (see p119)	MCyR surrogate with different hazard ratio for OS Exponential distribution fitted to third line CP cohort from Study 200 "Cumulative survival approach" (see p121)
	Hydroxycarbamide	Exponential distribution with mean OS = 3.5 years following Kantarjian (2007)[3]	Exponential distribution with different mean OS
	Interferon	Exponential distribution with mean OS = 3.6 years following Loveman (2012)[40]	*None*
	SCT	Exponential distribution fitted to Jabbour (2011)[10]	Weibull distribution fitted to Jabbour (2011)[10] Exponential distribution fitted to Oehler (2007)[12]
AP	Bosutinib	Exponential distribution fitted to AP cohort OS in Study 200	Extreme value distribution fitted to AP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 16 months to match length of time spent in AP and BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Jabbour (2011)[10]
BP	Bosutinib	Exponential distribution fitted to OS in Study 200	Weibull distribution fitted to BP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 6 months to match length of time spent in BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Saussele (2010)[13]

MCyR surrogate overall survival

Overall survival for bosutinib patients in the CP model was estimated using a MCyR surrogate approach. This approach was not used for OS for bosutinib patients in the AP and BP models as sufficiently mature OS data was available from Study 200 to fit parametric curves. A very similar MCyR approach has been used in a previous assessment, TA241,[2] which investigated nilotinib, dasatinib and high-dose imatinib for treatment of Ph^+ imatinib-resistant or imatinib-intolerant CML patients.

Following Rogers and colleagues (2012)[2] Pfizer assume a hazard ratio of overall mortality of 0.370 for patients achieving a MCyR versus those not achieving a MCyR. Pfizer assumed that the same hazard ratio would apply for patients achieving a MCyR using bosutinib as bosutinib is a TKI with a similar mode of action to imatinib.

Pfizer first extracted individual patient OS data from Jabbour and colleagues (2009),[44] which investigates the effectiveness of high-dose imatinib in patients after cytogenetic failure on standard-dose imatinib. Pfizer then fitted an exponential curve to the OS data using the maximum likelihood method. This curve, adjusted for general mortality, was then used as the basis for fitting a new curve with two components: survival for responders and survival for non-responders. These two components were both exponential curves with scale factors set such that the hazard ratio between matched 0.370. It was then assumed that the MCyR rate in Jabbour and colleagues (2009)[44] would be 41.7%, so that the overall survival in Jabbour would be equal to 41.7% × (OS for MCyR) + (100% − 41.7%) × (OS for no MCyR). The exponential parameters were chosen to achieve the best fit to the adjusted exponential curve fitted to the Jabbour OS data.

Finally OS for bosutinib was estimated by using the MCyR rate of 38.9%, which corresponds to the best cumulative response at a minimum follow up of 12 months for the entire 3rd-line population (not the post-hoc unmet clinical need population), i.e., 38.9% is the proportion of patients achieving a MCyR at any time or maintaining a MCyR present at baseline, with all patients followed up for at least 12 months (median follow-up 28.5 months).

Fitting parametric distributions to overall survival data

For bosutinib patients in the AP and BP models exponential distributions were fitted to individual patient data from the relevant cohorts in Study 200. The entire AP and BP cohorts were used (i.e., no post-hoc "unmet need" subpopulation was considered, nor were cohorts divided into imatinib-failure patients and multiple TKI-failure patients), but analysis was restricted to the first two years, since the study protocol stated that patients would only be followed up for two years post-discontinuation. In addition an exponential distribution was fitted to the CP cohort for a scenario analysis. Pfizer do not state explicitly that maximum likelihood methodology is used but it is very likely that this is the case.

For SCT patients in the CP model individual patient data was extracted from the relevant overall survival curve in Jabbour and colleagues (2011)[10] and an exponential distribution was fitted to this OS data. Again it is likely, but not explicitly stated, that the maximum likelihood methodology was used. The same methodology was used in the AP and BP models but fitted to OS data from Oehler and colleagues (2007).[12]

Choosing exponential distributions with desired mean overall survival

The method of moments was used to choose exponential distributions with desired mean OS for hydroxycarbamide in all three models and for interferon in the CP model. The method of moments involves simply setting the rate parameter λ to 1/(Mean OS).

Pfizer "cumulative survival approach"

Pfizer developed a "cumulative survival approach" for bosutinib overall survival in a scenario analysis of the CP model which they describe as similar to the cumulative survival approach used in TA251. Their approach involves estimating OS as PFS + 10 months in AP + 6 months in BP. We do not believe it is correct to describe this method as similar to the approach in TA251 as the cumulative survival approach in TA251 involved estimating OS as the sum of time spent on treatments, which is a different structural assumption.

Death due to non-CML mortality

Death due to non-CML mortality was originally calculated as follows for all treatments in the CP, AP and BP models, except for bosutinib in the CP model (Pfizer submission, Section 7.3.2, p124):

> For all three models, for all comparators, background mortality was incorporated into the model, to ensure that parametric curve fits did not over predict survival as patients aged.
>
> Background mortality was applied in the model by subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200), and adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012). The starting age in the AP and BP models are 50 and 47 respectively, so these ages are used to adjust for background mortality.
>
> As this component of mortality increases over time, it has the effect of ensuring survival curves do not asymptote to 0, estimating survival beyond what can be expected in clinical practice, where patients are likely to experience co-morbidities and competing risks.

The method for incorporating non-CML mortality for bosutinib in the CP model was changed following clarifications from the manufacturer in which they corrected an error in calculating CML mortality from the MCyR surrogate relationship (p119). Rather than using the above method, CML mortality was estimated accounting for general mortality (see p119) and then general mortality is added to CML mortality in a manner similar to that used in TA241 and described by Rogers and colleagues (2012).[2]

5.2.6.2 Time on treatment

Time on treatment has clinical relevance because treatments can reduce or improve health related quality of life. It is also very relevant to cost-effectiveness because higher drug acquisition costs are incurred while patients are on bosutinib or interferon rather than hydroxycarbamide.

Bosutinib and interferon are both discontinued when disease progresses (or the patient dies), the patient does not tolerate them or the technology is not efficacious. Hydroxycarbamide is received until death and is not discontinued; therefore for hydroxycarbamide time on treatment is equal to overall survival. Stem cell transplant patients have a one-off procedure followed by medical management, with medical management continuing until death.

Time on bosutinib

Time on bosutinib is incorporated into the model by fitting a lognormal distribution to the individual patient data for discontinuation in Study 200 for the relevant cohort, i.e., in the CP model the CP-3L cohort is used (Figure 13), in the AP model the AP cohort is used (

Figure 14) and in the BP model the BP cohort is used (

Figure 15).

Figure 13. [redacted]

Figure 14. [redacted]

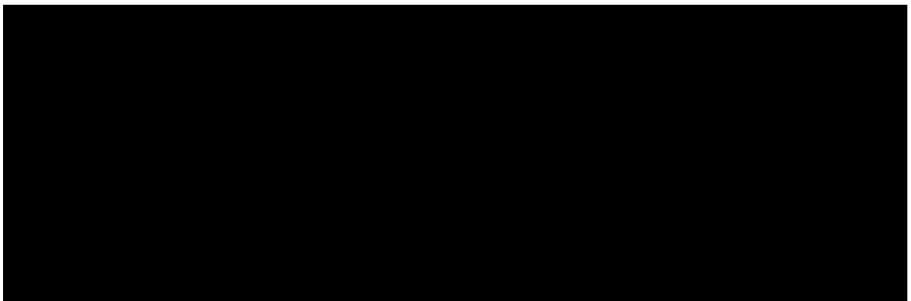


Figure 15. [redacted]

Time on interferon

Time on interferon is incorporated into the model using an exponential distribution, chosen such that the mean time on treatment (ignoring the effect of non-CML mortality) would be 0.5 years.[40] This estimate was not taken from any study, but on the basis of expert opinion.

5.2.7 Health related quality of life

5.2.7.1 Utilities in CP CML

For CP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. From patients on 1st-line imatinib in the IRIS RCT of imatinib vs. IFN. These values were reported in Reed and colleagues (2004),[45] and are estimated from a large sample of patients, using the EQ-5D, which is preferred in the NICE reference case. The mean utility is 0.85 at age 50. In TA251, we, PenTAG, applied this value to the utility for all 1st-line TKIs: imatinib, nilotinib and dasatinib in CP, given the lack of relevant high-quality utility data for these treatments, and based on clinical opinion and the similarity of the incidence of adverse events across treatments.
2. From patients in Study 200 of people on bosutinib. The weighted average utility for 3rd-line patients, mostly over the first two years of treatment, was [redacted] (p131 Pfizer submission). At baseline, [redacted] of 3rd-line CP patients completed the EQ-5D. The weighted average utility for 2nd-line patients also mostly over the first two years of treatment, was [redacted] (estimated by us from data on pp357-8 Pfizer submission). At baseline, [redacted] of 2nd-line CP patients completed the EQ-5D.

For their base case, Pfizer used the estimate from the IRIS trial.

Next, Pfizer found no relevant studies to estimate the utility for patients on HU in CP. They therefore assumed the same utility as for bosutinib. In TA251, we also found no relevant data for the utility for patients on HU in CP. We also set this value to equal the utility for the TKIs.

Next, Pfizer found two sources for utilities for patients after SCT in CP:

1. They correctly cite our TA251 analysis where we assumed a disutility vs. the general population of 0.041 for the 75% of patients in a "low risk" population and a disutility of 0.079 for the remaining 25% of patients in a "high risk" population. For details of our analysis, see our TA251 report.[17] In brief, the disutility of 0.079 was in respect of chronic graft-versus-host disease and was elicited from 12 US clinicians familiar with bone marrow transplantation. This therefore gave a mean utility at age 54 of 0.81 for patients in the "low risk" population and 0.76 for patients in the "high risk" population, giving a weighted mean of 0.80.
2. They cite utilities after SCT in CP of 0.60 from the BMS submission in TA241 and 0.81 from the Novartis submission in TA251 (p135 Pfizer submission). However, they give no further details on how these were estimated.

In their base case, Pfizer estimate a utility after SCT in CP of 0.71 at age 54.

Next, Pfizer assume a utility for patients on IFN in CP of 0.71, which they took from our analysis in TA241 (IFN was not a treatment in our TA251 analysis).

As in our TA251 analysis, all utilities are assumed to decrease gradually with age.

5.2.7.2 Utilities in AP CML

For AP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. 0.73 at age 54. We used this value in TA251 for treatment with HU (we did not model treatment with TKIs in AP). This value was originally reported in Dalziel and colleagues (2004).[46]
2. From patients in Study 200 of people on bosutinib. The weighted average utility, [redacted]. At baseline, [redacted] of AP patients completed the EQ-5D.

For their base case, Pfizer used the first value.

Next, Pfizer assumed the same value of 0.73 for patients on HU in AP.

Finally, for patients after SCT in AP, Pfizer assume a utility of 0.71 for patients age 54, the same as for patients after SCT in CP.

5.2.7.3 Utilities in BP CML

For AP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. 0.52 at age 54. We used this value in TA251 for treatment with HU (we did not model treatment with TKIs in BP). This value was originally reported in Dalziel and colleagues (2004).[46]
2. From patients in Study 200 of people on bosutinib. The weighted average utility, [redacted], was [redacted] (p132 Pfizer submission), which is only slightly less than the averages for 3rd-line CP and AP in Study 200. At baseline, [redacted] of BP patients completed the EQ-5D.

For their base case, Pfizer used the first value.

Next, Pfizer assumed the same value of 0.52 for patients in BP on HU and after SCT.

Table 42. Comparison of utilities used in TA251, used by Pfizer and measured in Study 200

Phase	Treatment	TA251	Study 200	Pfizer
CP	**Bosutinib**	For TKIs[a], 0.84 age 54, declining with age.	[redacted] at age [redacted] for 3rd-line, [redacted] for 2nd-line[d]	0.85 age 54, declining with age
	HU	0.84 age 54, declining with age	n/a	0.85 age 54, declining with age
	SCT	0.80 age 54, declining with age [b]		0.71 age 54, declining with age
	IFN	0.71, independent of age 51[c]		0.71 age 54, declining with age
AP	**Bosutinib**	n/a	[redacted]	0.73 age 54, declining with age
	HU	0.73 (declining with age from age 78)	n/a	0.73 age 54, declining with age
	SCT	n/a		0.71 age 54, declining with age
BP	**Bosutinib**	n/a	[redacted]	0.52 age 54, declining with age
	HU	0.52 (independent of age)	n/a	
	SCT	n/a		

a Bosutinib not modelled in TA251
b See text for derivation.
c From TA241; not modelled in TA251
d [redacted] calculated by PenTAG from data on p358 Pfizer submission

5.2.8 Adverse events

Adverse events are included only for bosutinib and are assumed to incur costs but not affect quality of life in any way not already reflected by utility values as specified in Section 5.2.7 (p124). Adverse events are assumed to occur in the first cycle only.

Resource use and costs associated with adverse events are discussed in Section 5.2.9.6 (p130).

5.2.9 Resources and costs

Resource use and cost data were drawn from multiple sources. Resource use data were largely drawn from TA251[17] (which were in turn based on a survey by Oxford Outcomes on behalf of Bristol-Myers Squibb), with most costs derived from the Department of Health National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts.[47]

5.2.9.1 Resource use systematic review

Pfizer conducted a systematic review for relevant resource use and cost data. The search was performed in October/November 2012 and used the same search strategy, inclusion and exclusion criteria as in Section 5.1 (p108), but with the study type criteria broadened to include any study that reported cost or resource data from the UK.

Abstracts were assessed by two reviewers for full paper retrieval. Full papers were obtained and assessed by two reviewers. Data extraction was conducted by one reviewer and checked by a second party.

Pfizer felt that insufficient resource use data had been identified and so sought data from first-line studies. As a result they included resource use and cost data from TA251.[17] Pfizer state that first-line data are appropriate as resource use is expected to be driven primarily by phase of disease rather than line of treatment (Pfizer submission, Section 7.4.18, p141).

Figure 16 shows the flow diagram of articles in the systematic review, and Table 43 shows the included studies.

Figure 16. Study flow diagram for resource use systematic review

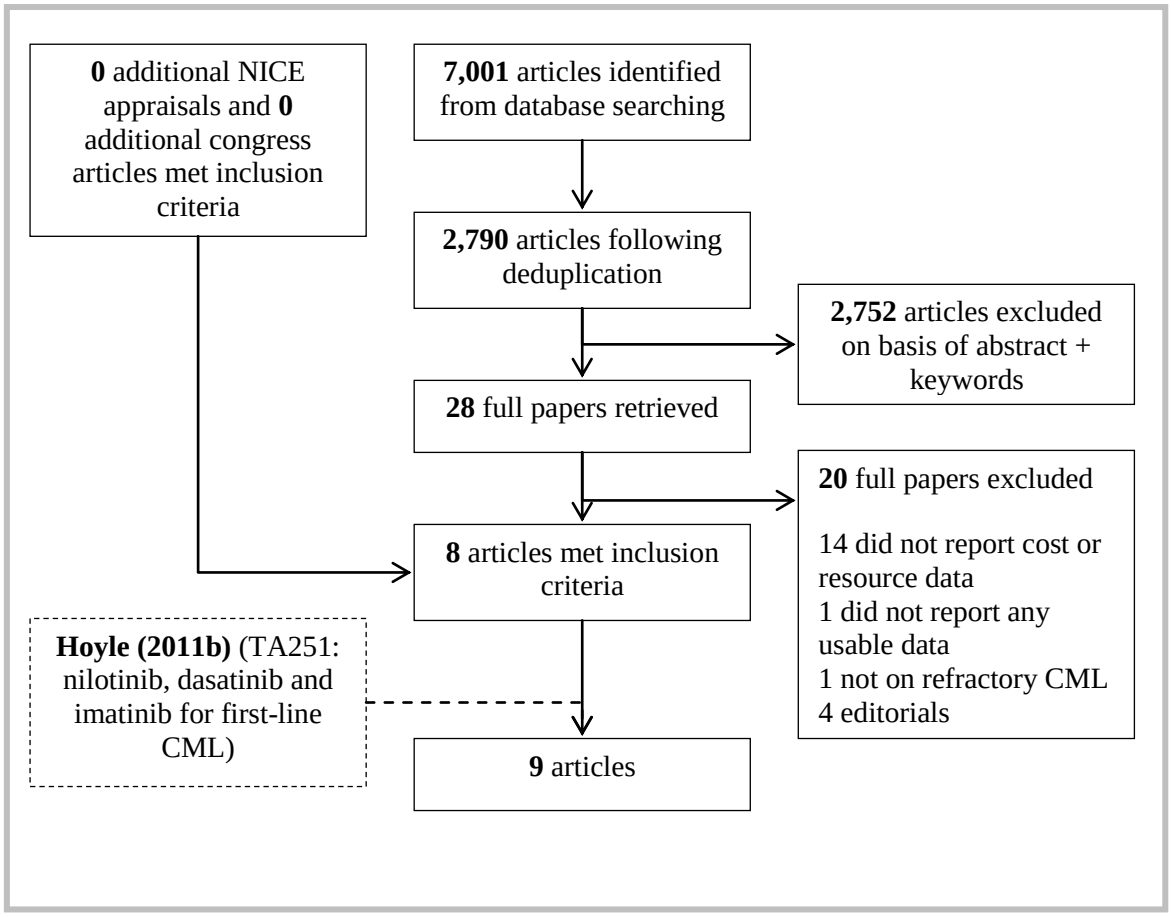


Table 43. Included studies in systematic review of resource use and cost data

Study	Resource use/cost included in Pfizer model base case	Notes
Hoyle (2011a)[39] Rogers (2012)[2] Loveman (2012)[40]	Interferon patients requiring assistance with injection Hydroxycarbamide and interferon dosing	TA241
Hoyle (2011b)[17]	Nurse-led outpatient appointments Consultant-led outpatient appointments Tests (various) Hospital inpatient bed days Hospital inpatient ICU days Adverse events	TA251
Darbà (2012)[48]	*None*	Not English language
Szabo (2009)[49]	*None*	Conference abstract
Taylor (2009a)[50]	*None*	Conference abstract
Taylor (2009b)[51]	*None*	Conference abstract
Warren (2004)[52]	*None*	

5.2.9.2 Drug acquisition

Drug acquisition costs per monthly model cycle were calculated by multiplying the expected dosage across the cycle by the drug cost per unit, to give monthly costs (costs per cycle) as shown in Table 44. Costs of stem cell transplant are discussed in Section 5.2.9.7 (p131).

Table 44. Costs per month of bosutinib, hydroxycarbamide and interferon

Intervention	Cost per month	Units per month	Source	Unit cost	Source
Bosutinib	£3,735.84	30.44	Recommended daily dose 500mg	£122.74	£3,436.67 for 28 tablet pack
Hydroxycarbamide	£12.75	121.75	Loveman (2012)[40]	£0.10	BNF 63[b]
Interferon	£1,296.03[a]	60.88	Rogers (2012)[2]	£21.29	BNF 63

a The Pfizer report states that the monthly cost of interferon including nurse assistance with injection for some patients is £648. We believe this assumes one unit daily, i.e., 30.44 units per month, and does not include the cost of nurse assistance. The Pfizer model assumes two injections per day.

b The Pfizer model cites the source as BNF 63 while the report cites the source as BNF 64

5.2.9.3 Drug administration

Pfizer assumed no drug administration costs for bosutinib and hydroxycarbamide. Pfizer assumed that 25% of interferon patients would require assistance with injection, following an assumption made by Rogers and colleagues (2012),[2] and that this would require a district nurse visit, each costing £39.[53]

The Pfizer model includes one nurse visit per cycle (i.e., per month) in drug administration costs for patients requiring assistance.

Stem cell transplant administration costs are discussed in Section 5.2.9.7 (p131).

5.2.9.4 Medical management, monitoring and tests

Pfizer included medical management costs as shown in Table 45 and a cost of palliative care before death (discussed in Section 5.2.9.5, p129). Medical management costs relating to stem cell transplant are discussed in Section 5.2.9.7 (p131).

Table 45. On-going medical management costs for patients on bosutinib, HU or IFN in Pfizer model

Item	Cost / month	Units / month[17]	Unit cost[47]
Chronic Phase			
Nurse-led outpatient appointment	£42	0.40	£106[a]
Consultant-led outpatient appointment	£111	0.90	£124[b]
Hospital inpatient ward day	£0	0.00	£322[c]
Hospital inpatient ward day	£0	0.00	£1,109[d]
Total	**£154**		
Accelerated Phase and Blast Crisis Phase			
Nurse-led outpatient appointment	£53	0.50	£106[a]
Consultant-led outpatient appointment	£161	1.30	£124[b]
Hospital inpatient ward day	£554	1.72	£322[c]
Hospital inpatient ward day	£111	0.10	£1,109[d]
Total	**£878**		

a Outpatient medical oncology - Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face
b Outpatient medical oncology - Consultant Led: Follow up Attendance Non-Admitted Face to Face
c Average of excess bed day – Non-elective inpatient - Malignant Disorders of Lymphatic or Haematological Systems, with/without CC
d Average of critical care unit costs – adult critical care (weighted by number of critical care periods)

Pfizer included costs of CML related tests (mostly bone marrow aspirations), separately for CP and for AP/BP, which were inflated from TA251[17] using the HCHS Pay and Prices index[53] to inflate from 2008/09 to 2011/12 prices. The resulting costs per cycle of tests in CP, AP and BP were £231, £377 and £377 respectively.

5.2.9.5 Palliative care

Pfizer used a cost of £6,004 for death based on a cost of £5,401 reported by Addicott and Dewar (2008)[54] and inflated from 2007/08 prices. The cost of £5,401 includes costs incurred in the acute and

community health sectors and is derived from 40 patients accessing a new programme of end of life choice.

5.2.9.6 Adverse events

Costs of adverse events were included for bosutinib but not for comparators. Pfizer state that this is in order to present a conservative estimate of the costs associated with bosutinib treatment. Frequencies of adverse events were estimated from the third-line CP cohort of Study 200 and included "treatment-emergent adverse events of grade 3 or 4 that occurred in 5% or more of the subpopulations contained within the third-line cohort of Study 200".

Table 46 shows the costs of adverse events for bosutinib in the Pfizer model, which are used for the CP model and also the AP and BP models. A one-off cost of £506.25 is assumed in the first cycle.

Table 46. Costs of adverse events for bosutinib in Pfizer model

AE	Proportion of patients (Study 200 CP-3L cohort, 28 March 2011 snapshot)	Cost per event	Cost source
Thrombocytopenia	25.4%	£503.99	TA251[17]
Neutropenia	14.4%	£506.13	
Anaemia	5.1%	£346.69	
Cardiac disorders	4.2%	£169.81	
Gastrointestinal disorders[a]	13.6%	£281.07	Erlotinib ERG report[55]
Hepatobiliary disorders	4.2%	£215.85	DH Reference costs 2011-12[47]
Infections and infestations	3.4%	£933.23	
Investigations	9.3%	£31.02	
Metabolism and nutrition disorders	3.4%	£1,576.37	
Musculoskeletal and connective tissue disorders	5.9%	£717.03	
Neoplasms benign, malignant and unspecified	3.4%	£1,570.14	
Nervous system disorders	4.2%	£1,091.02	
Respiratory, thoracic and mediastinal disorders[b]	2.5%	£32.10	TA251[17]
Skin and subcutaneous tissue disorders	1.7%	£138.76	Erlotinib ERG report[55]
Weighted average	**100%**	**£506.25**	

a Assumed to be diarrhoea
b Assumed to be pleural effusion

5.2.9.7 Stem cell transplant

Stem cell transplant costs were mainly drawn from the economic analysis performed for the NHS Blood and Transplant service[56] which estimated the upfront costs of SCT and the costs for three follow-up periods (1-6 months, 7-12 months and 13-24 months).

These costs were based on resource use in a Dutch cost study by van Agthoven and colleagues (2002)[57] into the costs of three forms of stem cell transplant for acute myeloid leukaemia and acute lymphoblastic leukaemia. The three forms were:

- BMT – Bone marrow transplant; stem cell graft harvested from the bone marrow of an HLA-identical sibling
- PBSCT – Peripheral blood stem cell transplant; stem cell graft harvested from the peripheral blood of an HLA-identical sibling
- MUD – Matched unrelated donor; stem cell graft from the bone marrow or peripheral blood of a voluntary matched unrelated donor

The study included direct medical costs for Personnel, Transplantation and Follow-up (two years), which importantly included outpatient clinic attendances and diagnostic tests during follow-up. The results of the study are shown in Table 47.

Table 47. Costs of stem cell transplant (1998 EUR, €) from van Agthoven and colleagues (2002)[57]

	BMT			**MUD**			**PBSCT**		
	Average cost per living patient	% alive	Average cost per transplant patient	Average cost per living patient	% alive	Average cost per transplant patient	Average cost per living patient	% alive	Average cost per transplant patient
Personnel	26,543		26,543	26,543		26,543	26,543		26,543
Transplantation	42,129	100	42,129	84,948	100	84,948	45,734	100	45,734
Follow-up phase 1 (1–6 months)	16,587	98	16,255	30,292	90	27,263	15,051	92	13,847
Follow-up phase 2 (7–12 months)	10,157	81	8,227	18,473	48	8,867	12,265	77	9,444
Follow-up phase 3 (13–24 months)	8,093	64	5,180	13,331	31	4,133	6,313	54	3,409
Total	**103,509**		**98,334**	**173,587**		**151,754**	**105,906**		**98,977**

In the economic analysis performed for the NHS Blood and Transplant service[56] unit costs were replaced with NHS costs (2009 prices) where possible, and where not possible were converted using the 1999 pound sterling / euro exchange rate and inflated at 3% per annum (Table 48).

Table 48. Costs of stem cell transplant (2009 GDP, £) from NHS Blood and Transplant service[56]

	Average cost per living patient	% alive	Weighted cost per transplant patient
Personnel	31,409	100	31,409
Transplantation	40,140	100	40,140
Follow-up phase 1 (1–6 months)	29,713	90	26,742
Follow-up phase 2 (7–12 months)	18,119	48	8,697
Follow-up phase 3 (13–24 months)	13,075	31	4,053
Total	**132,456**		**111,041**

The adaptation to NHS costs is not described in sufficient detail to be reproducible, but the researchers note that the weighted cost per transplant patient (£111k) is reassuringly close to the commissioning price (£101k).

Costs were then inflated by Pfizer using the HCHS Pay and Prices Index.[53]

Longer term follow-up was assumed to consist of 100 mg of ciclosporin twice daily. Costs per month used in Pfizer's model are presented in Table 49.

Table 49. Pfizer assumed costs associated with stem cell transplant

Item	Cost / month	Units / month	Unit cost
Initial treatment	£76,560	1	£76,560
Follow-up 1-6 months	£5,299	1	£5,299
Follow-up 7-12 months	£3,231	1	£3,231
Follow-up 13-24 months	£1,166	1	£1,166
Follow-up 25+ months	£140	60.88	£2.30

Patients receiving SCT in the blast crisis phase (i.e., SCT patients in the BP model) are assumed to receive two cycles of the FLAG-IDA chemotherapy regime before SCT, at a cost of £29,212. Table 50 gives a summary of costs for two cycles of the FLAG-IDA regime (further details available in Pfizer submission, Section 10.20, pp393-395).

Table 50. Summary of FLAG-IDA chemotherapy costs

Item	Item cost	Units	Unit cost
Drug acquisition			
Fludarabine	£1,471	10	£147.07
Cytarabine	£780	20	£39.00
Idarubicin	£1,048	12	£87.36
G-CSF	£1,922	Various	Various
Medical management			
Haematology tests	£3	1	£3.09
AML without CC: Elective inpatient stay	£4,866	1	£4,866
AML without CC: Elective excess bed day	£4,515	14	£322.34
Total (two cycles)	**£29,212**		

Abbreviations AML – acute myeloid leukaemia; CC – comorbidities and complications

5.2.9.8 Summary of costs

Table 51. Summary of costs per month in CP model

Intervention	Bosutinib	Hydroxy-carbamide	Interferon	SCT
Chronic Phase On Treatment				
Drug acquisition	£3,736	£13	£1,296	
Drug administration	£0	£0	£10	
Medical management	£154	£154	£154	£154
Tests	£231	£231	£231	£231
Adverse events	£506 first cycle only			
SCT costs				Month 0: £76,560 Months 1-6: £5,299 per month (p.m). Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£4,627** first cycle **£4,121** thereafter	**£398**	**£1,691**	Month 0: **£76,945** Months 1-6: **£5,684** p.m. Months 7-12: **£3,616** p.m. Months 13-24: **£1,551** p.m. Months 25+: **£525** p.m.
Chronic Phase Off Treatment				
Drug acquisition	£13		£13	
Drug administration	£0		£0	
Medical management	£154		£154	
Tests	£231		£231	
Total	**£398**		**£398**	
Accelerated & Blast Phases				
Drug acquisition	£13	£13	£13	
Drug administration	£0	£0	£0	
Medical management	£878	£878	£878	
Tests	£377	£377	£377	
Total	**£1,268**	**£1,268**	**£1,268**	
Death	**£6,004**	**£6,004**	**£6,004**	**£6,004**

Table 52. Summary of costs per month in AP model

Intervention	Bosutinib	Hydroxycarbamide	SCT
Accelerated Phase On Treatment			
Drug acquisition	**£3,736**	**£13**	
Drug administration	**£0**	**£0**	
Medical management	**£878**	**£878**	£878
Tests	**£377**	**£377**	£377
Adverse events	**£506 first cycle only**		
SCT costs			Month 0: £76,560 Months 1-6: £5,299 p.m. Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£5,498** first cycle **£4,991** thereafter	**£1,268**	Month 0: **£77,815** Months 1-6: **£6,554** p.m. Months 7-12: **£4,487** p.m. Months 13-24: **£2,421** p.m. Months 25+: **£1,396** p.m.
Accelerated Phase Off Treatment			
Drug acquisition	£13		
Drug administration	£0		
Medical management	**£878**		
Tests	**£377**		
Total	**£1,268**		
Blast Crisis Phase			
Drug acquisition	£13	£13	
Drug administration	£0	£0	
Medical management	**£878**	**£878**	
Tests	**£377**	**£377**	
Total	**£1,268**	**£1,268**	
Death	**£6,004**	**£6,004**	**£6,004**

Table 53. Summary of costs per month in BP model

Intervention	Bosutinib	Hydroxy-carbamide	SCT
Blast Crisis Phase On Treatment			
Drug acquisition	**£3,736**	**£13**	
Drug administration	**£0**	**£0**	
Medical management	**£878**	**£878**	£878
Tests	**£377**	**£377**	£377
Adverse events	**£506 first cycle only**		
SCT costs (including FLAG-IDA)			Month 0: £105,772 Months 1-6: £5,299 p.m. Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£5,498** first cycle **£4,991** thereafter	**£1,268**	Month 0: **£107,027** Months 1-6: **£6,554** p.m. Months 7-12: **£4,487** p.m. Months 13-24: **£2,421** p.m. Months 25+: **£1,396** p.m.
Blast Crisis Phase Off Treatment			
Drug acquisition	£13		
Drug administration	£0		
Medical management	**£878**		
Tests	**£377**		
Total	**£1,268**		
Death	**£6,004**	**£6,004**	**£6,004**

5.2.10 Cost-effectiveness results

This section presents the deterministic base case cost-effectiveness results.

Unless otherwise stated, positive Incremental cost-effectiveness ratios (ICERs) mean that the intervention is more costly and more effective than the comparator. Negative ICERs are not shown but instead it is stated whether the intervention "dominates" the comparator (is less costly and more effective) or is "dominated" by the comparator (is more costly and less effective).

Incremental net health benefits (INHBs) are also presented in units of QALYs. Incremental net health benefit is calculated as $INHB = \Delta QALYs - \Delta Costs/\lambda$ for a willingness-to-pay threshold λ. We present INHB at willingness-to-pay thresholds of £20,000 and £30,000 per QALY for all models, as well as INHB at willingness-to-pay threshold of £50,000 per QALY for the AP and BP models as Pfizer propose that bosutinib meets the end-of-life criteria in these patients. INHB are always shown relative to bosutinib, such that positive INHB for hydroxycarbamide (for example) means that hydroxycarbamide is cost-effective compared to bosutinib.

5.2.10.1 CP model deterministic results

Deterministic base case cost-effectiveness results from the CP model are shown in Table 54 (p138) and Figure 17 (p138). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 4.83 QALY (9.23 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted] (costs and QALYs discounted at 3.5% per annum, life years not discounted). The extra costs of bosutinib are mainly from drug acquisition, with smaller increases also due to additional medical management during the prolonged life expectancy. Interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib. Bosutinib is the most effective treatment, providing 3.56 QALYs more than the next most effective treatment, SCT.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000 and £30,000 per QALY are [redacted] and [redacted] QALYs respectively. At a willingness-to-pay threshold of £20,000 per QALY hydroxycarbamide gives the greatest expected net health benefit while at £30,000 per QALY bosutinib gives the greatest expected net health benefit.

Bosutinib patients spend longer in the chronic phase than other patients (11.54 years versus 2.58 for hydroxycarbamide, 2.67 for interferon and 6.60 for SCT) and also accrue more discounted QALYs in the chronic phase (6.77 QALYs versus 1.93 for hydroxycarbamide, 1.92 for interferon and 3.70 for SCT). Bosutinib patients also spend longer in the accelerated and blast phases than hydroxycarbamide and interferon patients (SCT patients are cured and do not progress to AP or BP), and accrue more discounted QALYs in the accelerated phase as a result, but not in the blast phase (due to greater discounting as BP is reached at a later time).

Bosutinib patients spend [redacted] life years in the CP off treatment state, in which they are treated with hydroxycarbamide.

[redacted]

Table 54. Deterministic CP model results

	Bosutinib	Hydroxycarbamide	Interferon	SCT
Life years (undiscounted)				
CP on treatment	[redacted]	2.58	0.54	6.60
CP off treatment	[redacted]	n/a	2.12	n/a
AP	0.73	0.51	0.52	n/a
BP	0.48	0.43	0.44	n/a
Total	**12.75**	**3.52**	**3.62**	**6.60**
Discounted QALYs				
CP on treatment	[redacted]	1.93	0.38	3.70
CP off treatment	[redacted]	n/a	1.53	n/a
AP	0.33	0.31	0.31	n/a
BP	0.16	0.19	0.19	n/a
Total	**7.26**	**2.43**	**2.42**	**3.70**
Discounted costs				
Technology cost	[redacted]	£490	£8,461	£141,132
Hydroxycarbamide following discontinuation	£1,053	n/a	£419	n/a
Monitoring	£24,372	£13,195	£13,386	£10,163
Tests	£27,315	£10,352	£10,583	£15,283
Palliative care	£4,174	£5,436	£5,419	£4,961
Adverse events	£506	n/a	n/a	n/a
Total	[redacted]	**£29,473**	**£38,268**	**£171,539**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified				
vs. hydroxycarbamide	[redacted]			
vs. interferon	[redacted]	Dominant		
vs. SCT	Dominant	111,511[a]	103,662[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)				
WTP £20,000/QALY	**n/a**	[redacted]	[redacted]	[redacted]
WTP £30,000/QALY	**n/a**	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 17. Cost-effectiveness plane in CP model, Pfizer base case

Note that (IFN, HU) and (Bosutinib, HU) denote that interferon and bosutinib are followed by hydroxycarbamide

5.2.10.2 AP model deterministic results

Deterministic base case cost-effectiveness results from the AP model are shown in Table 55 (p140) and

Figure 18 (p140). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 1.86 QALY (3.11 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted]. The extra costs of bosutinib are mainly drug acquisition and also due to additional medical management during the prolonged life expectancy. SCT is dominated by bosutinib as it is less effective and more costly. Bosutinib is the most effective intervention, providing a 0.80 QALY (1.45 life year) gain per patient over the next most effective intervention, SCT.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY are [redacted] QALYs respectively. At all three willingness-to-pay thresholds hydroxycarbamide therefore gives the greatest expected net benefit.

Bosutinib patients spend longer in the accelerated phase than patients receiving hydroxycarbamide and SCT (4.03 life years for bosutinib versus 1.02 life years for hydroxycarbamide and 3.02 life years for SCT), and accrue more discounted QALYs in the accelerated phase as well (2.56 QALYs for bosutinib versus 0.72 QALYs for hydroxycarbamide and 1.96 QALYs for SCT). Bosutinib patients spend slightly longer in the blast crisis phase than do hydroxycarbamide patients (0.45 versus 0.35 life

years; SCT patients do not transform to BP), and also accrue slightly more discounted QALYs in BP (0.20 versus 0.18).

Bosutinib patients spend [redacted] life years in the AP off treatment state, in which they are treated with hydroxycarbamide.

[redacted]

Table 55. Deterministic AP model results

	Bosutinib	Hydroxycarbamide	SCT
Life years (undiscounted)			
AP on treatment	[redacted]	1.02	3.02
AP off treatment	[redacted]	n/a	n/a
BP	0.45	0.35	n/a
Total	**4.48**	**1.37**	**3.02**
Discounted QALYs			
AP on treatment	[redacted]	0.72	1.96
AP off treatment	[redacted]	n/a	n/a
BP	0.20	0.18	n/a
Total	**2.76**	**0.90**	**1.96**
Discounted costs			
Technology cost	[redacted]	£204	£130,528
Hydroxycarbamide following discontinuation	£297	n/a	n/a
Monitoring	£41,726	£14,032	£29,414
Tests	£17,916	£6,025	£12,630
Palliative care	£5,280	£5,817	£5,520
Adverse events	£506	n/a	n/a
Total	[redacted]	**£26,078**	**£178,093**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified			
vs. hydroxycarbamide	[redacted]		
vs. SCT	Dominant	142,982[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)			
WTP £20,000/QALY	**n/a**	[redacted]	[redacted]
WTP £30,000/QALY	**n/a**	[redacted]	[redacted]
WTP £50,000/QALY	**n/a**	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 18. Cost-effectiveness plane in AP model, Pfizer base case

5.2.10.3 BP model deterministic results

Deterministic base case cost-effectiveness results from the BP model are shown in Table 56 (p142) and

Figure 19 (p142). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 0.60 QALY (1.23 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted]. The extra costs of bosutinib are drug acquisition and additional medical management during the prolonged life expectancy. SCT is more costly than bosutinib but more effective. The ICER for SCT versus bosutinib is [redacted] per QALY. SCT is the most effective intervention, providing a 0.40 QALY (0.87 life year) gain per patient over the next most effective intervention, bosutinib.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY are [redacted] QALYs respectively. The INHBs of SCT versus bosutinib at the same thresholds are [redacted] QALYs respectively.

Across all three willingness-to-pay thresholds hydroxycarbamide therefore gives the greatest expected net benefit.

Bosutinib patients spend [redacted] life years in the BP off treatment state, in which they are treated with hydroxycarbamide.

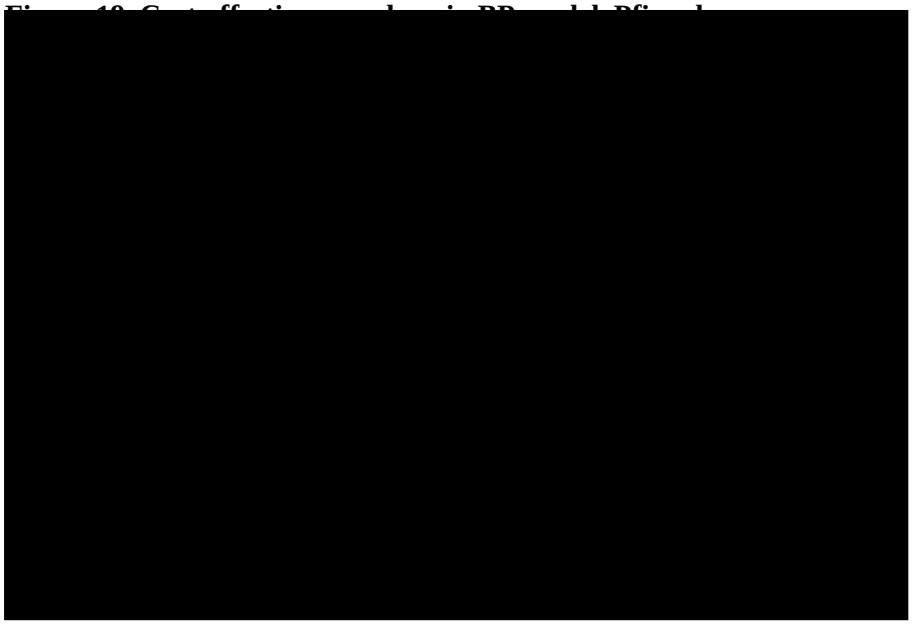
[redacted]

Table 56. Deterministic BP model results

	Bosutinib	Hydroxycarbamide	SCT
Life years (undiscounted)			
BP on treatment	[redacted]	0.54	2.64
BP off treatment	[redacted]	n/a	n/a
Total	**1.77**	**0.54**	**2.64**
Discounted QALYs			
BP on treatment	[redacted]	0.28	1.28
BP off treatment	[redacted]	n/a	n/a
Total	**0.88**	**0.28**	**1.28**
Discounted costs			
Technology cost	[redacted]	£82	£157,759
Hydroxycarbamide following discontinuation	£169	n/a	n/a
Monitoring	£17,935	£5,681	£26,011
Tests	£7,701	£2,439	£11,169
Palliative care	£5,743	£5,967	£5,586
Adverse events	£506	n/a	n/a
Total	[redacted]	**£14,170**	**£200,526**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified			
vs. hydroxycarbamide	[redacted]		
vs. SCT	[redacted]	186,265[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)			
WTP £20,000/QALY	**0.0**	[redacted]	[redacted]
WTP £30,000/QALY	**0.0**	[redacted]	[redacted]
WTP £50,000/QALY	**0.0**	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 19: Cost-effectiveness scatterplot in PBS model: Pfizer



5.2.11 Sensitivity analyses

5.2.11.1 One-way sensitivity analyses

Extensive one-way sensitivity analyses were not performed as Pfizer believed structural uncertainties were greater than parameter uncertainties. Scenario analyses were performed instead (see Section 5.2.11.3, p146).

5.2.11.2 Probabilistic sensitivity analysis

Pfizer conducted a probabilistic sensitivity analysis but cautioned that it could not capture all the uncertainty in the decision problems addressed by the economic models due to several sources of structural uncertainty.

Pfizer did not record the parameter values associated with probabilistic outputs and therefore no value of information analyses could be conducted.

CP model PSA

Table 57 gives a comparison of the key CP model deterministic and probabilistic results. The deterministic and mean probabilistic results are very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented graphically in the Pfizer report).

Further results are presented in Appendix R.

Table 57. Comparison of key CP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	Interferon	SCT
Deterministic results				
Total discounted QALYs	7.26	2.43	2.42	3.70
Total discounted costs	[redacted]	£29,473	£38,268	£171,539
ICER vs. hydroxycarbamide	[redacted]			
ICER vs. interferon	[redacted]	Dominant		
ICER vs. SCT	Dominant	111,511[a]	103,662[a]	
Probabilistic results				
Total discounted QALYs	7.15	2.43	2.39	3.84
Total discounted costs	[redacted]	£29,389	£36,091	£173,948
ICER vs. hydroxycarbamide	[redacted]			
ICER vs. interferon	[redacted]	Dominant		
ICER vs. SCT	Dominant	102,524[a]	104,118[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report

AP model PSA

Table 58 gives a comparison of the key AP model deterministic and probabilistic results. Deterministic results and mean probabilistic results were very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY, £30,000/QALY and £50,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented in the Pfizer report).

Further results are presented in Appendix R.

Table 58. Comparison of key AP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	SCT
Deterministic results			
Total discounted QALYs	2.76	0.90	1.96
Total discounted costs	[redacted]	£26,078	£178,093
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	Dominant	142,982[a]	
Probabilistic results			
Total discounted QALYs	2.75	0.91	1.95
Total discounted costs	[redacted]	£26,095	£175,420
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	Dominant	143,454[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	100.0%	0.0%
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £50,000/QALY[b]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report

BP model PSA

Table 59 gives a comparison of the key BP model deterministic and probabilistic results.

Deterministic results and mean probabilistic results were very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY, £30,000/QALY and £50,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented in the Pfizer report).

Further results are presented in Appendix R.

Table 59. Comparison of key BP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	SCT
Deterministic results			
Total discounted QALYs	0.88	0.28	1.28
Total discounted costs	[redacted]	£14,170	£200,526
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	[redacted]	186,265[a]	
Probabilistic results			
Total discounted QALYs	0.89	0.32	1.29
Total discounted costs	[redacted]	£15,262	£201,228
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	[redacted]	192,016[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	100.0%	0.0%
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £50,000/QALY[b]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report
c Note that in the Pfizer submission this was reported as [redacted]/QALY

5.2.11.3 Scenario analyses

Pfizer conducted a number of scenario analyses for each of the models. Some of these are parameter changes and would normally be considered one-way sensitivity analyses, while others are structural changes to the model. Here, we simply report the results of the analyses. Later (Section 5.3, p159), we comment on the appropriateness of the analyses.

[redacted]. Note that shading does not indicate whether bosutinib is more or less costly or more or less effective than the comparator.

Table 60. Shading used to denote cost-effectiveness of bosutinib

White background	[redacted]
Grey background	[redacted]
Black background	

CP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 61 (p148). In most scenarios interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib. Where this is not the case additional results are presented. Further details of scenario analyses can be found in the Pfizer submission, Section 10.22, pp467-476.

In most analyses interferon is dominated by hydroxycarbamide, which Pfizer state is in keeping with clinical practice. When bosutinib is compared to hydroxycarbamide, bosutinib is always more expensive, and more effective, with ICERs ranging from [redacted] per QALY. There were four scenarios where the ICER of bosutinib versus hydroxycarbamide was substantially reduced:

- Patient population set to second line for bosutinib
- Hydroxycarbamide overall survival set to two years
- Resource use from TA241 is assumed
- Hazard ratio for survival in MCyR surrogate method of 0.876 used

Pfizer suggest that resource use from TA241 may be more appropriate than resource use from TA251 (the base case) because TA241 and this decision problem involve patients who have failed imatinib treatment.

In most analyses bosutinib dominates SCT. When the time on bosutinib treatment is calculated using a similar method to TA241 SCT becomes cheaper than bosutinib but also less effective, with an ICER of [redacted] per QALY. When the cost per month in CP post-discontinuation is increased to £1,040 for bosutinib, SCT becomes cheaper than bosutinib but also less effective, with an ICER of [redacted] per QALY.

Table 61. Scenario analyses applied to CP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	Dominant
Patient population				
Bosutinib patient population	CP-3L from Study 200	CP-3L post-hoc "unmet need" subpopulation	[redacted]	Dominant
		CP-2L population	[redacted]	Dominant
		CP post-hoc "unmet need" subpopulation	[redacted]	Dominant
Cohort starting age	54 years (mean age in CP-3L Study 200)	49 years (−10%)	[redacted]	Dominant
		59 years (+10%)	[redacted]	Dominant
Overall survival				
Bosutinib overall survival	MCyR using hazard ratio for survival of 0.37[2]	MCyR using hazard ratio for survival of 0.156 (lower bound of 95% CI)	[redacted]	Dominant
		MCyR using hazard ratio for survival of 0.876 (upper bound of 95% CI)	[redacted]	Dominant
		Exponential curve fitted to CP-3L OS	[redacted]	Dominant
		"Cumulative survival approach" (OS = PFS + 10 months AP + 6 months BP)	[redacted]	Dominant
SCT overall survival	Exponential curve fitted to Jabbour (2011)[10]	Weibull curve fitted to Jabbour (2011)[10]	Unchanged	Dominant
		Exponential curve fitted to Oehler (2007)[12]	Unchanged	Dominant
Hydroxycarba-mide overall survival	Mean OS = 42 months	Mean OS = 38 months (see Pfizer submission, Section 10.22, pp469-470 for justification)	[redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		Mean OS = 24 months (lower bound of plausible range in Rogers 2012)[2]	[redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged
		Mean OS = 78 months (upper bound of plausible range in Rogers 2012)[2]	[redacted]	Unchanged
Transformation to AP and BP				
Time in blast phase	6 months	13 months[2]	[redacted]	Dominant
		3 months	[redacted]	Dominant
Transformation following SCT	Patients cannot transform to AP and BP, but remain in CP	Patients transform to AP and BP for 10 and 6 months respectively before death	[redacted]	Dominant
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to CP-3L cohort of Study 200	Loglogistic curve	[redacted]	Dominant
		Time on treatment equal to PFS minus discontinuation due to AEs[2]	[redacted]	[redacted]
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	Dominant
Costs				
Resource use	Medical management from TA251[17]	Medical management from TA241	[redacted]	Dominant
Cost of CP off treatment health state	Patients receive hydroxycarba-mide, costing £12.75 per month	Patients receive further treatment post-discontinuation in CP (e.g., other TKIs or SCT) costing £1,040 per month (similar to TA241)	[redacted]	[redacted]
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP & BP £2,536/month (doubled)[c]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		AP only doubled	[redacted]	Dominant
		BP only doubled	[redacted]	Dominant
Cost of death	£6,004	£569[17]	[redacted]	Dominant
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarba-mide arm only	[redacted]	Dominant
		Additional cost of £100/month in all arms wherever patients receive hydroxycarba-mide	[redacted]	Dominant
Utility values				
Source of utility for CP patients on bosutinib or hydr-oxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility at screening for CP-3L cohort in Study 200 used for all patients in CP on bosutinib and hydroxy-carbamide	[redacted]	Not reported
		Utility at screening for CP-3L cohort in Study 200 used for patients in CP on bosutinib only	[redacted]	Dominant
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251	Unchanged	Dominant
Interferon on-treatment utility value	Decrement to HRQL from interferon treatment	No decrement to HRQL from interferon treatment	Unchanged [redacted]bosutinib vs. interferon:[a] [redacted]	Unchanged
Utility values varying by age	Utility values adjusted to account for patient aging	No adjustment for aging	[redacted]	Dominant
Model settings				
Time horizon	50 years	2 years	[redacted]	Dominant
		5 years	[redacted]	Dominant
		10 years	[redacted]	Dominant
		25 years	[redacted]	Dominant

a In these scenarios interferon is not dominated by hydroxycarbamide
b In these scenarios SCT is cheaper than bosutinib
c Analysis conducted by PenTAG

AP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 62 (p152). In most scenarios (including the base case) bosutinib dominated SCT (i.e., bosutinib was cheaper and more effective than SCT). The ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] to [redacted] per QALY (ignoring scenario analyses where the time horizon is shortened). The ICERs for SCT versus hydroxycarbamide ranged from £98,279 to £195,626 per QALY (again, ignoring scenario analyses where the time horizon is shortened).

Notable scenarios in terms of impact on ICERs included:

- Increasing the time spent in BP to 13 months (as used in Rogers and colleagues 2012[2]) increases the ICERs of both bosutinib and SCT versus hydroxycarbamide to [redacted] and £195,626 per QALY respectively.
- Setting the time on bosutinib treatment equal to PFS from Study 200 results in bosutinib becoming more expensive than SCT. In this scenario the ICER of SCT versus hydroxycarbamide is unchanged at £142,982 per QALY and the ICER of bosutinib versus hydroxycarbamide is [redacted] per QALY. The ICER of bosutinib versus SCT is [redacted] per QALY but SCT would be deemed extended dominated by hydroxycarbamide and bosutinib and hence SCT would not be viewed as a proper comparator.
- Using medical management costs from TA241 instead of TA251 results in an ICER for bosutinib versus hydroxycarbamide of [redacted] per QALY.
- Doubling the cost per cycle of AP results in an increased ICER for bosutinib versus hydroxycarbamide of [redacted] per QALY.

Further details of scenario analyses can be found in the Pfizer submission, Section 10.23, pp477-483.

Table 62. Scenario analyses applied to AP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	Dominant
Patient population				
Cohort starting age	50 years (mean age in Study 200 AP cohort)	45 years (−10%)	[redacted]	Dominant
		55 years (+10%)	[redacted]	Dominant
Overall survival				
Bosutinib overall survival	Exponential curve fitted to Study 200 AP cohort OS	Extreme value curve fitted to Study 200 AP cohort OS (15 Feb 2012 snapshot)	[redacted]	Dominant
Stem cell transplant overall survival	Exponential curve fitted to AP cohort in Oehler (2007)[12]	Weibull curve fitted to AP cohort in Oehler (2007)[12]	Unchanged	Dominant
		Exponential curve fitted to AP cohort in Jabbour (2011)[10]	Unchanged	Dominant
Time spent in BP				
Time spent in blast phase	6 months	13 months[2]	[redacted]	Dominant
		3 months	[redacted]	Dominant
Transformation following SCT				
Transformation following SCT	Patients cannot transform to BP, but remain in AP	Patients transform to BP 6 months before death	[redacted]	Dominant
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200 AP cohort	Time on treatment equal to PFS from Study 200 (AP to BP)[a]	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 AP cohort	[redacted]	Dominant
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	Dominant
Costs				
Resource use	Medical management in TA251	Medical management in TA241	[redacted]	Dominant

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP and BP £2,536 (doubled)[b]	[redacted]	Dominant
		AP only doubled[c]	[redacted]	Dominant
		BP only doubled	[redacted]	Dominant
Cost of death	£6,004	£569[17]	[redacted]	Dominant
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	Dominant
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	Dominant
Utility values				
Source of utility for AP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for AP and BP cohorts from Study 200 used for all patients in AP and BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	Not reported
		Utility for AP in Study 200 only used for AP patients on bosutinib in the model (remainder as per base-case)	[redacted]	Dominant
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251[17]	Unchanged	Dominant
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	Dominant
Model settings				
Time horizon	50 years	2 years	[redacted]	Dominant
		5 years	[redacted]	Dominant
		10 years	[redacted]	Dominant

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		25 years	[redacted]	Dominant

a In these scenarios SCT was cheaper than bosutinib
b Analysis conducted by PenTAG
c Pfizer reported an ICER of £136,703/QALY for SCT vs. hydroxycarbamide, PenTAG calculated a different ICER of £168,310/QALY

BP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 63 (p155). In all scenarios SCT is more effective and more costly than bosutinib, which is in turn more costly and more effective than hydroxycarbamide. The ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] per QALY. The scenarios in which the ICER was lowest (i.e., in which bosutinib was most cost-effective) were:

- Utility values from Study 200 used for bosutinib (± hydroxycarbamide) patients (instead of IRIS trial utilities)
- Extreme value distribution used for bosutinib OS instead of exponential distribution

The scenarios in which the ICER for bosutinib versus hydroxycarbamide was highest were:

- Time spent in BP set to 13 months
- Time on treatment equal to PFS from Study 200
- Cost of BP health state doubled

The ICER for SCT versus bosutinib varied from [redacted] per QALY.

Further details of scenario analyses can be found in the Pfizer submission, Section 10.24, pp483-489.

Table 63. Scenario analyses applied to BP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	[redacted]
Patient population				
Cohort starting age	47 years (mean age in Study 200 BP cohort)	42 years (−10%)	[redacted]	[redacted]
		52 years (+10%)	[redacted]	[redacted]
Overall survival				
Bosutinib overall survival	Exponential curve fitted to Study 200 BP cohort OS	OS estimated by fitting 2nd best fitting curve (Weibull) to BP cohort from Study 200	[redacted]	[redacted]
Stem cell transplant overall survival	Exponential curve fitted to BP cohort in Oehler (2007)[12]	Weibull curve fitted to BP cohort in Oehler (2007)[12]	[redacted] Unchanged	[redacted]
		Exponential curve fitted to "advanced phase" cohort in Saussele (2010)[13]	[redacted] Unchanged	[redacted]
Time spent in BP				
Time spent in blast phase	6 months	13 months[2]	[redacted]	Unchanged
		3 months	[redacted]	Unchanged
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200 BP cohort	Time on treatment equal to PFS from Study 200	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 BP cohort	[redacted]	[redacted]
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	[redacted]
Costs				
Resource use	Medical management in TA251	Medical management in TA241	[redacted]	[redacted]
Cost of BP health state	BP £1,268/month	BP £2,536 (doubled)[b]	[redacted]	[redacted]
Cost of death	£6,004	£569[17]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	Unchanged (reported as [redacted] in Pfizer report)
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	[redacted] (reported as [redacted] in Pfizer report)
Cost of SCT	All patients incur cost of FLAG-IDA at £29,212	FLAG-IDA cost removed	Unchanged	[redacted]
Utility values				
Source of utility for BP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for BP cohort from Study 200 used for all patients in BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	Not reported
		Utility for BP in Study 200 only used for BP patients on bosutinib in the model (remainder as per base-case)	[redacted]	[redacted]
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251[17]	Unchanged	[redacted]
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	[redacted]
Model settings				
Time horizon	50 years	2 years	[redacted]	[redacted]
		5 years	[redacted]	[redacted]
		10 years	[redacted]	[redacted]
		25 years	[redacted]	[redacted]

a A wiring error was discovered in Pfizer's model meaning that the log-logistic curve for AP patients was used instead of the curve for BP patients. This gave an original erroneous ICER of [redacted] per QALY.

5.2.12 Model validation and face validity check

Pfizer describe the following model validation and face validity checks (Pfizer submission, Section 7.8.1, p185).

Model design

At the design stage of the model, it was presented to a leading clinician currently treating CML patients in the UK (October 2012), in order to ensure the model has face validity, and matched clinical practice. The key issues around the economic modelling such as time horizon, comparators, survival analysis, adverse events, and utility measures were discussed with other experts using at an advisory meeting in December 2012.

The subsequent model design and shell were then presented to a senior UK economist (and former member of the NICE appraisal committee), whose comments were then incorporated. After this the full economic model was developed, and a first draft of the submission document produced.

Model accuracy and calculations

A number of steps were taken to validate the technical accuracy of the model and submission.

Firstly, estimates of time on treatment and overall survival from the final model were checked against values calculated in a separate spreadsheet – results were the same.

Secondly, extensive one-way sensitivity analyses were conducted on all model inputs and results were reviewed to ensure that changes in cost and effectiveness measures were consistent with expectations.

Thirdly, random checks were made on model inputs compared with source data.

As a last step in the model validation process, the model was reviewed by a senior health economist not involved with the project, using the Drummond checklist, as well as a proprietary internal checklist from BresMed (who developed the model). Following this review a report was produced, with discussions held and changes made to the model and documented accordingly

Finally, in terms of internal validity, as discussed in Section 7.2.2 [of Pfizer submission] the survival functions used to generate estimates of time on treatment and overall survival for bosutinib, hydroxycarbamide and stem cell transplant are very close to those obtained based on the empirical (Kaplan-Meier) survival distributions (see Section 7.3.1 [of Pfizer submission]), and results seen in published NICE technology appraisals (TA241, TA251).

External review

Following the development of the model, the model and submission were reviewed by an independent UK economist not thus far involved with the project. This economist works in a department of a leading centre for health economics in the UK, and part of an Evidence Review Group. The economist reviewed the submission, highlighting areas for improvement and clarification, as well as any assumptions they did not agree with. Following this review, further changes were made (as well as amendments made to answers questions they raised), ahead of submission to NICE.

5.3 Critique of manufacturer's submitted evidence

5.3.1 Checking wiring of Pfizer's model

We checked the wiring of Pfizer's model in the following three ways:

- We built an independent, simplified version of Pfizer's model. This model did not use discrete model cycles. Instead, QALYs and costs were estimated by applying unit costs and utilities to the undiscounted life year estimates for each treatment in each arm in Pfizer's model. The results of the simplified model (e.g. total discounted costs and QALYs, ICERs) were similar to those from Pfizer's model. For example, the ICER for bosutinib vs. HU in CP was estimated as [redacted] vs. [redacted] from Pfizer's model. This provides strong evidence that there are no serious wiring errors in Pfizer's model in addition to the error we found in the original version of the model.
- We checked the key formulae in Pfizer's model.
- We checked that the model outputs were correct when input parameters were set to extreme values.

5.3.2 NICE reference case checklist

NICE reference case[43] requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	P	Population changed to reflect revised indication from the EMA for bosutinib. Population limited to include only patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	P	Does not include SCT following bosutinib (see Section 5.3.6, p162)
Perspective on costs	NHS and PSS	Y	See Section 5.3.7.1, p164
Perspective on outcomes	All health effects on individuals	Y	
Type of economic evaluation	Cost-effectiveness analysis	Y	
Synthesis of evidence on outcomes	Based on a systematic review	Y	
Measure of health benefits	QALYs	Y	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Y	*For bosutinib, hydroxycarbamide and interferon:* RCT of imatinib vs. combination of IFN-α and cytarabine. *For SCT:* Submissions to TA241 from Bristol-Myers Squibb and Novartis.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Y	
Discount rate	3.5% p.a. for costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	

Y – Yes; N – No; U – Unclear; P – Partially

5.3.3 Critical appraisal frameworks

Table 64. Critical appraisal checklist from Drummond and colleagues (1997)[58]

Item	Critical appraisal	Reviewer comment
Is there a well-defined question?	Y	
Is there a clear description of alternatives (i.e., who did what to whom, where and how often)?	Y	
Has the correct patient group / population of interest been clearly stated?	Y	
Is the correct comparator used?	P	Believe more appropriate to include SCT following bosutinib failure (see Section 5.3.6, p162)
Is the study type reasonable?	Y	
Is the perspective of the analysis clearly stated?	P	See Section 5.3.7.1, p164
Is the perspective employed appropriate?	Y	
Is effectiveness of the intervention established?	P	No evidence from RCT for specified population. Non-randomised evidence suggests bosutinib is capable of achieving cytogenetic response in some patients but no mature data on overall survival.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	Y	
Are the costs and consequences consistent with the perspective employed?	P	See Section 5.3.7.1, p164
Is differential timing considered?	Y	Discount rates for costs and QALYs 3.5% in line with NICE reference case
Is incremental analysis performed?	Y	
Is sensitivity analysis undertaken and presented clearly?	Y	

Y – Yes; N – No; U – Unclear; P – Partially

5.3.4 Model structure

The model structure chosen by Pfizer for bosutinib is very similar to the structure we, PenTAG, used in TA241[2] and importantly includes chronic phase states both on and off treatment and accelerated and blast crisis phase states. We believe the model structure is appropriate for the treatment sequence bosutinib followed by hydroxycarbamide, although in Section 5.3.6 (p162) we discuss how appropriate the selected treatment sequences are.

We also believe the model structure is appropriate for hydroxycarbamide and interferon.

The model structure for SCT is effectively a two state model with two states, alive and dead. SCT is assumed to be curative and therefore not followed by treatments expected in the event of SCT failure, i.e., TKI, hydroxycarbamide.

We believe the cycle length of one month is appropriate for the CP model. A shorter cycle length may have been marginally more appropriate for the AP model and would probably have been more appropriate for the BP model, however we doubt this would significantly impact on cost-effectiveness and changing the cycle length would require a great deal of work.

5.3.5 Population

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used as 2nd-line. However, as we say in Section 2.2.2 (p45), we believe that bosutinib will be used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis assumes 3rd-line use of bosutinib, and we consider the cost-effectiveness of bosutinib for use as 2nd-line in an important scenario analysis.

5.3.6 Intervention and comparators

As stated in Section 5.2.4, p117, Pfizer consider the following treatment sequences in the CP model:

- (Bosutinib, HU)
- HU
- SCT
- (IFN, HU)

The focus of our critique is on the first three sequences, as we understand that IFN is now virtually never used for CML in England & Wales due to poor quality of life.

For the AP and BP models, Pfizer consider the same treatment sequences with the exception of (IFN, HU), because they say that appropriate clinical effectiveness evidence is lacking.

Pfizer seem unsure whether HU or SCT is the main comparator for bosutinib. They say: "*It has been noted by clinicians that hydroxycarbamide is rarely, if ever used in CML patients and therefore SCT may be a more appropriate comparator*" (Pfizer submission, p104). This is later contradicted: "*No data was found on the uptake of SCT versus hydroxycarbamide (BSC) in the patient population under consideration in this license. Clinical experts have estimated that only 30% of this population would be eligible for SCT given the strict eligibility criteria and availability of donors, it is assumed that the rest will receive hydroxycarbamide*" (Pfizer submission, p190).

Our clinical expert, Dr Rudin, agrees with the second statement. We imagine that the actual proportion of patients who have a SCT may be less than 30% because this is a major operation which we assume some patients will not wish undergo. Furthermore, Pfizer later say "*Nonetheless, SCT remains the only 'cure' for CML and bosutinib is not expected to replace SCT for the minority of patients who are eligible to receive a SCT and who have a match*." (Pfizer submission, p192).

For all these reasons, we believe that HU is clearly the most important comparator treatment.

Pfizer assume that after patients become resistant or intolerant to bosutinib (as either 2nd-, 3rd- or 4th-line), they are then treated with HU until death. We agree that this is reasonable for those patients who are unsuitable for SCT or for those who are suitable for, but do not want SCT. However, our understanding is that patients who are suitable for and want a SCT may either proceed directly to transplant, or may try bosutinib first, and then when they become resistant or intolerant to bosutinib, they will likely then try SCT. Given that patients are predicted to take 3rd-line bosutinib for only about [redacted], we understand that if a patient is eligible for SCT before bosutinib treatment, they are very likely still to be eligible for SCT only [redacted] later. Indeed, Pfizer acknowledge this: "*However, in practice the impact of introducing another effective TKI option may result in a reduction in the numbers of SCT since patients or clinicians may prefer to try another TKI before or instead of SCT given the considerable cost, morbidity and mortality impact associated with SCT*" (Pfizer submission, p192).

In summary, we assume the following comparators for CP:

- (Bosutinib, HU)
- (Bosutinib, SCT) (only for those eligible for SCT)
- HU
- SCT (only for those eligible for SCT)
- (IFN, HU)

In other words, for those patients unsuited to SCT, the relevant comparators are:

- (Bosutinib, HU)
- HU
- (IFN, HU)

And for those suited to SCT, the main comparators are:

- (Bosutinib, SCT)
- SCT

But for completeness, we also model the following comparators:

- (Bosutinib, HU)
- HU
- (IFN, HU)

For AP and BP, we believe exactly the same arguments apply as for CP, except we do not model (IFN, HU).

In theory, it would be possible to additionally model the treatment sequence (IFN, SCT). However, we do not do this because IFN is rarely used now in England & Wales.

5.3.7 Perspective, time horizon and discounting

5.3.7.1 Perspective

Pfizer state (Section 5, p37) that a NHS/PSS perspective for costs is adopted in line with the NICE reference case, and this is reiterated on p39. In Section 7.2.6, p114, however it is stated that only NHS costs are included as "In this disease area there are not expected to be significant impacts on costs outside the NHS budget".

We believe that certain costs included in the economic analysis include costs incurred by PSS rather than NICE, e.g., the cost of palliative care prior to death is taken from Addicott and Dewar (2008)[54] and just over half of the cost is incurred in the community sector.

We do not believe that significant PSS costs have been excluded from the analysis and are therefore satisfied that the perspective adopted is appropriate, although reported inconsistently.

5.3.7.2 Time horizon

We are satisfied that a time horizon of 50 years is sufficient to account for all costs and benefits relevant to the decision problem.

5.3.7.3 Discounting

Discounting is applied at 3.5% per annum as per the NICE reference case.[43] We note that the discount factor is calculated on the basis of integer years from commencing treatment rather than months, which we feel would have been more appropriate and technically simple to implement. This however did not significantly impact on cost-effectiveness so we are satisfied that discounting is appropriate.

5.3.8 Treatment effectiveness and extrapolation

5.3.8.1 Overall survival (OS)

For the CP model, Pfizer's methods of estimating OS are not consistent across the four comparator treatments. OS for the bosutinib arm is estimated using a surrogate relationship using MCyR measured at minimum follow-up of 12 months in Study 200. This relationship was estimated as explained in Section 5.2.6.1 (p119). OS for the comparators: HU, SCT and IFN is estimated either by extrapolation directly from single arm trials (HU and SCT), or expert opinion (IFN) (Section 5.2.6.1, p118).

We believe that there are serious problems with Pfizer's methods of estimating OS for the four treatments because they involve numerous assumptions, for many of which there is little supporting evidence. Instead, we suggest that there is a superior method of estimating OS for all comparator treatments, which we describe as the Cumulative Survival method, not just in the CP model, but also in the AP and BP models. This is explained in detail in Section 6.1, p190.

Key assumptions underlying Pfizer's method of estimating OS for all comparators in CP are given in Table 65 below. All assumptions are important.

Table 65. Assumptions underlying Pfizer's methods of estimating OS for treatments in CP

Assumption	Description	Evidence to support
1. Lack of randomisation	Given that clinical effectiveness evidence is not randomised across treatments, we assume that estimated clinical effectiveness is similar to that which would be observed in a randomised trial of all treatments. This requires that many factors are similar across the single arm studies, e.g. patient baseline characteristics, medical management.	None given
2. Inconsistency in methods of estimated OS by treatment	OS is estimated using different methods across treatments: by a surrogate MCyR relationship for bosutinib and by extrapolating OS for HU, SCT and IFN. Assume that the MCyR surrogate relationship yields similar OS as extrapolation of mature OS for bosutinib	Very little
3. MCyR in model should refer to unmet need population	The MCyR value of 38.9% used to estimate OS for bosutinib in CP is taken from the whole population of Study 200. Pfizer report the corresponding MCyR value for the unmet need population as 43%. They say it is appropriate to use MCyR from the whole population because this is similar to the unmet need value. However, MCyR for the unmet need population is based on a sample of only 21 patients.	Some evidence, but limited due to small sample.
4. Validity of MCyR surrogate relationship:	The MCyR surrogate relationship is crucially dependent on MCyR and OS observed in a trial of patients on high-	Jabbour (2009)[44]

subsequent treatments	dose imatinib.[44] In particular, for the surrogate relationship to apply to bosutinib, Pfizer assume that all patients in Jabbour (2009) received only HU after high-dose imatinib, as they assume that all patients received HU after bosutinib. Furthermore, as explained in Section 5.3.6, p162, we believe it is appropriate to consider the treatment sequence (bosutinib, HU) for some patients and (bosutinib, SCT) for others.	
5. Validity of MCyR surrogate relationship: OS a function of MCyR only	Pfizer assume that OS is purely a function of MCyR. In particular OS is assumed independent of the duration and depth of response, and independent of treatment. In particular, the MCyR surrogate relationship is based on patients taking high-dose imatinib. However, Pfizer apply the relationship to MCyR achieved for patients taking bosutinib.	Unknown
6.Validity of MCyR surrogate relationship: unmet need population	The MCyR surrogate relationship estimated from Jabbour (2009)[44] is for patients who are both suited and unsuited to TKIs. However, Pfizer apply the relationship only to patients unsuited to TKIs.	Very little
7. 2nd-line OS from Jabbour (2009) appropriate for estimating OS for 3rd-line bosutinib	The MCyR surrogate relationship calibrates OS for 3rd-line using in CP for bosutinib to OS from Jabbour (2009)[44], but this is for a 2nd-line line population (after imatinib). OS for bosutinib is therefore probably over-estimated.	None

Pfizer claim that bosutinib OS estimated by MCyR is similar to that obtained by extrapolating bosutinib OS from Study 200 (Pfizer clarifications, Figure 7, p28; see also Appendix V). They then say that this validates their estimated bosutinib OS. However, we consider that the extrapolated OS is likely to be misleading for the following four reasons:

1. OS for bosutinib in CP is extremely immature, with approximately 85% patients still alive at 2 years. Any extrapolation of such immature OS data means that the estimated mean OS is extremely uncertain.
2. Whilst we require OS for bosutinib for patients unsuited to TKIs, most patients in Study 200 were suitable for TKIs. However, Pfizer estimate OS for bosutinib by extrapolating OS from Study 200.
3. Pfizer's model assumes that all patients in the bosutinib arm subsequently receive HU. However, Pfizer do not tell us the nature of subsequent treatments in Study 200. Given that the bosutinib OS data relates mostly to people who are suited to TKIs in Study 200, and not to those patients unsuited to TKIs (as required), these patients may have been treated with TKIs after bosutinib treatment. If so, this would likely lead to an over-estimate of OS for the bosutinib arm, as such subsequent TKIs are likely to extend OS.

4. As Pfizer acknowledge, OS for bosutinib in Study 200 may be over-estimated because of selective censoring of patients. In particular, patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, whereas all patients still on bosutinib were followed up whilst on bosutinib (Pfizer submission, p119).

In the current HTA, we believe that Pfizer's methods for estimating OS for treatments in CP result in the highly implausible result that the mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm and the time on 4th-line HU in the (IFN, HU) arm ([redacted] vs. 2.6 vs. 2.1 years respectively) (shown in Figure 20 below). We believe, and clinical expert advice has agreed, that this is unreasonable. Furthermore, this assumption acts dramatically in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU and (Bosutinib, HU) vs. (IFN, HU), because the price of HU is negligible. In Section 6.1, p190, we show how we correct for this under the Cumulative Survival method.

Figure 20.

[redacted]

Pfizer's surrogate relationship between MCyR and OS is very similar to the relationship that we, PenTAG, derived for TA241, to estimate OS for 2nd-line high-dose imatinib, nilotinib, dasatinib and IFN after imatinib failure for patients starting in CP CML. We believe that it was more appropriate to use the MCyR relationship in TA241 than in the current appraisal because fewer Assumptions were required in TA241. Specifically, although Assumptions 1, 4 and 5 above were required, Assumptions 2, 3, 6 and 7 were not. In particular, the crucial Assumption 2, was not required, i.e. the same method (MCyR) was used to estimate OS for all treatments. Nonetheless, with hindsight and with the experience of two previous HTAs in CML, we believe that it would have been useful to have

performed the Cumulative Survival method, at least as a sensitivity analysis, if not as the base case analysis.

By contrast, OS for bosutinib for the AP and BP models is not estimated using a MCyR relationship. Instead, it is extrapolated directly from OS from Study 200. Therefore, for the AP and BP models, the methods of estimating OS for the three treatments: bosutinib, HU and SCT are consistent. Furthermore, Assumptions 2–7 (Table 65, p165) are not required. However, we identify the following six criticisms with Pfizer's method of estimating OS for all treatments in the AP model:

1. Importantly, Assumption 1 still applies, i.e. randomisation is still lacking between comparator treatments.
2. OS for bosutinib in the AP model is very immature, with 65% of patients still alive at maximum follow up (Pfizer submission, p122). The means that the estimated mean OS in the bosutinib arm is highly uncertain.
3. Whilst we require OS for bosutinib for patients unsuited to TKIs, most patients in Study 200 were suitable for TKIs. However, Pfizer estimate OS for bosutinib by extrapolating OS from Study 200.
4. In their model, Pfizer assume that all patients receive HU after bosutinib failure. However, Pfizer do not state the nature of treatments after bosutinib failure in Study 200. Given that most patients in Study 200 were suited to TKIs, some patients may have had other TKIs after bosutinib failure, and this would likely increase their OS and hence lead to an over-estimate of OS for bosutinib for patients unsuited to TKIs.
5. As stated above when discussing CP, as Pfizer acknowledge, OS for bosutinib in Study 200 may be over-estimated because of selective censoring of patients.
6. In the AP model, as in the CP model, Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 1.0 years respectively) (Figure 21). As in CP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 21.

[redacted]

Similarly, in the BP model, the six criticisms for AP above also apply, although Criticism 2 is less of a problem between OS for bosutinib for BP (35% alive at maximum follow-up of 2 years) is more mature than for AP (65% alive). Criticism 6 again applies. Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 0.5 years respectively) (Figure 22). As in CP and AP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 22.

[redacted]

Under the Cumulative Survival method, we again correct for these imbalances, in an analogous way as for CP CML, described in Section 6.1 (p190).

Estimation of OS for bosutinib in CP using MCyR surrogate relationship

In addition to our belief that the use of a MCyR surrogate relationship to estimate OS for bosutinib patients in CP is inappropriate (as stated above), we also note some issues with the methodology used by Pfizer, although these do not significantly impact cost-effectiveness (see Appendix S).

Briefly, rather than fitting to data from Jabbour and colleagues (2009),[44] Pfizer instead fitted to an exponential curve fitted to the study. Pfizer also assumed a lower MCyR rate from Jabbour and colleagues (2009)[44] to the rate used in TA241.[2] Pfizer also use an inappropriate formula to calculate the monthly probability of death from non-CML causes. None of these shortcomings were judged significant enough to warrant changing Pfizer's base case and our objections to Pfizer's methodology as described above (p165) still stand.

Non-CML mortality

We identified a number of shortcomings with Pfizer's method of incorporating non-CML mortality but did not judge that these were significant enough to warrant significant changes to the model. See Appendix S for further details.

5.3.8.2 OS for HU in CP

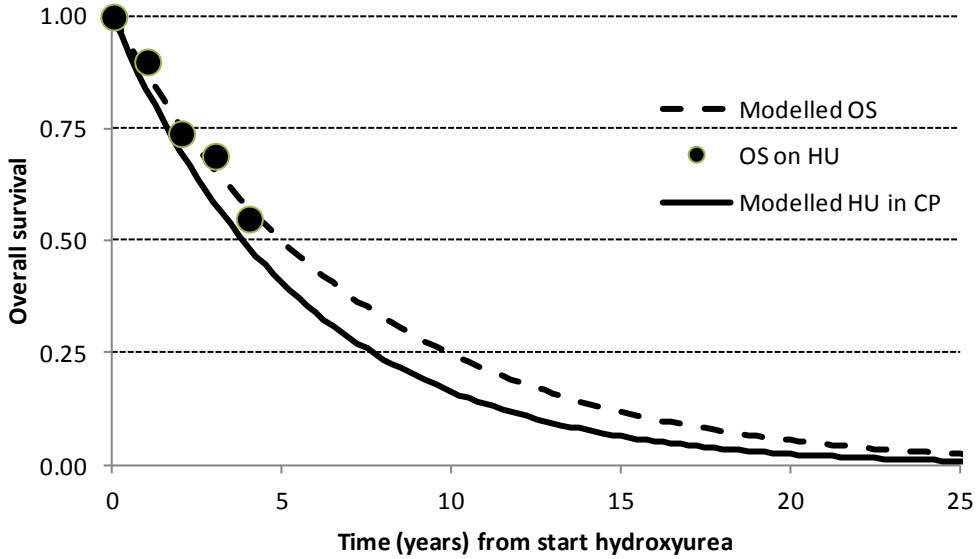
As stated in Section 5.2.6.1, p118, Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] Pfizer say that this study was used for the same purpose in TA241 and TA251 (Pfizer submission, p121). We agree that we, PenTAG, and Novartis, the manufacturer of nilotinib and imatinib used this study for this purpose in TA251. Furthermore, Novartis used this study for this purpose in TA241 (Novartis TA241 submission, p36). Our review of the literature at the time of TA251 suggested that this study was most appropriate for estimating OS for HU in CP.

This study enrolled patients in the USA from 1999 to 2005 who had failed on imatinib. Most (89%) were resistant to imatinib, but some (11%) were intolerant. For patients starting in CP, 8 subsequently received treatment with SCT, 35 with dasatinib/nilotinib and 61 'other' treatments. Of the 'other' treatment group, only 12 of the 61 patients received HU. The remaining patients received regimens including tipifarnib, ionafarnib, decitabine, cytarabine, homoharringtonine and IFN. The median age was 54 years, coincidentally and appropriately the same age as assumed in Pfizer's current model.

We also agree with Pfizer when they say that OS in the CP "other" treatment cohort was 77% at 2 years and 70% at 3 years (p94 Pfizer submission).

We agree with Pfizer when they state that an exponential curve was fitted to OS for CP HU in TA251 (Pfizer submission, p121). However, we disagree when they claim that the resulting mean OS was 3.5 years (Pfizer submission, p121). Instead, Novartis assumed a mean time on HU in CP (not OS) of 3.5 years (Novartis response document, 18th Oct 2011). Using Pfizer's estimated mean times in AP of 10 months and BP of 6 months, gives an estimated OS for HU of 3.5 + 0.8 + 0.5 = 4.8 years. Furthermore, we, PenTAG, estimated a mean OS for HU of 7.0 years (Hoyle and colleagues (2011),[17] p164). Below (Figure 23), we reproduce our exponential fit to the empirical data from Kantarjian and colleagues (2007)[3], taken from our TA251 Assessment report.[17]

Figure 23. PenTAG TA251 fit to CP HU OS data from Kantarjian and colleagues (2007)[3]



(Source: PenTAG TA251 submission,[17] Figure 29, p165)

From this figure, we can see clearly that Pfizer's estimate of OS on HU in CP of 3.5 years is far lower than indicated from Kantarjian and colleagues (2007).[3]

Clearly, the quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available to inform this parameter. We further note that clinical experts who advised Novartis in TA241 suggested that it was reasonable to assume that OS for HU is the same as OS for the "other" treatment group given the lack of available relevant data on HU in this setting (p164[17]).

Pfizer state that OS for HU in CP from Kantarjian and colleagues (2007)[3] should be viewed as an upper bound for the purposes of the current appraisal, given that the data from this study is for 2nd-line CML, whereas Pfizer's base case analysis is for 3rd-line, and we might expect OS to be lower for 3rd-line HU compared to 2nd-line HU. We agree that this is true for a 3rd-line analysis. However, as

stated in Section 5.3.5, p162, there is uncertainty as to whether bosutinib would be more likely to be used 2nd- or 3rd-line in England & Wales were it approved by NICE. If it is more likely to be used 2nd-line, then OS from Kantarjian and colleagues (2007)[3] is then appropriate.

Interestingly, our estimated mean OS of 7.0 years for HU in CP from TA251 is similar to Pfizer's base case estimate of [redacted] years for the mean survival on HU after bosutinib. Whilst this observation could be seen to corroborate our estimate of 7.0 years, we caution that we disagree with the derivation of Pfizer's estimate (Section 5.3.8.1, p165).

We adjust Pfizer's model to allow for a mean OS in the HU arm in CP of 7.0 years by changing the mean OS for HU, parameter "hu_cp_os" (cell E38 in worksheet "Efficacy") from 42 to 85 months. Note that we do not set this to 7.0 × 12 = 84 months, because Pfizer apply additional mortality due to background causes. Here, we do not change the mean times on HU after bosutinib or IFN failure. The ICERs are then as shown in Table 67 below. As explained above, we believe that the key comparison is (Bosutinib, HU) vs. HU, indicated in bold.

[redacted]

Note that shading does not indicate whether bosutinib is more or less costly or more or less effective than the comparator.

Table 66. Shading used to denote cost-effectiveness of bosutinib

Table 67. Pfizer's base case ICERs for CP CML adjusted for mean time in HU arm

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
Mean OS in HU arm increased from 3.5 to 7.0 years	[redacted]	Unchanged	Unchanged

5.3.8.3 OS for SCT in CP

Pfizer performed a literature review for studies that report OS after SCT. The results of this review suggest that relevant data for patients in CP is sparse. This is unfortunate since the cost-effectiveness of the comparison (bosutinib, HU) vs. SCT is strongly influenced by this parameter. There is substantial uncertainty in mean OS after SCT in CP because:

- OS for SCT is very immature, with maximum follow-up of 2 or 3 years, at which time at least 70% of patients are still alive. By contrast, mean OS is several years.
- This assessment concerns patients unsuited to TKIs other than bosutinib. However, all trial data refers to patients both suited and unsuited to TKIs.
- All trials of SCT have very small patient populations, in particular, all less than 100 patients.

As stated in Section 5.2.6.1, p118, Pfizer's base case estimate of OS after SCT for patients in CP was based on data from Jabbour and colleagues (2011).[10] Pfizer state that they chose this study "*because it was a full publication (rather than abstract), included the most comparable patient population (majority were third line) and presented OS curves.*" (Pfizer submission, p121) We agree with Pfizer that the Jabbour and colleagues (2011) patient population is mostly appropriate for the current HTA, given that patients were resistant to a TKI.[10] We further agree that most patients were 3rd-line, having previously received two TKIs. However, the sample size is extremely small, with only 16 CP patients (see Figure 3B of Jabbour and colleagues (2011)[10]) contributing to the estimates of OS, which is reflected in a very wide 95% confidence interval in the estimated 2-year OS of 72% (49%–96%). Also, the median age of 44 in this study is rather lower than that 54 years assumed in Pfizer's CP model.

Pfizer say that they digitised the OS data from Jabbour and colleagues (2011)[10] and then reconstructed the underlying patient level data. The exponential function fitted the patient level data best. Pfizer's fit to the Kaplan-Meier OS data from Jabbour and colleagues (2011)[10] appears reasonable. For example, the Kaplan-Meier estimate at 2 years of 72% is close to the 74% in the model.

Pfizer state (Pfizer submission, p121): "*The only other full-publication that reported OS in a format that was useable for our economic evaluation was Oehler 2007, but this was in a second-line population only and therefore deemed to be less relevant. Nonetheless, this is considered in a sensitivity analysis.*" In Oehler and colleagues (2007),[12] 145 patients in the US who received imatinib before allogeneic hematopoietic cell transplantation was retrospectively compared to 231 historical cohort patients who did not receive imatinib. Henceforth, we consider only the patients who previously received imatinib, as this is relevant to the current appraisal. As in Jabbour and colleagues (2011),[10] the median age (40 years) was lower than the starting age of 54 in Pfizer's CP model.

However, the sample size of 72 patients that informed the estimate of OS was far greater than the tiny sample of 16 patients in Jabbour and colleagues (2011).[10]

OS for CP patients was estimated as 78% at 3 years in Oehler and colleagues (2007).[12] Pfizer states that this study is less relevant than Jabbour and colleagues (2011)[10] because it concerns 2nd-line treatment, whereas Jabbour and colleagues (2011)[10] is mostly for 3rd-line treatment. However, as stated in Section 5.3.5, p162, we believe that bosutinib may be used for 2nd-line treatment and hence it is relevant to estimate OS for SCT in 2nd-line.

In addition, two further studies that report OS after SCT for patients starting in CP CML satisfy Pfizer's inclusion criteria (Pfizer submission, p90): Saussele and colleagues (2010)[13] and Schleuning and colleagues (2010).[14]

All patients in the study by Saussele and colleagues (2010)[13] had previously been treated with imatinib. Of the 37 CP patients, most, 32, were 2nd-line (after imatinib), and 5 were 3rd or 4th-line. The median age at transplantation was 37. OS at 3 years after SCT was 94.1% (95% CI 83.8–99.4%) in the 37 CP patients.

The retrospective registry study of Schleuning and colleagues (2010)[14] is published in abstract form only. All patients had been treated with nilotinib and/or dasatinib. Twenty-one patients were in CP and 20 patients in second or higher CP at the time of transplant. OS at 2 years was greater than 85% for the 15 patients in first CP.

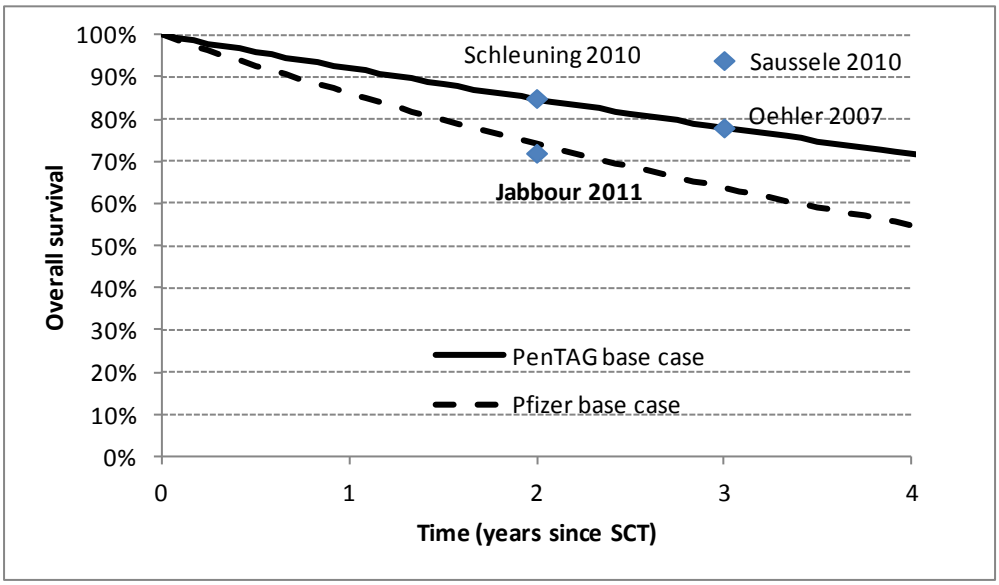
Whilst we acknowledge that there is no obviously superior source of data to estimate OS for SCT in CP, we believe that it is more appropriate to use the data from Oehler and colleagues (2007)[12] in preference to data from Jabbour and colleagues (2011),[10] which is Pfizer's preference, because:

- The sample size of 72 patients in Oehler and colleagues (2007)[12] that informs the estimate of OS is far greater than the tiny sample of 16 patients in Jabbour and colleagues (2011).[10]
- Whilst there is debate about the most appropriate line of treatment, we believe that it is reasonable to use the mostly 2nd-line data from Oehler and colleagues (2007)[12] as opposed to the mostly 3rd-line data from Jabbour and colleagues (2011).[10]
- The OS data from Oehler and colleagues (2007)[12] is clearly more consistent with that from Schleuning and colleagues (2010)[14] and Saussele and colleagues (2010)[13] (see Figure 24)

In summary, the PenTAG base case uses OS data from Oehler and colleagues (2007).[12]

In Figure 24, we can see clearly that Pfizer's base case estimate of OS after SCT in CP, shown by the dotted line, and which based on data from Jabbour and colleagues (2011),[10] is at the lower extreme of the data available, whereas our estimate of OS is more central (continuous line).

Figure 24. OS after SCT in CP



In Pfizer's model, we change the log(scale) parameter of the exponential distribution, cell E4 in worksheet "SCT parametric curves" from 1.897 to 2.491. The mean OS after SCT in CP then increases substantially, from 6.6 to 11.6 years. We notice that Pfizer estimate the log(scale) parameter of the exponential distribution using data from Oehler and colleagues (2007)[12] as 1.915, which is substantially different to our estimate of 2.491. However, it is impossible for us to reconstruct their analysis which led to this estimate. We do however note that the KM OS curve that Pfizer present on p381 appears inconsistent with the Kaplan-Meier curve shown in Figure 1A of Oehler and colleagues (2007).[12] In particular, Pfizer's figure shows OS at 3 years of approximately 0.72, whereas the figure from Oehler and colleagues (2007) is 0.78.[12]

The impact of our revised estimate of OS for SCT in CP on cost-effectiveness is given in Table 68 below. Note that while (Bosutinib, HU) continues to dominate SCT, the incremental costs and QALYs do change, as shown in Table 69.

Table 68. Pfizer's base case ICERs for CP CML adjusted for PenTAG preferred OS SCT

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
Mean OS in SCT arm increased from 6.6 to 11.6 years	Unchanged	Dominant	Unchanged

Table 69. Effect of PenTAG preferred OS on incremental outcomes, (Bosutinib, HU) vs. SCT

	Incremental discounted costs	Incremental discounted QALYs	INHB at WTP £20,000/QALY	INHB at WTP £30,000/QALY
Pfizer base case	[redacted]	+3.56	[redacted]	[redacted]
Mean OS of SCT increased to 11.6 years	[redacted]	+1.54	[redacted]	[redacted]

5.3.8.4 Time on treatment

The cost-effectiveness of bosutinib treatment sequences is very sensitive to the time on bosutinib treatment in all CML phase models. As stated in Section 5.2.6.2, p122, Pfizer estimate the time on bosutinib for all CML phases from Study 200. For 3rd-line CP CML, Pfizer fitted a log-normal distribution to the time on bosutinib treatment, and this appears reasonable. They estimate the mean time on 3rd-line bosutinib as [redacted] years. Fortunately, time on 3rd-line bosutinib data in Study 200 is rather mature, and so little extrapolation is required. However, this data is for the whole 3rd-line population in Study 200, whereas we are concerned with patients unsuited to TKIs. This therefore adds some uncertainty to the estimated time on bosutinib treatment.

Given that we believe that bosutinib may be used 2nd-line at least as often as 3rd-line, we asked Pfizer to provide Kaplan-Meier data for time on 2nd-line CP bosutinib. They agree, see Figure 25 below.

Figure 25. [redacted]

(a) Imatinib resistant (b) Imatinib intolerant

(Source: Pfizer clarifications, p35)

Later, we show that we estimate the mean time on 2nd-line bosutinib as approximately [redacted] years, far longer than the [redacted] years for 3rd-line treatment. This is a key parameter in our estimation of the cost-effectiveness of bosutinib treatment sequences in 2nd-line (Section 6.3.1, p214).

Our clinical advisor, Dr Rudin, believes that patients may often remain on bosutinib for the entire duration of CP in clinical practice. This would be in contrast to Study 200, where it appears that patients typically stopped bosutinib treatment well before progression to AP or BP. We consider this scenario in a sensitivity analysis (Section 6.3.1, p214).

Now turning to bosutinib use in AP, the time on bosutinib treatment is also rather mature, with approximately [redacted] of patients still on bosutinib at maximum follow-up (

Figure 14, p122). Therefore, little extrapolation is required. Pfizer again fitted a log-normal distribution to the time on bosutinib treatment, and this appears reasonable. They estimate the mean time on bosutinib in AP as [redacted] years.

The time on bosutinib treatment in BP is almost completely run off (

Figure 15, p123). Pfizer again fitted a log-normal distribution to the time on treatment, and this appears reasonable. They estimate the mean time on bosutinib in BP as [redacted] years.

Pfizer assume that HU is taken until death, which is appropriate.

As stated in Section 5.2.6.2, p123, Pfizer estimate the mean time on IFN was estimated as 0.5 years, on clinical advice. We believe this is a reasonable assumption.

5.3.9 Health related quality of life

Relevant sources for utility data, and Pfizer's base case utilities are given in Table 42, p126. First we note that there is uncertainty due to the fact that all sources of utilities were taken from patients who are both suited and unsuited to TKIs other than bosutinib, whereas we are interested in values appropriate for patients who are unsuited to TKIs.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 (Table 42, p126). In addition, they assume a utility for IFN in CP of 0.71, which is the same as our assumption in TA241. Their only departure from our previous assumptions is their estimate of the utility after SCT in CP, where they assume 0.71, versus our TA251 estimate of 0.80.

Importantly, Pfizer prefer the utilities that we have used previously to those from their Study 200. They justify this decision as follows (Pfizer submission, p137):

"*Whilst values taken directly from the intervention clinical trial is often more appropriate, the values in previous appraisals are from the IRIS study. This study collected arrange of utilities, in a large cohort of patients, including the utility of patients who progressed to AP and BP whilst not on active*

treatment. These utilities, though vital for modelling, are not available from Study 200. In addition the use of the IRIS values provides consistency with previous technology appraisals."

We agree that it is generally preferable to take utilities directly from the clinical trial of the intervention in question, in this case Study 200. Furthermore, the only source of utilities for bosutinib is Study 200 (IRIS gives utilities for imatinib), and this Study used the EQ-5D, which is preferred by NICE, and Study 200 is in the appropriate lines of treatment (2nd and 3rd-line vs. 1st-line in IRIS). But in this case, we are satisfied with Pfizer's decision because:

- Pfizer's utility of 0.85 for bosutinib in CP is only slightly higher than the Study 200 value of [redacted] for 3rd-line treatment. Furthermore, the Study 200 mean utility for 2nd-line [redacted] Pfizer's estimate of 0.85. As stated in Section 5.3.5, p162, the most relevant line of treatment for this appraisal is uncertain.
- Ideally, we would like a trial-based estimate of the utility of patients on bosutinib over the entire duration of treatment ([redacted]). However, utility measurements were heavily biased towards the start of bosutinib treatment. Therefore, this arguably limits the usefulness of the utilities from Study 200.
- The estimated utility of 0.85 for CP imatinib is based on a much larger study than Study 200.
- The mean utility from Study 200 for AP of [redacted] is the same as for 3rd-line CP. However, it is well know that quality of life is lower in AP. Therefore, arguably the Study 200 AP estimated utility lacks face validity.

We do not agree with Pfizer's justification of consistency with previous technology appraisals.

However, given that there is a reasonable argument to use utilities from Study 200, we perform the following sensitivity analysis:

- Utility bosutinib = [redacted] at age 54 (Study 200 value),
- Utility HU = Utility bosutinib = [redacted], and
- SCT, IFN unchanged from Pfizer base case.

Next, as stated above, Pfizer's only departure from our previous assumptions is their estimate of the utility after SCT in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Having inspected the source of our estimate, we believe that there is insufficient evidence to have a clear preference for our 0.80, and Pfizer's estimate is not unreasonable. Therefore, we accept Pfizer's base case estimate of 0.71, but we perform the following sensitivity analysis:

- Utility SCT = 0.80 at age 0.54 (increased from Pfizer base case 0.71),

- Utility bosutinib, HU, IFN = unchanged from Pfizer base case.

5.3.10 Adverse events

We are satisfied that using adverse event data from Study 200 is appropriate to the decision problem.

5.3.11 Resource use and costs

5.3.11.1 Resource use systematic review

Pfizer's systematic review of resource use and costs did not include first-line CML, but Pfizer include TA251[17] on the basis that they did not get sufficient data in their systematic review. It would have been more appropriate to conduct another systematic review but we are satisfied that TA251 should include the most relevant UK resource use and costs for first-line CML.

5.3.11.2 Drug acquisition

Pfizer have provided us with the acquisition cost of bosutinib (Table 44, p128) of £3,735.84 per month, or approximately £123 per day. We assume that this is indeed the price that the NHS would pay. In their base case analysis, Pfizer assume that all patients receive the licensed dose of bosutinib of 500mg per day, i.e. a dose intensity of 100%, in all CML phases. However, patients may increase the dose up to 600mg per day, or reduce the dose to 400mg or 300mg daily (Pfizer submission, p472), or may have dose interruptions. In short, we investigated Pfizer's assumption of a dose intensity of 100%, and we found it to be appropriate given the available data. The details are as follows.

Pfizer appropriately investigated the observed dose adjustments in Study 200. Specifically, they allowed for the proportion of Study 200 patients that received increased or decreased doses. As the duration of time at the new dose and time to new dose is not reported, they assumed that all patients received the adjusted dose for the entire duration of treatment with bosutinib. Given this, they estimated the mean daily cost for 3rd-line CP as [redacted] (Pfizer submission, p473), for AP as [redacted], and BP [redacted] and we agree with their calculations. Given that these costs are virtually identical to the mean cost assuming no dose adjustments, Pfizer assumed a dose intensity of 100% for all phases of CML.

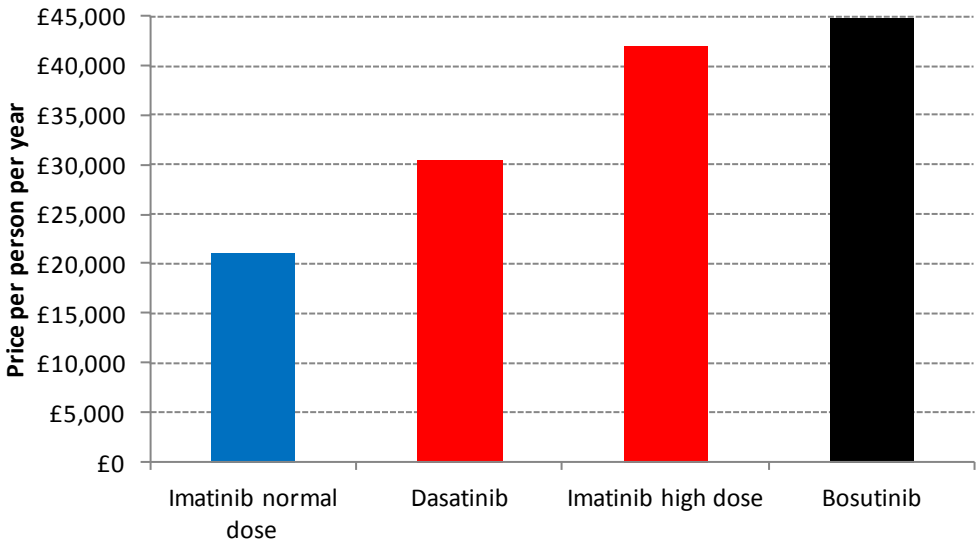
However, Pfizer's dose intensity calculation ignores (a) the possibility that people changed dose more than once and (b) treatment interruptions. Indeed, treatment interruptions are indicated for non-haematological adverse reactions (Pfizer submission, Table A1, p21), and some patients did have treatment with bosutinib interrupted due to adverse events (Pfizer submission, p359). We asked Pfizer to provide an indication of the mean time that patients were not receiving bosutinib due to dose interruptions. In response, they stated that in CP, approximately [redacted] of patients had at least one interruption of bosutinib treatment, and that for these patients, the mean total interruption period was

approximately [redacted]. The effect of modelling this is that the cost-effectiveness of bosutinib treatment sequences improves, but only incrementally. Specifically, the effect is to reduce the mean per patient cost in the bosutinib arms by approximately [redacted] × £44,830 / 12 = [redacted], where the annual acquisition cost of bosutinib is £44,830. Pfizer's base case ICER of (bosutinib, HU) vs. HU then improves very slightly, but still remains at [redacted] per QALY after rounding. The improvement in the ICERs for (bosutinib, HU) vs. HU in AP and BP are also slight. Given this, and given that the dose intensity of bosutinib whilst patients are actually taking the drug is slightly greater than 100%, we agree with Pfizer's assumption of a dose intensity of bosutinib of 100% for all phases of CML.

Given that bosutinib is given in packs of 28 tablets, there is scope for wastage. However, we estimate that if we allow for a plausible amount of wastage at the time the patient stops taking bosutinib, the ICERs for the bosutinib treatment sequences worsen only incrementally for all CML phases. Therefore, henceforth, we ignore wastage of bosutinib.

Figure 26 below shows the prices per person per year of TKI drugs for CML that have been assessed by NICE in the past and the price of bosutinib in this assessment. We are unable to cite the Patient Access price of nilotinib for reasons of confidentiality. Normal dose imatinib (blue shading) and nilotinib were recommended by NICE in TA251 and TA241 for 1st- and 2nd-line use. TKIs not recommended by NICE (red shading) are dasatinib for 1st- and 2nd-line use (TA251 and TA241) and high-dose imatinib for 2nd-line use (TA241). The price per patient per year is greatest for bosutinib (£44,830). The prices of the other TKIs are: normal dose imatinib = £20,994, dasatinib = £30,498, high dose imatinib = £41,989.

Figure 26. Prices of TKI drugs for CML assessed by NICE



Next, we are satisfied with Pfizer's estimation of the cost of HU as £12.75 per month (Table 44, p128). It is important to note that HU is extremely cheap.

We are also satisfied with Pfizer's estimation of the cost of IFN of £1,296 per month (Table 44, p128). We do however caution that the price that hospitals pay for IFN may be substantially lower due to discounted purchasing. However, we have no high quality evidence to support this claim, and so we accept Pfizer base case assumption. Furthermore, the cost-effectiveness of bosutinib versus IFN is rather insensitive to this parameter because Pfizer assume that IFN is taken for only about 0.5 years, far shorter than bosutinib, at about [redacted] years.

5.3.11.3 Stem cell transplant

As explained in Section 5.2.9.7, p131, Pfizer assume the cost of a SCT operation of £76,560, which was based on a 2010 NHS Blood and Transplant costing study,[56], which in turn was taken from van Agthoven and colleagues (2002).[57] In short, we are satisfied that the source of this cost and the cost itself are reasonable.

Pfizer also assume in the BP model that all patients receiving SCT first receive two cycles of FLAG-IDA chemotherapy. All patients are assumed to survive these cycles of chemotherapy and go on to incur SCT costs. The cost of FLAG-IDA was estimated based on Pastore and colleagues (2003),[59] in which 6.5% of patients died while undergoing one cycle of FLAG-IDA, which would suggest not all BP patients would go on to receive SCT. We investigated this and while the ICER for SCT versus bosutinib decreased it was not judged to have a significant impact.

5.3.11.4 Adverse events

Pfizer's assumptions regarding adverse events (i.e., adverse events incur costs but do not affect HRQL and are incurred in the first cycle) are broadly consistent with previous assessments of TKIs for CML. The PenTAG assessment in TA241[2] did not include costs for adverse events as these were expected to be low and could lend spurious accuracy. In previous assessments, adverse events have been used to estimate discontinuation rates, but this is not necessary in this assessment, as fairly mature discontinuation data is available from Study 200.

We note that the cost of adverse events in the AP and BP models are assumed to be the same as in the CP model. This is unrealistic as Table B29 of Pfizer's submission (Section 6.9.2, pp84-85) shows higher rates of adverse events for AP and BP patients than CP patients (Table B27, pp81-82). Using the same methodology as was used for CP to estimate a cost for AP and BP (combined) produced a value of £1,011 compared to the cost in CP of £506, i.e., the cost doubled. This however did not have a significant impact on cost-effectiveness.

We believe that adverse events are unlikely to have a significant impact on cost-effectiveness and are therefore satisfied by Pfizer's methodology.

5.3.11.5 Drug administration

Drug administration costs are incurred for interferon. We found an error in the calculation of the drug administration costs (see Appendix S) but it did not significantly impact cost-effectiveness.

5.3.11.6 Medical management, monitoring and tests

First, as explained in Section 5.2.9.7, p131, Pfizer assume the following follow-up costs after SCT: monthly costs for months 1–6 of £5,299, monthly costs for months 7–12 of £3,231 and monthly costs for months 13–24 of £1,166. In months 25 onwards, patients are assumed to receive 100mg of ciclosporin twice daily, giving a monthly cost of £140 (Pfizer submission, p145). As explained in Section 5.2.9.7, p131, these costs are taken from a NHS Blood and Transplant costing study,[56]. The underlying resource use for this study was taken from van Agthoven and colleagues (2002).[57] In short, we are satisfied that the source of these costs and the costs themselves are reasonable.

Pfizer's assumptions for medical management, monitoring and testing are given in Section 5.2.9.4, p129. These assumptions were based on those that we used originally in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey of 6 UK-based CML clinicians. However, Pfizer seem unaware that in TA251, our assumptions for medical management, monitoring and testing were challenged by Novartis, the manufacturer of nilotinib. In particular, in their response to our Assessment Report for TA251, Novartis submitted a response document, dated 18th October 2011, in which they stated that we over-estimated the frequencies of some resource use items. In response, we amended some of our assumptions for resource use in CP CML, as shown in Table 70.

Table 70. Selected resource use assumptions for CP CML

	Treatment	Nurse visits / month	Haematologist visits / month	Bone marrow aspirations / month
Pfizer current HTA	Bosutinib	0.4	0.9	0.3
	HU, IFN	0.4	0.9	0.3
	SCT	0.4	0.9	0.3
PenTAG TA251	Imatinib, dasatinib, nilotinib	0	0.33	0
	HU	0	0.72	0
	SCT	0	0	0
PenTAG current HTA	Bosutinib	0	0.33 per month, plus 2 at t = 0	0
	HU, IFN	0	0.72	0
	SCT	0	Many visits in months 0–24 included in ongoing costs from van Agthoven (2002)[57] 0.31 visits per month for month 24 onwards	0

Appendix U gives the full text of our response to Novartis' criticism of our original resource use assumptions in TA251. The NICE appraisal committee for TA251 were satisfied with our revised assumptions.

In April 2013, we asked our clinical expert, Claudius Rudin, to comment on our revised TA251 assumptions. His view of resource use whilst patients take TKIs is unchanged. However, as shown in Table 70 above, whilst patients are taking bosutinib, we now additionally include two haematologist visits at time zero. As stated in Appendix U, Dr Rudin believes that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly, i.e., there would be two more visits in the first three months than in subsequent three month periods. In TA251, we ignored the costs of the visits at 2, week 4, month 2 and month 4, because that appraisal was for 1st-line use of TKIs, and these costs cancelled between treatments almost exactly. In the current appraisal, we cost for these visits because a TKI, bosutinib, is used in just one treatment arm, and hence these costs do not cancel out in the other arms, HU and SCT. Also, we assume that all patients remain on bosutinib treatment, given that Pfizer's model predicts that [redacted] of patients are still on bosutinib treatment at 4 months.

Dr Rudin is still satisfied with our assumptions for patients whilst taking HU. Further, he believes that these are also appropriate for treatment whilst on IFN.

In TA251, we assumed no nurse visits, haematologist visits or bone marrow aspirations for patients after SCT. Dr Rudin agrees with the assumptions of no nurse visits or bone marrow aspirations, but disagrees with our assumption for frequency of haematologist visits after SCT. Specifically, he suggests that there are many such appointments in the first 100 days after SCT: twice a week after discharge at approximately day 28 until approximately day 60, then weekly until day 100, then monthly for the first year and if all goes well approximately every second month in the 2nd year, gradually extending to yearly after the 4th or 5th year. He advised that there would be much more frequent consultant-led clinic appointments, every 2 months if there is chronic graft versus host disease (cGvHD). Further, he agrees with the assumption that we and Novartis used in TA251 that 54% of patients get cGvHD after SCT.

We note that the follow-up costs assumed by Pfizer after SCT reflect a similar number of haematologist visits in the first 2 years as suggested by Dr Rudin. Specifically, in the period 0–6 months after transplant, patients visited an outpatient clinic an average of approximately 20 times, from 6–12 months after transplant, approximately 11 times, and from 12–24 months, approximately 10 times.[57] Therefore, on the basis of the suggested frequency of haematologist visits from Dr Rudin and the additional costs assumed by Pfizer after SCT, we first assume no haematologist visits in the first 2 years in addition to those already costs from the monthly follow up costs above. Second, we assume that all patients incur a background 0.31 visits per month from month 24 onwards, which is a weighted average of 0.50 per month for patients with cGvHD and the long term 0.08 per month for patients without cGvHD, with the weight being 54% of patients with cGvHD.

Note that whilst our estimate of consultant appointments in TA251 was incorrect, the cost-effectiveness of the 1st-line TKIs in this appraisal would have changed only marginally given the assumptions we now use in the current HTA. This is because SCT treatment was modelled as a downstream treatment in TA251, and costs of SCT largely cancelled between treatment arms. This is not the case in the current appraisal because SCT is one of the initial treatments.

As shown in Table 70 above, we assume no bone marrow aspirations. In TA251, we originally allowed for 0.3 bone marrow aspirations per month for all treatments. This constituted 94% of our estimated costs for tests of £216 per month. Pfizer's estimated cost for tests of £231 was based on the £216 per inflated to 2011/12 prices. Given that bone marrow aspirations constituted almost all test costs, in the current HTA, we assume zero test costs for all treatments.

When we alter Pfizer's model to reflect our preferred resource use assumptions shown in Table 70 above (see Appendix W for details), the cost-effectiveness of bosutinib improves versus hydroxycarbamide: Pfizer's ICER decreases from [redacted] per QALY. The costs of

bosutinib and SCT both decrease, although the costs of bosutinib decrease farther; as a result bosutinib continues to dominate SCT (Table 71).

Table 71. Pfizer's base case ICERs for CP CML adjusted for resource use assumptions preferred by PenTAG

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
PenTAG resource use assumptions in Table 49, p184.	[redacted]	Dominant	[redacted]

5.3.12 Cost-effectiveness results

We are satisfied that the results presented by Pfizer match those from the model supplied.

5.3.13 Sensitivity analyses

5.3.13.1 One-way sensitivity analyses

Pfizer conduct a number of one-way sensitivity analyses but by no means on all parameters. Tornado diagrams are not provided. Pfizer group their one-way sensitivity analyses along with explorations of structural uncertainty in Section 5.2.11.3, p146.

5.3.13.2 Probabilistic sensitivity analysis

We agree with Pfizer that probabilistic sensitivity analyses are not particularly useful as they do not account for the significant structural uncertainties in the decision problems, and we have therefore not critiqued the probabilistic sensitivity analyses in detail.

5.3.13.3 Scenario analyses

2nd-line use of bosutinib in CP patients

Pfizer's base case analysis assumes that bosutinib is used 3rd-line, but we feel it is likely that bosutinib will be used 2nd-line rather than 3rd-line due to the approval of nilotinib for 1st-line use, clinical opinion suggesting that imatinib is unlikely to be used in patients resistant to imatinib, and dasatinib not being approved 1st-line or post imatinib failure. Therefore as an important scenario analysis, we estimate the cost-effectiveness of bosutinib for 2nd-line CP. Pfizer did conduct a scenario analysis in which the 2nd-line cohort was used as the model population, however we do not believe that Pfizer's sensitivity analysis is appropriate as it includes only a change in the MCyR rate and does not include a change in the length of time patients spend on treatment – this biases the results in favour of cost-effectiveness of bosutinib.

We conduct our own scenario analysis based on treatment discontinuation curves provided by Pfizer in response to questions of clarification (Figure 25, p176) and on the MCyR rate for 2nd-line patients published in Cortes and colleagues (2011), in which the cumulative MCyR rate at a minimum follow-up of 12 months (median follow-up 24.2 months) was 140/266 = 52.6%.[24]

We estimated from Figure 25 (p176) that median time on 2nd-line bosutinib treatment would be [redacted] years for imatinib resistant patients and [redacted] years for imatinib intolerant patients. As there were 200 imatinib resistant patients versus 88 imatinib intolerant patients we estimated the median time on 2nd-line bosutinib treatment as (200 × [redacted] + 88 × [redacted]) / 288 = [redacted] years.

For simplicity, we then assumed an accelerated failure time model, i.e., the time to bosutinib treatment discontinuation for 2nd-line patients would be as for 3rd-line patients, but with time rescaled. This is achieved simply by adjusting the scale parameter μ of the log-normal distribution. The mean and median times on treatment are both scaled by the same factor. The median time on treatment from Study 200 in the 3rd-line CP cohort was 8.6 months = 0.72 years (15 February 2012 snapshot; Pfizer submission, Section 6.8.5, p72). We therefore estimated that the appropriate scaling factor was [redacted]/0.72 = [redacted].

To achieve the required [redacted] scaling of mean time on treatment we took mean time on treatment for 3rd-line patients from the model as [redacted] years and adjusted μ using Solver such that the mean time on 2nd-line treatment from the model was equal to [redacted] years when OS was adjusted using the MCyR rate of 52.6%, giving μ = [redacted].

Under this scenario analysis (and with no other alterations to the Pfizer model) we find that bosutinib is more costly and more effective than SCT and that the cost-effectiveness of bosutinib has worsened generally (see Table 72).

Table 72. Pfizer's base case ICERs for CP CML adjusted for 2nd-line patients

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
2nd-line CP cohort	[redacted]	[redacted]	[redacted]

It should be cautioned that, due to lack of evidence, no adjustments were made to survival or time on treatment for hydroxycarbamide and SCT to reflect the choice of a 2nd-line cohort (although the

estimate of effectiveness of hydroxycarbamide is already taken from a 2nd-line study), nor was the age adjusted for any patients.

Pfizer's "cumulative survival approach" to bosutinib OS in CP model

Pfizer present results of a "cumulative survival approach" in Table B64, Section 7.5.9, p160, and in Table B151, Section 10.22, p469. We believe this is a flawed analysis and that the methodology – while described as similar to an approach in TA251 – is not to be confused with the cumulative survival method we present in Section 6.1 (p190). Further discussion of this can be found in Section 6.1.4 (p202).

Bosutinib OS in BP model

We identified that there was a formula error in the scenario analysis where bosutinib OS in the BP model is based on fitting a Weibull distribution to Study 200 OS individual patient data. We corrected the formula error and re-fitted the Weibull distribution. The ICER for bosutinib versus hydroxycarbamide in this scenario increased from [redacted] per QALY.

5.4 Cost-effectiveness conclusions

No previous cost-effectiveness evaluations of bosutinib in refractory CML were identified in Pfizer's systematic review. The *de novo* economic evaluation submitted by Pfizer contains ICERs significantly lower than those calculated by PenTAG (see Section 6, p190), in which the following items were adjusted:

- The method of estimation of OS for all comparators using our "cumulative survival method"
- Mean overall survival on HU (CP model only)
- Mean overall survival after SCT (CP model only)
- Medical management resource use (CP model only)

The cumulative survival method also allows an estimation of the cost-effectiveness of bosutinib followed by SCT, which we believe is a relevant treatment sequence for patients able to receive SCT.

The cumulative survival method had the greatest impact on cost-effectiveness, with the additional items not affecting the cost-effectiveness of the PenTAG base case significantly (although some do affect the Pfizer base case significantly).

Table 73. Comparison of Pfizer and PenTAG base case ICERs

	Pfizer ICERs		**PenTAG ICERs**	
	(Bosutinib, HU) vs. HU	(Bosutinib, SCT) vs. SCT	(Bosutinib, HU) vs. HU	(Bosutinib, SCT) vs. SCT
CP model	[redacted]	n/a	[redacted]	[redacted]
AP model	[redacted]	n/a	[redacted]	[redacted]
BP model	[redacted]	n/a	[redacted]	[redacted]

n/a as not estimated by Pfizer

Although there is significant uncertainty regarding the effectiveness of HU and SCT and regarding which TKIs will be attempted before bosutinib, the PenTAG base case is fairly robust to these uncertainties as it is primarily driven by the drug acquisition cost of bosutinib.

6 ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Cumulative survival method

As explained in Section 5.3.8.1, p165 above, we believe that there are major problems with the methods Pfizer have used to estimate OS for all comparator treatments, especially for the CP model, but also for the AP and BP models. This leads to the implausible prediction that the mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm and the time on 4th-line HU in the (IFN, HU) arm for the CP, AP and BP models. Also as explained in Section 5.3.8.1, p165, in our base case, we have used a different method, the Cumulative Survival method, of estimating OS for all treatments in all model phases.

The Cumulative Survival method was used by us, PenTAG, in our base case analysis in TA251, of the cost-effectiveness of imatinib, nilotinib and dasatinib for 1st-line CML. In a sensitivity analysis, we estimated OS separately using a surrogate relationship based on CCyR and on MMR (major molecular response). In this appraisal, the method was also used by Novartis, the manufacturer of nilotinib. By contrast, Bristol-Myers Squibb, the manufacturer of dasatinib, estimated OS for all treatments using a surrogate relationship based on CCyR. In this appraisal, our base case analysis was accepted by the NICE Appraisal Committee as most appropriate.

6.1.1 Cumulative survival method CP

We first discuss the Cumulative Survival method applied to treatment starting in CP CML.

The motivation for performing the method in the CP is as follows. Pfizer estimate that the on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in arm and the time on 4th-line HU in the (IFN, HU) arm (versus 2.6 versus 2.1 years respectively) (

Figure 27). We believe, and clinical expert advice has agreed, that this is unreasonable. Furthermore, this assumption acts dramatically in favour of the cost-effectiveness of (Bosutinib, HU) versus HU and (Bosutinib, HU) versus (IFN, HU), because the price of HU is negligible.

Figure 27.

Under the Cumulative Survival method, we correct for this imbalance.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (IFN, HU) arm, the mean time, cost and QALY whilst on 3rd-line IFN treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

Clearly, not all patients in the (Bosutinib, HU) arm will survive to start 4th-line HU treatment. The key assumption of the Cumulative Survival method is that, in the (Bosutinib, HU) arm, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. None of Assumptions 1–7 (Table 65, p165), which are necessary for Pfizer's methods of estimating OS, are required.

Equivalently, we assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equals that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib. We believe that the life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib is probably an upper bound, as discussed in Section 6.1.4 (p202).

Similarly, in the (IFN, HU) arm, the life expectancy of those patients who start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm.

Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

In the next sections, we estimate the total life years, costs and QALYs for the (Bosutinib, HU), (IFN, HU) and (Bosutinib, SCT) treatment arms.

6.1.1.1 Cumulative survival method CP time on treatment

We denote T as the mean per patient undiscounted time. This is split in to four parts, corresponding to 3rd-line CP, 4th-line CP, AP and BP. Here, without loss of generality, we assume that all patients start 3rd-line treatment for CML. The notation of these time components is given in Table 74 below.

Table 74. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in CP.

	(Bosutinib, HU)	**HU**	**SCT**	**(IFN, HU)**	**(Bosutinib, SCT)**
3rd-line CP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{IFN,HU}}^{IFN\ 3}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line CP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{IFN,HU}}^{HU\ 4}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$
AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{AP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$		$\mathrm{T}_{\mathrm{IFN,HU}}^{AP}$	
BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$		$\mathrm{T}_{\mathrm{IFN,HU}}^{BP}$	

Then under the Cumulative Survival method, the component times are calculated as shown in Table 75, where S_{BOS} denotes the probability that a patient is still alive when he/she stops treatment with bosutinib, i.e. the probability that a patient in the (Bosutinib, HU) arm starts 4th-line HU treatment, which equals the probability that a patient in the (Bosutinib, SCT) arm starts 4th-line SCT treatment. S_{IFN} represents the analogous quantity for IFN.

Table 75. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in CP

	(Bosutinib, HU)	HU	SCT	(IFN, HU)	(Bosutinib, SCT)
3rd-line CP	unchanged	unchanged	unchanged	unchanged	unchanged
4th-line CP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$	
BP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$	

Unfortunately, S_{BOS} and S_{IFN} are not calculated in Pfizer's model. However, we estimate upper bounds for these quantities, 95.5% and 99.8% respectively, by assuming that the only mortality whilst patients are on bosutinib or IFN treatment is due to background causes. These estimates are based on Pfizer's base case estimates of time on 3rd-line bosutinib and 3rd-line IFN. These upper bounds in turn yield lower bounds for the ICERs of (Bosutinib, HU) versus HU and versus (IFN, HU).

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm and 4th-line HU in the (IFN, HU) arm are very similar (2.5 vs. 2.6 vs. 2.6 years respectively) (Figure 28). The mean time on HU in the (Bosutinib, HU) arm is slightly lower because not all patients (95.5%) reach HU treatment, whereas all patients start treatment in the HU arm and nearly all patients (99.8%) in the (IFN, HU) arm start HU treatment.

In addition, the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are very similar (6.3 vs. 6.6 years respectively) (Figure 28). Similarly, the time is slightly lower in the (Bosutinib, SCT) arm, again because only 95.5% reach SCT treatment.

Figure 28.

6.1.1.2 Cumulative survival method CP total costs and QALYs

Next, we denote C as the mean per patient discounted total costs. Then, as for T, this variable is split in to four parts, corresponding to 3rd-line CP, 4th-line CP, AP and BP, using exactly the same notation as for T, shown in Table 76, where d_{BOS} denotes the mean discount factor at the time of cessation of bosutinib treatment across all patients. Technically, this is the integral over all time of the probability density function of the bosutinib discontinuation function at time t multiplied by the discount factor at time t. d_{IFN} represents the analogous quantity for IFN.

d_{BOS} and d_{IFN} can be calculated directly from Pfizer's model and equal 93.0% and 99.4% respectively. These quantities are also based on Pfizer's base case estimates of time on 3rd-line bosutinib and 3rd-line IFN. They also assume a discount rate of 3.5% p.a.

Then under the cumulative survival method, the component costs are calculated as shown in Table 76.

Table 76. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in CP

	(Bosutinib, HU)	**HU**	**SCT**	**(IFN, HU)**	**(Bosutinib, SCT)**
3rd-line CP	unchanged	unchanged	unchanged	unchanged	unchanged
4th-line CP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{HU}}$	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{SCT}}$
AP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{AP}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{AP}}$	
BP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{BP}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{BP}}$	

The component QALYs are calculated in exactly the same way.

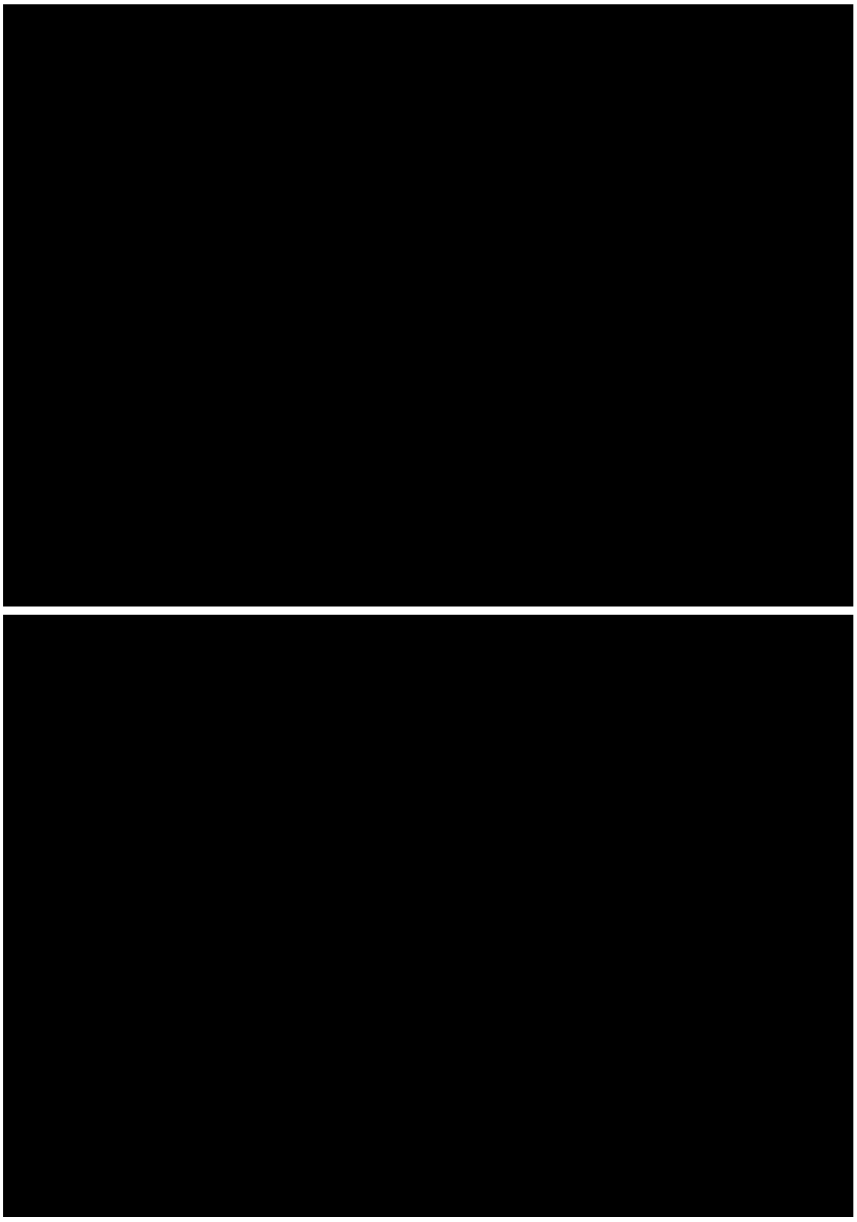
The ICERs are then as shown in Table 77 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT, indicated by bold font.

Table 77. PenTAG ICERs under the Cumulative Survival method for CP

Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

n/a as not estimated by Pfizer

Figure 29.



Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) and (IFN, HU) arms survive to start 4th-line HU treatment, i.e. $S_{\mathrm{BOS}} = S_{\mathrm{IFN}}$ = 100%, and
- no discounting of costs and QALYs, i.e. $d_{\mathrm{BOS}} = d_{\mathrm{IFN}}$ = 100%,

then the ICER for (Bosutinib, HU) versus HU is [redacted] per QALY and (Bosutinib, HU) versus (IFN, HU) is [redacted] per QALY. These ICERs only then depend on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm and IFN treatment in the (IFN, HU) arm. In other words, we ignore all costs and QALYs on HU treatment and in AP and BP in all arms, in particular ignoring all costs and QALYs in the entire HU arm.

Similarly, the ICER for (Bosutinib, SCT) versus SCT is [redacted] per QALY and then depends only on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, SCT) arm, i.e. ignoring all costs and QALYs in the entire SCT arm.

6.1.2 Cumulative survival method AP

We now discuss the Cumulative Survival method applied to treatment starting in AP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 1.0 years respectively) (Figure 30). As in CP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 30.

[redacted]

Under the Cumulative Survival method, we again correct for this imbalance, in an analogous way as for CP CML, described above. The details are given in Appendix T. The key assumptions are that the life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equals that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib, and in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm are very similar (1.01 vs. 1.02 years respectively) (Figure 31). The mean time on HU in the (Bosutinib, HU) arm is slightly lower because not all patients (98.9%) reach HU treatment, whereas all patients start treatment in the HU arm.

In addition, the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are very similar (2.99 vs. 3.02 years respectively) (Figure 31). Similarly, the time is slightly lower in the (Bosutinib, SCT) arm, again because only 98.9% reach SCT treatment.

Figure 31.

The ICERs are then as shown in Table 78 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT, indicated in bold.

Table 78. PenTAG ICERs under the Cumulative Survival method for AP CML

Intervention	(Bosutinib, HU) vs.	(Bosutinib, SCT) vs.

Comparator	***HU***	*SCT*	*HU*	***SCT***
Pfizer base case	[redacted]	Dominant	**n/a**	
Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]

n/a as not estimated by Pfizer

Figure 32.

[redacted]

Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) arm survival to start 4th-line HU treatment, i.e. S_{BOS} =100%, and
- no discounting of costs and QALYs, i.e. d_{BOS} = 100%,

then the ICERs for (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT are both [redacted] per QALY. This ICER only then depends on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm. In other words, we ignore all costs and QALYs on HU and SCT treatments in all arms, in particular ignoring all costs and QALYs in the entire HU and SCT arms.

6.1.3 Cumulative survival method BP

We now discuss the Cumulative Survival method applied to treatment starting in BP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 0.54 years respectively) (Figure 33). As in CP and AP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 33.

[redacted]

Under the Cumulative Survival method, we again correct for this imbalance, in an analogous way as for CP and AP CML. The details are given in Appendix T. The key assumptions are that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib, and in

the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm are virtually identical (0.54 vs. 0.54 years respectively) (Figure 34), and the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are virtually identical (2.64 vs. 2.64 years respectively) (Figure 34).

Figure 34.

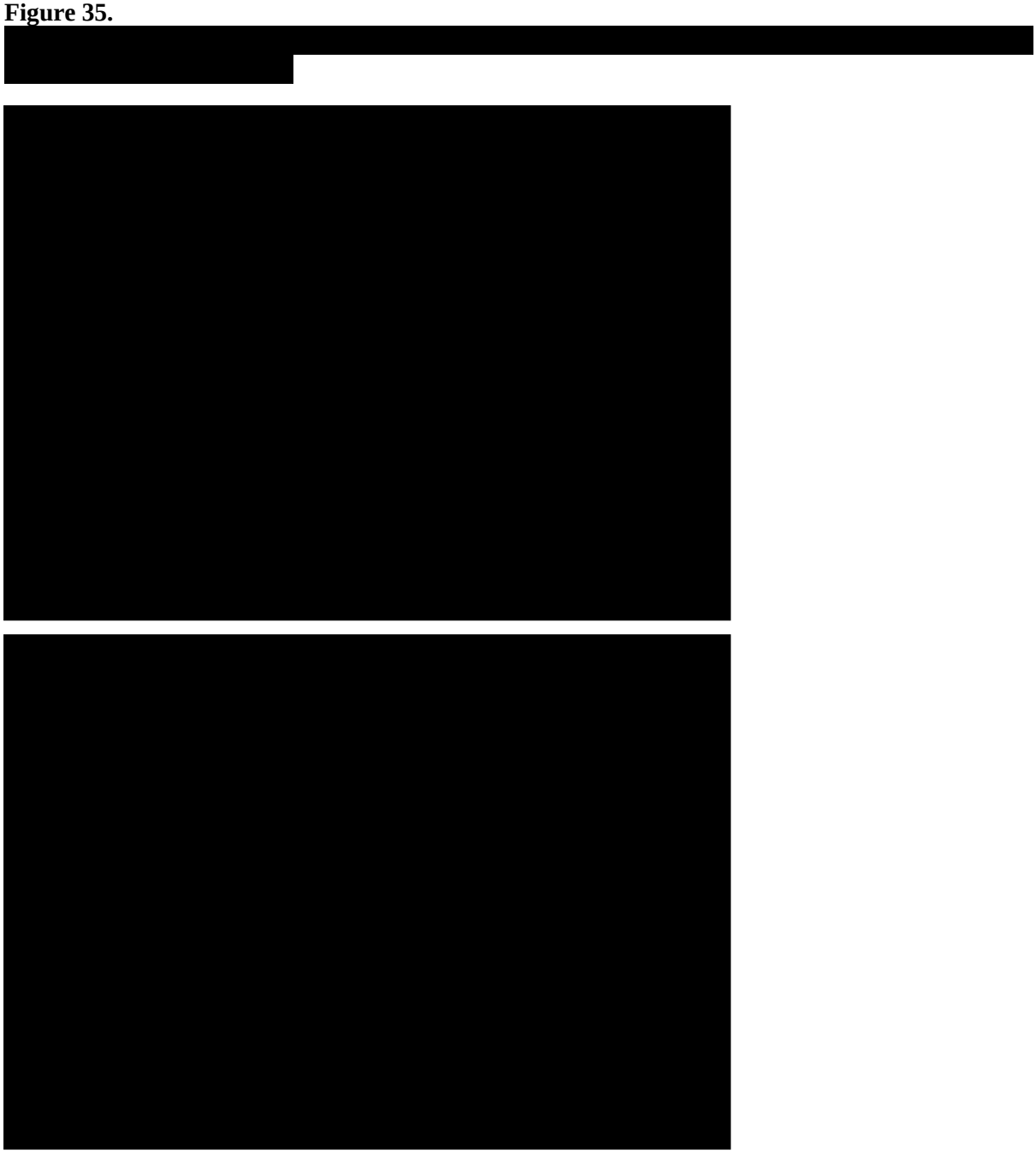
The ICERs are then as shown in Table 79 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT, indicated in bold.

Table 79. PenTAG ICERs under the Cumulative Survival method for BP CML

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
Pfizer base case			n/a	
Cumulative survival method				

n/a as not estimated by Pfizer
a (Bosutinib, HU) cheaper and less effective than SCT

Figure 35.



Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) arm survival to start 4th-line HU treatment, i.e. $S_{\mathrm{BOS}} = 100\%$, and
- no discounting of costs and QALYs, i.e. $d_{\mathrm{BOS}} = 100\%$,

then the ICERs for (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT are both [redacted] per QALY. This ICER only then depends on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm. In other words, we ignore all costs and QALYs on HU and SCT treatments in all arms, in particular ignoring all costs and QALYs in the entire HU and SCT arms.

6.1.4 Cumulative survival method discussion

We believe that the method to estimate OS for all treatments should be simple and parsimonious for the following reasons:

- Evidence for OS for all comparators is from single arm trials.
- The quality of evidence for OS for patients having failed a TKI for all comparators is poor.
- Worse still, there is no OS evidence whatsoever specifically for patients unsuited to TKIs for HU, SCT and IFN, and only limited evidence for bosutinib.

Pfizer's method for estimating OS involves numerous assumptions (Table 65, p165), for which there is little or no evidence. Furthermore, their results appear implausible. By contrast, the Cumulative Survival method requires just a single assumption and gives far more plausible estimates for the times on treatment. Therefore, we believe that the Cumulative Survival method should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The Cumulative Survival method additionally has the attractive property that the ICERs for the key comparisons of (bosutinib, HU) vs. HU and (bosutinib, SCT) vs. SCT depend almost exclusively on the costs and QALYs per unit time whilst patients are on bosutinib treatment. This leads to the following attractive predictions about the ICERs for the key comparisons of (bosutinib, HU) vs. HU and (bosutinib, SCT) vs. SCT under the Cumulative Survival method, none of which apply under Pfizer's method.

- They are very insensitive to the estimated mean time on HU and SCT. This is attractive because these quantities are highly uncertain due to the lack of quality clinical evidence.
- They are largely independent of line of treatment of bosutinib, as they are influenced heavily by the costs and QALYs on bosutinib per unit time, not over the entire duration of bosutinib treatment.
- They are insensitive to whether the clinical evidence relates just to those patients unsuited to TKIs or to all patients after imatinib failure.
- They are insensitive to the nature of subsequent treatments in the trials that inform OS for all comparator treatments.

Pfizer briefly mention a sensitivity analysis which they dub the "Cumulative survival approach" (p160 & p469) in which they estimate OS for bosutinib as PFS plus 10 months in AP and 6 months in BP. We agree with Pfizer that their "Cumulative survival approach" is "similar to the cumulative survival approach in TA251" (Pfizer submission, p469). We believe it is similar in that OS for bosutinib is not estimated by a surrogate approach, but instead is estimated as the sum of times in various health states. Nonetheless, their method is importantly different to the method we describe as the "Cumulative Survival" method for two main reasons. First, it is based on PFS, not on time on bosutinib treatment. Pfizer assume that OS is estimated as PFS plus time on AP plus time on BP. As we discussed in TA241, we disagree, because of the definition of progression. In Study 200, progression can indeed be due to progression to AP or BP, but also due to other events such as doubling of white blood cell count over at least 1 month with a second count >20 x 109/L confirmed at least 1 week later, loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss, loss of MCyR with an increase of ≥30% in Ph+ metaphases (p346 Pfizer submission). Therefore, we believe that Pfizer underestimate OS under their method. Second, Pfizer apply their "Cumulative survival approach" only to the bosutinib arm, not to the comparator arms. Therefore, the crucial Assumption 1 (Table 65, p165) remains, i.e. inconsistency in the method of estimating OS across comparators.

The Cumulative Survival method in the form we have just described is not mentioned by Pfizer in the current HTA. We find this puzzling, given that it was the accepted base case model structure in TA251 and given that Pfizer contrast their current analysis with the analyses from TA251 in great details in almost every other area, including choice of utilities, resource use and surrogate survival relationship.

If anything, the Cumulative survival method may slightly over-estimate OS in the bosutinib arm, and therefore is favourable to the cost-effectiveness of bosutinib, for three reasons.

First, the method assumes that the mean time on HU after bosutinib is approximately equal to the mean time on HU (without bosutinib). In other words, that the life expectancy on HU does not decrease at a later line of treatment. Conversely, life expectancy generally decreases with line of treatment.

Second, our estimate of S_{BOS}, the probability that a patient is still alive when he/she stops treatment with bosutinib, i.e. the probability that a patient in the (Bosutinib, HU) arm starts 4th-line HU treatment, which equals the probability that a patient in the (Bosutinib, SCT) arm starts 4th-line SCT treatment, is an upper bound since we assume that the only cause of mortality whilst patients are on bosutinib is background mortality, i.e. unrelated to CML. In reality, mortality is likely to be greater. In particular, an evidence-based estimate of the upper bound of S_{BOS} is 94.9%, which we derive as

follows. In the 3rd-line CP cohort of Study 200, by the 15th February 2012 snapshot, there had been 23 deaths overall, of which 6 occurred during bosutinib treatment or within 30 days of last dose, and 17 died more than 30 days after discontinuation of bosutinib (p83 Pfizer submission). Given that there were 118 3rd-line CP patients, if we assume that all patients were off bosutinib treatment at the data snapshot, this gives an upper bound of 100% − 6 / 118 = 94.9%. This is an upper bound because some patients were still taking bosutinib at the data cut off.

Third, the method does not allow for the fact that background mortality for patients starting 4th-line HU or SCT is slightly greater than for patients starting 3rd-line HU or SCT, reflecting an average time of [redacted] years on 3rd-line bosutinib in CP. However, we ignore this because exploratory calculations suggest that correcting this inaccuracy increases the ICER of bosutinib only very marginally.

Furthermore, we also do not allow for the fact that total QALYs on 4th-line HU will be slightly lower than on 3rd-line HU because utilities are assumed to reduce slightly with age. However, we ignore this for the same reason.

6.2 Derivation of PenTAG base case

In this section we present derivations of the PenTAG base cases in the CP, AP and BP models. The impacts of the individual components of our base case on cost-effectiveness are shown, as well as selected combinations of components and finally the base case which is composed of all components.

We also show more detailed results of the PenTAG base case and comparisons of the Pfizer and PenTAG base cases in the cost-effectiveness plane.

Unless otherwise stated, all ICERs lie in the first (NE) quadrant (i.e., the intervention is more costly and more effective than the comparator). We believe that the comparisons that are most relevant to the decision problem are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT. These ICERs are therefore highlighted in bold.

6.2.1 Derivation of PenTAG CP base case

Table 80 shows the derivation of the PenTAG base case in the CP model. Unless otherwise stated, IFN is dominated by HU.

Table 80. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
	Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	Dominant	[redacted]	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	[redacted]	n/a		
1+2[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+3[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+4[b]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+3+4		[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT
b Interferon is more costly and more effective than hydroxycarbamide

c Interferon is less costly and less effective than hydroxycarbamide

Our base case ICERs for (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT are [redacted] and [redacted] per QALY respectively. The cumulative survival method is the principal cause of the increase in the ICER for (Bosutinib, HU) versus HU from [redacted] per QALY, as individually it results in an ICER of [redacted] per QALY. The change in medical management costs improves the cost-effectiveness of bosutinib both when applied to Pfizer's base case and also as a component of the PenTAG base case. Increases in the overall survival for HU and SCT patients results in a significant worsening in the cost-effectiveness of bosutinib according to Pfizer's model but the change is less pronounced with the cumulative survival method as these OS gains are passed on to bosutinib patients also. Figure 36 shows the mean time on each treatment for each treatment arm in the PenTAG base case. Note that while SCT is now predicted to provide more life years than (Bosutinib, HU) (11.6 versus [redacted]), it is not predicted to provide more QALYs (5.7 versus [redacted]), although as stated before we believe the appropriate comparisons are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT.

Figure 36. [redacted]

[redacted]

The general effect of bosutinib in the PenTAG base case is to increase total QALYs by between [redacted] and [redacted] and increase discounted costs by around £100,000, as is shown in Figure 37. Comparisons of the cost-effectiveness planes in the Pfizer and PenTAG bases are shown in

Figure 38, in which it can be seen that HU and SCT become significantly more effective and marginally less costly. (Bosutinib, HU) by contrast becomes less effective and less costly. Further details are shown in Table 81.

Figure 37.

Figure 38.

Table 81. Life years, QALYs and costs in PenTAG CP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	(IFN, HU)	SCT
Life years (undiscounted)					
CP on treatment	[redacted]	[redacted]	5.87	0.54	11.59
CP off treatment	5.61	11.06	n/a	5.86	n/a
AP	0.62	n/a	0.65	0.65	n/a
BP	0.45	n/a	0.47	0.47	n/a
Total	[redacted]	[redacted]	**6.99**	**7.52**	**11.59**
Discounted QALYs					
CP on treatment	[redacted]	[redacted]	3.94	0.38	5.72
CP off treatment	3.50	5.08	n/a	3.90	n/a
AP	0.31	n/a	0.35	0.35	n/a
BP	0.16	n/a	0.18	0.18	n/a
Total	[redacted]	[redacted]	**4.47**	**4.82**	**5.72**
Discounted costs					
CP on treatment	[redacted]	[redacted]	£5,970	£9,038	£151,863
CP off treatment	£5,302	£134,862	n/a	£5,919	n/a
AP	£6,981	n/a	£7,861	£7,794	n/a
BP	£5,102	n/a	£5,745	£5,696	n/a
Palliative care	£4,356	£3,842	£4,905	£4,863	£4,326
Adverse events	£506	£506	n/a	n/a	n/a
Total	[redacted]	[redacted]	**£24,482**	**£33,311**	**£156,189**

6.2.2 Derivation of PenTAG AP base case

Table 82 shows the derivation of the PenTAG AP base case.

Table 82. Derivation of PenTAG base case AP CML

	Intervention	(Bosutinib, HU) vs.		(Bosutinib, SCT) vs.	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

[redacted]

The PenTAG AP base case is composed simply of the cumulative survival method. The effect of this change is to introduce the (Bosutinib, SCT) arm and to worsen slightly the cost-effectiveness of

(Bosutinib, HU) versus HU, with the ICER increasing from [redacted] per QALY. The ICER of (Bosutinib, SCT) versus SCT is estimated at [redacted] per QALY.

Figure 39 shows the mean time on each treatment in the PenTAG AP base case. It can be seen that the time spent on HU in AP in the (Bosutinib, HU) arm is similar to the time spent in AP in the HU arm, and likewise for SCT in the (Bosutinib, SCT) arm.

Figure 39.

[redacted]

Figure 40 shows the cost-effectiveness plane for the PenTAG AP base case. In this instance, bosutinib adds [redacted] QALYs and [redacted].

Figure 41 shows a comparison of the Pfizer and PenTAG base case cost-effectiveness planes, showing that the PenTAG base case reduces the effectiveness and cost of bosutinib and introduces the (Bosutinib, SCT) arm. Further details are shown in Table 83.

Figure 40.

[redacted]

Figure 41. [redacted]

[redacted]

Table 83. Life years, QALYs and costs in PenTAG AP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	SCT
Life years (undiscounted)				
AP on treatment	[redacted]	[redacted]	1.02	3.02
AP off treatment	1.01	2.99	n/a	n/a
BP	0.35	n/a	0.35	n/a
Total	[redacted]	[redacted]	**1.37**	**3.02**
Discounted QALYs				
AP on treatment	[redacted]	[redacted]	0.72	1.96
AP off treatment	0.68	1.83	n/a	n/a
BP	0.16	n/a	0.18	n/a
Total	[redacted]	[redacted]	**0.90**	**1.96**
Discounted costs				
AP on treatment	[redacted]	[redacted]	£15,117	£172,572
AP off treatment	£14,129	£161,294	n/a	n/a
BP	£4,808	n/a	£5,144	n/a
Palliative care	£5,437	£5,160	£5,817	£5,520
Adverse events	£506	£506	n/a	n/a
Total	[redacted]	[redacted]	**£26,078**	**£178,093**

6.2.3 Derivation of PenTAG BP base case

Table 84 shows the derivation of the PenTAG BP base case. In both the Pfizer base case and PenTAG base case (Bosutinib, HU) is less costly and less effective than SCT.

Table 84. Derivation of PenTAG base case BP CML

	Intervention	(Bosutinib, HU) vs.		(Bosutinib, SCT) vs.	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

As in the AP model, the only change is the introduction of the cumulative survival method. This results in the additional intervention arm (Bosutinib, SCT). The PenTAG base case ICERs for (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT are [redacted] and [redacted] per QALY

respectively. The ICER for (Bosutinib, HU) versus HU is increased from [redacted] per QALY in the Pfizer model because costs and QALYs are reduced in this arm but QALYs are more heavily reduced.

The mean time on each treatment for each treatment arm in the PenTAG BP base case is shown in Figure 42, which demonstrates that bosutinib provides an extra [redacted] life years.

Figure 42.

[redacted]

The PenTAG base case cost-effectiveness plane is shown in Figure 43, and demonstrates that bosutinib provides an extra [redacted] QALYs for an extra cost of around [redacted]. The SCT arms give approximately [redacted] extra QALY at an extra cost of approximately [redacted].

Figure 44 shows a comparison of the Pfizer and PenTAG BP base cases in the cost-effectiveness plane and demonstrate that the PenTAG base case introduces the (Bosutinib, SCT) arm and reduces the costs and QALYs of the (Bosutinib, HU) arm. Further details are shown in Table 85.

Figure 43.

Figure 44.

Table 85. Life years, QALYs and costs in PenTAG BP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	SCT
Life years (undiscounted)				
BP on treatment	[redacted]	[redacted]	0.54	2.64
BP off treatment	0.54	2.64	n/a	n/a
Total	[redacted]	[redacted]	**0.54**	**2.64**
Discounted QALYs				
BP on treatment	[redacted]	[redacted]	0.28	1.28
BP off treatment	0.28	1.27	n/a	n/a
Total	[redacted]	[redacted]	**0.28**	**1.28**
Discounted costs				
BP on treatment	[redacted]	[redacted]	£8,203	£194,940
BP off treatment	£8,117	£192,892	n/a	n/a
Palliative care	£5,904	£5,528	£5,967	£5,586
Adverse events	£506	£506	n/a	n/a
Total	[redacted]	[redacted]	**£14,170**	**£200,526**

6.3 Key sensitivity analyses applied to PenTAG and Pfizer base cases

In this section we select scenario analyses which we regard as key analyses either as explorations of potentially valid alternative base cases or of uncertainty in key parameters.

6.3.1 Key sensitivity analyses CP

We conducted a number of scenario analyses on both the Pfizer base case and the PenTAG base case (see Table 86 and Table 87). Some of these were performed because they were potentially valid as base cases (e.g., 2nd-line cohort, utilities from Study 200) while others were to explore the effect of uncertainty in key parameters.

When applied to the PenTAG base case, none of the sensitivity analyses have a significant impact on the relevant ICERs of (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT; in all scenarios, (Bosutinib, HU) is not cost-effective versus HU at cost-effectiveness thresholds of £20,000 or £30,000 per QALY, and likewise for (Bosutinib, SCT) versus SCT.

When applied to the Pfizer base case, some of the sensitivity analyses have a significant impact on the ICER of (Bosutinib, HU) versus HU. In particular, if bosutinib is used in a 2nd-line cohort we predict an ICER of [redacted] per QALY using Pfizer's base case; if bosutinib is received until transformation to AP (as might be the case if bosutinib is the last available TKI for a patient) we predict an ICER of [redacted] per QALY. In these two scenarios, it is also worth noting that (Bosutinib, HU) is no longer

cost-effective versus SCT, although we feel that a more appropriate comparison is (Bosutinib, SCT) vs. SCT.

Table 86. Important scenario analyses applied to PenTAG base case for CP model

Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	[redacted]	[redacted]	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	[redacted]	[redacted]	[redacted]
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
SCT utility set to TA251 utility	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT

Table 87. Important scenario analyses applied to Pfizer base case CP model

Intervention	**(Bosutinib, HU) vs.**		
Comparator	***HU***	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]
Mean OS HU decreased from 3.5 to 1.8 years (−50%)	[redacted]	n/c	n/c
Mean OS HU increased from 3.5 to 5.2 years (+50%)	[redacted]	n/c	n/c
Mean OS for SCT decreased from 6.6 to 3.3 years (−50%)	**n/c**	[redacted]	n/c
Mean OS for SCT increased from 6.6 to 9.9 years (+50%)	**n/c**	Dominant	n/c
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]
Bosutinib and HU utility set to Study 200 utility	[redacted]	n/c	[redacted]
SCT utility set to TA251 utility	**n/c**	Dominant	n/c

n/c – Not changed from base case
Shading as in Table 86

6.3.2 Key sensitivity analyses AP

We performed two sensitivity analyses on both the PenTAG and Pfizer base cases. In the first analysis, we increased the overall survival of HU from 1.37 to [redacted] years to match the time spent in AP off bosutinib treatment in the (Bosutinib, HU) arm. In the second analysis, we used utilities from Study 200. In both the PenTAG and Pfizer base cases, these sensitivity analyses did not significantly impact on the ICERs. Using Study 200 utilities improves cost-effectiveness as the HRQL under bosutinib is improved, but the ICERs remain well above the £20,000, £30,000 and £50,000 per QALY thresholds, at [redacted] per QALY in the PenTAG and Pfizer models respectively.

Table 88. Important scenario analyses applied to PenTAG base case for AP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]
HU OS = Time in Bosutinib AP Off Treatment [redacted]	[redacted]	n/c	[redacted]	[redacted]
Study 200 utilities	[redacted]	Dominant	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 89. Important scenario analyses applied to Pfizer base case for AP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	Dominant
HU OS = Time in Bosutinib AP Off Treatment [redacted]	[redacted]	n/c
Study 200 utilities	[redacted]	Dominant

n/c – Not changed from base case
Shading as in Table 88

6.3.3 Key sensitivity analyses BP

We performed similar sensitivity analyses in the BP model as in the AP model. We found that increasing the OS of HU to match the time spent off bosutinib in the (Bosutinib, HU) arm significantly worsened cost-effectiveness in the Pfizer model but had very little effect in the PenTAG model, as expected. Use of Study 200 utilities improved cost-effectiveness, but the ICER of (Bosutinib, HU) versus HU remained high, at [redacted] per QALY in the PenTAG and Pfizer models respectively. (Bosutinib, HU) was consistently less costly and less effective than SCT, except when the Pfizer base case was adjusted for Study 200 utilities.

Table 90. Important scenario analyses applied to PenTAG base case for BP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	[redacted]	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 200 utilities	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 91. Important scenario analyses applied to Pfizer base case for BP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	n/c
Study 200 utilities	[redacted]	Dominated

n/c – Not changed from base case

[redacted]

7 END OF LIFE

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML.

We agree that there is clearly no case for CP CML because life expectancy under the comparator treatments of HU and SCT are far greater than the threshold of 2 years.

We believe that bosutinib does not meet the End of Life criteria in any phase of CML, as demonstrated in Table 92 and Table 93 below.

Table 92. End of Life criteria for bosutinib in AP

Criterion	Pfizer comments	PenTAG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Pfizer claim life expectancy is approx. 1.3 years (p103 Pfizer submission)	In summary, it seems likely that the life expectancy for patients on an appropriate comparator treatment is close to the threshold of 24 months, as follows: First, we believe that the relevant comparator for most people is HU rather than SCT. Pfizer estimate life expectancy under HU as 1.4 years and after SCT as 3.0 years. We have no alternative value for SCT. We believe that the estimate of 1.4 years for HU is based on weak evidence. Also, Pfizer estimate a mean time on HU after bosutinib of [redacted] years.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pfizer claim extension to life expectancy is approx. 1.7 years (p103 Pfizer submission)	We believe that this criterion is probably satisfied. We understand that Pfizer's base case claims extension to life of 3.1 years for (Bosutinib, HU) vs. HU and 1.5 years vs. SCT. Under our Cumulative Survival method, the extension to life is [redacted] years.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Pfizer claim patient population < 8 p.a. (p103 Pfizer submission)	We believe that this criterion is clearly satisfied. Pfizer's estimate is not unreasonable.
The estimates of the extension to life are robust and can be shown or reasonably inferred from	No discussion	We believe that this criterion is not satisfied for the numerous reasons given in Section 5.3.8.1, p165.

either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)		For example, estimates of OS are not randomised, the method of estimation of OS is not consistent across treatments, OS is estimated from very small sample sizes, and largely from people suited to TKIs (whereas they should be for people unsuited to TKIs), OS data is immature.
The assumptions used in the reference case economic modelling are plausible, objective and robust.	No discussion in relation to End of Life	This criterion is difficult to evaluate. Most assumptions for the AP model are plausible, but not robust.
Overall qualification for End of Life	**Yes**	**No**

Table 93. End of Life criteria for bosutinib in BP

Criterion	Pfizer comments	PenTAG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Pfizer claim life expectancy is approx. 0.5 years (p103 Pfizer submission)	In summary, it seems likely that this criterion is satisfied, as follows: First, we believe that the relevant comparator for most people is HU rather than SCT. Pfizer estimate life expectancy under HU as 0.5 years and after SCT as 2.6 years. We have no alternative value for SCT. We believe that the estimate of 0.5 years for HU is based on weak evidence. Also, Pfizer estimate a mean time on HU after bosutinib of [redacted] years
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pfizer claim extension to life expectancy is approx. 1.2 years (p103 Pfizer submission)	We believe that this criterion is probably satisfied. Pfizer's base case extension to life is 1.2 years for (Bosutinib, HU) vs. HU (the most relevant comparator), but (Bosutinib, HU) reduces life expectancy vs. SCT. Under our Cumulative Survival method, the extension to life is [redacted] years.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in	Pfizer claim patient population < 8 p.a. (p103 Pfizer submission)	We believe that this criterion is clearly satisfied. Pfizer's estimate is not unreasonable.

England.		
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	No discussion	We believe that this criterion is not satisfied for the same reasons given for AP (Table 92).
The assumptions used in the reference case economic modelling are plausible, objective and robust.	No discussion in relation to End of Life	This criterion is difficult to evaluate. Most assumptions for the BP model are plausible, but not robust.
Overall qualification for End of Life	**Yes**	**No**

8 IMPLICATIONS FOR RESEARCH

Research in to the following would be welcome:

- The EMA's marketing authorisation is conditional on the following trial to be conducted, with final clinical study report due 30th September 2018[29]:

  "a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options."

  We agree that this would improve our understanding of bosutinib in the unmet need population.
- However, better still would be a randomised trial of bosutinib versus the comparators HU or SCT in the unmet need population.
- More mature OS data for bosutinib in all phases, specifically for patients in the patient population appropriate to this appraisal, i.e., those after TKIs failure, unsuited to imatinib, nilotinib and dasatinib. This would allow us to test our default assumption under the Cumulative Survival method that bosutinib does not affect mortality once it is discontinued. We assume that this will be recorded from Study 200. However, a larger patient population would be welcome from the single-arm trial recommended by the EMA.
- High quality estimate of OS on HU in all phases of CML for 2nd-line patients, and also for patients in the population appropriate to this appraisal, ideally from the randomised trial we recommend above, would be useful for modelling the cost-effectiveness of bosutinib (or other new TKIs in the future) versus HU. But we understand that this data may not be collected due to ethical reasons, as HU is not a potent treatment for CML.
- Similarly for OS after SCT in CP.
- Utilities for patients after SCT.

REFERENCES

1. Cortes J, Kantarjian H, Kim DW, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib: 36-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.

2. Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:1-410.

3. Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer 2007;109:1556-60.

4. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. Haematologica 2011;96:1779-82.

5. Benedicte D, Emmanuel B, Nicole R, et al. Impact of prior second-generation tyrosine kinase inhibitors on the outcome of hematopoietic stem cell transplantation for chronic myeloid leukemia In 52nd Annual Meeting of the American Society of Hematology, 2010.

6. Bornhauser M, Kroger N, Schwerdtfeger R, et al. Allogeneic haematopoietic cell transplantation for chronic myelogenous leukaemia in the era of imatinib: a retrospective multicentre study. Eur J Haematol 2006;76:9-17.

7. Holroyd A, Philips E, Szydlo R, et al. Response to tyrosine kinase inhibitor therapy in patients undergoing allogeneic hematopoietic stem cell transplantation for advanced phase chronic myeloid leukemia, In 52nd Annual Meeting of the American Society of Hematology, 2010, 2010.

8. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. Cancer 2007;110:340-4.

9. Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after Bcr-Abl kinase mutation-related imatinib failure. Blood 2006;108:1421-3.

10. Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-7.

11. Markiewicz M, Dzierzak-Mietla M, Wisniewska-Piaty K, et al. The favorable results of allo-HSCT in TKI-resistant CML, In 53rd Annual Meeting of the American Society of Hematology, In 53rd Annual Meeting of the American Society of Hematology, 2011, 2011.

12. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-9.

13. Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-5.

14. Schleuning M, Scholten M, van Bienzen A, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia after prior treatment with nilotinib or dasatinib, In 52nd Annual Meeting of the American Society of Hematology, 2010.

15. Weisser M, Schleuning M, Haferlach C, et al. Allogeneic stem-cell transplantation provides excellent results in advanced stage chronic myeloid leukemia with major cytogenetic response to pre-transplant imatinib therapy. Leuk Lymphoma 2007;48:295-301.

16. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol 2009;62:1253-1260 e4.

17. Hoyle M, Pavey T, Ciani O, et al. Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. National Institute for Health and Clinical Excellence (NICE): Peninsula Technology Assessment Group (PenTAG), University of Exeter 2011.

18. Bhamidipati PK, Kantarjian H, Cortes J, et al. Management of imatinib-resistant patients with chronic myeloid leukemia. Ther Adv Hematol 2013;4:103-17.

19. Haematological Malignancy Research Network. Chronic myelogenous leukaemia http://www.hmrn.org/Statistics/Cancer_Info.aspx?id=1 (last accessed 13 May 2013), 2013.

20. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.

21. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-8.

22. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011;118:686-92.

23. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol 2009;27:469-71.

24. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.

25. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403-12.

26. Trask PC, Cella D, Besson N, et al. Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia. Leuk Res 2012;36:438-42.

27. Pfizer. Study 200 Clinical Study Report.

28. Khoury HJ, Gambacorti-Passerini C, Kantarjian H, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Failure with Imatinib Plus Dasatinib and/or

Nilotinib: 24-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.

29. European Medicines Agency. Assessment report: bosulif, 2013.

30. Trask PC, Cella D, Powell C, et al. Health-related quality of life in chronic myeloid leukemia. Leuk Res 2013;37:9-13.

31. Dalziel K, Round A, Stein K, et al. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess 2005;9:iii-iv, 1-146.

32. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii-x, 1-173.

33. Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions (Available from www.cochrane-handbook.org): The Cochrane Collaboration, 2011.

34. Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Healthcare, 2009.

35. Porcher R, Desseaux K. What inference for two-stage phase II trials? BMC Med Res Methodol 2012;12:117.

36. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.

37. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP, 2011.

38. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. Lancet 1995;345:1392-7.

39. Hoyle M, Rogers G, Moxham T, et al. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. Value Health 2011;14:1057-67.

40. Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:iii-xiii, 1-137.

41. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006.

42. Hawkins N, Sculpher M, Epstein D. Cost-effectiveness analysis of treatments for chronic disease: using R to incorporate time dependency of treatment response. Med Decis Making 2005;25:511-9.

43. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. Process and methods guides, 2013.

44. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 2009;113:2154-60.

45. Reed SD, Anstrom KJ, Ludmer JA, et al. Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2004;101:2574-83.

46. Dalziel K, Round A, Stein K, et al. Effectiveness and cost-effectiveness of imatinib for first-line treatment of

chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technol Assess 2004;8:iii, 1-120.

47. Department of Health. Reference costs 2011-12 (available from: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012), 2012.

48. Darbà J, Kaskens L. Análisis coste-efectividad de dasatinib frente a imatinib a dosis alta en el tratamiento de la leucemia mieloide crónica en pacientes resistentes a dosis estándar de imatinib. PharmacoEconomics Spanish Research Articles 2012;9:63-71.

49. Szabo SM, Davis C, Sidhu S, et al. Characterizing resource use and treatment costs for chronic myelogenous leukemia (CML) in the UK (UK). Value Health 2009;12:A268.

50. Taylor M, Saxby R, Davis C. Using short-term response to predict long-term outcomes in patients with imatinib-resistent or imatinib-intolerant chronic myeloid leukaemia. Value Health 2009;12:A50.

51. Taylor MJ, Saxby RC, Davis C. An Economic Evaluation of Dasatinib for the Treatment of Imatinib-Resistant Patients with Chronic Myelogenous Leukaemia. ASH Annual Meeting Abstracts 2009;114:A4535.

52. Warren E, Ward S, Gordois A, et al. Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. Clin Ther 2004;26:1924-33.

53. Curtis L. Unit Costs of Health and Social Care 2012: Personal Social Services Research Unit, 2012.

54. Addicott R, Dewar S. Improving choice at end of life: a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice programme in Lincolnshire. London: King's Fund, 2008.

55. Bagust A, Boland A, Dundar Y, et al. Erlotinib for the treatment of relapsed non-small-cell lung cancer: Liverpool Reviews and Implementation Group, 2006.

56. NHS Blood and Transplant. The future of unrelated donor stem cell transplantation in the UK (report of the UK Stem Cells Strategic Forum), 2010.

57. van Agthoven M, Groot MT, Verdonck LF, et al. Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow Transplant 2002;30:243-51.

58. Drummond MF. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1997.

59. Pastore D, Specchia G, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed acute myeloid leukemia: single-center experience. Ann Hematol 2003;82:231-5.

9 APPENDICES

9.1 Appendix A: Incident population for bosutinib treatment in England & Wales

The following table is reproduced from Table C1, p188 of Pfizer's submission.

Table C1: Estimated annual, incident population for bosutinib treatment in England and Wales

Population	Estimated incidence	Assumption	Reference
Cases of chronic myeloid leukaemia in England and Wales	631	596 people in England and 35 people in Wales diagnosed with CML in 2010. Assuming that incidence has been stable since 2010.	Office of National Statistics Cancer Statistics Registrations, England, 2010 Welsh Cancer Intelligence and Surveillance Unit, Annual Publication No. SA12/01
People with Ph+ CML and treated with a 1st-line TKI (imatinib)	599	95% of those diagnosed with CML are Ph+. All diagnosed patients are treated with a 1st-line TKI (imatinib).	Goldman, 2009 Assumption
People for whom 1st-line imatinib treatment is unsuccessful and are treated with a 2nd-line TKI	234	39% of 1st-line patients discontinued imatinib (excluding those who discontinued due to mortality or receipt of a SCT) and all are treated with a 2nd-line TKI (usually nilotinib)	Deininger, 2009 Assumption
2nd-line patients for whom current 2nd-line TKIs are inappropriate options and therefore **eligible for bosutinib at 2nd-line**	12	5% of imatinib-resistant patients from Study 200 may have been unsuitable for treatment with nilotinib and dasatinib at 2nd-line, due to the presence of mutations conferring resistance or co-morbidities	Draft EPAR
Patients for whom 2nd-line TKI treatment is unsuccessful and are treated with a 3rd-line TKI	107	48% of 2nd-line patients discontinued nilotinib due to lack of efficacy (progression) or intolerance (adverse events) and treated with a 3rd-line TKI	Kantarjian (2011)
3rd-line patients whom the remaining TKI is not an appropriate option and therefore **eligible for bosutinib at 3rd-line**	19	18% of third-line patients from Study 200 may have been unsuitable for treatment with nilotinib or dasatinib at third-line (depending on previous treatment), due to the presence of mutations conferring resistance or co-morbidities, and therefore may be eligible for bosutinib at 3rd-line.	Draft EPAR
Patients for whom all currently available TKIs have been unsuccessful at 3rd-line and are therefore **eligible for bosutinib at 4th-line**	49	56% of 3rd-line patients (nilotinib and dasatinib) discontinue treatment excluding those discontinued due to mortality or receipt of a SCT) and have therefore exhausted all TKI options currently available.	Garg (2009)
Total incident population eligible to receive bosutinib under its proposed licensed indication	**80**	**80 patients per year may be eligible for bosutinib.**	

9.2 Appendix B: Pfizer search strategy

Embase 1974 to January 18th 2013: accessed January 21st 2013

# ▲	Searches	Results
1	exp chronic myeloid leukemia/	28150
2	exp myeloid leukemia/	94931
3	chronic.mp. or exp CHRONIC DISEASE/	1137090
4	2 and 3	37637
5	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	36017
6	1 or 4 or 5	40870
7	imatinib.mp. or exp IMATINIB/	25210
8	(gleevec or glivec).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	7043
9	(STI-571 or STI571 or CGP-57148B or CGP57148B).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3450
10	imatinib mes?late.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3959
11	7 or 8 or 9 or 10	25381
12	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1825148
13	11 and 12	8632
14	((second or third or fourth) adj2 line).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18247
15	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20661

16	exp hydroxycarbamide/	18838
17	exp stem cell transplantation/	73805
18	(HSCT or SCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	16373
19	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	80164
20	(best adj2 support*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2980
21	BSC.mp.	1903
22	exp alpha interferon/	42290
23	("roferon-a" or "intron-a").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4127
24	(interferon adj2 alpha).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	58762
25	exp bosutinib/	768
26	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	785
27	13 or 14	26479
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	164462
29	exp Meta Analysis/	68526
30	((meta adj analy$) or metaanalys$).tw.	64279
31	(systematic adj (review$1 or overview$1)).tw.	49775
32	or/29-31	126912
33	cancerlit.ab.	667
34	cochrane.ab.	29194
35	embase.ab.	26182

36	(psychlit or psyclit).ab.	960
37	(psychinfo or psycinfo).ab.	6477
38	(cinahl or cinhal).ab.	8859
39	science citation index.ab.	1924
40	bids.ab.	426
41	or/33-40	44645
42	reference lists.ab.	8707
43	bibliograph$.ab.	13958
44	hand-search$.ab.	4023
45	manual search$.ab.	2311
46	relevant journals.ab.	733
47	or/42-46	26833
48	data extraction.ab.	10705
49	selection criteria.ab.	19538
50	48 or 49	28886
51	review.pt.	1927821
52	50 and 51	17160
53	letter.pt.	810639
54	editorial.pt.	423694
55	animal/	1814965
56	human/	14033665
57	55 not (55 and 56)	1358614
58	or/53-54,57	2579283

59	32 or 41 or 47 or 52	158341
60	59 not 58	152465
61	Clinical trial/	880466
62	Randomized controlled trial/	338298
63	Randomization/	60597
64	Single blind procedure/	16904
65	Double blind procedure/	115252
66	Crossover procedure/	36027
67	Placebo/	224651
68	Randomi?ed controlled trial$.tw.	83038
69	Rct.tw.	10825
70	Random allocation.tw.	1244
71	Randomly allocated.tw.	18468
72	Allocated randomly.tw.	1879
73	(allocated adj2 random).tw.	797
74	Single blind$.tw.	13248
75	Double blind$.tw.	140106
76	((treble or triple) adj blind$).tw.	322
77	Placebo$.tw.	189572
78	Prospective study/	223692
79	or/61-78	1323025
80	Case study/	18387
81	Case report.tw.	246829

82	Abstract report/ or letter/	874710
83	or/80-82	1135017
84	79 not 83	1286701
85	Clinical study/	89188
86	Case control study/	73451
87	Family study/	9857
88	Longitudinal study/	57858
89	Retrospective study/	305071
90	Prospective study/	223692
91	Randomized controlled trials/	25395
92	90 not 91	222997
93	Cohort analysis/	138791
94	(Cohort adj (study or studies)).mp.	93662
95	(Case control adj (study or studies)).tw.	66302
96	(follow up adj (study or studies)).tw.	43659
97	(observational adj (study or studies)).tw.	50576
98	(epidemiologic$ adj (study or studies)).tw.	70019
99	(cross sectional adj (study or studies)).tw.	68258
100	or/85-89,92-99	1060706
101	60 or 84 or 100	2135162
102	6 and 27 and 28 and 101	634

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed January 21st 2013

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	14336
2	exp Leukemia, Myeloid/	73716
3	exp Chronic Disease/ or chronic.mp.	866224
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	22855
5	2 and 3	21552
6	1 or 4 or 5	26689
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9340
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1329087
9	7 and 8	3386
10	((second or third or fourth) adj2 line).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	12295
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9716
12	exp Hydroxycarbamide/	6966
13	exp Hematopoietic Stem Cell Transplantation/	24548
14	(HSCT or SCT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9314
15	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	52708
16	("roferon-a" or "intron-a").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease	602

	supplementary concept, unique identifier]	
17	(interferon adj2 alpha).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	34862
18	exp Interferon-alpha/	22848
19	(best adj2 support*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1940
20	BSC.mp.	1393
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	159
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	101858
23	9 or 10	15527
24	Randomized controlled trials as Topic/	82308
25	Randomized controlled trial/	337940
26	Random allocation/	75868
27	Double blind method/	117051
28	Single blind method/	16860
29	Clinical trial/	472870
30	exp Clinical Trials as Topic/	259509
31	or/24-30	838537
32	(clinic$ adj trial$1).tw.	186641
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	118891
34	Placebos/	31156
35	Placebo$.tw.	144503
36	Randomly allocated.tw.	14961

37	(allocated adj2 random).tw.	690
38	or/32-37	374411
39	31 or 38	967127
40	Case report.tw.	185707
41	Letter/	775875
42	Historical article/	288376
43	Review of reported cases.pt.	0
44	Review, multicase.pt.	0
45	or/40-44	1239238
46	39 not 45	940466
47	Epidemiologic studies/	5506
48	exp case control studies/	577770
49	exp cohort studies/	1213923
50	Case control.tw.	66232
51	(cohort adj (study or studies)).tw.	68832
52	Cohort analy$.tw.	3047
53	(Follow up adj (study or studies)).tw.	34614
54	(observational adj (study or studies)).tw.	35931
55	Longitudinal.tw.	121664
56	Retrospective.tw.	236529
57	Cross sectional.tw.	139952
58	Cross-sectional studies/	148552
59	or/47-58	1671329

60	Meta-Analysis as Topic/	12349
61	meta analy$.tw.	47037
62	metaanaly$.tw.	1193
63	Meta-Analysis/	36590
64	(systematic adj (review$1 or overview$1)).tw.	39507
65	exp Review Literature as Topic/	6473
66	or/60-65	95085
67	cochrane.ab.	22972
68	embase.ab.	20860
69	(psychlit or psyclit).ab.	844
70	(psychinfo or psycinfo).ab.	8116
71	(cinahl or cinhal).ab.	7677
72	science citation index.ab.	1607
73	bids.ab.	331
74	cancerlit.ab.	546
75	or/67-74	38173
76	reference list$.ab.	7893
77	bibliograph$.ab.	10357
78	hand-search$.ab.	3325
79	relevant journals.ab.	572
80	manual search$.ab.	1965
81	or/76-80	21577
82	selection criteria.ab.	16585

83	data extraction.ab.	8165
84	82 or 83	23449
85	Review/	1735402
86	84 and 85	15340
87	Comment/	518398
88	Letter/	775875
89	Editorial/	318524
90	animal/	4993336
91	human/	12521330
92	90 not (90 and 91)	3656512
93	or/87-89,92	4819761
94	66 or 75 or 81 or 86	121442
95	94 not 93	113116
96	46 or 59 or 95	2475570
97	6 and 22 and 23 and 96	198

EBM Reviews - Cochrane Central Register of Controlled Trials December 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2012, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2012, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2012: accessed January 21st 2012

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ ?	243
2	exp Leukemia, Myeloid/ ?	1243

3	exp Chronic Disease/ or chronic.mp. ?	55159
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	663
5	2 and 3 ?	322
6	1 or 4 or 5 ?	711
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	398
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	66651
9	7 and 8 ?	119
10	((second or third or fourth) adj2 line).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	1784
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	602
12	exp Hydroxycarbamide/ ?	289
13	exp Hematopoietic Stem Cell Transplantation/ ?	779
14	(HSCT or SCT).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	538
15	(stem adj2 cell adj2 transplant*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	2329
16	("roferon-a" or "intron-a").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	258
17	(interferon adj2 alpha).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	4044

18	exp Interferon-alpha/ ?	2264
19	(best adj2 support*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	437
20	BSC.mp. ?	175
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	3
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ?	7700
23	9 or 10 ?	1896
24	6 and 22 and 23 ?	26

(Source: Pfizer submission, Appendix 2, p201)

9.3 Appendix C: Quality assessment tool

Chambers criteria for quality assessment of non-RCTs

Criteria used for quality assessment
1 Were selection/eligibility criteria adequately reported?
2 Was the selected population representative of that seen in normal practice?
3 Was an appropriate measure of variability reported?
4 Was loss to follow-up reported or explained?
5 Were at least 90% of those included at baseline followed-up?
6 Were patients recruited prospectively?
7 Were patients recruited consecutively?
8 Did the study report relevant prognostic factors?

Using the above criteria, a study's quality could be scored as good, satisfactory or poor; good, if the answer is 'yes' to all of criteria 1 to 8; satisfactory, if the answer is 'yes' to criteria 2 and 4-7; poor, if the answer is not 'yes' to one or more of the criteria listed for 'satisfactory'

(Source: Pfizer submission, Appendix 7, p215)

9.4 Appendix D: Eligibility criteria for Study 200

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Signed and dated informed consent prior to any protocol-specific screening procedures • Cytogenetic- or PCR- based diagnosis of any phase of Ph^+ CML or Ph^+ ALL whose disease was resistant to full-dose imatinib (≥600 mg) or was intolerant of any dose of imatinib (please see Appendix 10.14 for definitions of resistance/intolerance) • Adequate duration of prior imatinib therapy • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for CP patients and 0, 1 or 2 for advanced phase leukaemia patients • No antiproliferative or antileukaemia treatment within 7 days of the first dose of bosutinib (except hydroxycarbamide and anagrelide) • At least three months post allogeneic stem cell transplantation • Recovery to grade 0/1, or to baseline, from any toxicities of prior anticancer treatment (excluding alopecia) • Able to take daily oral capsules or tablets reliably • Adequate bone marrow function (for imatinib-resistant patients in chronic phase only) o Absolute neutrophil count (ANC) >1000/mm3 (>1 x109/L) o Platelets ≥100,000/mm3 (≥100 x 109/L) and absence of any platelet transfusions during the preceding 14 days • Adequate hepatic function o AST/ALT ≤2.5 x ULN or ≤5 x ULN if attributable to liver involvement of leukaemia o Total bilirubin ≤1.5 x ULN • Adequate renal function o Creatine ≤1.5 x ULN • Willingness to use reliable birth control (if applicable) throughout the study and 30 days after the last dose • Documented normal INR if not on oral anticoagulant therapy, or if on oral anticoagulant therapy, consistent target INR ≤3 **<u>Additional inclusion criteria specific to Study 200 populations</u>** <u>Third-line CP CML population</u> • Imatinib-resistant or imatinib-intolerant CP	• Ph negative leukaemia or Bcr-Abl negative leukaemia • Overt leptomeningeal leukaemia (free of CNS involvement for <2 months) • Extramedullary disease only • GVHD (treated or untreated) within 60 days of study start • Documented history of the T315I Bcr-Abl mutation (this criterion added as of 10th June 2008 based on lack of efficacy in this group) • Pregnant or breastfeeding • Major surgery within 14 days or radiotherapy within 7 days before the first dose of bosutinib (recovery from any previous surgery should have been completed before day 1) • History of clinically significant or uncontrolled cardiac disease including: o history of or active congestive heart failure o uncontrolled angina or hypertension within 3 months o myocardial infarction within 12 months o clinically significant ventricular arrhythmia o diagnosed or suspected congenital or acquired prolonged QT syndrome o unexplained syncope o history of prolonged corrected QT interval (QTc) • Prolonged QTc (>0.45 seconds, average of triplicate readings at screening) • Concomitant use of or need for medications known to prolong the QT interval • Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval • Recent (within 30 days of study entry) or ongoing clinically significant gastrointestinal disorder • Evidence of serious active infection, or significant medical or psychiatric illness • Known seropositivity to human immunodeficiency virus or current acute or chronic hepatitis B or hepatitis C (antigen positive), cirrhosis or clinically significant abnormal laboratory findings that would, in the investigator's judgement, make the patient inappropriate for this study

Ph+ CML also previously treated with dasatinib and/or nilotinib, to which the patient developed resistance or intolerance <u>Advanced phase CML population</u> • Advanced phase Ph+ CML previously treated with 1 or more TKIs (imatinib only or imatinib and dasatinib and/or nilotinib)	
<u>Second-line CP CML patient population</u>	
• Imatinib-resistant or imatinib-intolerant CP Ph^+ CML • QTc interval <470 msec at screening	

(Source: Pfizer submission, Table B6, p53 and Appendix 15, p 349)

9.5 Appendix E: Outcome definitions used in Study 200

Outcome	Description/details
Cytogenetic Response	At least 20 metaphases were required for post-baseline assessment. If fewer than 20 metaphases were available, fluorescence in situ hybridisation (FISH) analysis of bone marrow aspirate for the presence of Bcr-Abl fusion protein could be used, provided ≥200 cells were analysed. Cytogenetics were performed within 14 days of registration and every 3 months thereafter. After 2 years, assessments were performed every 6 months. For CP patients, disease status was assessed at baseline and every 12 weeks during the first 2 years of treatment, every 24 weeks thereafter, and at the time of treatment completion. For advanced phase patients, cytogenetic assessments were performed monthly until week 12, or until the patient's status returned to chronic phase (whichever came first) and at week 24
Major cytogenetic response (MCyR)	0%—35% Ph^+ metaphases (0%—35% positive cells by FISH) MCyR = CCyR + PCyR
Complete cytogenetic response (CCyR)	0% Ph^+ metaphases (<1% positive cells by FISH)
Partial cytogenetic response (PCyR)	1%—35% Ph^+ metaphases (1%—35% positive cells by FISH)
Minor Cytogenetic Response (MiCyR)	36%—65% Ph^+ metaphases (36%—65% positive cells by FISH)
Minimal Cytogenetic Response	66%—95% (66%—95% positive cells by FISH)
No Cytogenetic Response	>95% positive cell (>95% positive cells by FISH)
Haematological Response	Haematological responses were based upon peripheral blood assessments (complete blood count, including 5-part differential, platelet count, absolute neutrophil count), bone marrow assessments (differential, clonal evolution) and clinical assessments of extramedullary disease. Peripheral blood assessments were performed at screening, weeks 1, 2, 3, 4, 8, 12, every 12 weeks during the first 2 years of treatment, every 24 weeks beginning with the third year of treatment and at the final visit
Complete haematological response (CHR)	For a patient to be deemed to possess a CHR, they must have fulfilled all of the following haematological criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in blood • White blood cell count (WBC) ≤ institutional ULN • Platelets <450 x 10^9/L • <20% basophils in blood • No extramedullary involvement (including hepato- or

Outcome	Description/details
	splenomegaly) • Platelets ≥100 x 10^9/L (only applicable to advanced phase) • Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (only applicable to advanced phase) • ≤5% bone marrow blasts (only applicable to advanced phase)
Overall haematological response (OHR)	A patient was defined as having an OHR if they met the criteria for any one of: CHR, no evidence of leukaemia (NEL) or return to chronic phase (RCP). <u>CHR</u> See above for criteria <u>NEL</u> A patient was defined as having NEL if they met all of the following criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in the blood • WBC ≤ institutional ULN • 450 x 10^9/L> platelets ≥20 x 10^9/L • ANC ≥0.5 x 10^9/L • <20% basophils in blood • No extramedullary involvement • ≤5% bone marrow blasts (only applicable to advanced phase) <u>RCP</u> To be defined as having achieved RCP, a patient had to meet all of the below criteria, with the exception of patients with CP CML who were not required to have post-baseline bone marrow samples taken. Disappearance of features defining accelerated and blast phases, but still in chronic phase as noted by: • <15% blasts in both peripheral blood and bone marrow • <30% blasts and promyelocytes in both peripheral blood and bone marrow • <20% basophils in both peripheral blood and bone marrow • No extramedullary involvement other than liver/spleen
Major haematological response (MHR)	A patient was defined as having a MHR if they met the criteria for either a CHR or NEL (see above)
Molecular Response	Assessed with non-nested RT-PCR for the BcrAbl transcript performed at a central laboratory (Quest Diagnostics) monthly for the first 3 months, every 3 months through 2 years and every 6 months thereafter
Major molecular response (MMR)	≥ 3 log reduction from standardised baseline (baseline based upon the PCR data of 120 previously untreated CML patients) in ratio of Bcr-Abl to Abl transcripts
Complete molecular response (CMR)	Undetectable Bcr-Abl transcript, with a PCR sensitivity of ≥5 log
Progression-free survival (PFS)	Within Study 200, PFS was calculated as the time from start of bosutinib therapy to disease progression (as assessed by an investigator), treatment discontinuation due to death or death within 30 days of the last dose. For patients who were

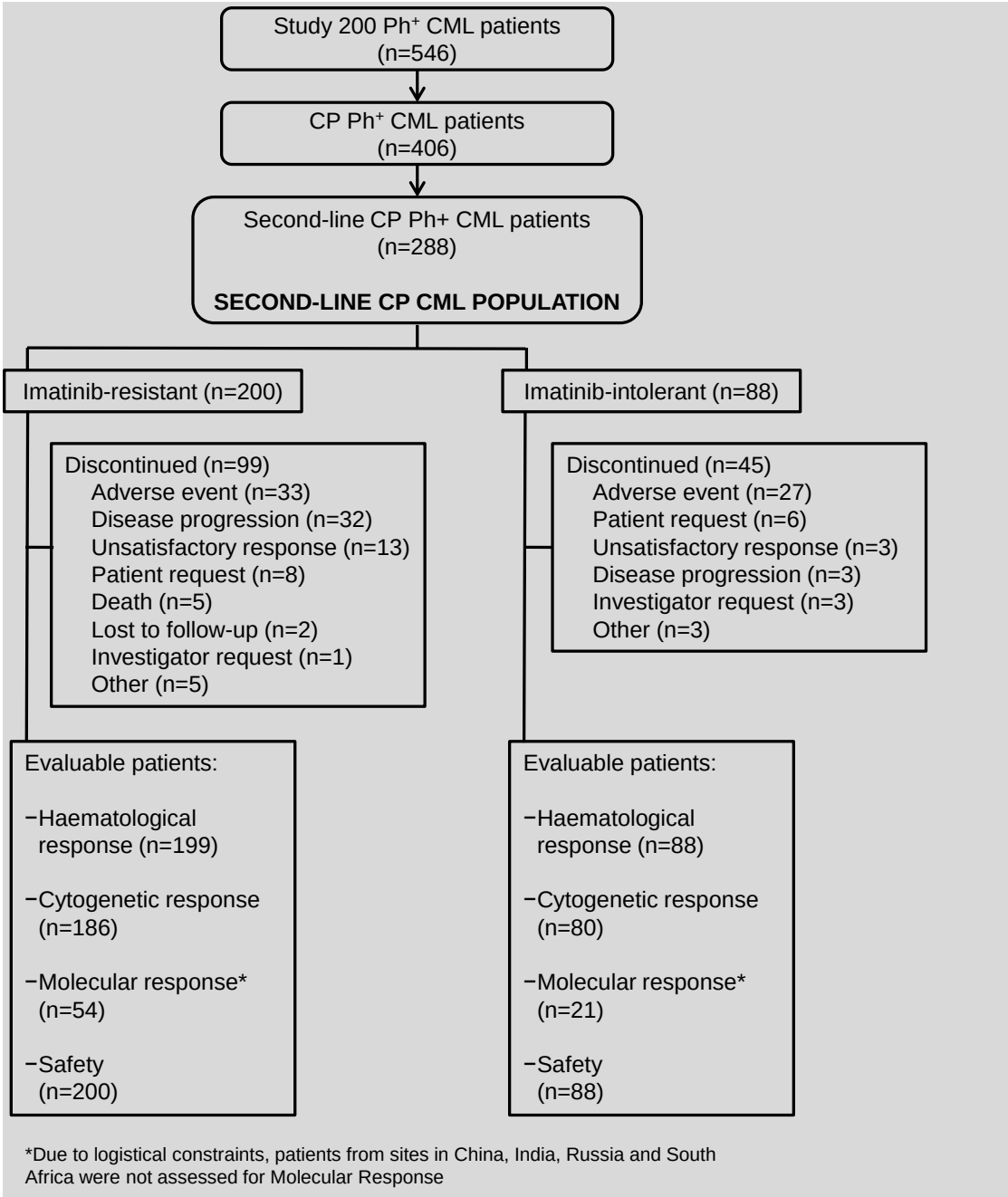
Outcome	Description/details
	last known to be alive and without progression, censoring was performed using the last date at which the patient was known to be progression free. Progression was defined by possession of any of the following criteria: • Entry in CP and clear progression to AP within the first 4 weeks of therapy (early progressor). To be considered a progressor to AP, a patient must have had an absolute increase of at least 10% in the count(s) qualifying the patient for accelerated phase • Evolution from initial CP, or from CP to which the patient returned, to AP or BP (evolution had to be measured on at least 2 consecutive assessments, at least 1 week apart) • Doubling of white blood cell count over at least 1 month with a second count >20 x 10^9/L confirmed at least 1 week later • Loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss • Loss of MCyR with an increase of ≥30% in Ph^+ metaphases
Overall survival (OS)	Overall survival was taken as the interval from the date of the first dose of bosutinib to the date of death, due to any cause. Patients who were not recorded as dead at the end of the study were censored at the last date at which they were known to be alive. The Study 200 protocol only required patients who discontinued treatment to be followed up for 24 months. It should therefore be noted that overall survival is truncated at 24 months for these patients and that this may bias the analysis with regards to this outcome
AP/BP Transformation Rate	Patients were considered to have undergone transformation if they experienced an evolution of disease from CP at study entry to AP or BP, or from AP at study entry to BP. This measure of transformation had to be present on 2 consecutive post-baseline assessments at least 1 week apart. In cases where the last haematological assessment did not confirm AP or BP status, then treatment discontinuation due to disease progression and death, or death within 30 days of last dose was considered a confirmation of transformation
FACT-Leu	The FACT-Leu is a 44-item, self-reported, reliable and valid assessment of health-related quality-of-life in patients with leukaemia. The FACT-Leu measures leukaemia specific health related quality of life and consists of 4 domains (27 items): • Physical well being (PWB) • Social well being (SWB) • Emotional well being (EWB) • Functional well being (FWB) The FACT-leu also measures a leukaemia subscale (LEUS) of additional concerns (17 items)

Outcome	Description/details
EQ-5D	EQ-5D is a patient-reported outcome which was obtained at screening, weeks 4, 8 and 12, every 12 weeks thereafter and at the end of treatment visit in countries where appropriate translations were available. EQ-5D assessments were also administered at the time of disease progression, grade 3 or 4 toxicitiy or at the time of early withdrawal. EQ-5D is a 5-item validated assessment of patient utility, consisting of: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Where each item takes an integral value from 1 (“no problems”) to 3 (“extreme problems”). The scores on these 5 items are summarised to create a single summary score. Since the questions may be answered differently in different countries/regions, for example due to different societal perspectives or customs, different weightings or tarrifs may be applied to the summary score. Study 200 EQ-5D data presented in this submission uses the UK summary score, such that the evidence is most relevant to the patient population covered in this submission i.e.patients in England and Wales. In addition, the EQ-5D has a general health visual anaolog scale (VAS): scores range from 0 to 100, where 0 is equivalent to the worst imaginable health state and 100 is equivalent to the best imaginable health state.
Adverse events (AEs)	Incidence and severity of AEs were reported at each study visit through 30 days after the last dose of bosutinib. Graded by use of the National Cancer Institute Common Terminology for Adverse Events Version 3.0[127]
Grade 3/4 adverse event	Unique clinical descriptions dictate the grading of each AE, but generally grade 3/4 AEs are considered severe (grade 3) or life-threatening or disabling (grade 4)

(Source: Pfizer submission, Appendix 14, p344)

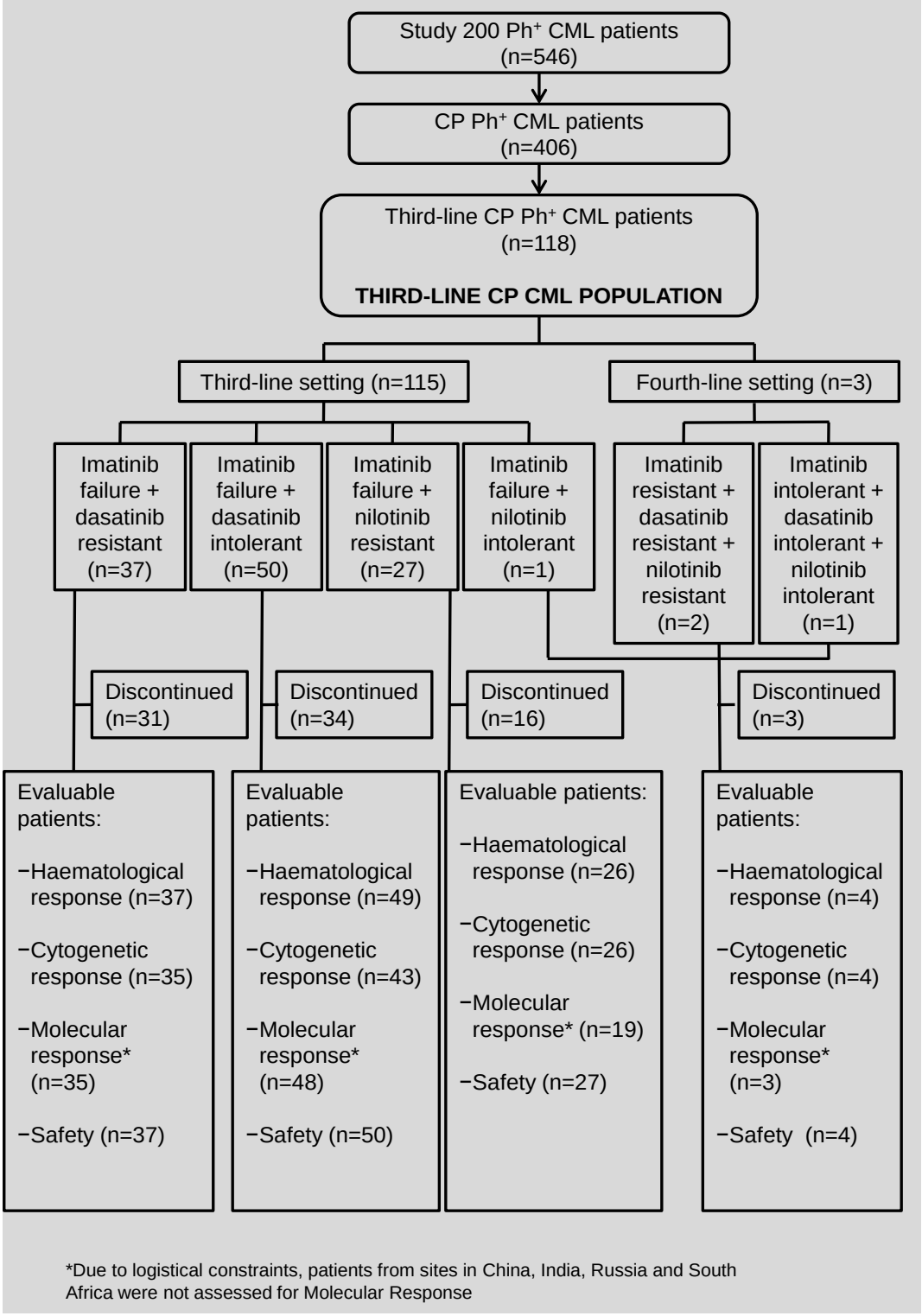
9.6 Appendix F: Participant flow diagrams

9.6.1 Participant flow for the second-line CP-CML population



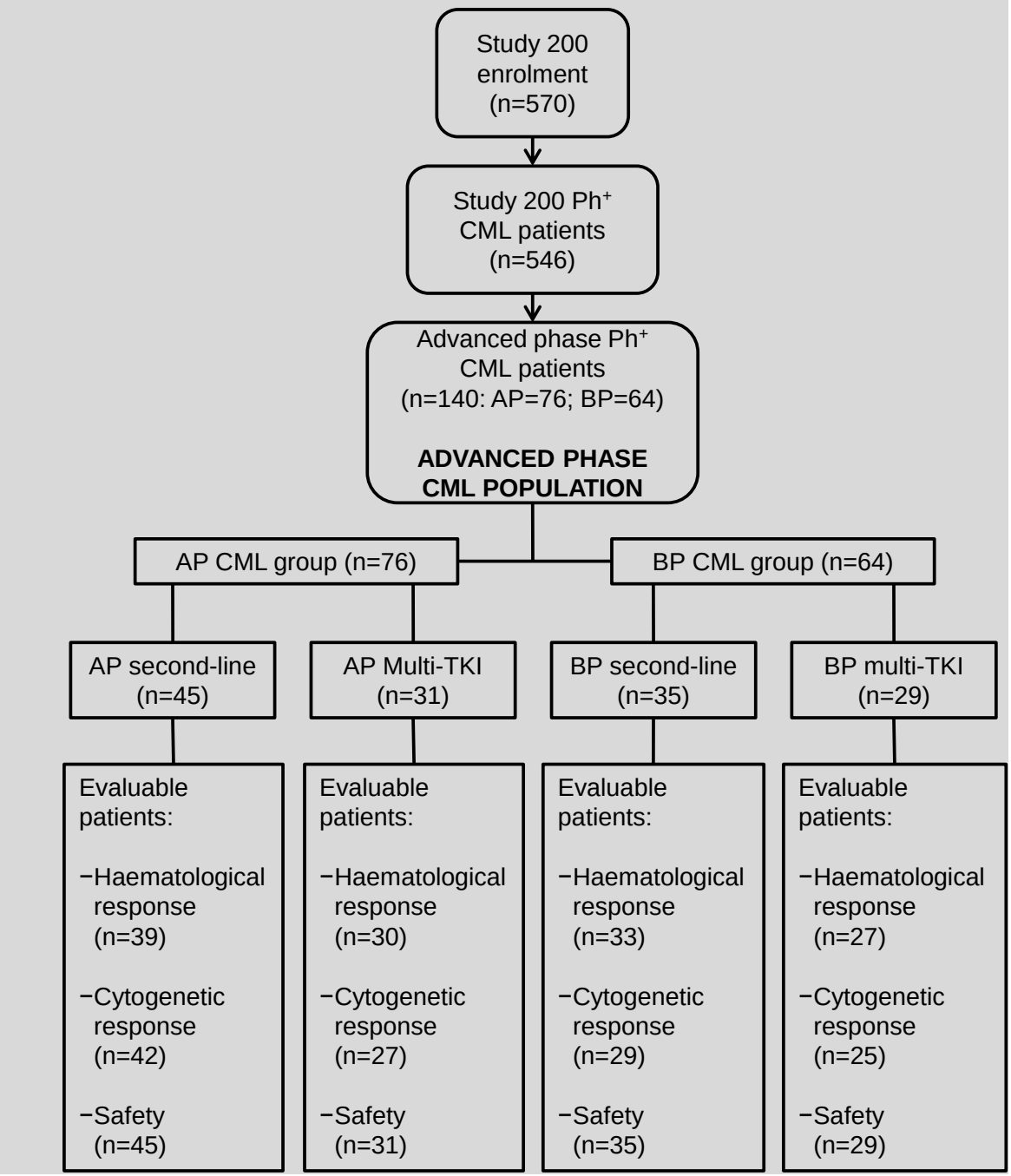
(Source: Pfizer submission, Figure B57, p352)

9.6.2 Participant flow for the third-line CP-CML population



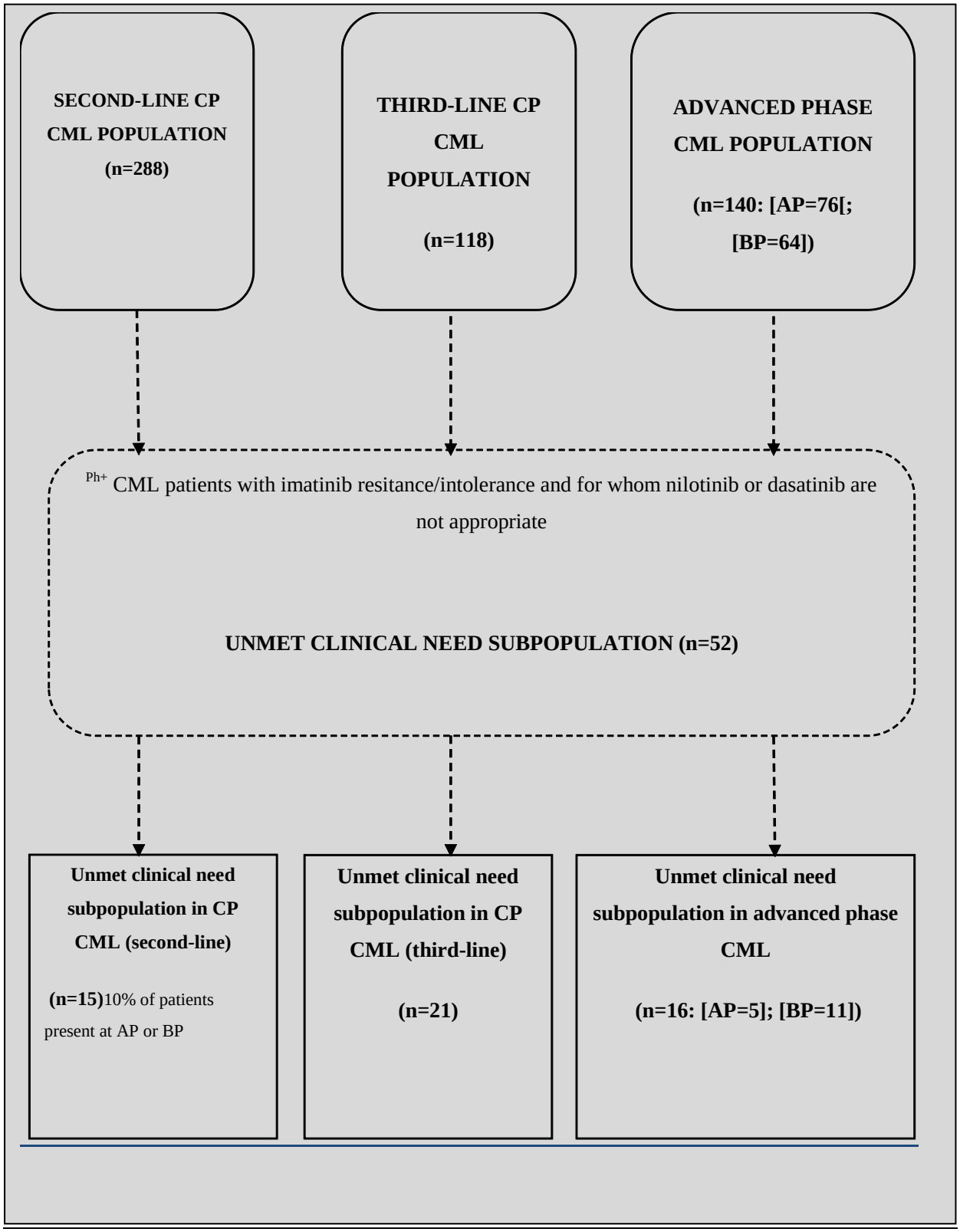
(Source: Pfizer submission, Figure B3, p60)

9.6.3 Participant flow for the advanced phases CML population



(Source: Pfizer submission, Figure B4, p61)

9.6.4 Participant flow for the unmet clinical need subpopulation



(Source: Pfizer submission, Figure B59, p362)

9.7 Appendix G: Unmet clinical need population eligibility; summary of mutations and medical conditions defining inappropriateness of nilotinib and dasatinib

	Nilotinib	**Dasatinib**
Mutation	Y253 E255 F359	F317 E255
Medical history or evidence of prior TKI intolerance	Coronary artery occlusion, coronary arterial stent insertion, arterial occlusive disease, coronary artery disease, arteriosclerosis, glucose tolerance impairment, coronary angioplasty, coronary artery bypass, hyperglycaemia, hypertriglyceridaemia, diabetes, pancreatitis	Pleural effusion, blood pressure increase, interstitial lung disease, chronic obstructive pulmonary disease, bronchitis chronic, pulmonary hypertension, pulmonary fibrosis, pulmonary oedema, emphysema, hypertension (Grade 3 or 4), cardiomyopathy, cardiac failure, ventricular failure, ventricular dysfunction, myocardial infarction., myocardial ischaemia, respiratory disorder

(Source: Pfizer submission, Table B109, p360)

9.8 Appendix H: Proportion of patients with T315I mutation at baseline

	N of patients assessed for mutations at baseline	**N of patients assessed with a T315I mutation at baseline**
CP2L	212/288 (74.6%)	9/212 (4.2%)
CP3L	83/118 (70.3%)	7/83 (8.4%)
Advanced phase	117/140 (83.6%)	15/117 (12.8%)

(Source: Pfizer response to clarification question A2)

9.9 Appendix I: Sample size calculations for Study 200

9.9.1 Sample size calculations for the second-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients resistant to imatinib and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a MCyR rate at 24 Weeks of 0.33 is of interest. Taking the interesting and uninteresting rates for MCyR rate at 24 Weeks to be p1=0.33 and p0=0.23, respectively, it was desired to test the null hypothesis of H0: p≤0.23 against the 1-sided alternative H1: p>0.23 Power calculation The hypothesis test was performed with a type I error rate of 0.05 and 80% power at p=0.33 Sample size calculation The design of the primary cohort incorporated a 4-stage group sequential design , requiring a maximum sample size of 167 evaluable patients, with a sample size of 82 expected under the null hypothesis, and a sample size of 115 expected when the true MCyR rate was p=0.33. Statistical analyses The test statistic, standardized using the empirical variance estimate, was assessed for efficacy at an overall 1-sided significance level of 0.05, and assessed for futility at an overall 1-sided significance level of 0.20. The decisions concerning stopping for efficacy or futility were based on the error spending functions at the actual number of enrolled patients at the interim analyses.
CP CML patients intolerant to imatinb and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a 73% MCyR rate at 24 Weeks was of interest. Taking the interesting and uninteresting MCyR rates at 24 Weeks to be p1=0.73 and p0=0.56, respectively, the null hypothesis H0: p ≤p0 was tested against the alternative H1: p≥p1. Sample size calculation The optimum Simon 2-stage design for alpha=0.05, beta=0.20, required a maximum of n=55 patients with 16 in the first stage. If the response rate was no greater than 9/16=0.56 at stage 1, consideration was given to early termination. The expected sample size under the null was 31.5 and probability of early termination under the null was 0.60.

(Source: Pfizer submission, Table B102, p351)

9.9.2 Sample size calculations for the third-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients previously treated with imatinib and who were resistant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.30 and p0=0.10 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=29 patients with 10 in the first stage. If the response rate was no greater than 1/10 at stage 1, consideration was given to early termination. The expected sample size under the null was 15.0 and probability of early termination under the null was 0.74.
CP CML patients previously treated with imatinib and who were intolerant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.37 and p0=0.17 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=35 patients with 12 in the first stage. If the response rate was no greater than 2/12=0.17 at stage 1, consideration was given to early termination. The expected sample size under the null was 19.7 and probability of early termination under the null was 0.67.
CP CML patients previously treated with imatinib who were resistant to nilotinib	Sample size calculation This cohort was sized using the same statistical considerations as in the dasatinib-resistant cohort, yielding a sample size of n=29 and an identical Simon 2-stage design. . Patients previously treated with imatinib who were either nilotinib intolerant or treated with both nilotinib and dasatinib were described. No testing was planned for this group.

(Source: Pfizer submission, Table B10, p58)

9.9.3 Sample size calculations for the advanced phase CML population

TKI exposure history	Statistical analysis details
Imatinib-resistant/intolerant CML patients in AP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.61 and p0=0.43 based on published nilotinib and dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=49 patients with 42 in the first stage. If the response rate was no greater than 22/42 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 42.6 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant patients in BP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.48 and p0=0.30 based on published dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=45 patients with 41 in the first stage. If the response rate was no greater than 16/41 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 41.3 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant CML patients, exposed to other TKIs	Both AP and BP patient populations fitting this description were analysed descriptively.

(Source: Pfizer submission, Table B11, p59)

9.10 Appendix J: Number of planned and enrolled patients

Subject Group Study Cohort	Planned	Expected Evaluable	Enrolled
Chronic Phase Second-line (Prior Imatinib)			
Imatinib Resistant	186	167	200
Imatinib Intolerant	61	55	88
Chronic Phase Third line (Prior Imatinib + ≥1 Additional TKI)			
IM + NI-Intolerant or IM + D and NI	Descriptively analysed – no testing planned		4
IM + D-Resistant	32	29	37
IM + D-Intolerant	39	35	50
IM + NI-Resistant	32	29	27
Advanced Leukaemia (≥1 Prior TKI)[a]			
AP CML – 2nd Line	55	49	45
BP CML – 2nd Line	50	45	35
AP/BP – Multi-TKI	Descriptively analysed – no testing planned		60

Abbreviations: AP=accelerated phase, BP=blast phase, CML=chronic myelogenous leukaemia, D=dasatinib, IM=imatinib, NA=not applicable, NI=nilotinib, Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukaemia, TKI=tyrosine kinase inhibitor

All subjects in the advanced leukaemia group received imatinib; some subjects also received at least 1 additional TKI. Date of Snapshot: 28MAR11

(Source: Pfizer response to clarification questions A4)

9.11 Appendix K: Baseline characteristics for Study 200

9.11.1 Second-line CP CML

Characteristic	Imatinib-resistant (n=200)	Imatinib-intolerant (n=88)	Total
Age, y			
Median	51.0	54.5	53.0
Range	18-86	23-91	18-91
Sex, n (%)			
Female	84 (42%)	50 (57%)	134 (47%)
Male	116 (58%)	38 (43%)	154 (53%)
Haematological analysis, 10^9/L			
White blood cell count			
Median	6.7	5.9	6.5
Range	2.1-151	2.1-160.7	2.1-151
Platelet count			
Median	261.5	202.5	237.5
Range	47-2436	48-2251	47-2436
Duration of disease, y			
Median	4.0	2.8	3.6
Range	0.1-15.1	0.1-13.6	0.1-15.1
Treatment history			
No. of previous therapies*, n (%)			
1	131 (66%)	65 (74%)	196 (68%)
2	69 (35%)	23 (26%)	92 (32%)
Previous IFN	69 (35%)	23 (26%)	92 (32%)
Previous SCT	6 (3%)	2 (2%)	8 (3%)
Features of imatinib treatment			
Duration of previous imatinib treatment, y			
Median	2.6	1.5	2.2
Range	0.4-8.8	<0.1-8.3	<0.1-8.8
Previous CHR with imatinib, n (%)	164 (82%)	55 (63%)	219 (76%)
Reason for stopping imatinib, n (%)			
Adverse event (intolerance)†	1 (1%)	86 (98%)	87 (33%)
Disease progression	163 (92%)	1 (1%)	164 (62%)
Regimen completed	7 (4%)	0 (0%)	8 (3%)
Other	7 (4%)	1 (1%)	7 (3%)
Missing‡	22	0	22
1 or more Bcr-Abl mutations detected§	57/83 (69%)	8/32 (25%)	65/115 (57%)

*Includes previous tyrosine kinase inhibitor therapies. Percentages may not total 100% because of rounding
†Patients simultaneously meeting the protocol definitions for imatinib resistance and imatinib intolerance are categorized as having imatinib resistance
‡The reason for stopping imatinib was not reported
§Total of 83 imatinib-resistant and 32 imatinib-intolerant patients assessed for mutation status at baseline
(Source: Pfizer submission, Table B101, p350)

9.11.2 Third-line CP CML

Characteristic	IM + DAS resistant (n=37)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NI (n=4)*	Total (n=118)
Median age, y (range)	54.0 (23-69)	58.0 (25-79)	52.0 (20-73)	54.5 (31-62)	56.0 (20-79)
Sex, n (%)					
Female	23 (62)	27 (54)	13 (48)	2 (50)	65 (55)
Male	14 (38)	23 (46)	14 (52)	2 (50)	53 (45)
Race, n (%)					
White	27 (73)	38 (76)	17 (63)	3 (75)	85 (72)
Asian	4 (11)	9 (18)	3 (11)	0	16 (14)
Other	6 (16)	3 (6)	7 (26)	1 (25)	17 (14)
Median duration of CML disease, y (range)	7.5 (1.2-17.6)	5.6 (0.6-18.3)	5.9 (1.2-16.3)	11.7 (2.2-11.9)	6.7 (0.6-18.3)
ECOG Performance Status, n (%)†					
0	28 (76)	31 (62)	25 (93)	2 (50)	86 (74)
1	9 (24)	18 (36)	2 (7)	2 (50)	31 (26)
Median duration of prior therapy, (range)					
Imatinib, years	2.6 (0.02-6.4)	3.3 (0.1-6.6)	2.5 (0.7-5.9)	3.0 (1.4-6.4)	2.7 (0.02-6.6)
Dasatinib, months	18.3 (1.7-47.9)	17.3 (1.1-35.7)	0	4.1 (1.3-6.9)	17.7 (1.1-47.9)
Nilotinib, months	0	0	12.7 (1.7-38.9)	5.4 (0.8-6.1)	9.2 (0.8-38.9)
Additional prior therapies, n (%)					
Interferon	25 (68)	24 (48)	10 (37)	2 (50)	61 (52)
SCT	2 (5)	5 (10)	0	2 (50)	9 (8)

IM = Imatinib; DAS = Dasatinib; NI = Nilotinib; ECOG = Eastern Cooperative Oncology Group
*Includes 3 patients who previously received all 3 inhibitors (2 DAS + NI resistant; 1 DAS + NI intolerant) and 1 patient with NI intolerance
†ECOG Performance Status at baseline was missing for 1 patient with DAS intolerance
(Source: Pfizer submission, Table B7, p54)

9.11.3 Advanced phase CML

Characteristic	**AP IM only (n=45)**	**AP Multi TKI (n=31)**	**AP Total (n=76)**	**BP IM only (n=35)**	**BP Multi TKI (n=29)**	**BP Total (n=64)**
Age, y						
Median	47.00	56.00	50. 50	37.00	53.00	48.50
Range	18.00-73.00	21.00-83.00	18.00-83.00	19.00-75.00	22.00-82.00	19.00-82.00
Sex, n (%)						
Female	21 (47)	13 (42)	34 (45)	11 (31)	12 (41)	23 (36)
Male	24 (53)	18 (58)	42 (55)	24 (69)	17 (59)	41 (64)
Race, n (%)						
Asian	15 (33)	5 (16)	20 (26)	12 (34)	2 (7)	14 (22)
Black	3 (7)	2 (6)	5 (7)	5 (14)	6 (21)	11 (17)

Characteristic	AP IM only (n=45)	AP Multi TKI (n=31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Other*	3 (7)	2 (6)	5 (7)	0	1 (3)	1 (2)
White	24 (53)	22 (71)	46 (61)	18 (51)	20 (69)	38 (59)
Duration of CML						
N	41	29	70	34	29	63
Median	3.85	8.25	5.06	1.75	5.75	3.08
Range	1.11-22.06	1.5 - 19.22	1.11-22.06	0.35 - 5.56	1.05 - 14.46	0.35-14.46
ECOG Performance Status, n (%)						
0	26 (58)	15 (48)	41 (54)	16 (46)	6 (21)	22 (34)
1	18 (40)	15 (48)	33 (43)	10 (29)	18 (62)	28 (44)
2	1 (2)	1 (3)	2 (3)	9 (26)	5 (17)	14 (22)
Number of prior therapies						
1	29 (64)	0	29 (38)	30 (86)	0	30 (47)
2	16 (36)	6 (19)	22 (29)	5 (14)	11 (38)	16 (25)
3	0	19 (61)	19 (25)	0	16 (55)	16 (25)
4	0	6 (19)	6 (8)	0	2 (7)	2 (3)
Prior interferon therapy						
No	29 (64)	9 (29)	38 (50)	30 (86)	15 (52)	45 (70)
Yes	16 (36)	22 (71)	38 (50)	5 (14)	14 (48)	19 (30)
Prior imatinib†						
Yes	45 (100)	31 (100)	76 (100)	35 (100)	29 (100)	64 (100)
Prior dasatinib†						
No	45 (100)	6 (19)	51 (67)	35 (100)	6 (21)	41 (64)
Yes	0	25 (81)	25 (33)	0	23 (79)	23 (36)
Prior nilotinib†						
No	45 (100)	16 (52)	61 (80)	35 (100)	17 (59)	52 (81)
Yes	0	15 (48)	15 (20)	0	12 (41)	12 (19)
Prior stem cell transplant						
No	41 (91)	28 (90)	69 (91)	34 (97)	26 (90)	60 (94)
Yes	4 (9)	3 (10)	7 (9)	1 (3)	3 (10)	4 (6)
Reasons for stopping imatinib						
Adverse event (intolerance)	3 (7)	6 (19)	9 (12)	5 (14)	7 (24)	12 (19)
Disease progression/ Inadequate response	41 (91)	24 (77)	65 (86)	30 (86)	22 (76)	52 (81)
Other‡	0	1 (3)	1 (1)	0	0	0
Regimen completed	1 (2)	0	1 (1)	0	0	0

IM only= only prior TKI exposure is to imatinib; Multi TKI = Multiple TKI exposure
*Race Other: Afghan (1), Hispanic (7), Turkish (1)
†If a patient received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the patient is only counted once for the respective treatment
‡Other reason for discontinuing imatinib: Unknown
(Source: Adapted from Pfizer submission, Table B8, p55 and Pfizer response to clarification questions A3)

9.12 Appendix L: Response by baseline mutation status, Study 200

9.12.1 Response by baseline mutation status in the second-line CP evaluable population (15 May 2012 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)	
		CHR	MCyR
No mutation	132	119/132 (90)	70/120 (58)
≥1 mutation	78	65/77 (84)	44/77 (57)
≥2 mutations	11	8/11 (73)	3/10 (30)
Most common individual mutations[b]			
T315I[c,d]	9	2/9 (22)	2/9 (22)
M351T	9	9/9 (100)	8/9 (89)
F359V[d]	9	8/9 (89)	4/9 (44)
G250E	6	5/6 (83)	3/5 (60)
M244V	6	6/6 (100)	3/6 (50)
L248V	5	5/5 (100)	3/5 (60)
F317L[c]	4	4/4 (100)	3/4 (75)
E255K[d]	3	0/2	2/3 (67)
Y253H[d]	2	2/2 (100)	2/2 (100)
E255V[d]	2	2/2 (100)	1/2 (50)
F311I	2	2/2 (100)	1/2 (50)
F311L	2	2/2 (100)	2/2 (100)
E355G	2	2/2 (100)	1/2 (50)
H396P	2	2/2 (100)	2/2 (100)
H396R	2	1/2 (50)	0/2

[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint
[b] Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
(Source: Pfizer submission, Table B105, p356)

9.12.2 Response by baseline mutation status in the third-line CP CML population

	17 May 2011 snapshot			15 February 2012 snapshot		
Bcr-Abl mutation status	**n**	**Cumulative response, n/n evaluable[a] (%)**		**n**	**Cumulative response, n/n evaluable[a] (%)**	
		CHR	**MCyR**		**CHR**	**MCyR**
No mutation	44	34/44 (77)	15/43 (35)	46	35/45 (78)	18/45 (40)
≥1 mutation	39	26/39 (67)	11/35 (31)	40	26/39 (67)	14/37 (38)
≥2 mutations	9	3/9 (33)	2/9 (22)	9	3/9 (33)	2/9 (22)
Most common individual mutations[b]						
F317L[c]	8	4/8 (50)	1/7 (14)	8	4/8 (50)	1/7 (14)
T315I[c,d]	7	2/7 (29)	0/6	7	2/7 (29)	1/7 (14)[e]
G250E	6	3/6 (50)	0/5	6	3/6 (50)	0/5
Y253H[d]	6	5/6 (83)	4/6 (67)	6	5/6 (83)	5/6 (83)
M244V	3	3/3 (100)	2/3 (67)	3	3/3 (100)	2/3 (67)
F359V[d]	2	0/2	1/2 (50)	3	1/3 (33)	2/3 (67)
V299L[c]	2	1/2 (50)	0/2	2	1/2 (50)	0/2
F359C[d]	2	2/2 (100)	1/2 (50)	2	1/1 (100)	1/2 (50)
F359I	2	2/2 (100)	2/2 (100)	2	2/2 (100)	2/2 (100)

[a]Evaluable patient had received ≥1 bosutinib dose and had a valid baseline disease assessment for the corresponding endpoint
[b]Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
[e]The patient with the T315I mutation at baseline who responded with a MCyR had a PCyR at baseline that was maintained at Week 12 allowing the patient to be counted as a responder. The patient discontinued treatment due to an AE around Week 24 and did not have any further cytogenetic assessments

(Source: Pfizer submission, Table B19, p71)

9.12.3 Response by baseline mutation status in the advanced phase CML population (17 May 2011 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)		
		CHR	OHR	MCyR
No mutation	52	19/49 (38.8)	23/49 (46.9)	16/43 (37.2)
≥1 mutation	65	10/59 (16.9)	21/59 (35.6)	13/55 (23.6)
Most common individual mutations[b]				
T315I[c,d]	15	0/13	1/13 (7.69)	1/13 (7.69)
F317L[c]	9	0/9	2/9 (22.2)	0/6
G250E	7	4/6 (66.7)	4/6 (66.7)	2/7 (28.6)
Y253H[d]	7	1/7 (14.3)	2/7 (28.6)	2/7 (28.6)
E255V[d]	5	0/4	0/4	1/3 (33.3)
M351T	5	2/5 (40.0)	3/5 (60.0)	1/4 (25.0)
E255K[d]	4	0/4	1/4 (25.0)	1/3 (33.3)
M244V	3	1/2 (50.0)	2/2 (100)	1/2 (50.0)
F359I	2	0/2	1/2 (50.0)	1/2 (50.0)
F359V[d]	2	0/2	1/2 (50.0)	0/2
F486S	2	1/2 (50.0)	1/2 (50.0)	2/2 (100)

[a]The evaluable population includes patients who had a valid baseline disease assessment
[b]Includes all mutations reported for ≥2 patients assessed at baseline
(Source: Pfizer submission, Table B26, p77)

9.13 Appendix M: Cytogenetic response rates, Study 200

9.13.1 Cytogenetic response rates for the second-line CP CML population

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]
Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.
(Source: Pfizer response to clarification questions A7)

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
(Source: Pfizer response to clarification questions A7)

9.13.2 Cytogenetic response rates for the third-line CP CML population

	12 months minimum follow-up 28 Mar 2011 Snapshot			24 months minimum follow up-15 February 2012 Snapshot		
Cohort	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**
Post-hoc analysis: patients who attained a response or maintained a response present at BL[c]						
IM + D resistant	35	12 (34.3) (19.1, 52.2)	6 (17.1) (6.6, 33.7)	36	12 (33.3) (18.6, 51.0)	7 (19.4) (8.2, 36.0)
IM + D intolerant	43	19 (44.2) (29.1, 60.1)	18 (41.9) (27.0, 57.9)	44	21 (47.7) (32.5, 63.3)	19 (43.2) (28.4, 59.0)
IM + NI resistant	26	9 (34.6) (17.2, 55.7)	7 (26.9) (11.6, 47.8)	26	10 (38.5) (20.2, 59.4)	7 (26.9) (11.6, 47.8)
IM + (NI + D) or IM + NI intolerant*	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)
Total	**108**	**42 (38.9) (29.7, 48.8)**	**33 (30.6) (22.1, 40.2)**	**110[d]**	**45 (40.9) (31.6, 50.7)**	**35 (31.8) (23.3, 41.4)**

Abbreviations: CI=confidence interval; CCyR= complete cytogenetic response; D=dasatinib; IM=imatinib; MCyR=major cytogenetic response; n=number of patients; NI=nilotinib; BL = baseline
*Includes 3 patients who previously received all 3 inhibitors and 1 patient with NI intolerance
[a]Evaluable patients had a baseline disease assessment
[c]Note: Percentages are based on number of patients in each analysis. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with MCYR at baseline who were allowed to maintain best response post-baseline.
[d]Includes Patients 200-060-001446 and 200-075-001612. Patient 200-075-001612 had a valid baseline cytogenetic assessment in 15FEB2012 but not 28MAR2011

(Source: Pfizer submission, adapted Table B13, p54)

9.13.3 Cytogenetic response rates for the advanced phase population

Cytogenetic response rates for the advanced phase CML population (28 Mar 2011 snapshot)

Cytogenetic response, n (%)	Accelerated phase			Blast phase		
	Second-line (n=42)	Multi-TKI (n=27)	Total (n=69)	Second-line (n=29)	Multi-TKI (n=25)	Total (n=54)
MCyR	20 (47.6)	4 (14.8)	24 (34.8)	13 (44.8)	3 (12.0)	16 (29.6)
CCyR	14 (33.3)	3 (11.1)	17 (24.6)	9 (31.0)	2 (8.0)	11 (20.4)
PCyR	6 (14.3)	1 (3.7)	7 (10.1)	4 (13.8)	1 (4.0)	5 (9.3)

(Source: Pfizer submission, Table B23, p75)

9.14 Appendix N: Haematological response rates, Study 200

9.14.1 CHR rates for the second-line CP CML population

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]
Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.
(Source: Pfizer response to clarification questions A7)

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
(Source: Pfizer response to clarification questions A7)

9.14.2 CHR rates for the third-line CP CML population

Cohort	28 Mar 2011 Snapshot n	28 Mar 2011 Snapshot CHR N (%) (95% CI)	15 February 2012 Snapshot n	15 February 2012 Snapshot CHR N (%) (95% CI)
CHR including subjects with CHR at baseline[a,b]				
IM + (NI + D) or IM + NI Intolerant	4	3 (75.0) (19.4, 99.4)	4	3 (75.0) (19.4, 99.4)
IM + D Resistant	37	23 (62.2) (44.8, 77.5)	37	23 (62.2) (44.8, 77.5)
IM + D Intolerant	49	39 (79.6) (65.7, 89.8)	49	39 (79.6) (65.7, 89.8)
IM + NI Resistant	26	20 (76.9) (56.4, 91.0)	25	19 (76.0) (54.9, 90.6)
Total	**116**	**85 (73.3) (64.3, 81.1)**	**115[c]**	**84 (73.0) (64.0, 80.9)**

Abbreviations: CHR=major hematologic response; CI=confidence interval; D=dasatinib; IM=imatinib; n=number of patients; NI=nilotinib.
[a]Analysis includes patients who have a valid baseline hematologic measurement.
[b]Subjects with CHR at baseline are eligible for response post-baseline. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with CHR at baseline who were allowed to maintain best response post-baseline.
[c]Analysis includes Patient 200-060-001446 but excludes Patients 200-093-002244 and 200-093-002246 due to missing baseline hematologic assessment in 15 February 2012

(Source: Pfizer submission, Table B14, p65)

9.14.3 CHR rates for the advanced phase CML population (28 Mar 2011 snapshot)

Haematological response, n (%) [95% CI]	Accelerated phase			Blast phase		
	Second-line (n=39)	Multi-TKI (n=30)	Total (n=69)	Second-line (n=33)	Multi-TKI (n=27)	Total (n=60)
OHR	25 (64.1) [47.2-78.8]	13 (43.3) [25.5-62.6]	38 (55.1) [42.6-67.1]	12 (36.4) [20.4-54.9]	5 (18.5) [6.3-38.1]	17 (28.3) [17.5-41.4]
MHR	21 (53.9) [37.2-69.9]	11 (36.7) [19.9-56.1]	32 (46.4) [34.3-58.8]	8 (24.2) [11.1-42.3]	3 (11.1) [2.4-29.2]	11 (18.3) [9.5-30.4]
CHR	16 (41.0) [25.6-57.9]	8 (26.7) [12.3-45.9]	24 (34.8) [23.7-47.2]	8 (24.2) [11.1-42.3]	1 (3.7) [0.1-19.0]	9 (15.0) [7.1-26.6]

(Source: Pfizer submission, Table B22, p75)

9.15 Appendix O: Overall survival, Study 200

9.15.1 OS second-line CP CML population

Kaplan-Meier Estimate of Overall Survival Chronic Phase Second-line All-treated Population, 28 March 2011 snapshot

OS, K-M estimates, % (95%CI)	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Year 1	96.8 (94.0,98.3)	95.9 (92.0,97.9)	98.8 (92.0,99.8)
Year 2	90.6 (86.5,93.5)	87.6 (82.1,91.5)	97.6 (90.9,99.4)

(Source: Pfizer response to clarification questions A7)

9.15.2 OS third-line CP CML population

K-M estimate of OS in third-line CP all-treated population

	28 March 2011 Snapshot			15 February 2012 Snapshot		
Cohort	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**
IM + (NI + D) or IM + NI Intolerant	4	N/A	N/A	4	N/A	N/A
IM + D Resistant	37	82.8 (65.6, 91.9)	75.2 (56.1, 86.9)	38	83.6 (67.0, 92.3)	77.4 (59.7, 88.0)
IM + D Intolerant	50	93.9 (82.3, 98.0)	85.4 (71,7, 92.8)	50	93.9 (82.3, 98.0)	85.4 (71.7, 92.8)
IM + NI Resistant	27	96.3 (76.5, 99.5)	91.7 (70.5, 97.9)	27	96.3 (76.5, 99.5)	92.4 (73.0, 98.1)
Total	**118**	**91.2 (84.3, 95.2)**	**82.9 (74.1, 88.9)**	**119**	**91.4 (84.6, 95.3)**	**84.0 (75.8, 89.6)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; N/A=not applicable; n=number of patients; NI=nilotinib.
a. The sample size is too small to suggest accurate estimates.
Note: One year is assumed to have 12 months.

(Source: Pfizer submission, Table B18, p70)

9.16 Appendix P: Efficacy and safety studies

Protocol number	Study design	Treatment groups	No of subjects	Demographics	Duration of treatment
Phase I/II Study 200 (NCT00261846; 3160A4-200).	Phase 1/2 open-label 2-part study in subjects with Ph+ leukemia. Part 1: dose escalation. Part 2: efficacy study at the selected Phase 2 dose. To determine safety, tolerability, MTD, PK, PD, and efficacy in subjects with chronic phase and advanced phase Ph+ leukaemias. To explore pharmacogenomic effects.	Parts 1 and 2: bosutinib 100-mg capsules or 100-mg tablets Part 1: Dose levels studied were 400, 500, and 600 mg Part 2: selected dose=500 mg.	Randomised: 571 Treated: 570 - 18 in Part 1 - 553 in Part 2		QD until disease progression, unacceptable toxicity, or withdrawal of consent.
		CP CML Second line	288	Sex: 135F/153M Mean Age (min/max): 52 (18/91) years Race, % W/B/A/O: 64/5/19/12	
		CP CML Third line	118	Sex: 65F/53M Mean Age (min/max): 54 (20/79) years Race, % W/B/A/O: 72/3/11/14	
		Advanced phase Ph+ leukaemias (AP and BP CML; Ph+ ALL)	164	Sex: 69F/95M Mean Age (min/max): 50 (18/84) years Race, % W/B/A/O: 63/11/13/13	
Phase III Study 3000 (NCT00574873; 3160A4-3000)	Phase 3 randomised open-label trial. 1/ to compare the efficacy (rate of CCyR at 1 year) of bosutinib vs imatinib in subjects with chronic phase (CP) CML. 2/ to compare MMR at 1 year, duration of CCyR, CHR, and MMR, time to transformation to	Bosutinib 500 mg QD (100-mg tablets).	Randomised: 250 Treated: 248	Sex: 101F/149M Mean Age (min/max): 47 (19/91) years Race, % W/B/A/O: 64.5/1.0/24.15/ 10.4	QD until completion of 8 years or early discontinuation due to treatment failure, unacceptable toxicity, death, or withdrawal of consent
		matinib 400 mg QD (100-mg and/or 400-mg tablets).	Randomised: 252 Treated: 251	Sex: 117F/135M Mean Age (min/max): 46 (18/89) years Race, % W/B/A/O: 65/1/23/11	

	AP and BP; to assess the population PK; to assess the comparative safety of bosutinib vs imatinib.		Total: Randomised: 502 Treated: 499	Sex: 218F/284M Mean Age (min/max): 47 (18/91) years Race, % W/B/A/O: 65/1/24/10	
Phase I/II in Japanese subjects (NCT00811070; 3160A4-2203)	Phase 1/2 open-label, continuous daily dose administration, 2-part study in subjects with Ph+ leukaemia. To determine safety, tolerability, MTD, PK, PD, and efficacy of bosutinib in Japanese subjects with Ph+ leukaemias.	Part 1: bosutinib capsules (100 mg). Part 2: bosutinib tablet (100 mg). Part 1: Starting dose of 400 mg (up to max. 600 mg). Part 2: MTD=500 mg. Continuous oral dose administration from Day 1 onwards.	Part 1 Treated: 17 Part 2 Treated: 35	Sex: 20F /32M Mean Age (min/max): 54 (78/20) years Race, %: A: 100	QD until disease progression, unacceptable toxicity, or withdrawal of consent.

Note: Table information taken from Bosulif EMA assessment report,[29] study status is as of 15 Nov 2010. A=Asian; AP=Accelerated phase; B = Black; BA =Bioavailability; BE = Bioequivalence; BID = Twice daily; BMI=Body mass index; BP = Blast phase; CCyR=Complete cytogenetic response; CHR=Complete haematologic response; CML=Chronic myelogenous leukaemia; CP=chronic phase; CYP3A=Cytochrome P450 isoenzyme 3A; DB = Double-blind; ER=estrogen receptor; erbB2=epidermal growth factor receptor 2; F = Female; FR=fast release; HRQoL=health-related quality of life; M = Male; MBC=metastatic breast cancer; MMR=Major molecular response; MTD = Maximum tolerated dose; No = Number; O=other; ORR= objective response rate; OS= overall survival; PC = Placebo-controlled; PD = Pharmacodynamic; PG = Parallel-group; PgR=progesterone receptor; Ph+ = Philadelphia chromosome positive; PK = Pharmacokinetic; PFS=progression-free survival; QD=once a day; SR=low-release; TR=target release; vs = versus; "+" = Positive (for receptors);"-" = Negative (for receptors); W = White.

9.17 Appendix Q: Treatment discontinuation and adverse effects, Study 200

9.17.1 Second-line CP CML population

Treatment discontinuation in the second-line CP CML population, 28 March 2011 snapshot

Reason for discontinued treatment[a]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Discontinued treatment, n (%)	159 (55.2)	108 (54.0)	51 (58.0)
AE	64 (22.2)	33 (16.5)	31 (35.2)
Disease progression	41 (14.2)	35 (17.5)	6 (6.8)
Lack of efficacy	21 (7.3)	17 (8.5)	4 (4.5)
Patient request	18 (6.3)	11 (5.5)	7 (8.0)
Death	5 (1.7)	5 (2.5)	0
Investigator Request	1 (0.3)	1 (0.5)	0
Lost to follow-up	2 (0.7)	2 (1.0)	0
Other[b]	7 (2.4)	4 (2.0)	3 (3.4)

(a) Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
(b) Other: For imatinib resistant: no CCyR at Week 48 (1 subject), non-compliance (1 subject), T315I mutation (1 subject), no CCyR, investigator/subject request, loss of CCyR, and increasing transcript levels (1 subject); For imatinib intolerant: transplant (2 subjects), non-compliance (1 subject).

(Source: Pfizer response to clarification questions A7)

Treatment discontinuation in the second-line CP CML population, 15 May 2012 snapshot

Reason for discontinued treatment	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Discontinued treatment, n (%)	166 (58)	109 (56)	57 (63)
AE	66 (23)	30 (15)	36 (40)
Disease progression	41 (14)	35 (18)	6 (7)
Lack of efficacy	24 (8)	19 (10)	5 (6)
Patient request	17 (6)	11 (6)	6 (7)
Death	6 (2)	6 (3)	0
Investigator Request	2 (1)	2 (1)	0
Lost to follow-up	2 (1)	2 (1)	0
Other	8 (3)	4 (2)	4 (4)

(Source: Pfizer response to clarification questions A7)

Rates of most common (≥20%) adverse events in the second-line CP CML population

AE[a], n (%)	IM-R (n=195)		IM-I (n=91)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhoea	165 (85)	18 (9)	79 (87)	10 (11)
Nausea	83 (43)	1 (1)	47 (52)	3 (3)
Rash	63 (32)	16 (8)	40 (44)	11 (12)
Vomiting	70 (36)	3 (2)	35 (39)	8 (9)
Pyrexia	57 (29)	1 (1)	16 (18)	1 (1)
Fatigue	47 (24)	1 (1)	23 (25)	2 (2)
Abdominal pain	46 (24)	2 (1)	24 (26)	2 (2)
Cough	44 (23)	0	17 (19)	0
Elevated ALT	41(21)	14 (7)	22 (24)	8 (9)
Upper abdominal pain	40 (21)	1 (1)	17 (19)	0
Elevated AST	36 (19)	7 (4)	19 (21)	5 (6)
Headache	34 (17)	0	18 (20)	0

IM-R = imatinib-resistant; IM-I = imatinib-intolerant; ALT = alanine aminotransferase; AST = aspartate aminotransferase

(Source: Pfizer submission, Table B108, p 359)

9.17.2 Third-line CP CML population

Rates of TEAEs (all grades) occurring in ≥10% and of TEAEs (grade 3/4) occurring in ≥5% of the third-line CP CML population

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
Any adverse event	118 (100)	74 (62.7)
Blood and lymphatic system disorders	58 (49.2)	35 (29.7)
Thrombocytopaenia	41 (34.7)	30 (25.4)
Neutropaenia	21 (17.8)	17 (14.4)
Anaemia	18 (15.3)	6 (5.1)
Cardiac disorders	13 (11.0)	5 (4.2)
Eye disorders	14 (11.9)	-
Gastrointestinal disorders	111 (94.1)	16 (13.6)
Diarrhoea	98 (83.1)	10 (8.5)
Nausea	56 (47.5)	-
Vomiting	46 (39.0)	-
Abdominal pain	23 (19.5)	-
Abdominal pain upper	20 (16.9)	-
Constipation	15 (12.7)	-
General disorders and administration site conditions	59 (50.0)	-
Fatigue	28 (23.7)	-
Pyrexia	18 (15.3)	-
Oedema peripheral	12 (10.2)	-
Hepatobiliary disorders	-	5 (4.2)
Infections and infestations	46 (39.0)	4 (3.4)
Injury, poisoning and procedural complications	15 (12.7)	-
Investigations	45 (38.1)	11 (9.3)
Alanine aminotransferase increased	18 (15.3)	8 (6.8)
Lipase increased	-	4 (3.4)
Aspartate aminotransferase increased	-	3 (2.5)
Metabolism and nutrition disorders	38 (32.2)	4 (3.4)
Decreased appetite	14 (11.9)	-
Musculoskeletal and connective tissue	50 (42.4)	7 (5.9)

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
disorders		
Arthralgia	17 (14.4)	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	-	4 (3.4)
Nervous system disorders	43 (36.4)	5 (4.2)
Headache	30 (25.4)	-
Dizziness	15 (12.7)	-
Psychiatric disorders	13 (11.0)	-
Respiratory, thoracic and mediastinal disorders	47 (39.8)	5 (4.2)
Cough	20 (16.9)	-
Pleural effusion	12 (10.2)	-
Skin and subcutaneous tissue disorders	59 (50.0)	8 (6.8)
Rash	34 (28.8)	5 (4.2)
Pruritus	17 (14.4)	-
Vascular disorders	12 (10.2)	-

[a]Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA)
[1]For 'All grades' adverse events, the incidence threshold of ≥10% was applied to the entire third-line CP CML population (n=118)
[1]For 'All grades' adverse events, only adverse events occurring in ≥10% of the entire third-line CP cohort (n=118)
[2] For grade 3/4 adverse events, adverse events occurring in ≥5% of any of the constituent subpopulations

(Source: Pfizer submission, Table B27, p 81)

Number (%) of Subjects Reporting ≥10% TEAEs (CP3L Safety Population) (15 Feb 2012 snapshot)

System Organ Class a Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	4 (100)	38 (100)	50 (100)	27 (100)	119 (100)
Blood and lymphatic system disorders	2 (50.0)	20 (52.6)	23 (46.0)	14 (51.9)	59 (49.6)
Thrombocytopenia	2 (50.0)	9 (23.7)	18 (36.0)	12 (44.4)	41 (34.5)
Neutropenia	1 (25.0)	8 (21.1)	7 (14.0)	7 (25.9)	23 (19.3)
Anaemia	1 (25.0)	7 (18.4)	7 (14.0)	6 (22.2)	21 (17.6)
Leukopenia	0	4 (10.5)	0	0	4 (3.4)
Cardiac disorders	0	4 (10.5)	10 (20.0)	2 (7.4)	16 (13.4)
Ear and labyrinth disorders	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Eye disorders	2 (50.0)	5 (13.2)	8 (16.0)	3 (11.1)	18 (15.1)
Eye oedema	1 (25.0)	0	0	0	1 (0.8)
Scleral haemorrhage	1 (25.0)	0	0	0	1 (0.8)
Gastrointestinal disorders	4 (100)	37 (97.4)	47 (94.0)	24 (88.9)	112 (94.1)
Diarrhoea	4 (100)	30 (78.9)	41 (82.0)	23 (85.2)	98 (82.4)
Nausea	2 (50.0)	21 (55.3)	22 (44.0)	13 (48.1)	58 (48.7)
Vomiting	0	15 (39.5)	24 (48.0)	8 (29.6)	47 (39.5)
Abdominal pain	0	6 (15.8)	12 (24.0)	6 (22.2)	24 (20.2)
Abdominal pain upper	0	8 (21.1)	8 (16.0)	4 (14.8)	20 (16.8)
Constipation	2 (50.0)	4 (10.5)	6 (12.0)	3 (11.1)	15 (12.6)
Dyspepsia	0	7 (18.4)	4 (8.0)	1 (3.7)	12 (10.1)
Flatulence	0	4 (10.5)	2 (4.0)	2 (7.4)	8 (6.7)
Toothache	1 (25.0)	2 (5.3)	2 (4.0)	0	5 (4.2)
Haemorrhoids	0	1 (2.6)	0	3 (11.1)	4 (3.4)
Gingival pain	1 (25.0)	2 (5.3)	0	0	3 (2.5)
Gastrointestinal sounds abnormal	1 (25.0)	0	1 (2.0)	0	2 (1.7)
General disorders and administration site conditions	3 (75.0)	19 (50.0)	28 (56.0)	10 (37.0)	60 (50.4)
Fatigue	3 (75.0)	8 (21.1)	14 (28.0)	3 (11.1)	28 (23.5)
Pyrexia	1 (25.0)	6 (15.8)	7 (14.0)	4 (14.8)	18 (15.1)
Oedema peripheral	1 (25.0)	1 (2.6)	5 (10.0)	4 (14.8)	11 (9.2)
Asthenia	1 (25.0)	1 (2.6)	2 (4.0)	4 (14.8)	8 (6.7)
Pain	2 (50.0)	1 (2.6)	2 (4.0)	1 (3.7)	6 (5.0)
Chest pain	1 (25.0)	0	3 (6.0)	0	4 (3.4)
Temperature intolerance	1 (25.0)	0	0	0	1 (0.8)
Hepatobiliary disorders	1 (25.0)	0	3 (6.0)	2 (7.4)	6 (5.0)
Hyperbilirubinaemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Immune system disorders	0	5 (13.2)	2 (4.0)	3 (11.1)	10 (8.4)
Infections and infestations	3 (75.0)	15 (39.5)	20 (40.0)	11 (40.7)	49 (41.2)
Nasopharyngitis	1 (25.0)	2 (5.3)	5 (10.0)	4 (14.8)	12 (10.1)

Influenza	0	4 (10.5)	3 (6.0)	3 (11.1)	10 (8.4)
Upper respiratory tract infection	2 (50.0)	2 (5.3)	5 (10.0)	0	9 (7.6)
Lower respiratory tract infection	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Respiratory tract infection viral	0	0	0	3 (11.1)	3 (2.5)
Pharyngitis	1 (25.0)	1 (2.6)	0	0	2 (1.7)
Wound infection	1 (25.0)	0	0	0	1 (0.8)
Injury, poisoning and procedural complications	1 (25.0)	6 (15.8)	8 (16.0)	0	15 (12.6)
Procedural pain	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Investigations	2 (50.0)	15 (39.5)	18 (36.0)	12 (44.4)	47 (39.5)
Alanine aminotransferase increased	1 (25.0)	7 (18.4)	5 (10.0)	6 (22.2)	19 (16.0)
Blood creatinine increased	0	4 (10.5)	4 (8.0)	3 (11.1)	11 (9.2)
Aspartate aminotransferase increased	0	2 (5.3)	3 (6.0)	5 (18.5)	10 (8.4)
Blood alkaline phosphatase increased	0	2 (5.3)	0	3 (11.1)	5 (4.2)
White blood cells urine positive	1 (25.0)	0	0	0	1 (0.8)
Metabolism and nutrition disorders	2 (50.0)	9 (23.7)	18 (36.0)	9 (33.3)	38 (31.9)
Decreased appetite	0	3 (7.9)	6 (12.0)	4 (14.8)	13 (10.9)
Hyperuricaemia	1 (25.0)	1 (2.6)	4 (8.0)	0	6 (5.0)
Hyperkalaemia	0	0	1 (2.0)	3 (11.1)	4 (3.4)
Hypophosphataemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal and connective tissue disorders	3 (75.0)	17 (44.7)	21 (42.0)	9 (33.3)	50 (42.0)
Arthralgia	0	5 (13.2)	9 (18.0)	4 (14.8)	18 (15.1)
Back pain	1 (25.0)	5 (13.2)	4 (8.0)	3 (11.1)	13 (10.9)
Bone pain	0	5 (13.2)	3 (6.0)	1 (3.7)	9 (7.6)
Pain in extremity	0	1 (2.6)	5 (10.0)	3 (11.1)	9 (7.6)
Musculoskeletal pain	0	4 (10.5)	1 (2.0)	1 (3.7)	6 (5.0)
Joint swelling	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal stiffness	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Nervous system disorders	1 (25.0)	12 (31.6)	21 (42.0)	14 (51.9)	48 (40.3)
Headache	1 (25.0)	9 (23.7)	13 (26.0)	8 (29.6)	31 (26.1)
Dizziness	1 (25.0)	5 (13.2)	8 (16.0)	3 (11.1)	17 (14.3)
Dysgeusia	1 (25.0)	0	1 (2.0)	1 (3.7)	3 (2.5)
Paraesthesia	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Neuropathy peripheral	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Sensory disturbance	1 (25.0)	0	0	0	1 (0.8)
Psychiatric disorders	1 (25.0)	2 (5.3)	9 (18.0)	1 (3.7)	13 (10.9)
Insomnia	1 (25.0)	2 (5.3)	4 (8.0)	1 (3.7)	8 (6.7)
Renal and urinary disorders	0	5 (13.2)	4 (8.0)	5 (18.5)	14 (11.8)
Reproductive system and breast disorders	0	2 (5.3)	2 (4.0)	4 (14.8)	8 (6.7)
Respiratory, thoracic and mediastinal disorders	2 (50.0)	13 (34.2)	26 (52.0)	8 (29.6)	49 (41.2)
Cough	1 (25.0)	5 (13.2)	11 (22.0)	4 (14.8)	21 (17.6)
Pleural effusion	0	2 (5.3)	11 (22.0)	1 (3.7)	14 (11.8)
Dyspnoea	0	1 (2.6)	10 (20.0)	1 (3.7)	12 (10.1)
Oropharyngeal pain	1 (25.0)	3 (7.9)	3 (6.0)	2 (7.4)	9 (7.6)
Dyspnoea exertional	1 (25.0)	1 (2.6)	3 (6.0)	0	5 (4.2)

Productive cough	0	0	5 (10.0)	0	5 (4.2)
Skin and subcutaneous tissue disorders	1 (25.0)	22 (57.9)	28 (56.0)	12 (44.4)	63 (52.9)
Rash	1 (25.0)	9 (23.7)	19 (38.0)	3 (11.1)	32 (26.9)
Pruritus	0	10 (26.3)	7 (14.0)	2 (7.4)	19 (16.0)
Dry skin	0	1 (2.6)	2 (4.0)	3 (11.1)	6 (5.0)
Alopecia	1 (25.0)	1 (2.6)	2 (4.0)	0	4 (3.4)
Skin depigmentation	1 (25.0)	0	0	0	1 (0.8)
Vascular disorders	1 (25.0)	1 (2.6)	9 (18.0)	2 (7.4)	13 (10.9)
Hypertension	0	1 (2.6)	6 (12.0)	0	7 (5.9)
Flushing	1 (25.0)	0	0	0	1 (0.8)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

(Source: Pfizer response to clarification questions A5)

Number (%) of Subjects Reporting ≥5% TEAEs Grades 3 or 4 AEs Only (CP3L Safety Population) (Data snapshot 15 Feb 2012)

System Organ Class [a] Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	1 (25.0)	22 (57.9)	38 (76.0)	15 (55.6)	76 (63.9)
Blood and lymphatic system disorders	1 (25.0)	11 (28.9)	16 (32.0)	8 (29.6)	36 (30.3)
Thrombocytopenia	0	7 (18.4)	15 (30.0)	8 (29.6)	30 (25.2)
Neutropenia	1 (25.0)	5 (13.2)	7 (14.0)	4 (14.8)	17 (14.3)
Anaemia	0	2 (5.3)	4 (8.0)	1 (3.7)	7 (5.9)
Cardiac disorders	0	1 (2.6)	7 (14.0)	0	8 (6.7)
Gastrointestinal disorders	0	7 (18.4)	7 (14.0)	2 (7.4)	16 (13.4)
Diarrhoea	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Hepatobiliary disorders	0	0	3 (6.0)	2 (7.4)	5 (4.2)
Infections and infestations	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Investigations	0	2 (5.3)	5 (10.0)	4 (14.8)	11 (9.2)
Alanine aminotransferase increased	0	1 (2.6)	3 (6.0)	4 (14.8)	8 (6.7)
Lipase increased	0	1 (2.6)	1 (2.0)	2 (7.4)	4 (3.4)
Aspartate aminotransferase increased	0	0	1 (2.0)	2 (7.4)	3 (2.5)
Metabolism and nutrition disorders	0	2 (5.3)	1 (2.0)	1 (3.7)	4 (3.4)
Musculoskeletal and connective tissue disorders	0	1 (2.6)	4 (8.0)	2 (7.4)	7 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (6.0)	1 (3.7)	4 (3.4)

Nervous system disorders	0	1 (2.6)	4 (8.0)	0	5 (4.2)
Headache	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6)	5 (10.0)	0	6 (5.0)
Pleural effusion	0	0	3 (6.0)	0	3 (2.5)
Skin and subcutaneous tissue disorders	0	2 (5.3)	6 (12.0)	0	8 (6.7)
Rash	0	0	3 (6.0)	0	3 (2.5)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the
incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject
may report two or more different adverse events within the higher level category.

(Source: Pfizer response to clarification questions A5)

9.17.3 Advanced phase CML population

Summary of adverse events for the advanced phase CML population

Event	AP IM only (n=45)	AP Multi TKI (n-31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Any TEAE	45 (100)	31 (100)	76 (100)	34 (97.1)	29 (100)	63 (98.4)
TEAEs related to study drug	45 (100)	30 (96.8)	75 (98.7)	34 (97.1)	26 (89.7)	60 (93.8)
Grade 3 or 4 TEAEs	36 (80)	30 (96.8)	66 (86.8)	26 (74.3)	23 (79.3)	49 (76.6)
Grade 3 or 4 TEAEs related to study drug	25 (55.6)	22 (71)	47 (61.8)	19 (54.3)	15 (51.7)	34 (53.1)
SAEs	23 (51.1)	18 (58.1)	41 (53.9)	18 (51.4)	17 (58.6)	35 (54.7)
TEAEs leading to discontinuation	10 (22.2)	8 (25.8)	18 (23.7)	1 (2.9)	5 (17.2)	6 (9.4)
TEAEs leading to dose reduction	17 (37.8)	14 (45.2)	31 (40.8)	11 (31.4)	6 (20.7)	17 (26.6)
TEAEs leading to dose delay	23 (51.1)	21 (67.7)	44 (57.9)	17 (48.6)	11 (37.9)	28 (43.8)

(Source: Pfizer response to clarification questions A6)

Rates of most common (≥10%) treatment-emergent adverse events in the advanced phase CML population

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	76 (100)	45(100)	31(100)	63 (98.4)	34 (97.1)	29 (100)
Blood and lymphatic system disorders	56 (73.7)	32 (71.1)	24 (77.4)	35 (54.7)	19 (54.3)	16 (55.2)
Anaemia	32 (42.1)	15 (33.3)	17 (54.8)	18 (28.1)	10 (28.6)	8 (27.6)
Thrombocytopaenia	32 (42.1)	16 (35.6)	16 (51.6)	18 (28.1)	9 (25.7)	9 (31.0)
Neutropaenia	12 (15.8)	4 (8.9)	8 (25.8)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	3 (4.7)	3 (8.6) 0	0
Leukopenia	6 (7.9)	3 (6.7)	3 (9.7)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	6 (7.9)	4 (8.9)	2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Cardiac disorders	14 (18.4)	7 (15.6)	7 (22.6)	8 (12.5)	5 (14.3)	3 (10.3)
Eye disorders	15 (19.7)	7 (15.6)	8 (25.8)	8 (12.5)	6 (17.1)	2 (6.9)
Gastrointestinal disorders	72 (94.7)	42 (93.3)	30 (96.8)	53 (82.8)	28 (80.0)	25 (86.2)
Diarrhoea	65 (85.5)	38 (84.4)	27 (87.1)	42 (65.6)	23 (65.7)	19 (65.5)
Nausea	34 (44.7)	17 (37.8)	17 (54.8)	32 (50.0)	18 (51.4)	14 (48.3)
Vomiting	34 (44.7)	23 (51.1)	11 (35.5)	25 (39.1)	11 (31.4)	14 (48.3)
Abdominal pain	20 (26.3)	16 (35.6)	4 (12.9)	11 (17.2)	9 (25.7)	2 (6.9)
Abdominal pain upper	10 (13.2)	7 (15.6)	3 (9.7)	5 (7.8)	2 (5.7)	3 (10.3)
Constipation	13 (17.1)	8 (17.8)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
General disorders and administration site conditions	47 (61.8)	24 (53.3)	23 (74.2)	41 (64.1)	23 (65.7)	18 (62.1)
Pyrexia	28 (36.8)	16 (35.6)	12 (38.7)	22 (34.4)	16 (45.7)	6 (20.7)
Fatigue	15 (19.7)	3 (6.7)	12 (38.7)	12 (18.8)	5 (14.3)	7 (24.1)
Asthenia	10 (13.2)	6 (13.3)	4 (12.9)	4 (6.3)	4 (11.4)	0
General physical health deterioration	1 (1.3)	0	1 (3.2)	3 (4.7)	0	3 (10.3)
Oedema peripheral	3 (6.7)	4 (12.9)	7 (9.2)	0	4 (13.8)	4 (6.3)
Hepatobiliary disorders	5 (6.6)	3 (6.7)	2 (6.5)	4 (6.3)	4 (11.4)	0
Hyperbilirubinaemia	-	-	-	-	-	-
Infections and infestations	42 (55.3)	23 (51.1)	19 (61.3)	34 (53.1)	19 (54.3)	15 (51.7)
Pneumonia	8 (10.5)	4 (8.9)	4 (12.9)	10 (15.6)	4 (11.4)	6 (20.7)
Sepsis	-	-	-	-	-	-
Upper respiratory tract infection	8 (10.5)	6 (13.3)	2 (6.5)	2 (3.1)	1 (2.9)	1 (3.4)
Investigations	38 (50.0)	20 (44.4)	18 (58.1)	31 (48.4)	18 (51.4)	13 (44.8)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	10 (13.2)	5 (11.1)	5 (16.1)	4 (6.3)	4 (11.4)	0
Neutrophil count decreased	-	-	-	-	-	-
Aspartate aminotransferase increased	11 (14.5)	7 (15.6)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Lipase increased	-	-	-	-	-	-
Metabolism and nutrition disorders	27 (35.5)	17 (37.8)	10 (32.3)	22 (34.4)	11 (31.4)	11 (37.9)
Decreased appetite	6 (7.9)	4 (8.9)	2 (6.5)	12 (18.8)	5 (14.3)	7 (24.1)
Hypokalaemia	2 (2.6)	0	0 2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Hypophosphataemia	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	26 (34.2)	18 (40.0)	8 (25.8)	24 (37.5)	13 (37.1)	11 (37.9)
Arthralgia	10 (13.2)	8 (17.8)	2 (6.5)	7 (10.9)	6 (17.1)	1 (3.4)
Pain in extremity	10 (13.2)	7 (15.6)	3 (9.7)	6 (9.4)	4 (11.4)	2 (6.9)
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	11 (14.5)	6 (13.3)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
Blast crisis in myelogenous leukaemia	-	-	-	-	-	-
Nervous system disorders	24 (31.6)	14 (31.1)	10 (32.3)	26 (40.6)	16 (45.7)	10 (34.5)
Headache	12 (15.8)	9 (20.0)	3 (9.7)	13 (20.3)	9 (25.7)	4 (13.8)
Dizziness	8 (10.5)	4 (8.9)	4 (12.9)	9 (14.1)	6 (17.1)	3 (10.3)
Psychiatric disorders	16 (21.1)	6 (13.3)	10 (32.3)	11 (17.2)	6 (17.1)	5 (17.2)
Renal and urinary disorders	11 (14.5)	5 (11.1)	6 (19.4)	8 (12.5)	5 (14.3)	3 (10.3)
Renal failure acute	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	35 (46.1)	19 (42.2)	16 (51.6)	23 (35.9)	14 (40.0)	9 (31.0)
Dyspnoea	14 (18.4)	8 (17.8)	6 (19.4)	12 (18.8)	7 (20.0)	5 (17.2)
Cough	13 (28.9)	8 (25.8)	21 (27.6)	6 (17.1)	3 (10.3)	9 (14.1)
Oropharyngeal pain	8 (10.5)	4 (8.9)	4 (12.9)	2 (3.1)	1 (2.9)	1 (3.4)
Pleural effusion	9 (11.8)	5 (11.1)	4 (12.9)	4 (6.3)	2 (5.7)	2 (6.9)
Skin and subcutaneous tissue disorders	42 (55.3)	25 (55.6)	17 (54.8)	30 (46.9)	17 (48.6)	13 (44.8)
Rash	25 (32.9)	16 (35.6)	9 (29.0)	20 (31.3)	10 (28.6)	10 (34.5)
Vascular disorders	11 (14.5)	4 (8.9)	7 (22.6)	7 (10.9)	7 (20.0)	0
Hypertension	7 (9.2)	3 (6.7)	4 (12.9)	2 (3.1)	2 (5.7)	0

(Source: Pfizer response to clarification questions A6)

Rates of TEAEs (grade 3/4) occurring in ≥5% of the advanced phase populations

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	66 (86.8)	36 (80.0)	30 (96.8)	49 (76.7)	26 (74.3)	23 (79.3)
Blood and lymphatic system disorders	42 (55.3)	20 (44.4)	22 (71.0)	29 (45.3)	18 (51.4)	11 (37.9)
Anaemia	23 (30.3)	11 (24.4)	12 (38.7)	12 (18.8)	7 (20.0)	5 (17.2)
Thrombocytopaenia	25 (32.9)	11 (24.4)	14 (45.2)	17 (26.6)	9 (25.7)	8 (27.6)
Neutropaenia	11 (14.5)	4 (8.9)	7 (22.6)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Leukopenia	3 (3.9)	1 (2.2)	2 (6.5)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	3 (3.9)	2 (4.4)	1 (3.2)	2 (3.1)	0	2 (6.9)
Cardiac disorders	5 (6.6)	3 (6.7)	2 (6.5)	3 (4.7)	1 (2.9)	2 (6.9)
Eye disorders	0	0	0	3 (4.7)	1 (2.9)	2 (6.9)
Gastrointestinal disorders	14 (18.4)	7 (15.6)	7 (22.6)	14 (21.9)	5 (14.3)	9 (31.0)
Diarrhoea	3 (3.9)	1 (2.2)	2 (6.5)	4 (6.3)	2 (5.7)	2 (6.9)
Nausea	-	-	-	-	-	-
Vomiting	3 (3.9)	1 (2.2)	2 (6.5)	2 (3.1)	0	2 (6.9)
Abdominal pain	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Abdominal pain upper	-	-	-	-	-	-
Constipation	-	-	-	-	-	-
General disorders and administration site conditions	7 (9.2)	1 (2.2)	6 (19.4)	10 (15.6)	4 (11.4)	6 (20.7)
Pyrexia	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Fatigue	3 (3.9)	0	3 (9.7)	2 (3.1)	0	2 (6.9)
Asthenia	-	-	-	-	-	-
General physical health deterioration	0	0	0	2 (3.1)	0	2 (6.9)
Hepatobiliary disorders	2 (2.6)	1 (2.2)	1 (3.2)	3 (4.7)	3 (8.6)	0
Hyperbilirubinaemia	0	0	0	3 (4.7)	3 (8.6)	0
Infections and infestations	12 (15.8)	5 (11.1)	7 (22.6)	14 (21.9)	4 (11.4)	10 (34.5)
Pneumonia	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	1 (2.9)	3 (10.3)
Sepsis	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9) 0	1 (2.9) 0
Upper respiratory tract infection	-	-	-	-	-	-
Investigations	14 (18.4)	8 (17.8)	6 (19.4)	11 (17.2)	5 (14.3)	6 (20.7)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	6 (7.9)	3 (6.7)	3 (9.7)	1 (1.6)	1 (2.9)	0
Neutrophil count decreased	1 (1.3)	1 (2.2)	0	0	0	0
Aspartate aminotransferase increased	4 (5.3)	3 (6.7)	1 (3.2)	0	0	0

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Lipase increased	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Metabolism and nutrition disorders	9 (11.8)	4 (8.9)	5 (16.1)	7 (10.9)	3 (8.6)	4 (13.8)
Decreased appetite	-	-	-	-	-	-
Hypokalaemia	1 (1.3)	0	1 (3.2)	3 (4.7)	1 (2.9)	2 (6.9)
Hypophosphataemia	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9)	0
Musculoskeletal and connective tissue disorders	4 (5.3)	3 (6.7)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Arthralgia	-	-	-	-	-	-
Pain in extremity	-	-	-	-	-	-
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)
Blast crisis in myelogenous leukaemia	2 (2.6)	0	0 2 (6.5)	1 (1.6)	1 (2.9)	0
Nervous system disorders	4 (5.3)	1 (2.2)	3 (9.7)	6 (9.4)	2 (5.7)	4 (13.8)
Headache	2 (2.6)	1 (2.2)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Dizziness	-	-	-	-	-	-
Psychiatric disorders	1 (1.3)	0	1 (3.2)	2 (3.1)	0	2 (6.9)
Renal and urinary disorders	1 (1.3)	0	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Renal failure acute	0	0	0	2 (3.1)	2 (5.7)	0
Respiratory, thoracic and mediastinal disorders	8 (10.5)	3 (6.7)	5 (16.1)	6 (9.4)	4 (11.4)	2 (6.9)
Dyspnoea	6 (7.9)	2 (4.4)	4 (12.9)	2 (3.1)	2 (5.7)	0
Cough	-	-	-	-	-	-
Pleural effusion	4 (5.3)	1 (2.2)	3 (9.7)	2 (3.1)	1 (2.9)	1 (3.4)
Skin and subcutaneous tissue disorders	3 (3.9)	3 (6.7)	0	5 (7.8)	2 (5.7)	3 (10.3)
Rash	3 (3.9)	3 (6.7)	0	2 (3.1)	1 (2.9)	1 (3.4)
Vascular disorders	5 (6.6)	1 (2.2)	4 (12.9)	1 (1.6)	1 (2.9)	0
Hypertension	4 (5.3)	1 (2.2)	3 (9.7)	1 (1.6)	1 (2.9)	0

(Source: Pfizer response to clarification questions A6)

9.17.4 Post-hoc analyses of patients with unmet clinical need

Incidence rates of adverse events by type for the unmet clinical need subpopulation

Event	CP (second-line) (n=15)	CP (third line) (n=21)	Total CP CML (n=36)	AP CML (n=5)	BP CML (n=11)	Total advanced phase CML (n=16)	Total subpopulation of unmet clinical need (n=52)
Any TEAE (N, %)	15 (100)	21 (100)	36 (100)	5 (100)	11 (100)	16 (100)	52 (100)
Grade 3 or 4 TEAEs (N, %)	11 (73.3)	12 (57.1)	23 (63.9)	5 (100)	8 (72.7)	13 (81.3)	36 (69.2)
TEAEs leading to discont. (N, %)	4 (26.7)	5 (23.8)	9 (25.0)	1 (20)	3 (27.3)	4 (25.0)	13 (25)
SAEs (N, %)	6 (40.0)	10 (47.6)	16 (44.4)	4 (80.0)	8 (72.7)	12 (75.0)	28 (53.8)

(Source: Pfizer submission, Table B110, p 365)

9.17.5 Study 3000, number (%) of subjects experiencing drug related treatment-emergent adverse events with an incidence of ≥5%

	Treatment		
System Organ Class Preferred Term	**Bosutinib N=248**	**Imatinib N=251**	**Total N=499**
ANY ADVERSE EVENT	227 (91.5)	218 (86.9)	445 (89.2)
Blood and lymphatic system disorders	94 (37.9)	118 (47.0)	212 (42.5)
Thrombocytopenia	65 (26.2)	67 (26.7)	132 (26.5)
Neutropenia	29 (11.7)	65 (25.9)	94 (18.8)
Anaemia	37 (14.9)	45 (17.9)	82 (16.4)
Leukopenia	21 (8.5)	50 (19.9)	71 (14.2)
Eye disorders	8 (3.2)	34 (13.5)	42 (8.4)
Eyelid oedema	2 (0.8)	18 (7.2)	20 (4.0)
Gastrointestinal disorders	181 (73.0)	106 (42.2)	287 (57.5)
Diarrhoea	163 (65.7)	45 (17.9)	208 (41.7)
Nausea	66 (26.6)	81 (32.3)	147 (29.5)
Vomiting	61 (24.6)	22 (8.8)	83 (16.6)
Abdominal pain upper	24 (9.7)	10 (4.0)	34 (6.8)
Abdominal pain	21 (8.5)	7 (2.8)	28 (5.6)
General disorders and administration site conditions	54 (21.8)	68 (27.1)	122 (24.4)
Fatigue	22 (8.9)	22 (8.8)	44 (8.8)
Oedema peripheral	4 (1.6)	21 (8.4)	25 (5.0)
Investigations	123 (49.6)	75 (29.9)	198 (39.7)
Alanine aminotransferase increased	73 (29.4)	14 (5.6)	87 (17.4)
Aspartate aminotransferase increased	59 (23.8)	12 (4.8)	71 (14.2)
Lipase increased	25 (10.1)	20 (8.0)	45 (9.0)
Blood creatine phosphokinase increased	10 (4.0)	22 (8.8)	32 (6.4)
Blood alkaline phosphatase increased	14 (5.6)	9 (3.6)	23 (4.6)
Gamma-glutamyltransferase increased	14(5.6)	1 (0.4)	15 (3.0)
Metabolism and nutrition disorders	39 (15.7)	43 (17.1)	82 (16.4)
Hypophosphataemia	12 (4.8)	25 (10.0)	37 (7.4)
Decreased appetite	19 (7.7)	3 (1.2)	22 (4.4)
Musculoskeletal and connective tissue disorders	19 (7.7)	80 (31.9)	99 (19.8)
Muscle spasms	1 (0.4)	44 (17.5)	45 (9.0)
Myalgia	6 (2.4)	21 (8.4)	27 (5.4)
Bone pain	2 (0.8)	16 (6.4)	18 (3.6)
Nervous system disorders	34 (13.7)	18 (7.2)	52 (10.4)
Headache	13 (5.2)	6 (2.4)	19 (3.8)
Skin and subcutaneous tissue disorders	80 (32.3)	69 (27.5)	149 (29.9)
Rash	45 (18.1)	28 (11.2)	73 (14.6)
Periorbital oedema	0	34 (13.5)	34 (6.8)
System organ class totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same system organ class. Date of snapshot: 31AUG2010			

(Source: Pfizer response to clarification questions A1)

9.18 Appendix R: Detailed results of probabilistic sensitivity analyses

This section details results of the probabilistic sensitivity analyses which were not felt important enough to include in the main report.

9.18.1 CP model results

Figure 45. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer clarification, Figure 9, p30)

Figure 46. Cost-effectiveness acceptability curve, all strategies (note dotted line is interferon)

(Source: Pfizer clarification, Figure 10, p30)

Figure 47. Pairwise comparison of hydroxycarbamide and bosutinib in PSA (incremental costs and QALYs of bosutinib versus hydroxycarbamide)

(Source: Pfizer clarification, Figure 11, p31)

9.18.2 AP model results

Figure 48. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer submission, Section 7.6.8, p171)

Figure 49. Cost-effectiveness acceptability curve, all strategies

(Source: Pfizer submission, Section 7.6.8, p171)

Figure 50. Pairwise comparison of hydroxycarbamide and bosutinib intervention

(Source: Pfizer submission, Section 7.6.8, p172)

9.18.3 BP model results

Figure 51. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer submission, Section 7.7.8, p181)

Figure 52. Cost-effectiveness acceptability curve, all strategies

(Source: Pfizer submission, Section 7.7.8, p182)

Figure 53. Pairwise comparison of bosutinib versus hydroxycarbamide

(Source: Pfizer submission, Section 7.7.8, p182)

9.19 Appendix S: Shortcomings in Pfizer's analysis with minimal effect on cost-effectiveness

Here, we discuss three aspects of Pfizer's model with which we agree. We do not adjust the model for our base case analysis because, when corrected, the cost-effectiveness of bosutinib changes only incrementally.

9.19.1 Death from non-CML causes

We believe that death due to all-cause mortality (in fact, due to non-CML mortality) for bosutinib patients is not correctly incorporated in the Pfizer model. The Pfizer report states that all-cause mortality is incorporated using the following method (except for bosutinib in CP model):

1. Overall survival is initially estimated by extrapolating from trial data
2. Background mortality already incorporated in the overall survival from the MCyR surrogate method is removed by "subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200)"
3. Age-appropriate background mortality is incorporated by "adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012)"

This contrasts with the method used by PenTAG in TA241[2] in which CML and non-CML mortality were jointly calibrated to OS in Jabbour and colleagues,[44] estimating non-CML mortality from UK Life Tables. We believe this is a more consistent method of estimating CML mortality and hence overall survival, but in reality neither method is ideal as both rely on accounting for the non-CML mortality that would be experienced by an average patient, rather than the average non-CML mortality that would have been experienced by the heterogeneous population described in Jabbour and colleagues.[44] As both methods are subject to the same criticism and the same methodology is applied across all interventions hence not introducing bias, we were content to accept the general methodology, with a few further considerations.

We do not believe that simple addition and subtraction of monthly probabilities of death from survival curves is logical. Instead we believe it is appropriate to estimate hazard rates and cumulative hazard functions, which may be added and subtracted, and then use the net cumulative hazard function to calculate overall survival, as follows:

1. Overall survival is initially estimated using the MCyR surrogate method, and denoted $S_{surrogate}(t)$
2. The cumulative hazard from the MCyR surrogate method is then $\Lambda_{surrogate}(t) = -\ln S_{surrogate}(t)$

3. The cumulative hazard experienced by a patient consistently feeling the force of non-CML mortality as experienced at age 54 is calculated as $\Lambda_{Non-CML|54}(t) = \lambda_{Non-CML|54} \times t$ where $\lambda_{Non-CML|54} = -\ln(1 - q_{54})$ where q_{54} is the probability of dying before age 55 if one is alive at age 54
4. The cumulative hazard experienced by a patient due to non-CML mortality as experienced at the appropriate age is calculated as $\Lambda_{Non-CML}(t_i) = \Lambda_{Non-CML}(t_{i-1}) - \ln\big(1 - q(x_{i-1})\big) \times (t_i - t_{i-1})$ where $q(x_{i-1})$ is the probability of dying before age $x_{i-1} + 1$ if one is alive at age x_{i-1} and x_0 is the starting age (54 years)
5. The net cumulative hazard is calculated as $\Lambda_{OS}(t) = \Lambda_{surrogate}(t) - \Lambda_{Non-CML|54}(t) + \Lambda_{Non-CML}(t)$
6. The overall survival is calculated as $S_{OS}(t) = \exp\{-\Lambda_{OS}(t)\}$

Furthermore, the Pfizer model does not appear to correctly implement the method described in the Pfizer report, as it calculates the monthly probability of death as $(1 + q_x)^{\frac{1}{12}} - 1$ rather than the correct calculation of $1 - (1 - q_x)^{\frac{1}{12}}$. This results in an underestimate of the monthly probability of death, particularly in older patients where q_x is greater. Note that this is in fact irrelevant as we do not consider that a simple correction to this monthly probability calculation would result in a correct and logical overall incorporation of non-CML mortality.

In addition we do not believe that the overall survival should be adjusted according to the mean age of the third-line CP cohort in study 200, since this study does not form the basis of the overall survival estimates, which instead come from Jabbour and colleagues.[44] The mean age of patients is not reported in Jabbour and colleagues, but the median age is reported as 54 years.[44] We also do not believe that simply adjusting according to any average age is ideal as the rate of non-CML mortality is nonlinearly related to age, but in the absence of any further data demonstrating the effect of age on overall survival within Jabbour and colleagues we believe it is a suitable approximation to adjust according to the median age.

Finally we note that in the Pfizer model the age used to adjust overall survival is 56 years rather than 54 years but this has a negligible impact.

We estimate that correct incorporation of non-CML mortality results in a 0.22 year decrease in mean OS for bosutinib from the Pfizer calculation. We felt this was unlikely to result in a significant impact on cost-effectiveness and it would require substantial changes to the model, so we have not pursued further.

9.19.2 Interferon drug administration resource use

Pfizer assume that 25% of interferon patients require assistance with injecting, following the assumption made in Rogers and colleagues (2012),[2] but the model includes only one district nurse visit per cycle for those patients requiring assistance. Rogers and colleagues by contrast assume one district nurse visit per day, which we believe is appropriate. The drug administration cost for interferon per cycle is therefore equal to 25% × £39 × 30.4 = £296.77 (compared to an original cost of £9.75).

Correcting this error results in a change in the Pfizer base case CP model ICER of bosutinib versus interferon from [redacted] per QALY, although interferon continues to be dominated by hydroxycarbamide. ICERs of bosutinib versus hydroxycarbamide and SCT in the CP model are unchanged, as are ICERs in the AP and BP model. As this results in only a small change in the ICER of bosutinib versus interferon (which is not the main comparison in the decision problem as interferon is dominated by hydroxycarbamide which is more reflective of clinical practice) we do not correct this in the base case.

9.19.3 Estimation of OS for bosutinib in CP using MCyR surrogate relationship

As described in Section 5.2.6.1 (p118) Pfizer fit a single curve (denoted curve A in this section) to OS from Jabbour and colleagues (2009)[44] before fitting a weighted combination of curves (denoted curve B in this section) to an adjusted version of curve A (A'). While we are satisfied that curve A is fitted appropriately, we note that Pfizer then use equal weighting across the curve when fitting curve B to curve A', which is particularly inappropriate when the underlying OS data is immature (maximum follow-up 7.7 years) and curve A' is extrapolated for 50 years. We note however that curve B is closely fitted to A' for the first 20 years, and hence although we do not agree with the methodology we do not believe a materially different estimate of cost-effectiveness would be obtained through a more appropriate methodology.

Pfizer assumed that 35/84 = 41.7% of patients in Jabbour and colleagues (2009)[44] achieved or maintained a MCyR, whereas in TA241 it was decided that the appropriate figure was 37/84 = 44.0%.[2] Substituting this value and re-calibrating as described in the Pfizer clarifications we calculated the CP model ICER of bosutinib versus hydroxycarbamide increased marginally from [redacted] per QALY.

Pfizer's model additionally had some logical errors:

- Curve A was adjusted to curve A' by adding and subtracting monthly mortality probabilities from a survival distribution, which is not logical. The more appropriate method is very

similar to the method employed to incorporate CML and non-CML mortality as conducted by Pfizer.

- Monthly probabilities of dying from non-CML causes were incorrectly estimated from annual probabilities taken from life tables. The correct formula is $q_{monthly} = 1 - \left(1 - q_{yearly}\right)^{1/12}$ while Pfizer used $q_{monthly} = \left(1 + q_{yearly}\right)^{1/12} - 1$ which underestimates non-CML mortality.
- Different methods were now used to incorporate non-CML mortality for bosutinib and for the comparators. This inconsistency could introduce bias.

We conducted an exploratory analysis where we corrected all the logical errors, including changing the method to incorporate non-CML mortality for hydroxycarbamide to match the method used for bosutinib. The resulting ICER for bosutinib versus hydroxycarbamide was [redacted] per QALY (up marginally from [redacted] per QALY). We also investigated the joint effect of changing the MCyR rate and correcting the logical errors and obtained an ICER of [redacted] per QALY. We did not feel this was a sufficiently important change in the ICER to warrant changing the base case for the analysis.

9.20 Appendix T: Cumulative survival method for AP and BP models

9.20.1 Cumulative survival method AP

Here, we discuss the Cumulative Survival method applied to treatment starting in AP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

We assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib.

Similarly, in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

We estimate the total life years, costs and QALYs for the (Bosutinib, HU), and (Bosutinib, SCT) treatment arms.

The notation of the time components is given in Table 94 below.

Table 94. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in AP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$
BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$		

Then under the Cumulative Survival method, the component times are calculated as shown in Table 95, where S_{BOS} and d_{BOS} have the analogous meanings as described in Section 6.1.1 (p190).

Table 95. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in AP

	(Bosutinib, HU)	HU	SCT	(Bosutinib, SCT)
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
BP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			

From Pfizer's model, we estimate an upper bound for S_{BOS} as 98.9% by assuming that the only mortality whilst patients are on bosutinib treatment is due to background causes. This estimate is based on Pfizer's base case estimates of time on 3rd-line bosutinib.

d_{BOS} = 94.5% from Pfizer's model, based on Pfizer's base case estimate of time on 3rd-line bosutinib and a discount rate of 3.5% p.a.

Under the cumulative survival method, the component costs are calculated as shown in Table 96.

Table 96. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in AP

	(Bosutinib, HU)	HU	SCT	(Bosutinib, SCT)
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
BP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			

The component QALYs are calculated in exactly the same way.

9.20.2 Cumulative survival method BP

Here, we discuss the Cumulative Survival method applied to treatment starting in BP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

We assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib.

Similarly, in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

We estimate the total life years, costs and QALYs for the (Bosutinib, HU), and (Bosutinib, SCT) treatment arms.

The notation of the time components is given in Table 97 below.

Table 97. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$

Then under the Cumulative Survival method, the component times are calculated as shown in Table 98, where S_{BOS} and d_{BOS} have the analogous meanings as described in Section 6.1.1 (p190).

Table 98. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$

From Pfizer's model, we estimate an upper bound for S_{BOS} as 99.9% by assuming that the only mortality whilst patients are on bosutinib treatment is due to background causes. This estimate is based on Pfizer's base case estimates of time on 3rd-line bosutinib.

d_{BOS} = 97.9% from Pfizer's model, based on Pfizer's base case estimate of time on 3rd-line bosutinib and a discount rate of 3.5% p.a.

Under the cumulative survival method, the component costs are calculated as shown in Table 99.

Table 99. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}} d_{\mathrm{BOS}} \mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}} d_{\mathrm{BOS}} \mathrm{T}_{\mathrm{SCT}}$

The component QALYs are calculated in exactly the same way.

9.21 Appendix U: Correspondence from TA251 concerning medical management

The following text is reproduced from our document "Addendum to PenTAG report for TA251: Prepared and sent by PenTAG, 3rd November 2011".

Novartis correctly state that during chronic phase CML, alongside other monitoring test costs, we originally assumed a monthly frequency of:

0.4 visits with a nurse

0.9 visits with a haematologist/oncologist, and

0.3 bone marrow aspirations.

These figures were taken from the 2009 Oxford Outcomes survey of 6 UK-based CML clinicians (see p179 our report).

Novartis claim that this is an overestimate the frequency of outpatient visits. They claim that it is more reasonable to assume one visit per 3 to 6 months, based on current ELN guidelines. They also claim that we over-estimate the frequency of bone marrow aspirations.

We have presented Novartis' criticisms to our clinical advisor, and he agrees that we have over-estimated these quantities. He believes that it is more likely that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly. Patients on hydroxyurea would be seen about every 6 weeks. Furthermore, patients would rarely be seen by a nurse (without a consultant). Our advisor claims that clinical practice for bone marrow aspiration varies from only a single test, to tests at month 0, 3, 6, 12, 18 and 24 or until CCyR, but not after 24 months.

Given this new information and current European treatment guidelines, we have calculated revised base case cost-effectiveness estimates assuming lower medical management costs during the chronic phase. The modelling for our revised estimates now assumes:

- one visit to a haematologist/oncologist every 3 months for patients on a TKI, i.e. 0.33 visits per month.
- one visit to a haematologist/oncologist every 6 weeks for patients hydroxyurea, i.e. 0.72 visits per month.
- no outpatient nurse visits.
- no bone marrow aspirations (given that some clinicians give no repeat tests and given that for those cases when repeat aspirations are given, costs would cancel to a large extent between treatment arms).

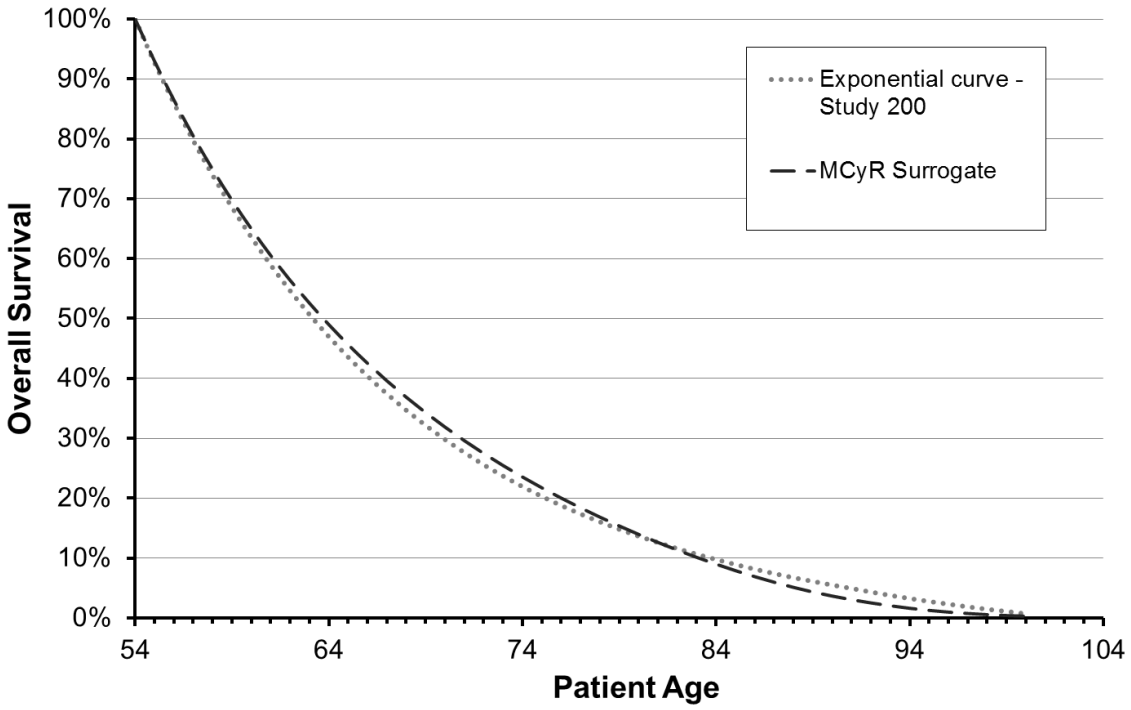
We can safely ignore the initial higher frequency of visits when patients start taking TKIs, as these costs effectively cancel out between treatment arms (because virtually all patients on 1st-line TKIs are still on treatment at 4 months). We leave all other assumptions for the costs of medical management unchanged (see p180 our report), although these contribute only marginally.

These new cost assumptions give a mean medical management cost of £169 per month per patient on TKIs in chronic phase and £317 per patient on HU in chronic phase.

9.22 Appendix V: Comparison of overall survival in CP model calculated by MCyR surrogate, Study 200 Kaplan-Meier and exponential fit

Pfizer state (Pfizer clarification, Figure 7, p28) that the overall survival (OS) obtained by the MCyR surrogate method was validated by comparing it to the exponential curve fitted to Study 200 CP-3L cohort OS, with the curves being very similar:

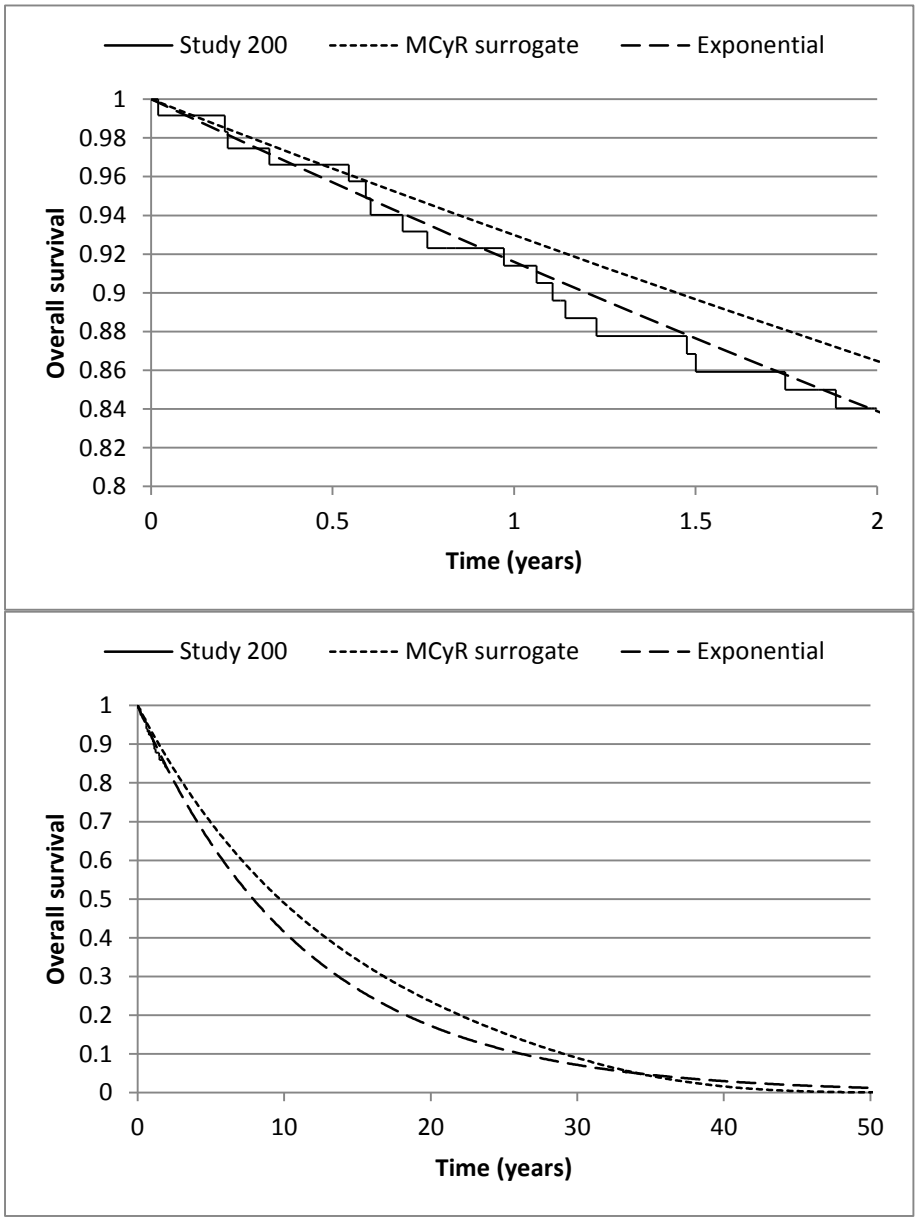
Figure 54. OS in CP model calculated by exponential curve and MCyR surrogate method



(Source: Pfizer clarifications, Figure 7, p28)

We believe this figure is not an accurate reflection of the exponential curve used in Pfizer's model. Figure 55 shows the actual OS in the CP model and demonstrates that the MCyR surrogate method is overestimating the OS.

Figure 55. Actual OS in CP model



Note that we do not accept that the Study 200 OS is good quality data for the purposes of estimating OS for patients on bosutinib in the unmet need population; indeed we identify a number of issues with the data (see Section 5.3.8.1, p165). This is presented only to demonstrate the shortcomings of the MCyR surrogate method (since we believe Study 200 OS is already likely to be biased upwards). As the MCyR surrogate method is a key component of Pfizer's CP base case we believe this is further reason to not accept Pfizer's base case estimate of OS for patients on bosutinib in CP.

9.23 Appendix W: Adjusting Pfizer's model for PenTAG preferred medical management resource use

Table 100. Changes to Pfizer's model to achieve PenTAG preferred medical management resource use

Worksheet	Cell(s)	Change

PF_Bosutinib	AG11	Change from
		`=ae_bosutinib_cost+AB11*c_cpt_bos`
		to
		`=ae_bosutinib_cost+AB11*c_cpt_bos+2*p_clin_onc`

Costs	C117	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$57`
		to
		`=1/3*p_clin_onc+$F$57`

	D117	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$59`
		to
		`=0.72*p_clin_onc+$F$59`

	C118, D118, D119	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$59`
		to
		`=0.72*p_clin_onc+$F$59`

	C119	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55) + Parameters!$N$56 + $F$61 + (1-Parameters!$N$34)*Parameters!$N$33`
		to
		`=0.72*p_clin_onc+$F$61+(1-Parameters!$N$34)*Parameters!$N$33`

	C84, D84	Set to 0

PF_Interferon	BE11:BE610	Change from (row 11)
		`=SUM(Z11:AA11)*SUMPRODUCT( Parameters!$N$37:$N$40, Parameters!$N$52:$N$55) + AB11*SUMPRODUCT(Parameters!$N$42:$N$45, Parameters!$N$52:$N$55) + AC11*SUMPRODUCT(Parameters!$N$47:$N$50, Parameters!$N$52:$N$55)`
		to
		`=SUM(Z11:AA11)*0.72*p_clin_onc + AB11*SUMPRODUCT(Parameters!$N$42:$N$45, Parameters!$N$52:$N$55) + AC11*SUMPRODUCT(Parameters!$N$47:$N$50, Parameters!$N$52:$N$55)`

	BF11:BF610	Change from (row 11)

		`=SUM(Z11:AA11)*Parameters!$N$56 + SUM(AB11:AC11)*Parameters!$N$57`
		to
		`=SUM(AB11:AC11)*Parameters!$N$57`

PF_StemCellTransplant	AE11:AE610	Replace `c_sct_25` with `c_sct_25+(0.54*0.5+0.46*0.08)*p_clin_onc`

Bosutinib for previously treated chronic myeloid leukaemia: a single technology appraisal

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Martin Hoyle	Project manager, led the critique of Pfizer's economic analysis, and contributed to the writing of the clinical and cost-effectiveness chapters.
Tristan Snowsill	Critiqued Pfizer's economic model and contributed to the writing of the cost-effectiveness chapters. Collated the final report.
Marcela Haasova	Critiqued clinical effectiveness evidence and wrote most of the clinical effectiveness chapter.
Chris Cooper	Critiqued Pfizer's searches for clinical and cost-effectiveness evidence.
Claudius Rudin	Advised on possible use of bosutinib in England and Wales and on CML in general.

About the Peninsula Technology Assessment Group (PenTAG)

PenTAG is part of the Institute of Health Service Research at the University of Exeter Medical School. PenTAG was established in 2000 and currently has two major work streams: independent health technology assessments (HTAs) for NICE and the NIHR HTA programme, and evidence synthesis work in relation to the needs of the SW Peninsula Collaboration for Applied Health Research and Care (PenCLAHRC), as well as for other local and national decision-makers.

The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics.

Website: http://sites.pcmd.ac.uk/pentag/

Disclosure of information

This report contains information designated by the manufacturer as 'commercial in confidence' and 'academic in confidence' (data awaiting publication). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

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Certain figures in this report are designated as commercial in confidence and this is indicated both by underlining and highlighting the caption and underlining and highlighting the figure (although the latter is not always obvious).

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LIST OF ABBREVIATIONS

AE/SAE/TEAE	Adverse event/ Serious adverse event/ Treatment-emergent adverse event
ALL	Acute lymphoblastic leukaemia
SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BC	Blast crisis
Bcr-Abl	Breakpoint cluster region-Abelson (an oncogene fusion protein consisting of BCR and ABL)
BMS	Bristol-Myers Squibb
BMT	Bone marrow transplant
BNF	British National Formulary
BP	Blast phase
BSC	Best supportive care
C(A)T	Computerised (axial) tomography
CC	Complication/comorbidity (HRG code)
CCyR	Complete cytogenetic response
CENTRAL	The Cochrane Central Register of Controlled Trials
cGvHD	Chronic graft versus host disease
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
DARE	The Database of Abstracts of Reviews of Effects
DET	Data extraction table
ECOG	Eastern Cooperative Oncology Group
EHA	European Haematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-	European Organisation for Research and Treatment of Cancer Quality of Life

C30	Questionnaire-Core 36
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life- 5 Dimensions questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EWB	Emotional well-being
FACT-Leu	Functional Assessment of Cancer Therapy- Leukemia
FDA	US Food and Drug Administration
FISH	Fluorescence *in situ* hybridisation
FLAG-IDA	Fludarabine, cytarabine, idarubicin and G-CSF chemotherapy regimen
FWB	Functional well-being
GBP	Great British Pounds (currency)
G-CSF	Granulocyte-colony stimulating factor
GP	General Practitioner
GVHD	Graft versus host disease
HCHS	Hospital and community health services
HDI	High-dose imatinib
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HTA	Health Technology Assessment
HTN	Hypertension
HU	Hydroxyurea/hydroxycarbamide
ICER	Incremental cost-effectiveness ratio
ICLLM	International Congress on Leukemia Lymphoma Myeloma
ICU	Intensive-care unit
IFN	Interferon alpha
IFR	Individual funding requests
IM-I	Imatinib-intolerant
IM-R	Imatinib-resistant
INHB	Incremental net health benefit
INR	International Normalised Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LEUS	Leukaemia subscale
MCyR	Major cytogenetic response
mg	Milligrams
MHR	Major haematological response
MiCyR	Minor cytogenetic response
MMR	Major molecular response

MUD	Matched unrelated donor
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	No evidence of leukaemia
NHB	Net health benefit
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation Database
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Clinical Excellence / National Institute for Health and Care Excellence
NR	Not reported
OHR	Overall haematological response
ONS	Office for National Statistics
OS	Overall survival
PAOD	Peripheral arterial occlusive disease
PAS	Patient Access Scheme
PB	Peripheral Blood
PBSCT	Peripheral blood stem cell transplant
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
Ph^+	Philadelphia chromosome-positive
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PWB	Physical well-being
QALY	Quality-adjusted life year
QTc	Corrected QT interval
RCP	Return to chronic phase
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
SmPC/SPC	Summary of Product Characteristics
STC	Stem cell transplant
SWB	Social well-being
TA[number]	Technology appraisal [number]
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor

UK	United Kingdom
ULN	Upper limit of normal
USA/US	United States of America
WBC	White blood cell
WHO	World Health Organisation
WTP	Willingness to pay

(Adapted from Pfizer submission, pp8–12)

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency.

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML)
- Hydroxycarbamide
- Interferon alpha
- Best supportive care

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 1.5.2, p30).

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence of bosutinib (Bosulif®) in treatment of adult patients with Ph+ CML was reviewed. The entire clinical evidence for bosutinib comes from a single arm, phase I/II multi-centre trial, Study 200. Because no RCT evidence was identified, separate clinical effectiveness evidence was submitted for the Scope defined comparators. Thirteen non-randomised comparator studies were included.

1.2.1 Bosutinib

Study 200 (Phase II) examined the efficacy and safety of bosutinib 500mg daily in 546 Ph+ CML patients with previous imatinib failure. Patients in all three phases of Ph+ CML were recruited; second line CP (N=288), third line CP (N=118), AP (N=76) and BP (N=64). In addition, based on

EMA recommendation, a subgroup of patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (population of unmet clinical need) was identified and analysed post hoc. Baseline characteristics across all phases of the disease and lines of treatment are summarised in Table 1.

Table 1. Study 200 baseline patient characteristics

Population	**Age (years) [Median (range)]**	**Male [N (%)]**	**CML duration (years) [Median (range)]**	**IM duration (years) [Median (range)]**	**ECOG performance status N (%)**		
					0	*1*	*2*
CP2L (n=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.11–22.06)	NR	41 (54%)	33 (43%)	2 (3%)
BP (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.35–14.46)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need (N=52)[b]	58 (19-81)	31 (605)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NR = not reported

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

In the complete population of Study 200, bosutinib was associated with good cytogenetic and haematological response rates and overall survival (Table 2). However, the OS data from Study 200 for CP patients is very immature. Cytogenetic and haematological responses were also observed among participants with mutations that would confer the use of nilotinib or dasatinib inappropriate (Table 3). Apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical need population. For example, MCyR was 60%, 42.9%, 60% and 18.2 % for second and third line CP and AP and BP unmet clinical need population respectively. However these response rates are based on very small sample sizes (N=3–21) and are therefore uncertain.

Table 2. Study 200 cytogenetic and haematological response rates for full Study 200 population

	Evaluable population			
	MCyR March 2011	*CCyR March 2011*	*CHR March 2011*	*K-M estimates of OS at 2 years*
CP2L	53.4%	41.4%	84.7%	90.6%[a]
CP3L	38.9%	30.6%	73.3%	84.0%[a]
AP	34.8%	24.6%	34.8%	65.6%[b]
BP	29.6%	20.4%	15%	35.4%[c]

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a 24 month minimum follow-up, median OS had not yet been reached

b 12 month minimum follow-up, median OS had not yet been reached

c 18 month minimum follow-up, median OS for BP patients was 11.1 months

Table 3. Study 200 response rates by baseline mutation

Mutation	**CP2L CHR [n/N %]**	**CP2L MCyR [n/N %]**	**CP3L CHR [n/N %]**	**CP3L MCyR [n/N %]**	**AP & BP CHR [n/N %]**	**AP & BP MCyR [n/N %]**
Y253	2/2 100%	2/2 100%	5/6 83%	4/6 67%	1/7 14.3%	2/7 28.6%
E255	0/2 0%	2/3 67%	NA	NA	0/4 0%	1/3 33.3%
F317	4/4 100%	3/4 75%	4/8 50%	1/7 14%	0/9 0%	0/6 0%
F359	8/9 89%	4/9 44%	0/2 0%	1/2 50%	0/2 0%	1/2 50%

Notes: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, n = numbers of participants with response, N = number of participants with mutation, NA = not applicable

Bosutinib was found to have an acceptable safety profile across all phases of the disease and lines of treatment. Low rates of transformation to the next phase of CML were observed on bosutinib treatment for both chronic and advanced phase populations (Table 4). Adverse events were mainly restricted to gastrointestinal toxicities (Table 4) and in the majority of cases these toxicities were mild in severity. The most common haematological events across all phases of the disease and lines of treatments in both the chronic and advanced phases of the disease were thrombocytopaenia, neutropaenia and anaemia. Severe cases of anaemia seemed to be more pronounced at the more advanced stages of the disease (Table 4). The profile of AE associated with bosutinib appears to be more similar to those associated with nilotinib than with dasatinib. In comparison, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections,

haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI.

Table 4. Study 200 safety

	CP2L	CP3L	AP	BP
Rates of disease transformation to the next phase of CML	3.8%	4%	6.4%	NA
Treatment discontinuation	58% (36 months minimum follow-up)	76% (24 months minimum follow-up)	NR	NR
Treatment discontinuation due to AE	23%	22%	23.7%	9.4%
Diarrhoea	85.3%	82.4%	85.5%	65.6%
Nausea	45.5%	48.7%	44.7%	50%
Vomiting	36.7%	39.5%	44.7%	39.1%
Rash	36%	26.9%	32.9%	31.3%
Thrombocytopenia Grade 3/4	24%	25.4%	32.9%	26.6%
Neutropenia Grade 3/4	18%	14.4%	14.5%	20.3%
Anaemia Grade 3/4	13%	5.1%	30.3%	18.8%

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable, NR = not reported

EQ-5D data were collected in Study 200. The mean EQ-5D utilities, averaged mostly over the first two years of treatment, were [redacted] in the CP 2nd-line, 3rd-line, AP and BP populations respectively.

1.2.2 Comparator treatments

No studies reporting on interferon alpha in a refractory setting were identified. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] However only 7 studies[3, 4, 6, 7, 10, 12, 13] were considered in Pfizer's submission as five SCT studies did not stratify results by disease phase.

In summary, the clinical effectiveness evidence for the comparator treatments is very poor. Hydroxycarbamide was considered to be a proxy for best supportive care. Participants in the comparator studies appear to be younger, and most of the comparator studies are small and the outcomes reported vary. Pfizer describe the HU comparator studies as "not strictly eligible" (p89 Pfizer Submission) for inclusion and only three included SCT studies[7, 10, 13] are considered to be a good quality evidence according to the Chambers (2009)[16] criteria (Pfizer submission, p216). This

further highlights the difficulty inherent to such naïve comparisons and impedes any comparisons of Study 200 with comparator studies.

The CP cost-effectiveness model used data from Kantarjian (2007)[3] for the clinical effectiveness of HU and Jabbour (2011)[10] for the clinical effectiveness of SCT. Of particular importance for the model are:

- OS after SCT in CP of 72% at year 2 in Jabbour (2011)[10]
- OS for HU in CP of 77% at year 2 and 70% at year 3 in Kantarjian (2007)[3]

No safety data were reported for HU, and the grade 3–4 graft versus host disease reported in SCT studies varied across the lines of treatment as well as the studies from 6.25% to 40%.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

First, the main weakness of the clinical effectiveness evidence is the fact that no RCT evidence was identified. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML. Similarly, the evidence for comparator treatments comes from 13 non-randomised comparator studies.

Second, the bosutinib licence is intended for treatment of adult patients with CP, AP and BP Ph+ CML patients previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. However only 52 of the 546 patients in Study 200 fulfilled the criteria for this unmet need population.

Third, Pfizer do not state the nature of treatments given after bosutinib failure. This means that the relevance of the OS data from Study 200 is uncertain, because many patients may have proceeded to take a different TKI on bosutinib failure. Also, the OS data in CP is very immature, which means that it is difficult to estimate mean OS, a key driver of the cost-effectiveness of bosutinib.

Fourth, we cannot stress enough, that the naïve comparison of the single arm Study 200 with non-randomised comparator studies is predisposed to bias. The evidence for the two comparator treatments, HU and SCT, is taken from small studies with populations that mostly did not meet the unmet need criteria.

Fifth, Pfizer present no evidence for the clinical effectiveness of IFN, which is one of the comparator treatments in the CP economic model.

1.4 Summary of cost-effectiveness evidence submitted by the manufacturer

Pfizer conducted a systematic review for cost-effectiveness evidence relating to the decision problem. This did not identify any relevant studies for bosutinib.

Pfizer therefore developed a *de novo* economic model to answer the decision problem. The model developed was an "area-under-the-curve" cohort model where patients could be on or off the principal treatment in the treatment arm and patients could undergo transformation to later disease phases (accelerated and blast crisis phase). Patients could start in either the chronic phase, accelerated phase or blast crisis phase and these are denoted the CP, AP and BP models.

Pfizer consider the following four treatment sequences in the CP model:

- Bosutinib followed by hydroxycarbamide, denoted (Bosutinib, HU),
- Hydroxycarbamide, denoted HU,
- Stem cell transplant, denoted SCT,
- Interferon followed by hydroxycarbamide, denoted (IFN, HU).

For the AP and BP models, they consider the same treatment sequences but without (IFN, HU).

Overall survival was estimated for (Bosutinib, HU) in the CP model using a MCyR surrogate method, which has been used previously by PenTAG in TA241. They did not however use this method to estimate overall survival for comparator treatments, instead extrapolating from trials and using clinical expert opinion. Overall survival for (Bosutinib, HU) in the AP and BP models was estimated by extrapolating from Study 200.

Time on bosutinib treatment was estimated by extrapolating from Study 200. Time on interferon treatment was extrapolated from clinical expert opinion. Patients did not discontinue hydroxycarbamide treatment and patients who received a stem cell transplant were assumed to receive no further drug treatment.

Resource uses and costs were generally based on previous assessments by PenTAG, TA241 and TA251.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 and TA241. Their only departure from our previous assumptions is their estimate of the utility after stem cell transplant in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Importantly, for the estimated utility under bosutinib treatment, they prefer the utilities that we have used previously for utilities for TKIs to those from their Study 200.

1.4.1 CP model results

Pfizer's analysis showed that (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY), and more effective and less costly than SCT, i.e., (Bosutinib, HU) dominates. Pfizer found that (IFN, HU) was less effective and more costly than HU (HU dominates). The ICER of (Bosutinib, HU) versus (IFN, HU) was [redacted] per QALY.

Table 5. Pfizer CP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	(IFN, HU)	SCT
Life years	12.75	3.52	3.62	6.60
QALYs	7.26	2.43	2.42	3.70
Costs	[redacted]	£29,473	£38,268	£171,539

QALYs and costs discounted at 3.5% per annum

1.4.2 AP model results

Pfizer's AP base case results showed that similar to the CP model (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY), and that (Bosutinib, HU) dominates SCT.

Table 6. Pfizer AP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	4.48	1.37	3.02
QALYs	2.76	0.90	1.96
Costs	[redacted]	£26,078	£178,093

QALYs and costs discounted at 3.5% per annum

1.4.3 BP model results

Pfizer's BP base case results showed that (Bosutinib, HU) was more effective and more costly than HU (ICER [redacted] per QALY). The results also showed that (Bosutinib, HU) was less effective and less costly than SCT (ICER [redacted] per QALY).

Table 7. Pfizer BP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	1.77	0.54	2.64
QALYs	0.88	0.28	1.28
Costs	[redacted]	£14,170	£200,526

QALYs and costs discounted at 3.5% per annum

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

In this section, we highlight our key areas of disagreement with Pfizer's analysis. As a result of our critique of their model, we have developed PenTAG base case ICERs (Section 1.7, p35) for each of the CP, AP and BP models. In order to develop our base case, we have adjusted the following items in Pfizer's CP model:

- The method of estimation of OS for all comparators using our "cumulative survival method",
- Mean overall survival on HU,
- Mean overall survival after SCT,
- Resource use in CP CML.

We have changed just the first item in Pfizer's AP and BP models.

1.5.1 Model wiring errors

We discovered an important wiring error in the version of the model that Pfizer originally sent us on 14th March 2013. Pfizer sent as a corrected version of their model on 19th April 2013. Their base case ICER for bosutinib versus HU in CP then decreased from [redacted] per QALY.

In order to check the wiring of Pfizer's cost-effectiveness model, we built a model that is completely independent of their model. We feel confident that there are no major wiring errors in Pfizer's corrected model because the results from our independent model are very similar to those of Pfizer's model.

1.5.2 Comparator treatment sequences

Pfizer model the four treatment sequences in CP in Section 1.4, p28. In addition, we believe it is important to model the sequence (Bosutinib, SCT) for patients eligible for SCT. In summary, we assume the following comparator treatment sequences for CP:

- (Bosutinib, HU),
- (Bosutinib, SCT) (only for those eligible for SCT),
- HU,
- SCT (only for those eligible for SCT),
- (IFN, HU).

For the AP and BP models, we assume the same comparators, but without (IFN, HU).

We believe that the most important comparison in all model phases is (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Furthermore, we understand that a minority of patients (<30%) will be eligible for SCT and hence (Bosutinib, HU) versus HU is the most important treatment comparison in all disease phases.

1.5.3 Method of overall survival (OS) estimation

As stated in Section 1.4, p28, in the CP model, Pfizer use very different methods to estimate OS across treatments in the CP model. We believe that this lack of consistency, the lack of randomised evidence, and problems specific to the estimation of OS for bosutinib using the MCyR surrogate relationship leads to the following important prediction that lacks face validity. The mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) (shown in Figure 1 below). We believe, and clinical expert advice confirms, that this is unreasonable. Furthermore, this assumption dramatically biases the cost-effectiveness in favour of (Bosutinib, HU) versus HU because the price of HU is negligible.

Figure 1.

[redacted]

Although OS for all treatments is consistently estimated by extrapolating trial data in the AP and BP model, we believe there are still serious problems with Pfizer's method of estimating OS for all treatments in AP and BP. This similarly leads to the implausible prediction that, in both the AP and BP models, the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm.

Instead, we suggest that a far more parsimonious method is required to estimate OS across comparators. Indeed, we suggest such a method, which we describe as the Cumulative Survival method. We believe that it is far preferable for estimating OS for all comparator treatments for all

model phases. We believe that it should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The key assumption of the Cumulative Survival method is that in the (Bosutinib, HU) and (IFN, HU) arms, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. In Figure 1, the heights of the HU sections then become approximately equal. Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

The revised cost-effectiveness results are then:

- In the CP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases substantially, from [redacted] to [redacted] per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY.
- In the AP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY.
- In the BP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY. In their base case, Pfizer estimate an ICER of [redacted] for (Bosutinib, HU) versus SCT, with (Bosutinib, HU) cheaper and less effective than SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is [redacted] per QALY, i.e. (Bosutinib, SCT) gives poor value versus SCT.

Of all the changes we make to Pfizer's model, this has the largest impact on the estimated cost-effectiveness of bosutinib.

1.5.4 OS for HU in CP

Relevant data for OS on HU for patients in CP is sparse. Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] We used this study for this purpose in TA251. Pfizer claim that the agreed estimate of mean OS for HU in CP was 3.5 years in TA251, and they therefore use this value in their base case. However, we disagree. Instead,

we calculated a mean OS of 7.0 years in TA251.[17(p164)] Furthermore, the 3.5 years estimated by Pfizer is clearly incompatible with the Kaplan-Meier OS curve from this study.

The quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is clearly poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available for this purpose.

Pfizer's base case ICER for (Bosutinib, HU) versus HU then increases from [redacted] to [redacted] per QALY, and the cost-effectiveness of (Bosutinib, HU) versus SCT is unchanged.

1.5.5 OS after SCT in CP

Relevant data for OS after SCT for patients in CP is also sparse. Pfizer's base case estimate of OS after SCT for patients in CP was based on data from the study Jabbour and colleagues (2011).[10] Whilst we agree that this study is relevant, the sample size is extremely small, with only 16 CP patients contributing to the estimates of OS. Instead, we use data from the study by Oehler and colleagues (2007),[12] in our base case, as it is relevant, has a much larger sample of 72 patients and reports OS that is more consistent with the OS from two other relevant studies. Our estimated OS of 11.6 years is far greater than Pfizer's estimate of 6.6 years.

Pfizer's base ICER for (Bosutinib, HU) versus HU then remains unchanged, and (Bosutinib, HU) still dominates SCT, but the cost-effectiveness of (Bosutinib, HU) deteriorates versus SCT.

1.5.6 Medical management costs in CP

Pfizer's assumptions for medical management, monitoring and testing are based on those that we originally used in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey. However, Pfizer seem unaware that after the first NICE committee meeting for TA251, our assumptions were challenged by Novartis, the manufacturer of nilotinib. In response, we amended some of our assumptions for resource use in CP CML in TA251, and these were accepted by the NICE committee.

These changes plus changes to resource use assumptions for patients after SCT are reflected in our base case assumptions. When we amend Pfizer's model, their ICER for (Bosutinib, HU) versus HU decreases from [redacted] to [redacted] per QALY and (Bosutinib, HU) continues to dominate SCT.

1.5.7 Line of treatment

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used 2nd-line. However, we believe that bosutinib will be

used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis also assumes 3rd-line use of bosutinib, and we consider use of bosutinib in 2nd-line in an important scenario analysis.

Pfizer estimate the mean time on 3rd-line bosutinib in CP from Study 200 as [redacted]. Based on the Kaplan-Meier data from Study 200 we requested from Pfizer, we estimate the mean time on 2nd-line bosutinib as being far longer, at [redacted].

Changing Pfizer's model for this estimate and for the 2nd-line MCyR from Study 200, Pfizer's base case ICER for (Bosutinib, HU) versus HU for CP increases substantially, from [redacted] to [redacted] per QALY and (Bosutinib, HU) changes from dominating SCT to being more costly and more effective than SCT (ICER [redacted] per QALY).

1.5.8 Utilities

In short, we accept Pfizer's utilities. However, we believe that there are strong arguments that we should instead use the utilities from Study 200 for bosutinib treatment, and our estimate of 0.80 after SCT in CP in preference to their estimate of 0.71.

In the first case, Pfizer's ICER for (Bosutinib, HU) versus HU in CP increases marginally, from [redacted] to [redacted] per QALY.

In the second case, based on Pfizer's analysis, (Bosutinib, HU) still dominates SCT in CP, but to a lesser extent.

1.5.9 End of Life criteria

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML. By contrast, we believe bosutinib does not meet the criteria in any phase of CML. We believe that bosutinib does not quality in AP and BP due to lack of robustness of the estimates of extension to life.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- Pfizer's analysis was clearly described in their report.
- We found only one important wiring error in Pfizer's model.
- The structure of Pfizer's model is mostly consistent with the natural history of CML.
- With the exception of the Cumulative Survival method, Pfizer clearly studied TA241 and TA251 in detail and adapted their model accordingly.
- The time on bosutinib treatment from Study 200 is mature.

- Extrapolations for time on bosutinib treatment appear reasonable.
- The modelled unit costs seem appropriate.
- The modelled utilities are plausible.

1.6.2 Weaknesses

- The clinical effectiveness evidence is taken from a single non-randomised trial (Study 200).
- Only a small subset of the patient population in Study 200 reflects the population indicated for bosutinib.
- Although some effectiveness results are presented for the patients indicated for bosutinib, some key effectiveness results, such as time on bosutinib treatment, are not.
- OS for patients on bosutinib in CP is very immature.
- In Pfizer's model, all patients were assumed to receive hydroxycarbamide following bosutinib failure. Instead, we believe that some patients would receive SCT after bosutinib.
- Pfizer's important prediction that the mean time in the CP model on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) lacks face validity.
- We believe that Pfizer's estimate of mean OS on HU in CP is logically flawed, as described in Section 1.5.4, p32.
- We believe that Pfizer's estimate of mean OS after SCT in CP is biased, as described in Section 1.5.5, p33.

1.6.3 Areas of uncertainty

There is substantial uncertainty in almost all the key parameters of Pfizer's model. Much of this has already been discussed above, but some of the key parameters which are uncertain include:

- The line of treatment that clinicians would use bosutinib if it were recommended by NICE,
- Mean OS on bosutinib in all phases, specifically for patients unsuited to TKIs,
- Mean time on bosutinib treatment in all phases, specifically for patients unsuited to TKIs,
- Mean OS on HU in all phases of CML,
- Mean OS after SCT in all phases of CML,
- Utilities for patients after SCT.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Summaries of the derivation of our base case ICERs and sensitivity analyses are given in the following tables below:

- Table 8 and Table 9 (CP)

- Table 10 (AP)
- Table 11 (BP)

The key treatment comparisons are highlighted in bold: (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Our base case ICERs for these key comparisons are as follows:

- CP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY
- AP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY
- BP model
    - (Bosutinib, HU) versus HU [redacted] per QALY
    - (Bosutinib, SCT) versus SCT [redacted] per QALY

Table 8. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) versus**			**(Bosutinib, SCT) versus**		
	Comparator	*HU*	*SCT*	*IFN*	*HU*	*SCT*	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	n/c	n/c	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	n/c	n/a		
1+2[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+3[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+4[b]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+3+4		[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from Pfizer base case

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT

b Interferon is more costly and more effective than hydroxycarbamide
c Interferon is less costly and less effective than hydroxycarbamide

Table 9. Important scenario analyses applied to PenTAG base case for CP model

Intervention	(Bosutinib, HU) versus			(Bosutinib, SCT) versus		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	[redacted]	[redacted]	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	[redacted]	Dominant	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	[redacted]	[redacted]	[redacted]
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
SCT utility set to TA251 utility	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]

n/c – Not changed from PenTAG base case
Shading as in Table 8
a (Bosutinib, HU) is less costly and less effective than SCT

Table 10. Derivation of PenTAG base case AP CML

	Intervention	(Bosutinib, HU) versus		(Bosutinib, SCT) versus	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

Shading as in Table 8

Table 11. Derivation of PenTAG base case BP CML

	Intervention	(Bosutinib, HU) versus		(Bosutinib, SCT) versus	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

Shading as in Table 8
a Bosutinib is less costly and less effective than SCT

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

Leukaemia is a form of cancer affecting blood. Chronic myeloid leukaemia (CML) is characterised by excessive proliferation of white blood cells (mainly granulocytes) in the bone marrow, and an initial slow disease progression.[2] The Haematological Malignancy Research Network (HMRN) estimates that 560 cases of CML are newly diagnosed in the UK each year; an annual age-standardised rate of 1.2 per 100,000 for men and 0.7 per 100,000 for women (based on HMRN 2004-11 and 2001 UK census data). Natural history and epidemiology of CML, technologies and clinical pathways available, as well as the patients' life expectancy were described in Sections 2.1–2.6 of the manufacturer's submission.

2.1.1 Natural history of CML

The introduction of TKIs in the treatment of CML has changed the management and outcome of this disease dramatically. Although a true cure for CML is not generally achieved, CML was transformed from an immediately life-threatening cancer, with a 10–20% mortality rate per year, to a disease, managed with oral medications, and with 1–2% mortality per year.[18]

CML is characterised by the presence of the BCR-ABL fusion gene as the result of a reciprocal chromosome translocation between chromosomes 9 and 22; t(9q34;22q11). This acquired (non-inherited) translocation results in a truncated derivative chromosome 22 known as the Philadelphia chromosome. Approximately 90–95% of the CML population are Philadelphia chromosome positive (Ph+). A further 5% do not exhibit the characteristic Philadelphia chromosome, but have cryptic chromosomal rearrangements resulting in the BCR-ABL fusion gene. The resulting Bcr-Abl fusion protein is a constitutively active tyrosine kinase, resistant to apoptosis (programmed cell death). It phosphorylates numerous substrates, disrupting the regulation of intracellular signal transduction pathways, promoting proliferation and genetic instability.

CML has three phases: chronic (CP), accelerated (AP) and blast (BP), each corresponding to increasing leukaemic blast counts in the blood and bone marrow and clinical severity ([Pfizer submission] Table 3). Blast is a term which describes an immature blood cell of any type. Normally, a blast will develop into a mature blood cell, but in CML these cells are abnormal and do not fully develop, becoming known as leukaemic blasts.

Approximately 90% of patients are diagnosed while in CP, 9% in AP and 1% in the BP. If left untreated, the average time a patient would remain in CP, AP and BP is 3–5 years, 6–24 months and 6 months, respectively.

(Source: Pfizer submission, p23)

2.1.2 Epidemiology

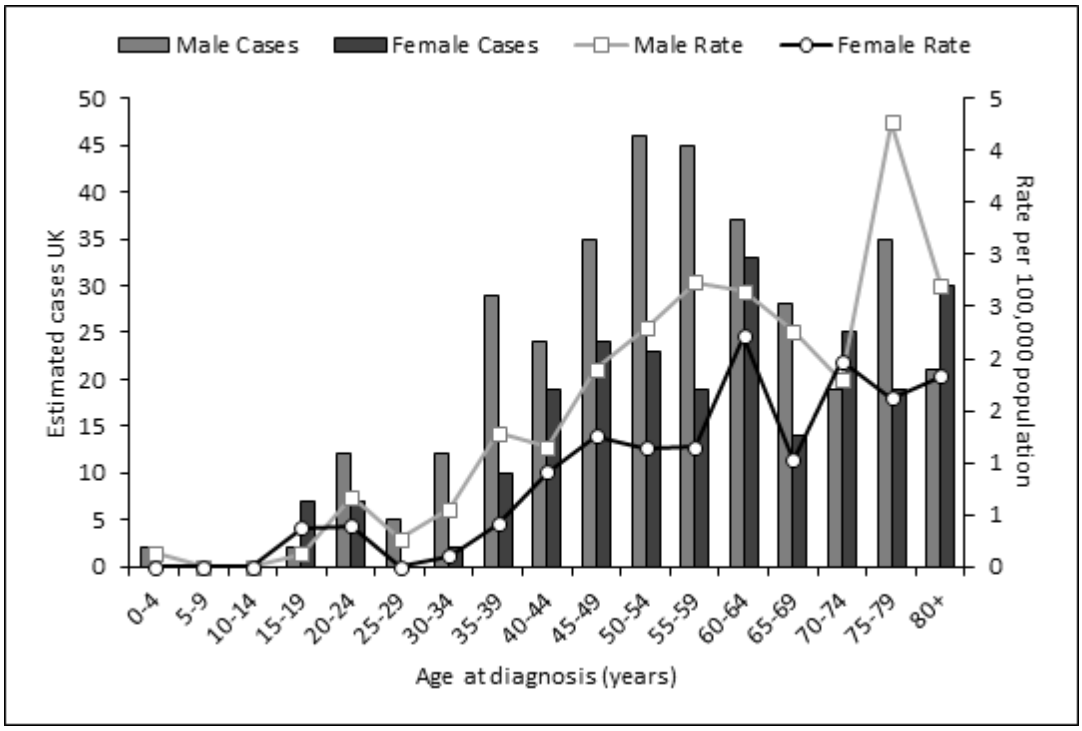
CML occurs in all age groups, but is most common in older adults and the median age at diagnosis is 59.1 years. A French study has shown that the prevalence of CML is increasing. In the pre-imatinib era, prevalence increased 4.1% annually (from 1998 to 2002), however, since the introduction of imatinib a mean annual increase of 9.3% has been observed (from 2003 to 2007). Apart from the impact of imatinib, better diagnosis and an aging population may play a part in increasing prevalence.

In 2003, the prevalence of CML in England and Wales was estimated at 2,660. Therefore, assuming a mean annual increase in cases of 9.3% since then, current prevalence of CML in England and Wales is estimated at 5,922.

(Source: Pfizer submission, p24)

Figure 2 shows the HMRN gender and age specific incidence estimates for CML.

Figure 2. Estimated age-specific incidence of CML[19]



Pfizer's estimates of the annual incidence of patients in the unmet need population at each phase of CML are given in Appendix A. In summary, they assume that bosutinib will be used mostly 4th-line, after 3 previous lines of TKIs: 12 patients p.a. 2nd-line, 19 p.a. 3rd-line and 49 p.a. 4th-line.

2.1.3 Prognosis

> If left untreated CML will typically progress from the CP to the AP in 3-5 years, and then to BP within 6-24 months. Median survival in the BP, without treatment, is around 6 months. As such, the typical life expectancy for a CML patient diagnosed in CP is around 4-7 years without treatment.
>
> The majority (>90%) of patients are diagnosed with CML in CP. Imatinib currently represents the established first-line treatment for these CP CML patients in clinical practice, having replaced interferon alpha upon its introduction. This new treatment paradigm has led to a dramatic improvement in the prognosis for patients diagnosed with CP CML. The estimated median survival with imatinib exceeds 25 years with median age of diagnosis of almost 60 years.
>
> Patients who respond well to standard-dose imatinib treatment (approximately 55% of patients) will often continue to receive this treatment for life and have a normal life expectancy.

(Source: Pfizer submission, p24)

We agree with Pfizer's statement above. However, our clinical advisor suggests that whilst imatinib used to be the 1st-line treatment of choice, nilotinib is now preferred given the recent NICE TA251 guidance. Treatments and clinical pathways are discussed in detail in Section 2.2.1, p43.

Two prognostic staging scores, developed prior TKI treatments, are available: the Sokal[20] and the Hasford[21] scores. Risk factors are used to determine if a patient is at a low, intermediate or high risk of death. In addition, The European Treatment and Outcome Study (EUTOS) prognostic scoring system was developed after the first TKI was introduced.[22] Although the Sokal and Hasford scores were briefly mentioned in the submission (Pfizer submission, p24), no risk factors were reported for Study 200 participants. While risk factors may allow comparisons across studies, our clinical advisor suggests they are not used to make treatment decisions.

2.1.4 Quality of life

We agree with Pfizer's description of HRQL for CML patients:

> Patients in the CP may experience mild and non-specific symptoms such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss. Approximately 40% of CP patients are asymptomatic and diagnosed as a result of a routine blood test. Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising,

bleeding and infections. In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease.

Health-Related Quality of Life (HRQL) for CML patients can vary greatly, depending on the treatment regime used. The introduction of effective therapies such as those of the TKI class has led to improvements in the HRQL of CML patients. In contrast, there is some evidence that CML patients treated long-term with interferon alpha may experience reduced HRQL.

(Source: Pfizer submission, p23)

2.1.5 Rationale for bosutinib

Treatment options are limited for patients who have previously tried all three currently available TKIs (i.e. fourth-line patients) or second- and third-line patients for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. There is a clear unmet need for an effective treatment for these patients, the majority of who will currently be managed with hydroxycarbamide, which represents best supportive care (BSC).

(Source: Pfizer submission, p25)

Mutations in the BCR-ABL kinase domain often lead to imatinib resistance, particularly secondary resistance, and are often responsible for treatment failure:

The proposed indication for bosutinib is as a treatment for patients who have been previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are inappropriate. In some cases, a patient may be inappropriate for one of these TKIs as a result of the presence of Bcr-Abl mutations that confer resistance to currently available TKIs. Bosutinib has demonstrated clinical activity in CML patients with mutations that confer resistance to currently available TKIs. In a study of CP CML patients, treatment with bosutinib in the third-line setting resulted in complete haematological responses and major cytogenetic responses across a broad range of Bcr-Abl mutants, including those conferring clinical resistance to nilotinib (Y253H, E255K/V, F359C/I/V) and dasatinib (F317L). Efficacy of bosutinib in CML patients with a broad range of Bcr-Abl mutations have also been demonstrated for bosutinib in a second-line setting. Bosutinib is therefore innovative in its potential to treat a patient group, with unmet needs, which is identifiable by its genetic characteristics: Bcr-Abl kinase mutations conferring resistance to current TKIs.

(Source: Pfizer submission, p33)

Unfortunately Bosutinib was found to be ineffective in patients with the T315I gatekeeper mutation.[23]

2.2 Critique of manufacturer's overview of current service provision

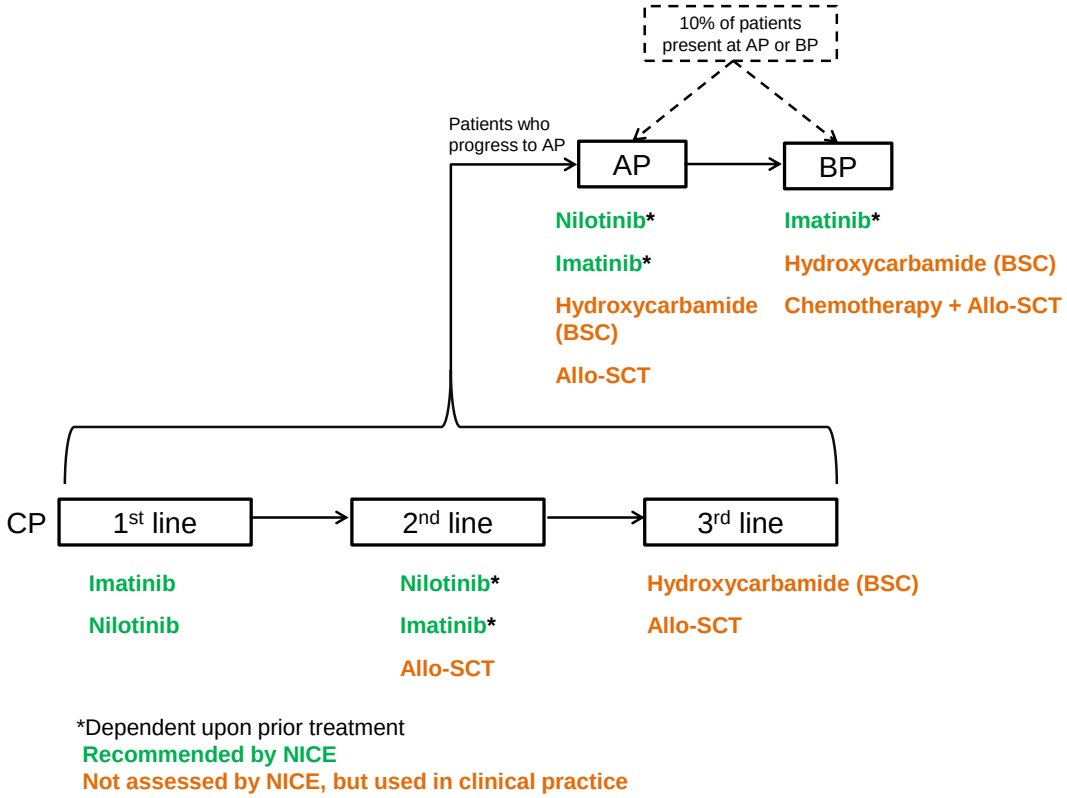
2.2.1 Current treatments for CML

We agree with Pfizer's assertion (Pfizer submission, p27) that the previous NICE technology appraisals that are relevant to the current appraisal are:

- TA251, 2012, 'Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)'.
- TA241, 2012, 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review TA70) and dasatinib and nilotinib for people with chronic myeloid leukaemia for whom treatment with imatinib has failed because of intolerance'.
- TA70, 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia. This guidance has now been partially updated by TA241 and TA251.

We further agree with Pfizer's summary of NICE recommended treatments for Ph+ CML, as shown in Figure 3 and in the text below (p28 Pfizer submission, p28).

Figure 3. NICE recommended clinical pathway of care



(Source: Pfizer submission, Figure A2)

NICE recommendations for 1st-line treatment are as follows (Figure 3):

- Nilotinib and standard-dose imatinib in CP CML (TA251).
- Dasatinib is not recommended for 1St-line use in CP, despite having an EMA marketing authorisation (TA251).
- Imatinib for CML that initially presents in AP or BP or that initially presents in CP and then progresses to AP or BP if imatinib has not been used previously.

NICE recommendations for 2nd-line treatment are as follows (Figure 3):

- Nilotinib for the treatment of CP or AP that is resistant or intolerant to standard dose imatinib (TA241).
- Dasatinib is not recommended for 2nd-line use for any phase of CML, despite having an EMA marketing authorisation (TA241).
- High-dose imatinib is not recommended for 2nd-line use for any phase of CML (TA241).
- NICE recommendations allow for the use of standard-dose imatinib 2nd-line after treatment with 1st-line nilotinib.
- NICE does not make any recommendations for treatment of patients in BP that is resistant or intolerant to standard-dose imatinib.

The following claim from Pfizer (Pfizer submission, p29) seems reasonable:

> There remains significant unmet need in the treatment of CP, AP and BP CML. Development of resistance, progression of disease despite treatment and intolerance to the currently recommended TKIs (imatinib, nilotinib and dasatinib) pose a significant challenge in the treatment of these patients and may cause withdrawal of therapy and can adversely affect compliance and outcomes. Furthermore, the presence of specific mutations or co-morbidities may render current therapies inappropriate. Hydroxycarbamide represents the main option in this patient population and therefore equates to best supportive care (BSC) for these patients. Given the limited efficacy of hydroxycarbamide (BSC), these patients represent a population of significant unmet need, for whom bosutinib offers an effective alternative.

We also agree with Pfizer's statements concerning the use of allogeneic stem cell transplantation (SCT) as follows (Pfizer submission, pp30–31):

> SCT is a treatment option for patients in CP, AP and BP and may be used in patients who have failed (due to lack of efficacy or tolerability) on currently available TKIs or for whom TKIs are inappropriate. In BP, SCT is typically preceded by treatment with acute leukaemia-style chemotherapy to try and establish haematological control. Bosutinib may therefore be considered as an alternative to SCT in CP, AP and BP patients, however as noted in Section 2.3 [Pfizer submission],

SCT is restricted by the number of matched donors available and is associated with high levels of morbidity and mortality.

The probability of success of this procedure is influenced by many factors, including (but not limited to): patient age, timing of the transplant, availability of a matched donor and level of progression of the disease. Therefore, SCT does not occupy a single, well-defined space in the CML pathway of care and could be applied at various stages of this pathway depending upon a complement of patient-related factors and the preference of the responsible physicians. This tends to be reflected in the evidence base for SCT, whereby the population is frequently heterogeneous including patients at different lines of treatment and even phases of CML. Additionally, its use in patients who are not suitable for or who have failed on all currently available TKIs is not known.

2.2.2 Bosutinib use in 2nd-, 3rd- and 4th-line treatment

Here we discuss the likely relative use of bosutinib across 2nd-, 3rd- and 4th-line lines of treatment. This is important because this dictates the most relevant clinical data to use in the economic model.

Pfizer assume that bosutinib will be used mostly 4th-line, after 3 previous lines of TKIs. In particular, they assume 12 patients p.a. 2nd-line, 19 p.a. 3rd-line and 49 p.a. 4th-line (Appendix A). For their economic model, Pfizer use clinical data from 3rd-line bosutinib as justified below:

With regards to the use of bosutinib in CP in practice, very few second-line patients are likely to be unsuitable for imatinib, nilotinib and dasatinib. As such, the third-line cohort from Study 200 is the focus for this submission as this is more likely to be representative of the patients expected in clinical practice, the majority of whom will likely be at least third-line. Data from the second-line CP CML patient population are only presented in Appendix 10.15 [Pfizer submission] for completeness.

(Source: Pfizer submission, p46)

Pfizer indicate that if 4th-line data were available from Study 200, they would have used this in their model (Pfizer submission, Section 7.2.1, p108).

Pfizer assume that most patients will receive imatinib 1st-line, and that dasatinib will be available in England & Wales, despite not being recommended by NICE in TA241 and TA251. They justify this by its current use under the Cancer Drugs Fund or individual funding requests (IFR).

By contrast, we believe that, if recommended by NICE, bosutinib will be used most often either as 2nd- or 3rd-line treatment, but rarely 4th-line.

Both imatinib and nilotinib, but not dasatinib, are recommended by NICE as 1st- and 2nd-line treatments in CP. Since NICE's TA251 recommendations, we understand that nilotinib has replaced imatinib as the 1st-line TKI of choice because it is similar in action to, but more potent than imatinib. Further, we understand that clinicians would be unlikely to use imatinib after nilotinib failure for the same reason. Dr Byrne, representing the Royal College of Pathologists and the BSH, appears to agree, stating (in a statement to NICE for this appraisal):

> Since an increasing number of patients are now receiving Nilotinib as a 1st-line treatment, this limits its usefulness as a 2nd-line agent in these patients. Furthermore as Nilotinib is generally accepted as a more potent bcr-abl inhibitor than Imatinib, with activity in many but not all the known mutations, there is little point in switching patients who have failed Nilotinib to Imatinib. However, Imatinib may be useful as a 2nd-line agent for patients experiencing toxicity on Nilotinib.

In contrast to Pfizer, we assume that dasatinib will be used only rarely from 2014 because we understand that the Cancer Drugs Fund is due either to end completely or to be scaled down in 2014, and because NICE have not recommended it for 1st- or 2nd-line use.

We imagine that if bosutinib were recommended by NICE in this appraisal, it will be used most heavily 2nd-line, after nilotinib, given that clinicians would be disinclined to use imatinib 2nd-line as it is less potent than nilotinib and given that dasatinib would not be available. However, it is possible that, at least initially, clinicians may prefer to delay use of bosutinib because they will be unfamiliar with it and because of the rather high treatment discontinuation rates. In this case, the preferred treatment sequence may be nilotinib then imatinib then bosutinib, i.e. bosutinib 3rd-line.

Bosutinib has a licence for patients who are unsuitable for imatinib, nilotinib and dasatinib. If it did not have this restriction, we imagine that it would be the 2nd-line treatment of choice after nilotinib. In particular, it is possible that most of the predicted 234 p.a. patients who Pfizer predict to fail on a 1st-line TKI would be treated with bosutinib 2nd-line. However, most patients who fail on 1st-line nilotinib will be suited to either imatinib or dasatinib. Given the restriction of the licence for bosutinib, these patients would then not be eligible for bosutinib, and they would instead likely receive 2nd-line imatinib, HU or SCT.

[redacted]. However, for the reasons given above, we imagine these sequences of treatment will be less likely to be relevant from 2014, given

that now most patients receive 1st-line nilotinib and we predict that dasatinib will rarely be used from 2014.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency (see Section 3.2 below).

The clinical evidence for bosutinib is taken entirely from Study 200, a single arm trial. The fitness of patients in this trial, as measured by ECOG, is representative of patients in clinical practice in England & Wales. However, the main weakness in the relevance of this evidence to the patient population in question is that most patients in this trial were suited to imatinib, nilotinib or dasatinib. Indeed, only 52 out of a total of 546 patients in Study 200 were not suited to all TKIs.

Other, probably more minor, weakness of Study 200 are that: (a) approx. 40% of patients had previously taken IFN, but IFN is now virtually never given for CML in the UK and (b) all patients had previously been treated with imatinib, but we understand that since TA251, 1st-line treatment for CML is now usually nilotinib.

3.2 Intervention

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

Pfizer state (Pfizer submission, p18):

> European Medicines Agency (EMA) filing originally occurred on 29th July 2011 for the indication stated below. This application was initially based on data from a pivotal phase III study, 3160A4-3000-WW (Study 3000). This was a randomised, open-label study comparison with imatinib. At this time the proposed indication applied for was:
>
> Bosutinib is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph^+ CML) in chronic phase (CP).

In this RCT, bosutinib failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib. Furthermore, toxicity with bosutinib was more pronounced than with imatinib. (EMA assessment report for bosutinib, Jan 2013).

Pfizer continue (p18 submission):

> Following ongoing discussions with the EMA, Pfizer agreed to revise the indication for bosutinib to:
>
> Bosutinib is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
>
> On the 17th January 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for bosutinib in this indication.
>
> In addition, the COMP adopted a positive opinion on the maintenance of orphan designation for bosutinib in EU in this indication on February 13th 2013

The final EPAR is now available on the EMA website.

3.3 Comparators

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML),
- Hydroxycarbamide,
- Interferon alpha,
- Best supportive care.

The comparators in the submission are as in the Scope, but without "best supportive care". Pfizer justify this by saying that hydroxycarbamide is accepted as best supportive care (Pfizer submission, p31), and we agree.

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 2.2.2, p45).

3.4 Outcomes

The outcomes in the Final Scope are as follows:

- overall survival,
- event-free survival,
- progression-free survival,
- time to progression,
- response rates: cytogenetic, haematological and molecular, including time to response and duration of response
- time to treatment failure
- adverse effects of treatment
- health-related quality of life

Pfizer consider all these outcomes in their submission. In addition, they consider rates of transformation from CP to AP/BP CML.

One important limitation of Pfizer's economic analysis is that, given that overall survival (OS) is immature for CP patients in Study 200, they estimate OS using a surrogate relationship based on the rate of major cytogenetic response.

The EQ-5D was used in Study 200, which is NICE's preferred instrument for measured health-related quality of life.

3.5 Other relevant factors

Pfizer present a discussion on matters of equity (Pfizer submission, p33) in which they state:

> There are no specific equality issues relating to bosutinib itself, however, the inclusion of bosutinib as an additional treatment option in the clinical pathway of care may help to address some of the equality issues associated with SCT, […]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

We validated the search strategy, critically appraised the systematic reviews described in Pfizer submission and critically appraised both the single arm phase I/II trial Study 200, the base of clinical effectiveness for bosutinib, as well as the studies with comparator data evidence. The power calculations for Study 200 were also re-run. The work has been undertaken between 11 March and 15 May 2013.

4.1.1 Searches

Pfizer provided detailed information on the search strategy. The complete search strategy (as included in Pfizer submission) is presented in Appendix B. In summary, the following search approach was used in Pfizer submission:

The following electronic databases were searched:

Medline (R) In-Process & Other Non-Indexed Citations
(searched from 1946 to January 21st 2013)
Ovid MEDLINE (R) 1946 to present (via OVID; searched from 1946 to January 21st 2013)
EMBASE, 1980 to present (via OVID; searched from 1974 to January 18th 2013)
The Cochrane Library (via OVID), searching the following databases:
The Cochrane Central Register of Controlled Trials (CENTRAL; searched to December 2012)
The Cochrane Database of Systematic Reviews (Cochrane Reviews; searches from 2005 to December 2012)
The Database of Abstracts of Reviews of Effects (DARE; searched 4th Quarter 2012)
The Health Technology Assessment Database (HTA; searched 4th Quarter 2012)
NHS Economic Evaluation Database (searched 4th Quarter 2012)

The following conference proceedings were searched (2010-2012):

American Society of Haematology (ASH)
American Society of Clinical Oncology (ASCO)
European Haematology Association (EHA)

(Source: Pfizer submission, adapted from Appendix 2, p201)

The searches were run in January 2013. The search strategy for the electronic databases took terms for CML and combined this with terms for imatinib (though this was restricted to incidences of intolerance, failure or resistance), hydroxycarbamide, stem cell transplantation, interferon, and bosutinib. A limit to systematic reviews and trials was used for this search. No separate searches were conducted for adverse event (AE). This could have compromised AE information.

In summary, the literature searching and search methods were found appropriate to the research question.

4.1.2 Inclusion criteria

Because of the lack of RCT evidence, the submission included separate clinical evidence for bosutinib and bosutinib comparators. The following study designs were included:

No RCTs were identified in the systematic review that specifically matched the licensed population for bosutinib. The data on which the license has been derived comes from a single-arm study, Study 200. The Study 200 Clinical Study Report (CSR), provides data across four cohorts of patients recruited separately into the study. In addition, a number of publications and conference abstracts/posters based on Study 200 are also available and are presented in this submission.

(Source: Pfizer submission, p44)

Comparators

No studies specifically evaluating comparator treatments in patients for whom imatinib, nilotinib and dasatinib are unsuitable were found. However, the systematic review identified 13 comparator studies that, like bosutinib, considered the use of the comparators in the broad second-line or later populations, in CP, AP and BP.

(Source: Pfizer submission, p48)

Inclusion and exclusion criteria as described in Table 12 are appropriate.

Table 12. Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years) with CP, AP and/or BP CML who have failed imatinib treatment	
Interventions/Comparators	• Bosutinib • Interferon alpha • Hydroxycarbamide (hydroxyurea) • SCT	
Outcomes	Efficacy: • Treatment response rates (including molecular, cytogenetic and haematological responses) • Time to- and duration of response • Overall survival • Event-free survival • Progression-free survival • Time to treatment failure • Health-related quality of life Safety/Tolerability: • Adverse events (all grades) • Incidence of serious adverse events	
Study design	• Prospective randomised controlled trials (RCTs) • Observational studies	Single case studies
Language	English abstracts of foreign language publications	Non-English publications

(Source: Pfizer submission, Table B1, p43)

4.1.3 Critique of data extraction

The submission explains the processes used in study selection and data extraction which is in line with the standard review process. The screening of the literature was performed by one reviewer and inclusion and exclusion criteria were verified by a second reviewer. Any disputes were resolved by a third party. The following data extraction strategy was used:

Results from database searches were downloaded into a bespoke Access® database, which was used to manage citation screening. Following full-text review and identification of studies to be included, data was extracted into a Data Extraction Table (DET). The DET included, but was not limited to, the following column headings:

- Country
- Study design
- Number of patients
- Key inclusion and exclusion criteria including subgroups
- Baseline characteristics
- Outcomes reported as summarised on page 6
- Likelihood of bias (quality components)

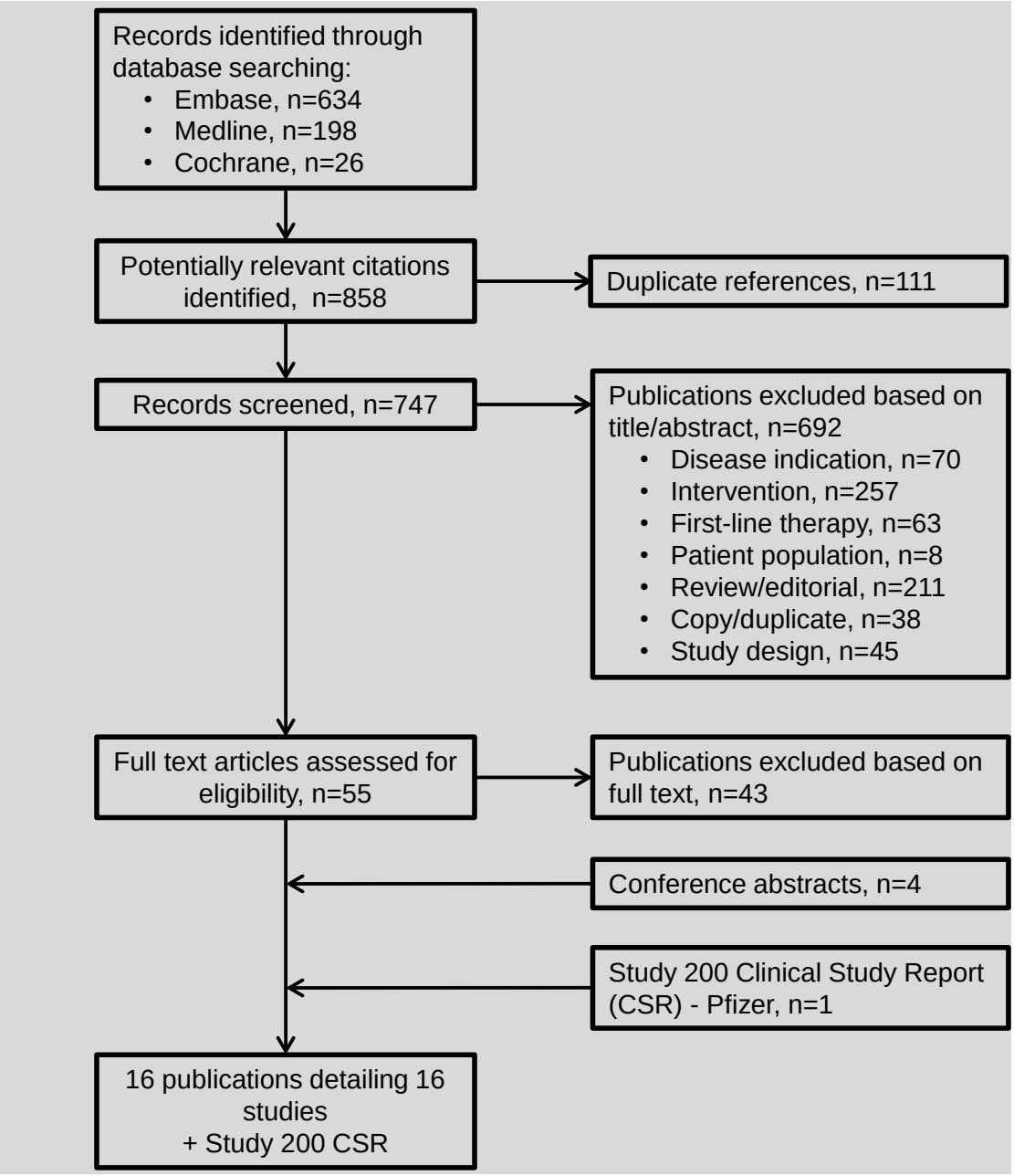
This data extraction was performed by one reviewer and verified by a second party.

(Source: Pfizer submission, Appendix 10.2.7, p212)

Overall, 16 studies were identified (Figure 4, p55), of these 13[3-15] reported on comparator treatments, and three[24-26] reported on bosutinib. All bosutinib studies are related to phase I/II Study 200 (NCT00261846; 3160A4-200). Further information on Study 200 was extracted from the Pfizer CSR,[27] and two conference posters based on Study 200 were identified.[1, 28] In addition, a similar on-going phase I/II study trial (NCT00811070; 3160A4-2203) evaluating bosutinib in Japanese subjects is expected to be completed in September 2014. Both Study 200 and the trial evaluating bosutinib in Japanese subjects, are Pfizer funded studies.

[redacted] Pfizer did not supply us with any information about the results from the Japanese trial. However, we found that some information on this phase I/II trial was reported in the EMA assessment report for Bosulif.[29] Given that Study 200 is a large multi-centre trial (conducted in North America, the European Union, Eastern Europe, Africa and Asia), and includes patients in all stages of CML, we believe that the lack of the results from the Japanese population (N=53) is not a significant weakness of the submission. In addition, one more study based on Study 200 and not identified in the submission, a study reporting baseline HRQL,[30] was identified.

Figure 4. Flow diagram of included studies



(Source: Pfizer submission, Figure B1, p44)

4.1.4 Quality assessment

We will now discuss Study 200, the clinical evidence for the comparator treatments is discussed in 4.3 (p95). Pfizer's quality assessment of Study 200 was performed according to the Chambers (2009) criteria for case series studies.[16] Further information on the quality assessment criteria can be found in Appendix C.

The most challenging aspect of the Study 200 quality assessment critique is its non-randomised single arm design. The design of single-arm studies makes it difficult to assess and generalise results. Results from non-randomised studies may differ from RCT evidence and case series design is considered to be the weakest source of clinical effectiveness evidence in the hierarchy of study designs. Interestingly, case series evidence was considered in 14 out of 47 Heath Technology Assessment reports.[31] While RCTs are designed to maximise internal validity, it can be argued that large, prospective and comprehensive case series may achieve high external validity. Study 200 was a multicentre trial and recruited people consecutively, which could reduce the risk of bias. There is no agreed 'gold standard' appraisal tool for the assessment of non-randomised studies.[32] The Cochrane handbook suggests that reviewers should select and modify or develop a tool that is most appropriate to their topic and the study design.[33] Similarly, the Centre for Reviews and Dissemination (CRD)[34] recommends considering the appropriateness of study design to the research objective, risk of bias, other issues related to study quality, choice of outcome measure, statistical issues, quality of reporting, quality of the intervention and generalizability in a quality assessment of any study. Therefore we will comment on both internal and external validity of Study 200 in addition to the Chambers (2009) criteria.[16] Details of the manufacturer's critical appraisal of Study 200 alongside our critique can be seen in Table 13.

Table 13. Quality assessment of Study 200 using Chambers (2009)[16] criteria

Study	1. Eligibility criteria adequately reported?	2. Study population representative of a normal population?	3. An appropriate measure of variability reported?	4. Loss to follow-up reported or explained?	5. At least 90% included at baseline followed-up?	6. Were patients recruited prospectively?	7. Were patients recruited consecutively?	8. Did the study report relevant prognostic factors?	Quality score
Bosutinib, advanced disease study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 2nd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Bosutinib, 3rd-line CP CML study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
PenTAG comment	Yes	Yes	Yes	Partially, see section below for more details.	Yes	Yes.	Yes, based on information in this table.	Partially, no risk factors reported.	Good, assuming "partially" is "yes".

4.1.4.1 Internal validity

Selection bias

Full details of Study 200 recruitment procedures are not given. It is not clear whether all eligible patients were invited, or if investigators' discretion affected those included. However, Pfizer states that participants were recruited consecutively in the quality assessment of Study 200 (Pfizer submission, p246) and details for recruited participants are given. Analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. Table 14 shows the difference between recruited and evaluable populations for CML disease phases at different snapshots.

The eligibility criteria allowed investigators to exclude participants if they were considered unable to take daily oral medication reliably. While this is reasonable, it may have allowed some potential for investigators to influence which participants were included.

Table 14. Recruited and evaluable population in Study 200

Population	**CP2L (N=288)**		**CP3L (N=118)**		**AP(N=76)**	**BP(N=64)**
Outcome	March 2011 snapshot evaluable population	February 2012 snapshot evaluable population	March 2011 snapshot evaluable population	February 2012 snapshot evaluable population	March 2011 snapshot evaluable population	March 2011 snapshot evaluable population
Cytogenetic	266	264	108	110	69	54
Haematological	288	285	116	115	69	60
Molecular	200	NR	105[a]	NR	NR	NR

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, N = number of participants, NR = not reported

a Excluded 13 subjects from China, India, Russia and South Africa, where molecular assessment was not performed due to logistical constraints

Performance bias

The dosage of bosutinib in Study 200 was 500mg once daily. Escalation to 600mg in case of haematological or cytological resistance, or reduction to 400 mg and 300mg once daily in case of AE was possible and the protocol for drug dosage was described. Eighty five subjects (15.2%) who started treatment at ≤ 500 mg (n=558) received dose escalations to 600 mg. Detailed information on treatment interruption was requested by PenTAG (Table 15). However, only some information is given for bosutinib dose reduction.

Table 15. Mean days of treatment interruption in Study 200

	CP2L (N=288)	CP3L (N=118)	AP (N=76)	BP (N=64)
Patients with an interruption [N (%)]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days interrupted [Mean (SD)]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Pfizer clarifications, question B5)

Patients were allowed to receive hydroxycarbamide and anagrelide while taking part in Study 200. In addition, patients after SCT or with previous interferon alpha therapy were eligible to take a part. It is not clear if anagrelide or previous SCT and interferon alpha treatment may have an effect on the expected outcomes in Study 200. In fact, 52% of 3rd-line CP patients and 32% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy. Since other than as a bridge to SCT, interferon alpha therapy is hardly used in England and Wales, it increases the uncertainty of Study 200 relevance to the expected clinical population.

Only some data were available on patient compliance with the treatment regiments. One participant (1%) was excluded based on protocol violation in the third line CP CML population.

Detection and reporting bias

No blinding was reported; investigators, care providers and patients were aware that bosutinib was the test drug. This could influence outcomes reporting, especially AE and HRQL, reflecting an understandable enthusiasm for a new drug therapy. However, since the main outcomes are measured objectively, they are less likely to be affected.

Attrition bias

Only 2 patients (0.7%) were lost to follow up in the March 2011 snapshot of second line CP CML patients. Similarly, 2 patients (2%) were lost to follow up in the March 2011 snapshot of third line CP CML patients. At the same snapshot, 3 participants requested treatment discontinuation in third line CP CML. No data are available on the numbers of patients lost to follow up in advanced phase CML.

4.1.4.2 External validity

Patients' characteristics

The full baseline characteristics are discussed in Section 4.2.5 (p69); here we discuss potential threats to external validity. Firstly, Study 200 was not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate (population of unmet clinical need appropriate for

this appraisal). The submission assumes that Study 200 is representative of the population expected in clinical practice. Although based on EMA recommendation, post-hoc analyses of the population of unmet clinical need are available; only 52 patients from Study 200 were eligible. In addition, the submission assumes that mostly third and fourth line patients would be eligible, thus the cost-effectiveness model is based on third-line CP, and combined second-line and multiple TKI AP and BP Study 200 sub-populations. However, we believe that based on current practice, if recommended, bosutinib would be mostly used in second and third line setting (see Section 2.2.2, p45).

Secondly, all patients in Study 200 had previously taken imatinib. Pfizer report the median duration of previous imatinib in the 2nd-line bosutinib chronic phase population as 2.6 years for imatinib-resistant people and as 1.5 years for imatinib-intolerant people (Pfizer submission, p350). Similarly, they report the median duration of previous imatinib in the 3rd-line CP population as 2.7 years (Pfizer submission, p54). However, these durations are much lower than the median of 8 years on 1st-line imatinib in the IRIS trial.[17] We are unable to account for this large discrepancy. We believe that if patients in Study 200 were truly representative of people who fail on imatinib, their median duration of imatinib should be approximately 8 years.

In addition, in third line CP CML, 37 patients were resistant to dasatinib, 50 were intolerant to dasatinib, 27 were resistant to nilotinib and only 1 was intolerant to nilotinib. The patients' characteristics for the third line CP subgroups were similar (Section 4.2.5, p69) to those of all patients in Study 200 (Table 16). We cannot explain why there was only 1 third line patient intolerant to nilotinib. While we cannot comment on treatment effects for nilotinib resistant patients in third line CP CML, the lack of participants in the nilotinib resistant sub-group may have been due to a small sample size.

Table 16. Baseline characteristics for Study 200

	CP2L (N=288)	**CP3L (N=118)**	**AP (N=76)**	**BP (N=64)**	**Unmet clinical need (N=52)**
Age (years) [Median (range)]	53 (18–91)	56 (20–79)	50.5 (18–83)	48.5 (19–82)	58 (19–81)
Male [N (%)]	154 (53%)	53 (45%)	42 (55%)	41 (64%)	31 (60)
Duration of CML disease (years) [Median (range)]	3.6 (0.1–15.1)	6.7 (0.6–18.3)	5.06 (1.11–22.06)	3.08 (0.35–14.46)	NR

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, N = number of participants, NR = not reported

Unsuitability was determined based on Bcr-Abl kinase domain mutations that would be reasonably expected to confer resistance to dasatinib (F317, E255) or nilotinib (E255, Y253, F359) and expected to have sensitivity to bosutinib, or the presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatinib therapy (for more details see Appendix G). Although Pfizer does not propose bosutinib use in patients with T315I mutation, no exclusion criteria for bosutinib use in CML patients was included in the submission.

Mutations T315I and V299L appear to be resistant to bosutinib,[23] Pfizer acknowledged this (Pfizer submission, p14). Indeed, patients with a documented history of prior T315I Bcr-Abl mutation were excluded from Study 200 as of 10 June 2008 due to a lack of efficacy in this group. This change in eligibility criteria resulted in inclusion of some participants with T315I mutation in Study 200. In addition, some participants with V299L may have been included. In fact, 2 participants with V299L were identified in third line CP CML population. Table 17 summarises the efficacy based on the different mutations. Although the numbers of recruited patients with a baseline T315I mutation were small (Appendix H), it may have caused more stringent efficacy estimates.

Table 17. Efficacy in full Study 200 evaluable populations versus those with a baseline T315I and V299L mutations

	Evaluable population		**T315I subpopulation**		**V299L subpopulation**	
	CHR	*MCyR*	*CHR*	*MCyR*	*CHR*	*MCyR*
CP2L	85.0%	53.4%	22.2%	22.2%	50%	0%
CP3L	73.3%	38.9%	28.6%	0%	NA	NA
Advanced phase	25.6%	32.5%	0%	7.7%	NA	NA

Abbreviations: CHR = Complete Haematological Response, MCyR = Major Cytogenetic Response, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable (no patients with V299L mutation identified)
(Source: Pfizer clarifications, question A2; Pfizer submission, Table B19, p71)

Co-morbidity

Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 were excluded from CP CML population and patients with a score of 3 were excluded from advanced phase leukaemia population. Thus 74% and 77% patients were ECOG 0 and 26% and 23% were ECOG 1 in third and second line CP CML respectively. Similarly, in accelerated phase, 54% were ECOG 0, 43% ECOG 1, 3% ECOG 2, and in blast phase, 34% were ECOG 0, 44% ECOG 1, 22% ECOG 2. Our clinical expert believes that these values are similar to those expected in clinical population. Patients

with liver, kidney and severe cardiac disease were excluded; for details on co-morbidities exclusion criteria see Appendix D.

Duration of response

The length of follow up for patients in Study 200 varied. Patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, whereas all patients still on bosutinib were followed up whilst on bosutinib. Thus the OS may be over-estimated because of selective censoring of patients, and this is acknowledged by Pfizer (Pfizer submission, p119).

Statistical analyses

For all populations (disease phases), analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. Intention-to-treat analyses were not reported; this may have resulted in more generous response estimates. PFS and OS were calculated based on all enrolled patients who received at least one dose of bosutinib. All patients who received at least 1 dose of bosutinib (the all-treated population) were also included in the analysis of safety. In addition, no adjustments for multiple comparisons were made for secondary or exploratory analyses (Pfizer response to clarification question A4).

4.2 Critique of clinical evidence for bosutinib

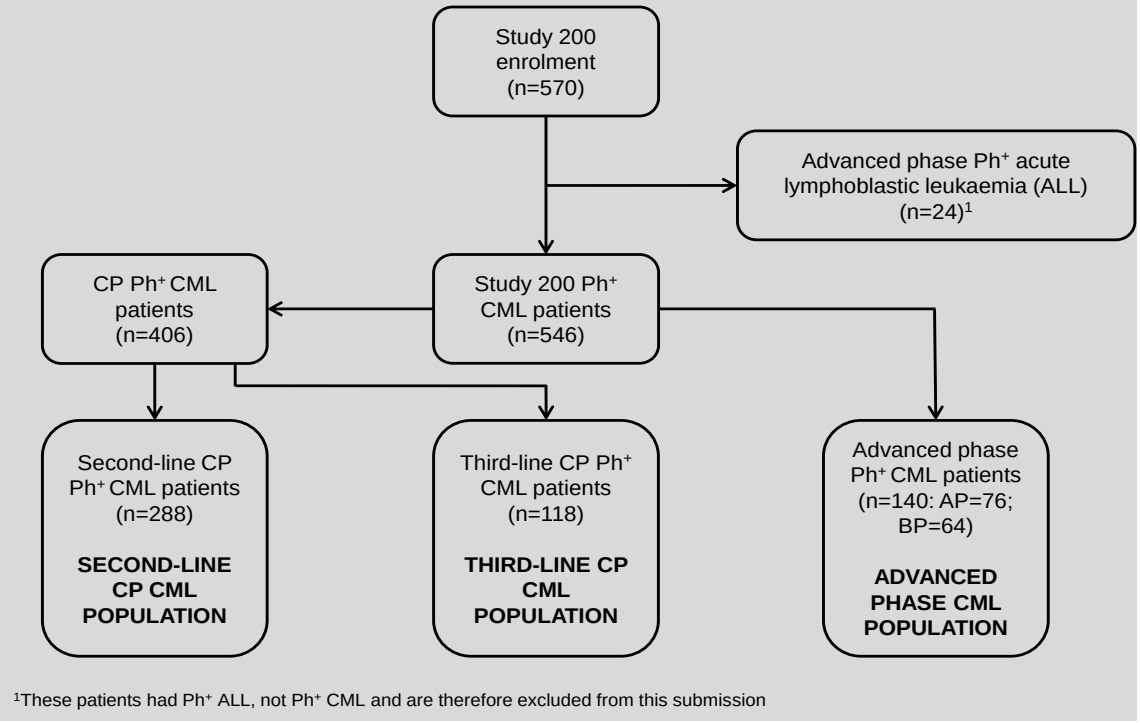
The search results presented by the manufacturer did not identify any randomised controlled trials directly comparing bosutinib with an appropriate comparator. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML:

- **Phase I** of this study defined the maximum tolerated dose of bosutinib in 18 Chronic Phase (CP) CML patients refractory to imatinib
- **Phase II** (n=570, including 18 patients enrolled in Phase I) investigates the efficacy and safety of bosutinib 500mg daily in four clinical sub-populations:
    - Second-line CP CML: Patients in CP CML with imatinib resistance or intolerance (n=288)
    - Third-line CP CML: Patients with imatinib resistance/intolerance followed by dasatinib resistance/intolerance or nilotinib resistance/intolerance or both dasatinib and nilotinib resistance/intolerance (n=118). This population also includes 3 patients who had prior exposure to imatinib, dasatinib and nilotinib, thus received bosutinib in fourth-line setting.

- Advanced phase CML: Patients with imatinib resistance/intolerance or resistance/intolerance to imatinib, dasatinib and/or nilotinib (n=140). This population includes patients receiving bosutinib second line or later:
  - Second line AP CML (n=45)
  - Multi TKI AP CML (n=31)
  - Second line BP CML (n=35)
  - Multi TKI BP CML (n=29)
- Acute lymphoblastic leukaemia: Patients with imatinib resistance or intolerance (n=24)

Figure 5 represents participants' flow in Study 200.

Figure 5. Study 200 participant flow diagram



(Source: Pfizer submission, Figure B2, p50)

Pfizer submission acknowledges that Study 200 was not specifically designed to evaluate patients for whom imatinib, dasatinib and nilotinib are inappropriate (population of unmet clinical need). However, Study 200 is the only study that evaluates bosutinib in patients who have tried one or more prior TKI therapy (i.e. received bosutinib at second-line or later). The Committee for Medicinal Products for Human Use (CHMP) accepted Study 200 to be representative of the population of unmet clinical need. In addition, based on EMA (European Medicines Agency) recommendations, post-hoc analyses of patients with unmet clinical need from Study 200 were performed.

We agree that after excluding Phase I and the sub-population of acute lymphoblastic leukaemia (Phase II), the results from Study 200 are relevant to the research question. For participant flow of the sub-populations please see Appendix F. A total of 52 patients were eligible for inclusion in the post-hoc analysis of unmet clinical need population based on the presence of a mutation, a medical condition, or prior toxicities that may predispose patients to be unsuitable to nilotinib or dasatinib therapy (Appendix F).

Even though there is only one study assessed in the clinical effectiveness review, multiple references and various data snapshots of Study 200 are available (Table 18).

Table 18. Data sources for Study 200 populations

Third-line CP CML population	Second-line CP CML population	Advanced phase population (AP and BP)
Data snapshot 28 Mar 2011 (minimum/median follow-up: 12/28.5 months): • Khoury (2012)[25] • CSR[27] Data snapshot 15 Feb 2012 (minimum/median follow-up: 24/31.4 months): • Khoury (2012)[28]	Data snapshot 3rd June 2010 (24.2 months median follow-up): • Cortes (2011)[24] Data snapshot 28th March 2011 (24 month minimum follow-up): • CSR[27] Data snapshot 15th May 2012 (36 month minimum follow-up update): • Cortes (2012)[1] HRQL data • Trask (2012)[26]	Data snapshot 28 Mar 2011 (minimum follow-up: 12 months for AP; 18 months for BP): • CSR[27]
Baseline HRQL data • Trask (2013)[30]		

4.2.1 Eligibility criteria

Study 200 evaluates bosutinib in patients who have tried one or more prior TKI therapy. Appendix D lists the Study 200 eligibility criteria. The difference between the Study 200 population and the population defined in Pfizer submission (population of unmet clinical need) was already noted. In addition, criteria that we felt may have an effect on the generalizability of the Study 200 results to the population expected in clinical practice were discussed in Section 4.1.4.2 (p59).

The similarity and differences between the Study 200 and population of the unmet clinical need subpopulation (Appendix G) are discussed in Section 4.2.6 (p72).

4.2.2 Outcomes

Table 19 (p66) summarises primary and secondary outcomes for the three clinical sub-populations considered. Study 200 outcomes definitions are presented in Appendix E. The primary outcome for second and third line CP CML population was the rate of major cytogenetic response (MCyR) by 24 weeks, while the rate of overall haematological response (OHR) by 48 weeks was the primary outcome for the advanced phase populations. Cytogenetic responses (MCyR, CyR), haematological responses (mainly CHR), survival (mainly OS), HRQL and safety outcome (AE) at the March 2011 snapshot and at longer follow up are discussed. No data are available on patients' treatment after bosutinib failure, which adds to the uncertainty in the relevance of the OS data from Study 200.

Table 19. Summary of the methodology applied to Study 200 populations

	Second-line CP CML population (n=288)	Third-line CP CML population (n=118)	Advanced phase CML population (n=140; AP=76, BP=64)
Location	Multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. The 5 countries enrolling the most patients were the United States (147), Russia (66), Italy (53), China (43) and Germany (39).		
Design	Patients were treated with bosutinib 500mg once-daily until disease progression, unacceptable toxicity or withdrawal of consent. Dose escalation to bosutinib 600 mg once daily was permitted in cases of lack of efficacy (CHR not reached by week 8 or CCyR not reached by week 12) and dosage could be reduced in increments of 100 mg, as necessary in accordance with observed toxicities, down to a minimum of 300 mg/day. The dosing regimen used in Study 200 is reflective of the SPC recommendations, discussed in Table 1 [Pfizer submission]. Study 200 was a single-arm trial with no randomisation or blinding procedures. The only intervention was bosutinib 500mg once daily. There were no comparators.		
Duration of study	Study 200 began in January 2006 and is currently still on-going. Patients remain in the trial until death or lost to follow-up.		
Primary outcomes	Rate of MCyR by 24 weeks		Rate of attainment or maintenance of OHR by Week 48
Secondary outcomes	• Further response rates for efficacy endpoints: CCyR, CHR, MMR and CMR • Median duration of MCyR and CHR • Median time to MCyR and CHR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • Transformation Rate • HRQL: FACT-Leu & EQ-5D Safety outcomes were also considered: • Incidence rate of any AEs	• Further response rates for efficacy endpoints: CCyR, MiCyR, CHR, CMR and MMR • Median duration of MCyR, CCyR and CHR • Median time to MCyR • Probability of retaining MCyR and probability of retaining CHR • PFS at 1 year and 2 years • OS at 1 year and 2 years • HRQL: FACT-Leu & EQ-5D Safety outcomes were also considered • Incidence rate of any AEs • Incidence rate of Grade 3/4 AEs • Rate of patient deaths	• Duration of OHR, CHR and MCyR • Median time to confirmed (attained or maintained) OHR and CHR • Cumulative haematological response (for OHR, MHR and CHR) • Cumulative MCyR • BP transformation rate • PFS at 1 year and 2 years • OS at 1 year and 2 years • Time to treatment failure • HRQL: FACT-Leu & EQ-5D

4.2.3 Sample size calculation

The manufacturer used Simon two-stage design for sample size calculation which is often used for phase II cancer clinical trials.[35] The first stage requires a small sample size and sets a benchmark number of successes above which the trial enters the second stage.[36] The power calculations were determined separately for different patient populations, dependent upon their experience with prior TKI therapy and disease progression. The sample size calculation was based on primary outcomes; the rate of MCyR by 24 weeks for second and third line CP CML population and the rate of OHR by 48 weeks for the advanced phase populations (Appendix I). The MCyR rates for third line CP CML populations were based on clinical estimates, and the MCyR rates for second line CP CML as well as the OHR rates for AP and BP populations were based on published dasatinib and nilotinib data. We requested further information on the source of the OHR and MCyR rates used in the sample size calculation:

Due to the paucity of data available in the third line CP CML population when the study was designed, we were unable to provide sample size estimates based on specific clinical trial data. Although the original expectations for the treatment effect for this heavily pre-treated population were based on 2L clinical experience, the response rates observed were considered clinically meaningful within this heavily pre-treated cohort.

The published dasatinib data upon which the accelerated phase sample size calculation was based was taken from the three references below, whilst the blast phase sub-group estimates were based on the first two publications.

1. Talpaz M, Apperley JF, Kim DW, et al. Dasatinib (D) in patients with accelerated phase chronic myeloid leukemia (AP-CML) who are resistant or intolerant to imatinib: Results of the CA180005 'START-A' study. J Clin Oncol. 2006;24: 6526

2. Cortes JE, Kim DW, Rosti G, et al. Dasatinib (D) in patients (pts) with chronic myelogenous leukemia (CML) in myeloid blast crisis (MBC) who are imatinib-resistant (IM-R) or IM intolerant (IM-I): Results of the CA180006 'START-B' study. J Clin Oncol. 2006;24:6529

3. le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or –intolerant accelerated-phase chronic myelogenous leukemia. Blood. 2008;111:1834 -1839

(Source: Pfizer clarifications, response to question A4)

It is not clear how Pfizer arrived at the rates of MCyR and OHR used in the sample size calculation. However based on the results of a systematic review of clinical effectiveness of dasatinib and nilotinib,[2] the estimates used in the submission appear to be within the range of reported results.

Interestingly, while no sample size calculation for imatinib and nilotinib intolerant third line CP CML patients was included in the submission, the response to clarification questions states that no statistical analyses of these patients were planned (Appendix J). Also no post-hoc sample size calculation for the unmet clinical need population was provided.

Study 200 recruitment was closed without reaching planned sample sizes for AP and BP CML patients due to slow accrual. Patients in second and third line CP CML were over-recruited because of a change in the evaluable population definition.

4.2.4 Statistical analysis

As already mentioned in Section 4.1.4, analyses of the primary and key secondary outcomes, except for PFS and OS, were performed using the evaluable population. The evaluable population was defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. Table 14 (p58) showed the difference between recruited and evaluable populations for CML disease phases at different snapshots. OS and AE were calculated for all patients who received at least 1 dose of bosutinib (the all-treated population). No intention-to-treat analyses or adjustments for multiple comparisons were reported.

Importantly, the analyses defined in the protocol have changed. The protocol pre-defined analyses considered patients with baseline MCyR or CCyR as non-responders. The new analyses consider patients who maintained or achieved a cytogenetic or haematological response as responders. Using the two approaches, 32%, or 38.9% of third-line CP CML patients, achieved, or attained and achieved MCyR at 12 months minimum follow up respectively. The results of the post-hoc analyses, with higher response rates, when both achieved and maintained response are considered to be a response, were reported in Pfizer submission, and are used in the cost-effectiveness model.

Of note is that the definition of evaluable patients has changed, from all treated patients with a valid baseline and post-baseline measurement or early death or progression, to all enrolled patients who received at least one dose of bosutinib and had an adequate baseline outcome assessment. The first definition was found to produce a biased analysis, as subjects who discontinued early due to adverse events are ‘unevaluable’.

The outcomes used in the cost effectiveness model: MCyR, OHR, overall survival (OS), treatment discontinuation, HRQL and adverse events (AE) rates, are discussed in Section 4.2.6 (p72). The

results are described separately for the Study 200 sub-populations, and the post hoc analyses of patients that may have an unmet clinical need according to the proposed EMA indication.

4.2.5 Baseline characteristics

Study 200 baseline characteristics are summarised in Table 20 (p70). The full characteristics as supplied by Pfizer are included in Appendix K. We discussed some of the participants' characteristics in Section 4.1.4. ECOG performance status of Study 200 appears to be similar to the one expected in clinical population. The median age seems to be close to 50 years for all subpopulations, with the exception of second line BP patients. The post imatinib BP population (n=35) median age is 37 years (range 19–79), which is particularly low probably due to a small sample size. The proportion of male patients differs from 38% to 69% across the Study 200 subpopulations.

Baseline mutation status was recorded for 210 second-line CP, 117 third-line CP and 86 advanced phase CML patients. Based on May 2011 snapshot evaluable population, 78 (37%) second-line CP participants had ≥1 of 42 unique Bcr-Abl kinase domain mutations, of these 9 (4%) with the T315I mutation. Similarly, 65 (55.6%) third-line CP participants had Bcr-Abl kinase domain mutations, of these 15 (12.8%) with the T315I mutation. Forty (47%) advanced phase participants had ≥1 of 19 unique Bcr-Abl kinase domain mutations, including 7 (8%) with the T315I mutation. Information on cytogenetic and haematological response by baseline mutation status is included in Appendix L.

An important comparison is between the complete Study 200 population with the population of unmet clinical need (Appendix G). The results of the Study 200 populations and the population of the unmet clinical need sub population are discussed in Section 4.2.6 (p72).

Table 20. Study 200, baseline characteristics

Population		Age (years) [Median (range)]	Male [N (%)]	CML duration (years) [Median (range)]	IM duration (years) [Median (range)]	ECOG Performance Status [N (%)]		
						0	*1*	*2*
CP2L (N=288)	IM-R CP2L (N=200)	51.0 (18–86)	116 (58%)	4.0 (0.1–15.1)	2.6 (0.4–8.8)	151[a] (77%)	44[a] (23%)	0[a] (0%)
	IM-I CP2L (N=88)	54.5 (23–91)	38 (43%)	2.8 (0.1–13.6)	1.5 (<0.1–8.3)	68[a] (76%)	21[a] (23%)	1[a] (1%)
	Total CP2L (N=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	IM + DAS resistant CP3L (N=37)	54.0 (23–69)	14 (38%)	7.5 (1.2–17.6)	2.6 (0.02–6.4)	28 (76%)	9 (24%)	NA
	IM + DAS intolerant CP3L (N=50)	58.0 (25–79)	23 (46%)	5.6 (0.6–18.3)	3.3 (0.1–6.6)	31 (62%)	18 (36%)	NA
	IM + NI resistant CP3L (N=27)	52.0 (20–79)	14 (52%)	5.9 (1.2–16.3)	2.5 (0.7–5.9)	25 (93%)	2 (7%)	NA
	IM + DAS ± NI CP3L (N=4)	54.5 (31–62)	2 (50%)	11.7 (2.2–11.9)	3.0 (1.4–6.4)	2 (50%)	2 (50%)	NA
	Total CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	AP IM only (N=45)	47.0 (18–73)	24 (53%)	3.85 (1.1–22.1)	NR	26 (58%)	18 (40%)	1 (3%)
	AP Multi TKI (N=31)	56.0 (21–83)	18 (58%)	8.25 (1.5–19.2)	NR	15 (48%)	15 (48%)	1 (3%)
	AP Total (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.1–22.1)	NR	16 (46%)	10 (29%)	9 (26%)
BP (N=64)	BP IM only (N=35)	37.0 (19–75)	24 (69%)	1.75 (0.4–5.6)	NR	16 (46%)	10 (29%)	9 (26%)
	BP Multi TKI	53.0 (22–82)	17 (59%)	5.75 (1.1–14.6)	NR	6 (21%)	18 (62%)	5 (17%)

	(N=29)							
	BP Total (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.4–14.5)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need[b](N=52)	CP2L (N=15)	65 (24-81)	10 (67%)	NR	NR	6 (40%)	9 (60%)	0
	CP3L (N=21)	58 (30-79)	11 (52%)	NR	NR	13 (62%)	8 (38%)	0
	AP (N=5)	66 (48-73)	6 (60%)	NR	NR	1 (20%)	4 (80%)	0
	BP (N=11)	51 (19-80)	7 (64%)	NR	NR	2 (18%)	6 (55%)	3 (27%)
	Total (N=52)	58 (19-81)	31 (60%)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

4.2.6 Results

4.2.6.1 Cytogenetic response

As mentioned in Section 4.2.4 (p68), the protocol pre-defined analyses considering patients with baseline MCyR or CCyR as non-responders were not used. The post-hoc analyses (when both achieved and maintained MCyR or CCyR are considered to be a response) were used. The MCyR in the third line CP population was used in the cost-effectiveness model to estimate OS for bosutinib in CP CML. Because of the number of snapshots available and the multiple results reported, we collated the various results and calculated 95% Clopper-Pearson confidence intervals using Stata v.12[37] (Table 21). The cytogenetic response tables supplied in the submission are included in Appendix M. The rate of MCyR and CCyR increases only slightly as the duration of minimum follow-up increases, and the rate decreases with disease progression (Table 21). The imatinib resistant population seems to achieve similar rates as imatinib intolerant second line CP CML population (Appendix M), while dasatinib and nilotinib resistant patients seem to have slightly lower response rates than dasatinib intolerant third line CP CML patients (Appendix M).

It is interesting to compare the different sup-populations with the unmet clinical need sub-groups. It seems that apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical population. This would act to give a conservative estimate of the cost-effectiveness of bosutinib use in CP, given that Pfizer estimate OS for bosutinib in CP based on MCyR. However due to the very small numbers of participant in the unmet clinical need populations, any assumptions based on the unmet clinical need result have a high degree of uncertainty.

Table 21. Cytogenetic responses for all subpopulations at different snapshots

Population		Responding/N	MCyR% (95%CI)	Responding/N	CCyR% (95%CI)
CP2L	CP2L June 2010[24]	140/266[a]	52.6%[a] (46.4, 58.8)	110/266[a]	41.4%[a] (35.4, 47.5)
	CP2L March 2011[27]	142/266	53.4% (47.2, 59.5)	114/266	42.9 (36.8, 49.0)
	CP2L February 2012[27][b]	168/286	58.7% (52.8, 64.5)	141/286	49.3% (43.4, 55.3)
	CP2L May 2012[1]	155/264	58.7% (52.5, 64.7)	130/264	49.3% (43.1, 55.4)
	CP2L unmet clinical need population[27]	9/15	60% (32.3, 83.7)	8/15	53.3% (26.6, 78.7)
CP3L	CP3L March 2011[25, 27]	42/108	38.9%[c] (29.7, 48.7)	33/108	30.6%[d] (22.1, 40.2)
	CP3L February 2012[27, 28]	45/110	40.9%[e] (31.6, 50.7)	35/110	31.8%[f] (23.3, 41.4)
	CP3L unmet clinical need population[27]	9/21	42.9%[g] (21.8, 66.0)	7/21	33.3% (14.6, 57.0)
AP	AP March 2011[27]	24/69	34.8% (23.7, 47.2)	17/69	24.6% (15.1, 36.5)
	AP February 2012[27][b]	30/77	39.0% (28.0, 50.8)	23/77	29.9% (20.0, 41.4)
	AP unmet clinical need population[27]	3/5	60.0% (14.7, 94.7)	3/5	60.0% (14.7, 94.7)
BP	BP March 2011[27]	16/54	29.6% (18.0, 43.6)	11/54	20.4% (10.6, 33.5)
	BP February 2012[27][b]	21/64	32.8% (21.6, 45.7)	16/64	25% (15.0, 37.4)
	BP unmet clinical need population[27]	2/11	18.2%[h] (2.3, 51.8)	2/11	18.2% (2.3, 51.8)

Abbreviations: AP = accelerated phase, BP= blast phase, CP2L= second line chronic phase, CP3L= third line chronic phase

a Only patients attaining cytogenetic response counted as responders, not directly comparable with the rest of the table (protocol pre-specified analyses)

b Information extracted from the cost-effectiveness model supplied with the submission

c Results for the protocol pre-specified analysis for MCyR were 32.4% (23.7, 42.1)

d Results for the protocol pre-specified analysis for CCyR were 24.1% (16.4, 33.3)

e Different results found in Pfizer's economic model: 41.2% (32.1, 50.6)

f Different results found in Pfizer's economic model: 32.8% (24.4, 42.0)

g Different results found in Pfizer's economic model: 47.6% (25.7, 70.2)

h Different results found in Pfizer's economic model: 36.4% (10.9, 69.2)

4.2.6.2 Haematological response

Similarly to cytogenetic responses, not the protocol pre-defined analyses considering patients with baseline CHR as non-responders, but new analyses when both, achieved and maintained response, are considered to be a response, are discussed. Because of the number of snapshots available and the multiple results reported, we collated the various results and calculated 95% Clopper-Pearson confidence intervals using Stata v.12[37] (Table 22). The haematological response tables supplied in the submission are included in Appendix N. While the rate of CHR does not seem to change with increased duration of minimum follow-up, the rates decrease with disease progression. Again, it seems that the results of the post-hoc unmet clinical need population show slightly higher response rates. However, due to the very small numbers of participant in the unmet clinical need populations, any assumptions based on the unmet clinical need result have a high degree of uncertainty.

Table 22. Haematological responses for all sub-populations at different snapshots

Population		Responding/N	CHR% (95%CI)
CP2L	CP2L June 2010[24]	247/287	86.1% (81.5, 89.9)
	CP2L March 2011[27]	244/288	84.7% (80.0, 88.7)
	CP2L February 2012[27][a]	245/286	85.7% (81.1, 89.5)
	CP2L May 2012[1]	244/285	85.6%[b] (81.0, 89.5)
	CP2L unmet clinical need population[27][a]	12/15	80% (51.9, 95.7)
CP3L	CP3L March 2011[25, 27]	85/116	73.3% (64.3, 81.1)
	CP3L February 2012[27]	87/119	73.1% (64.2, 80.8)
	CP3L February 2012[27, 28]	84/115	73.0% (64.0, 80.9)
	CP3L unmet clinical need population[27]	18/21	85.7%[c] (63.7, 97.0)
AP	AP March 2011[27]	24/69	34.8% (23.7-47.2)
	AP unmet clinical need population[27]	4/5	80% (28.4, 99.5)
BP	BP March 2011[27]	9/60	15% (7.1, 26.6)
	BP unmet clinical need population[27]	3/11	27.3% (6.0, 61.0)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a Information extracted from Pfizer's economic model

b Reported in submission as 85%

c Different results found in Pfizer's economic model: 81.0% (58.1, 94.6)

4.2.6.3 Overall survival

Overall survival (OS) results were based on all enrolled patients who received at least one dose of bosutinib. Table 23, Table 24 and Table 25 detail the Kaplan-Meier (K-M) estimates of Study 200 subpopulations based on different snapshots. As expected, the estimated OS is shorter for more advanced disease phases. The OS tables supplied in the submission are included in Appendix O. In addition, as mentioned earlier, patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, while patients on bosutinib were followed up whilst on bosutinib. Thus the OS may be overestimated beyond 2 years because of selective censoring of patients.

Table 23. Kaplan-Meier estimate of overall survival in CP2L subpopulation at different snapshots

CP2L	**OS at 1 year (95%CI)**			**OS at 2 years (95%CI)**		
	Total N	**IM resistant N**	**IM intolerant N**	**Total N**	**IM resistant N**	**IM intolerant N**
June 2010[24]	97% 288	NR	NR	92% 288	92% 200	98% 88
March 2011[27[a]]	96.8% (94.0, 98.3) 288	95.9% (92.0, 97.9) 200	87.6% (82.1, 91.5) 88	90.6% (86.5, 93.5) 288	98.8% (92.0, 99.8) 200	97.6% (90.9, 99.4) 88
May 2012[1]	NR	NR	NR	NR 286	88% (83, 92) 195	98% (91, 99) 91
Unmet clinical need[27]	NR	NR	NR	NR	NR	NR

Abbreviations: CP2L = second line chronic phase, OS = overall survival, CI = confidence interval, IM = imatinib, N = number of participants, NR = not reported

a Source: Pfizer clarifications

Table 24. Kaplan-Meier estimate of overall survival in CP3L subpopulation at different snapshots

CP3L	OS at 1 year (95%CI)				OS at 2 years (95%CI)			
	Total N	IM + DAS resistant N	IM + DAS intolerant N	IM + NI resistant N	Total N	IM + DAS resistant N	IM + DAS intolerant N	IM + NI intolerant N
March 2011[25, 27]	91.2% (84.3, 95.2) 118	82.8% (65.6, 91.9) 37	93.9% (82.3, 98.0) 50	96.3% (76.5, 99.5) 27	82.9% (74.1, 88.9) 118	75.2% (56.1, 86.9) 37	85.4% (71.7, 92.8) 50	91.7% (70.5, 97.5) 27
February 2012[27, 28]	91.4% (84.6, 95.3) 119	83.6% (67.0, 92.3) 38	93.9% (82.3, 98.0) 50	96.3% (76.5, 99.5) 27	84.0% (75.8, 89.6) 119	77.4% (59.7, 88.0) 38	85.4% (71.7, 92.8) 50	92.4% (73.0, 98.1) 27
Unmet clinical need[27]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CP3L = third line chronic phase, OS = overall survival, CI = confidence interval, IM = imatinib, DAS = dasatinib, NI = nilotinib, N = number of participants, NR = not reported

Table 25. Kaplan-Meier estimate of overall survival in AP and BP subpopulations at different snapshots

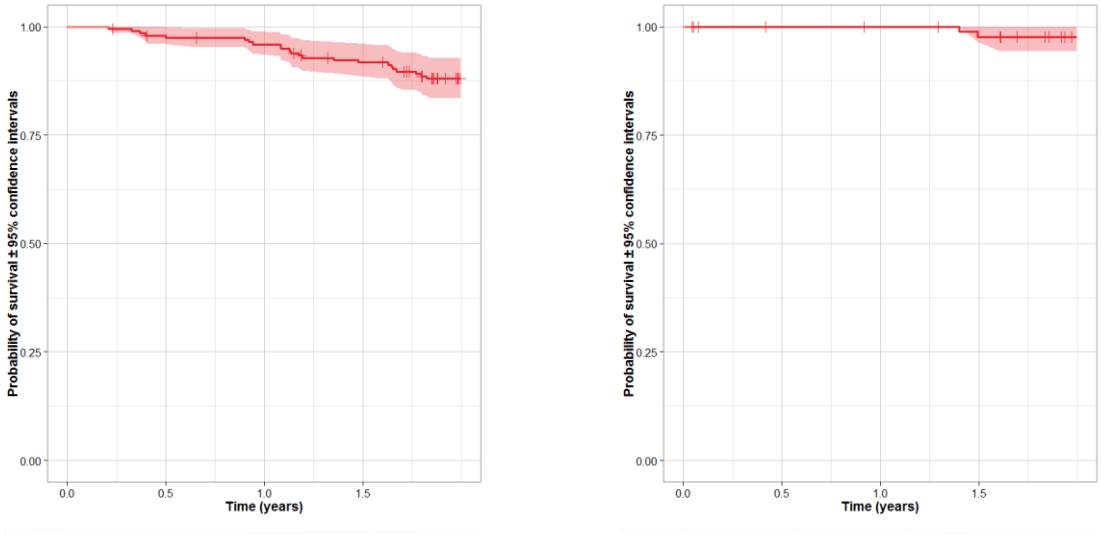
AP and BP	OS at 1 year (95%CI)			OS at 2 years (95%CI)		
	Total N	IM N	Multi TKI N	Total N	IM N	Multi TKI N
AP March 2011[27]	76.0% (64.7, 84.2) 76	NA	NA	65.6% (53.4, 75.4) 76	NA	NA
AP unmet clinical need[27]	NR	NR	NR	NR	NR	NR
BP March 2011[27]	43.8% (31.3, 55.6) 64	NA	NA	35.4% (23.8, 47.3) 64	NA	NA
BP unmet clinical need[27]	NR	NR	NR	NR	NR	NR

Abbreviations: AP = accelerated phase, BP = blast phase, OS = overall survival, CI = confidence interval, IM = imatinib, TKI = tyrosine kinase inhibitor, N = number of participants, NR = not reported

The imatinib-intolerant population seems to achieve better OS than the imatinib-resistant second line CP CML population. The nilotinib-resistant population seems to have the highest, while dasatinib-resistant populations seem to have the lowest OS estimates in third line CP CML population. Figure

6, Figure 7 and Figure 8 show the K-M estimates of OS for all three subpopulations (as included in Pfizer submission and Pfizer response to clarification questions).

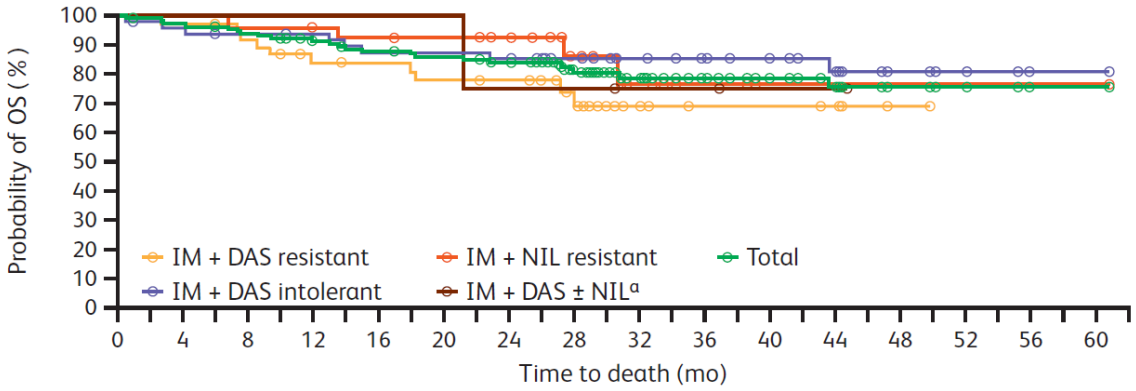
Figure 6. Kaplan-Meier estimates of overall survival for the 2nd-line CP all-treated population



Imatinib-resistant Imatinib-intolerant

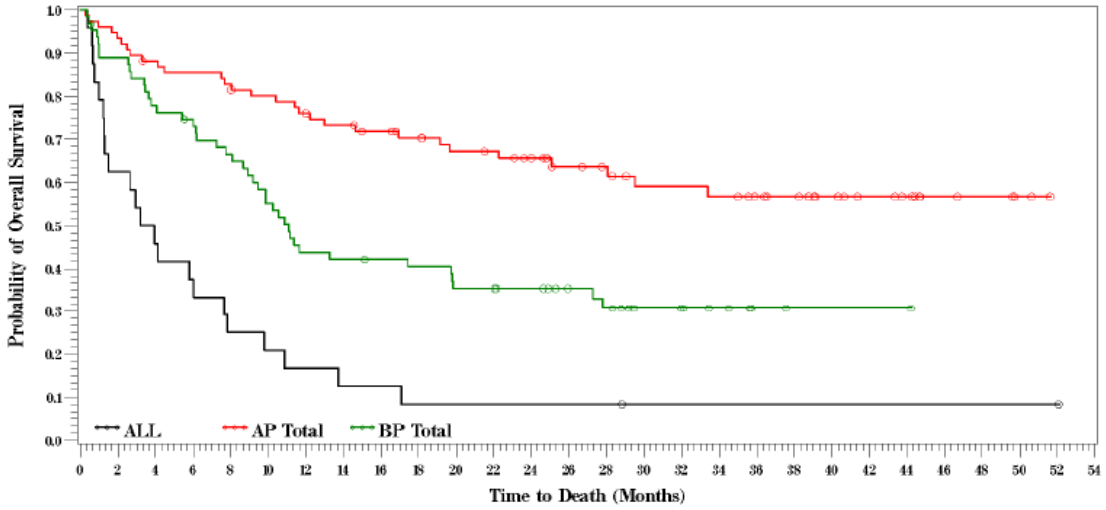
(Source: Pfizer response to clarification question B3)

Figure 7. Kaplan-Meier estimate of overall survival for the 3rd-line CP all-treated population (15 Feb 2012 snapshot)



(Source: Pfizer submission, Figure B12, p70)

Figure 8. Overall survival for the advanced phase CML population (28 Mar 2011 snapshot)



(Source: Pfizer submission, Figure B12, p79)

4.2.6.4 Treatment discontinuation and adverse events

All toxicities, up to 30 days after the last dose of bosutinib, were assessed according the National Cancer Institute Common Terminology for Adverse Events Version 3.0. We have already mentioned that no separate searches were conducted to search for adverse events evidence. However safety data are also available from a Phase III Study 3000 (NCT00574873; 3160A4-3000), a two-arm, randomized, open-label trial designed to evaluate the efficacy and safety of bosutinib compared to imatinib in subjects newly diagnosed with chronic phase CML (bosutinib n=248 and imatinib N=251). In addition, the Summary of Product Characteristics (SPC) for bosutinib combined evaluation of AE from the following three studies: Study 300 (248 patients treated with bosutinib), Study 200 (n=570, including 24 patients with acute CML) and 53 patients in the Japanese phase I/II trial (a dose-escalation study in CP CML patients followed with an evaluation study of safety and efficacy of the maximum tolerated dose in CML patients); all patients received at least 1 dose of single agent bosutinib. A summary of the three efficacy and safety studies is in Appendix P.

The treatment discontinuation and adverse events tables as supplied in the submission and response to clarification questions (including results from Study 3000) are presented in Appendix Q. Table 26 summarises reasons for treatment discontinuation in Study 200, the results reported are medians, not Kaplan-Meier estimates. While Table 27 and Table 28 summarise AE reported in Study 200 for different subpopulations. Finally Table 29 shows the combined AE from the three efficacy studies as reported in SPC. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (CP3L subgroup, n=4).

Adverse events were mainly restricted to gastrointestinal toxicities in both the chronic and advanced phases of the disease and in the majority of cases these toxicities were mild in severity. Overall, grade 3–4 non-haematological AE appear rare; diarrhoea was reported in patients in all lines of treatment: imatinib resistant CP2L 9%, imatinib intolerant CP2L 11%, CP3L 8.5%, AP 3.9% and BP 6.3%. Similarly rash was reported in imatinib resistant CP2L 8%, imatinib intolerant CP2L 12%, CP3L 4.2%, AP 3.9% and BP patients 3.1%. In addition, vomiting was reported in imatinib resistant CP2L 2%, imatinib intolerant CP2L 9%, AP 3.9% and BP 3.1%, but not among CP3L patients. In the advanced phases, fatigue (3.9 % and 3.1 % for AP and BP respectively), pleural effusion (5.3 % and 3.1 % for AP and BP respectively), and dyspnoea (7.9 % and 2.3 % for AP and BP respectively) were also reported. Fatigue was also reported in CP 2L; imatinib resistant CP2L 1%, imatinib intolerant CP2L 2%. The most common haematological events were thrombocytopaenia, neutropaenia and anaemia. In comparison with other TKIs, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] While the most commonly reported nilotinib AEs were thrombopenia, neutropenia , anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase, and bilirubin. In addition, the FDA has stipulated that nilotinib carry a 'black box' warning for possible heart problems that may lead to an irregular heart beat and possibly sudden death.[2]

Table 26. Treatment discontinuation in Study 200

Reason for discontinued treatment	Second line CP[a]			Third line CP[b]					Advanced CML[c]		Unmet clinical need population[d]
	15 May 2012 snapshot			15 February 2012 snapshot					28 March 2011 snapshot		28 March 2011 snapshot
	IM-R (n=200)	IM-I (n=88)	Total (n=288)	IM + DAS resistant (n=38)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NIL[a] (n=4)	Total (n=119)	AP CML (n=76)	BP CML (n=64)	Total (n=52)
Discontinued treatment, n (%)	109 (56)	57 (63)	166 (58)	32 (84)	37 (74)	18 (67)	3 (75)	90 (76)	61 (80)	61 (95)	NR
AE	35 (18)	6 (7)	66 (23)	6 (16)	17 (34)	3 (11)	0	26 (22)	18 (23.7)	6 (9.4)	13 (25)
Lack of efficacy	19 (10)	5 (6)	24 (8)	12 (32)	7 (14)	5 (19)	1 (25)	25 (21)	NR	NR	NR
Disease progression	35 (18)	6 (7)	41 (14)	7 (18)	4 (8)	7 (26)	2 (50)	20 (17)	NR	NR	NR
Patient request	11 (6)	6 (7)	17 (6)	2 (5)	3 (6)	1 (4)	0	6 (5)	NR	NR	NR
Death	6 (3)	0	6 (2)	2 (5)	2 (4)	0	0	4 (3)	NR	NR	NR
Investigator Request	2 (1)	0	2 (1)	0	0	2 (7)	0	2 (2)	NR	NR	NR
Lost to follow-up	2 (1)	0	2 (1)	2 (5)	0	0	0	2 (2)	NR	NR	NR
Protocol violation	NR	NR	NR	0	1 (2)	0	0	1 (1)	NR	NR	NR
Other	4 (2)	4 (4)	8 (3)	1 (3)	3 (6)	0	0	4 (3)	NR	NR	NR

Abbreviations: CP = chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

a Pfizer response to clarification questions A1

b Pfizer submission, Table B19, p73

c Pfizer response to clarification questions A6 and Pfizer submission Table B21, p74

d Pfizer submission Table B110, p366

Table 27. Non-haematological bosutinib AEs for all sub-populations at different snapshots

Population		Diarrhoea % (n/N)	Nausea % (n/N)	Vomiting % (n/N)	Rash % (n/N)	Dose reduction due to AE % (n/N)	Treatment discontinuation due to AE % (n/N) [% of participants with treatment discontinuation (n/N)]
CP2L	CP2L Total	85.3%* (244/286)	45.5%* (130/286)	36.7%* (105/286)	36%* (103/286)	47%[g] (135/288)	23%[a] (66/286) [58% (168/286)]
	CP2L IM-R	85%* (165/195)	43%* (83/195)	36%* (70/195)	32%* (63/195)	43%[g] (86/200)	15%[a] (30/195) [56% (109/195)]
	CP2L IM-I	87%* (79/91)	52%* (47/91)	39%* (35/91)	44%* (40/91)	56%[g] (49/88)	40%[a] (36/91) [63% (578/91)]
CP3L	CP3L total	82.4%[b] (98/119)	48.7%[b] (58/119)	39.5%[b] (47/119)	26.9%[b] (32/119)	63%[f]	22%[e] (26/119) [76% (90/119)]
	CP3L IM+NI resistant	85.2%[b] (23/27)	48.1%[b] (13/27)	29.6%[b] (8/27)	11.1%[b] (3/27)	NR	11%[e] (3/27) [67% (18/27)]
	CP3L IM+DAS resistant	78.9%[b] (30/38)	55.3%[b] (21/38)	39.5%[b] (15/38)	23.7%[b] (9/38)	NR	16%[e] (6/38) [84% (32/38)]
	CP3L IM+DAS intolerant	82%[b] (41/50)	44%[b] (22/50)	48%[b] (24/50)	38%[b] (19/50)	NR	34%[e] (17/50) [74% (37/50)]

AP	AP total	85.5%[c] (65/76)	44.7%[c] (34/76)	44.7%[c] (34/76)	32.9%[c] (25/76)	40.8%[c] (31/76)	23.7%[c] (18/76)
	AP IM	84.4%[c] (38/45)	37.8%[c] (17/45)	51.1%[c] (23/45)	35.6%[c] (16/45)	37.8%[c] (17/45)	25.8%[c] (10/45)
	AP Multi TKI	87.1%[c] (27/31)	54.8%[c] (17/31)	35.5%[c] (11/31)	29%[c] (9/31)	45.2%[c] (14/31)	29%[c] (8/31)
BP	BP total	65.6%[c] (42/64)	50%[c] (32/64)	39.1%[c] (25/64)	31.3%[c] (20/64)	26.6%[c] (17/64)	9.4%[c] (6/64)
	BP IM	65.7%[c] (23/35)	51.4%[c] (18/35)	31.4%[c] (11/35)	28.6%[c] (10/35)	31.4%[c] (11/35)	2.9%[c] (1/35)
	BP Multi TKI	65.5%[c] (19/29)	48.3%[c] (14/29)	48.3%[c] (14/29)	34.5%[c] (10/29)	20.7%[c] (6/29)	17.2%[c] (5/29)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor

* Subjects reporting ≥20% treatment-emergent adverse events (Pfizer submission table B108, p359)

a May 2012 snapshot (Pfizer response to clarification questions A7)

b Subjects reporting ≥10% treatment-emergent adverse events, Feb 2012 snapshot (Pfizer response to clarification questions A5)

c Subjects reporting ≥10% treatment-emergent adverse events (Pfizer response to clarification questions A6)

d Patients with an interruption (Pfizer response to clarification question B5)

e Treatment discontinuation, February 2012 snapshot (Pfizer submission, Table B19, p73)

Table 28. Haematological bosutinib adverse effects for all subpopulations at different snapshots

Population		Thrombocytopenia	Neutropenia	Anaemia	Thrombocytopenia Grade 3/4	Neutropenia Grade 3/4	Anaemia Grade 3/4
CP2L	CP2L Total	66%[a] (191/288)	40%[a] (116/288)	90%[a] (258/288)	24%[a] (68/288)	18%[a] (53/288)	13%[a] (36/288)
	CP2L IM-R	68%[a] (60/88)	48%[a] (42/88)	86%[a] (76/88)	33%[a] (29/88)	28%[a] (25/88)	18%[a] (16/88)
	CP2L IM-I	66%[a] (131/200)	37%[a] (74/200)	91%[a] (182/200)	20%[a] (39/200)	14%[a] (28/200)	10%[a] (20/200)
CP3L	CP3L Total	34.7%[b] (41/118)	17.8%[b] (21/118)	15.3%[b] (18/118)	25.4%[b] (30/118)	14.4%[b] (17/118)	5.1%[b] (6/118)
	CP3L IM+NI resistant CP3L IM+DAS resistant CP3L IM+DAS intolerant	NR					
AP	AP Total	42.1%[c] (32/76)	15.8%[c] (12/76)	42.1%[c] (32/76)	32.9%[c] (25/76)	14.5%[c] (11/76)	30.3%[c] (23/76)
	AP IM / Multi TKI	NR					
BP	BP total	28.1%[c] (18/64)	20.3%[c] (13/64)	28.1%[c] (18/64)	26.6%[c] (17/64)	20.3%[c] (13/64)	18.8%[c] (12/64)
	BP IM / Multi TKI	NR					

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, DAS = dasatinib, IM = imatinib, N = number of participants, NI = nilotinib, NR = not reported, TKI = tyrosine kinase inhibitor, NR = not reported, subjects reporting ≥10% treatment-emergent adverse events, and subjects reporting ≥5% treatment-emergent adverse events

a Cortes (2011)

b March snapshot (Pfizer submission, Table B27, p81)

c March snapshot (Pfizer submission, Table B29, p81)

Table 29. Adverse reactions for bosutinib from SPC

System Organ Class	Frequency	Adverse reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations	Very common	Respiratory tract infection[a]	99 (11.4)	4 (0.5)	0
	Common	Pneumonia[b]	45 (5.2)	21 (2.4)	5 (0.6)
		Influenza	47 (5.4)	2 (0.2)	0
		Bronchitis	27 (3.1)	1 (0.1)	0
		Nasopharyngitis	81 (9.3)	0	0
Blood and lymphatic system disorders	Very common	Thrombocytopenia	335 (38.5)	127 (14.6)	94 (10.8)
		Neutropenia	141 (16.2)	67 (7.7)	33 (3.8)
		Anaemia	238 (27.4)	82 (9.4)	25 (2.9)
		Leukopenia	94 (10.8)	31 (3.6)	8 (0.9)
	Common	Febrile Neutropenia	13 (1.5)	8 (0.9)	3 (0.3)
	Uncommon	Granulocytopenia	2 (0.2)	0	2 (0.2)
Immune system disorders	Common	Drug hypersensitivity	12 (1.4)	7 (0.8)	0
	Uncommon	Anaphylactic shock	2 (0.2)	0	2 (0.2)
Metabolism and nutrition disorders	Very Common	Decreased appetite	109 (12.5)	4 (0.5)	0
	Common	Dehydration	20 (2.3)	2 (0.2)	0
		Hyperkalaemia	23 (2.6)	2 (0.2)	1 (0.1)
		Hypophosphataemia	54 (6.2)	18 (2.1)	0
Nervous system disorders	Very common	Headache	148 (17.0)	9 (1.0)	3 (0.3)
	Common	Dizziness	74 (8.5)	2 (0.2)	0
		Dysgeusia	18 (2.1)	0	0
Ear and labyrinth disorders	Uncommon	Tinnitus	8 (0.9)	0	0
Cardiac disorders	Common	Pericardial effusion	16 (1.8)	2 (0.2)	1 (0.1)
		Electrocardiogram QT prolonged[c]	10 (1.1)	1 (0.1)	0
	Uncommon	Pericarditis	1 (0.1)	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	125 (14.4)	0	0
	Common	Dyspnoea	82 (9.4)	15 (1.7)	3 (0.3)
		Pleural effusion	52 (6.0)	14 (1.6)	1 (0.1)
	Uncommon	Respiratory failure	5 (0.6)	1 (0.1)	1 (0.1)
		Acute pulmonary oedema	3 (0.3)	1 (0.1)	1 (0.1)
		Pulmonary hypertension	4 (0.5)	1 (0.1)	0

Gastrointestinal disorders	Very common	Diarrhoea	683 (78.5)	78 (9.0)	1 (0.1)
		Vomiting	323 (37.1)	25 (2.9)	0
		Nausea	366 (42.1)	10 (1.1)	0
		Abdominal pain[d]	291 (33.4)	15 (1.7)	0
	Common	Gastritis	25 (2.9)	3 (0.3)	1 (0.1)
	Uncommon	Acute pancreatitis	3 (0.3)	2 (0.2)	1 (0.1)
		Gastrointestinal haemorrhage[e]	6 (0.7)	5 (0.6)	0
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	194 (22.3)	79 (9.1)	10 (1.1)
		Aspartate aminotransferase increased	160 (18.4)	41 (4.7)	3 (0.3)
	Common	Hepatotoxicity[f]	15 (1.7)	5 (0.6)	1 (0.1)
		Hepatic function abnormal	27 (3.1)	8 (0.9)	3 (0.3)
		Blood bilirubin increased	33 (3.8)	8 (0.9)	0
		Gamma-glutamyltransferase increased	29 (3.3)	7 (0.8)	0
	Uncommon	Liver Injury	2 (0.2)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	Very common	Rash[g]	282 (32.4)	51 (5.9)	2 (0.2)
	Common	Urticaria	26 (3.0)	2 (0.2)	1 (0.1)
		Acne	25 (2.9)	0	0
		Pruritus	71 (8.2)	3 (0.3)	0
	Uncommon	Erythema multiforme	1 (0.1)	0	1 (0.1)
		Exfoliative rash	6 (0.7)	1 (0.1)	0
		Drug eruption	5 (0.6)	1 (0.1)	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	96 (11.0)	3 (0.3)	0
	Common	Myalgia	49 (5.6)	3 (0.3)	0
		Back pain	72 (8.3)	7 (0.8)	1 (0.1)
Renal and urinary disorders	Common	Renal failure	13 (1.5)	2 (0.2)	1 (0.1)
	Uncommon	Renal failure acute	7 (0.8)	3 (0.3)	1 (0.1)
		Renal impairment	8 (0.9)	1 (0.1)	0
General disorders and administration site conditions	Very common	Pyrexia	204 (23.4)	6 (0.7)	1 (0.1)
		Oedema[h]	100 (11.5)	1 (0.1)	0
		Fatigue[i]	169 (19.4)	14 (1.6)	1 (0.1)
	Common	Chest pain[j]	61 (7.0)	4 (0.5)	1 (0.1)
		Pain	41 (4.7)	5 (0.6)	0

		Asthenia	86 (9.9)	7 (0.8)	2.(0.2)
Investigations	Common	Lipase increased	76 (8.7)	41 (4.7)	4 (0.5)
		Blood creatinine increased	42 (4.8)	2 (0.2)	0
		Blood amylase increased	31 (3.6)	7 (0.8)	0
		Blood creatine phosphokinase increased	28 (3.2)	3 (0.3)	2 (0.2)

The following terms have been combined:

a Respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral
b Pneumonia, bronchopneumonia, primary atypical pneumonia, lobar pneumonia
c Electrocardiogram QT prolonged, long QT syndrome
d Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain
e Gastrointestinal haemorrhage, gastric haemorrhage, upper gastrointestinal haemorrhage
f Hepatotoxicity, toxic hepatitis, cytolytic hepatitis
g Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash
h Oedema, face oedema, localized oedema, peripheral oedema
i Fatigue, malaise
j Chest pain, chest discomfort

(Source: Pfizer response to clarification question A1)

Cross-intolerance and cross-resistance

The reported cross-intolerance between bosutinib and dasatinib showed that 8% patients discontinued treatment with bosutinib as a result of same AE:

> This study included a retrospective evaluation of cross-intolerance between dasatinib and bosutinib. This retrospective evaluation provides an indication of how likely it is that the reason(s) for inappropriateness of dasatinib may also render bosutinib inappropriate, where the reason(s) are based on intolerance due to adverse events. This is therefore highly relevant to the scope of this submission, since the indication for bosutinib includes patients for whom dasatinib is not appropriate.
>
> Of 50 patients with dasatinib intolerance, 11 (22%) were found to experience the same adverse event as a grade 3/4 event when treated with bosutinib. Of 50 patients, 4 (8%) discontinued treatment with bosutinib as a result of the same AE.

(Source: Pfizer submission, p83)

No data on bosutinib and nilotinib cross-intolerance are available (only 1 third line patient intolerant to nilotinib was recruited in Study 200). However, the EMA highlighted a high degree of cross-resistance between bosutinib and dasatinib or nilotinib.[29] The reported MCyR for CP 3L dasatinib

intolerant subgroup was 47.7%, in comparison dasatinib resistant and nilotinib resistant patients achieved 33.3% and 38.5% respectively. Advanced phase patients treated with bosutinib at second line reported better MCyR than patients receiving bosutinib at third line or later. In fact, AP patients achieved 47.6% and 14.8% MCyR at second line and multi TKI respectively, while BP patients achieved 44.8% and 12.6% MCyR at second line and multi TKI respectively (March 2011 snapshot). We can argue, that at least some of the difference between the results could be explained by cross-resistance between second generation TKIs. The results of the retrospective evaluation of dasatinib cross-intolerance are presented in Table 30.

Table 30. Cross-intolerance between dasatinib and bosutinib for third-line CP CML population

AE, n (%)[a]	Dasatinib intolerant	Grade 3/4 event	Discontinued bosutinib because of event
Any AE	50	11 (22)	4 (8)
Haematological events	20	8 (40)	2 (10)
Thrombocytopaenia	8	6 (75)	1 (13)
Pancytopenia	5	0	0
Neutropaenia	4	4 (100)	1 (25)
Haematoxicity	3	0	0
Cardiovascular events	3	0	1 (33)
Gastrointestinal events	6	0	0
Diarrhoea	3	0	0
Musculoskeletal events	4	0	0
Respiratory events	23	3 (13)	1 (4)
Pleural effusion	19	2 (11)	0
Dyspnoea	3	1 (33)	1 (33)
Skin disorders	5	0	0

a Includes all AEs with ≥3 patients categorized as intolerant on prior dasatinib
(Source: Pfizer submission, Table B28, p83)

4.2.6.5 Quality of life

Tyrosine kinase inhibitors have revolutionised the treatment of CML and led to improvements in HRQL:

CML is a chronic disease and unless a patient is able to receive a SCT, patients remain on medication for many years. The estimated median survival with imatinib exceeds 25 years in patients with a median age of diagnosis of almost 60 years. Quality of life is not significantly impaired in the chronic phase of CML compared to those of a similar age without CML, indeed approximately 40% of CP

patients are asymptomatic and diagnosed as a result of a routine blood test. For those that do experience symptoms in the chronic phase they tend to be mild and non-specific, such as tiredness, anaemia, enlarged spleen (and associated tenderness to left side of abdomen), night sweats and weight loss.

Although quality of life is not assumed to be very different for CML patients on and off treatment, low grade chronic AEs can be debilitating, particularly if experienced over long periods of time, such as fatigue, oedema, muscle aches, rash or diarrhoea. Some more serious AEs may have a more significant impact on quality of life and may require intervention, for example a pleural effusion requiring steroids, pleural taps or pleural drains, PAOD requiring surgical bypass or balloon angioplasty or pulmonary HTN requiring cardiac catheterisation and medication.

Patients in the AP experience a worsening of symptoms and additional symptoms such as bruising, bleeding and infections.18 In the BP, symptoms include fever, sweats, pain, weight loss, hepato-splenomegaly, enlarged lymph nodes and extramedullary disease. For patients, symptoms such as breathlessness, tiredness, bleeding and infections can seriously affect patients' quality of life.

Please describe how a patient's HRQL is likely to change over the course of the condition.

Quality of life is expected to worsen as the disease progresses from chronic phase to accelerated phase and again to blast crisis phase.

In the chronic phase of the disease, previous studies have found that quality of life is not seriously impaired compared to those of a similar age without CML. In the advanced phases, HRQL is expected to be significantly worse.

(Source: Pfizer submission, p130)

A disease specific, The Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale, and a general, European Quality of Life- 5 Dimensions questionnaire (EQ-5D), were reported in Study 200. Since EQ-5D is NICE's preferred instrument, the submission commented on these results only. The EQ-5D was valued using the UK tariff.

The mean EQ-5D for CP patients across the trial was [redacted] and [redacted] (estimated by us from data on p357-8 Pfizer submission) for second and third- line for patients respectively. The mean utility values at screening were [redacted] and [redacted] for second and third-line respectively. Similarly, the mean EQ-5D for advanced phase patients across the trial was [redacted] and [redacted] for AP and BP for patients respectively. The mean utility values at screening were [redacted] and [redacted] for AP and BP respectively. In comparison, the average utility used in TA251 and TA241 for first and second- line CP patients

(based on IRIS study) was 0.85 (SE 0.004) at diagnosis (Pfizer submission, p135). Interestingly, the mean EQ-5D values did not differ much across the disease phases.

Pfizer reports improvements in HRQL in all disease phases at the March 2011 snapshot:

> Improvements in overall health status as assessed by the EQ-5D were observed for second-line CP patients over the course of treatment, as of 28 Mar 2011 snapshot.
>
> Imatinib-resistant subjects experienced a significant improvement in overall health status from baseline starting at Week 8 ($p<0.05$) and continuing at each subsequent assessment until Week 48 (all $p<0.001$). Imatinib-intolerant subjects experienced significant improvement from baseline by Week 24 ($p<0.001$) that continued until Week 48 ($p<0.001$).

(Source: Pfizer submission, p 357)

> *3L CP:*
>
> Improvements or maintenance of baseline levels of overall health status as assessed by the EQ-5D was observed for dasatinib-intolerant, dasatinib-resistant and nilotinib-resistant patients over the course of treatment, as of the 28 March 2011 snapshot. Subjects who were nilotinib-intolerant and those who had received prior nilotinib and dasatinib were ignored for this evaluation as a result of the small sample size (n=4).

(Source: Pfizer submission, p 72)

> Improvements in overall health status as assessed by the EQ-5D were observed for the AP CML and BP CML subjects over the course of treatment, as of the 28 Mar 2011 snapshot.
>
> The mean and median EQ-5D scores, and the number of patients with an EQ-5D score at each observation, are presented along with cost-effectiveness data in Section 7.4.3 [Pfizer submission].

(Source: Pfizer submission, p 79)

However as can be seen in the following tables (Table 31, Table 32, Table 33 and Table 34), the numbers of patients reporting at each week varied significantly.

Table 31. Summary of EQ-5D results by visit for second-line CP patients, n=288 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					

(Source: Pfizer submission, Table B107, p357)

Table 32. Summary of EQ-5D results by visit for third-line CP CML patients, n=118 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					

(Source: Pfizer submission, Table B39, p131)

Table 33. Summary of EQ-5D results by visit for AP patients, n=76 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]		

(Source: Pfizer submission, Table B40, p131)

Table 34. Summary of EQ-5D results by visit for BP patients, n=64 (28 Mar 2011 snapshot)

Week	n	Median	Mean	Std Dev	95% CI
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
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[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

(Source: Pfizer submission, Table B42, p132)

4.3 Critique of the clinical evidence for comparator treatments

As previously mentioned – because of the lack of RCT evidence – the submission included separate studies to inform clinical effectiveness for bosutinib and bosutinib comparators. The following comparators were considered in the literature searches:

- Hydroxycarbamide (HU; as a proxy for best supportive care)
- Allogeneic stem cell transplantation (SCT)
- Interferon alpha

The submission identified 13 non-RCT comparator studies (Table 35). Again we cannot emphasize enough, that the naïve comparison of single arm Study 200 with non-randomised comparator studies is strongly susceptible to bias. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] The submission did not identify any studies reporting on interferon alpha in a refractory setting (post-TKI or post-other treatments). The submission further excluded 5 SCT studies from the review as they did not stratify results according to CML disease phase.[5, 8, 9, 11, 15] Studies that reported combined results for AP and BP CML patients were included in the Pfizer submission.[6, 10, 13]

Table 35. Summary of studies of hydroxycarbamide and stem cell transplant

Study	Patients (Disease phase at transplantation)	Survival	Response	Safety	Pfizer analysis	PenTAG comments
Benedicte (2010)[5]* Median follow-up: 27 months (range 1.2-50.2).	N=31 (median age 39.8 years), (CP 21 (including second CP), AP 10) Received SCT at: • 3rd-line (imatinib and dasatinib or nilotinib) • 4th-line (imatinib, dasatinib and nilotinib)	**OS:** CP and AP combined • 1 year: 79.2% (95% CI 64.3-94.1) Estimated: • 2 years: 55.5% (95% CI 35.0-75.9)	NR	**GVHD** CP and AP combined Grade 2–4: 37.9% Grade 3–4: 20.6% Chronic: 60%	Excluded: Mixed phases.	Only abstract with limited information available. Combined results for CP and AP CML patients.
Bornhäuser (2006)[6] Median follow-up: 18 months (range 2–62).	N=61 (CP 47 (including second CP), AP 8, BP 6), (mean age=45, 57% male) Received SCT at: • 2nd-line (imatinib)	**OS** CP, AP and BP combined (N=61) • 18 months: 37% **Disease Free Survival at 18 months:** CP (N=47) = 34.6% AP and BP combined (N=14) = 29.4% CP, AP and BP combined (N=61) = 33.0%	CP, AP and BP combined Molecular response recorded in 25 from 26 participants alive at last follow up: molecular remission achieved in 19 participants.	**GVHD** CP AP and BP combined Grade 2–4: 66% Grade 3–4: 38% Chronic: 29%	Included: Second-line (post-imatinib failure)	Although 32 (50%) patients were at high risk for transplant-related deaths Gratwohl score of 5-7, 47(77%) patients were in chronic phase at the time of transplantation.
Holroyd (2010)[7]* Median follow-up: NR.	N=43, (CP 17 (including second CP), AP 24, BP 2), (median age 40.8 years) Received SCT at: • 2nd-line: 35	**OS** Estimated: CP (N=17) • 1 year: 49.4%	11 patients relapsed post SCT.	**GVHD** CP, AP and BP combined Grade 2–4: 24%	Included: Multiple lines.	Only abstract with limited information available. Small numbers of participants in all disease cohorts.

	participants (34 imatinib and 1 dasatinib) • 3rd-line: 6 participants (imatininb and dasatinib) • 4th-line: 2 participants (imatinib, dasatinib and nilotinib) Some patients received chemotherapy.	• 3 years: 29.6% <u>AP (N=24)</u> • 1 year: 54.2% • 3 years: 50% <u>BP (N=2)</u> • 1 year: 0% • 3 years: 0% The impact of maximal disease stage, AP(n=23) vs. BP (n=20): • 3 years: 61% and 33% respectively.		Chronic: 54%		
Ibrahim (2011)[4] Median follow-up: 50.4 months (range 2-202)	N=293 (57.3 % male) Subpopulation of interferon alpha versus chemotherapy RCT for CP CML[38]. 247 patients failed to response to interferon alpha. Of these, 117 CP patients received HU after: • interferon alpha treatment failure.	**OS** Estimated: <u>CP(N=246)</u> • 7 years: 34.4 %	NR	NR	Included: Second-line (post-IFN failure)	Results given for all 246 patients who failed to response to interferon alpha; of these only 117 received HU, 122 remained on interferon alpha till disease progression and 7 received bosutinib.
Jabbour (2006)[9] Median follow-up: 19 months (range 13-24).	N=10 (CP 3, AP 4, BP 2, acute 1), (median age 44 years, 80% male) Received SCT at: • 2nd-line: 10 participants (imatinib)	**OS** <u>CP, AP and BP combined</u> • 1 year: 70%	<u>CP, AP and BP combined</u> 2 patients relapsed post SCT. CMR=66.7% MMR=77.8%	**GVHD** <u>CP, AP and BP combined</u> Acute: 44% Chronic: 60%	Excluded: Mixed phases.	Very small study (N=10). Results are reported for all participants, including the one acute CML patient.

Jabbour (2007)[8]	N=12 (CP 7 (including second CP), AP 1, BP 4), (median age 41 years, 58% male) Received SCT at: • 2nd-line: 9 participants (dasatinib (2) and nilotinib (7)) • 3rd-line: 3 participants (dasatinib and nilotinib)	**OS** CP, AP and BP combined • Median follow up of 6 months (2, 11): 58%	CP, AP and BP combined Median follow-up: 10 months: Molecular response in 58% participants.	**GVHD** CP, AP and BP combined Acute: 58.3% Chronic: 50%	Excluded: Mixed phases.	Very small study (N=12).
Jabbour (2011)[10] Median follow-up: 22 months (range 5–53).	N= 47 (CP 26 (10 second CP), AP 12, BP 9), (median age 44 years; 57% male) Received SCT • 2nd-line: 18 (38%) patients received imatinib only • 3rd-line: 29 (62%) patients received imatinib and nilotinib (13), dasatinib (13) or bosutinib (30) • 4th-line: 5 (11%) patients received imatinib and two more TKIs	**OS** CP(N=16) • 2 years: 72% (95% CI 49–96) Advanced (N=31; include 10 second CP patients) • 2 years: 59% (95% CI 41–77) ALL combined (N=47) • 2 years: 63% (95% CI 49–78)	**CMR** CP (N=16) 87.5% Advanced (including second CP) (N=31) 54.8% All combined (N=47) 66% **CCyR** CP (N=16) 6.25% Advanced (including second CP) (N=31) 32.3% CP, AP and BP combined (N=47)	**GVHD** CP, AP and BP combined (N=47) Grade 2–4: 42% Grade 3–4: 17% Chronic: 46%	Included: Multiple lines. Pfizer Base case:	Small study, only 16 patients in CP and advanced phase cohort (N=31) included 10 second CP patients. Submission (p384) shows OS is very immature, therefore poor data source.

			23%			
Kantarjian (2007)[3]	N=574 (CP 321, AP 161, BP 92) participants who discontinued imatinib therapy. Results reported for 104 CP CML participants post-imatinib failure who received: • SCT (n=8) • TKI (n=35) • Other treatment, (n=61), of these 12 participants received HU. Outcome for 127 participants is missing	**OS** Estimated: <u>CP SCT cohort (N=8)</u> • 2 years: 60.0 % • 3 years: 45.0 % <u>CP other treatment cohort (N=61)</u> • 2 years: 77.0 % • 3 years: 70.0 % **Mortality** <u>CP SCT cohort (N=8)</u> CP: 4/10 (40%) AP: 1/5 (20%) BP: 5/8 (63%) <u>Other treatment cohort (N=61):</u> CP: 24/68 (35%) AP: 53/64 (83%) BP: 85/95 (90%)	NR	NR	Included: Second-line (post-imatinib failure)	Data for large number of patients are missing (N=127). A very small SCT cohort (N=8), and in the HU cohort (N=61) only 12 patients received HU.
Markiewicz (2011)[11]*	N= 48 (NR), (median age 33 years) Received SCT at: • 2nd-line: 39 Imatinib (37), dasatinib (2) • 3rd-line: 6 Imatinib and dasatinib or nilotinib	**OS:** Estimated •5 years: 79%	NR	**GVHD** <u>Disease progression NR</u> Grade 3–4: 6.25% Chronic, limited: 35.4% Chronic, extensive: 18.75%	Excluded: Mixed phases.	Only abstract with limited information available. Disease stage not reported.

	• 4th-line: 3 patients, imatinib and dasatinib and nilotinib					
Oehler (2007)[12]	N= 145 (CP 72, AP (or second CP) 60, BP 13), (median age= 40.1; 64% male) Received SCT at: • 2nd-line: after imatinib (not after imatinib failure, 23 patients had previous INF)	**OS:** Estimated: <u>CP(N=72)</u> • 3 years: 78.0 % <u>AP and second CP(N=60)</u> • 3 years: 48.0 % **Mortality** <u>BP</u> 6/12 (follow up 542-1593 days) **Mortality** **by response to imatinib:** <u>69 CP patients with available data:</u> *Suboptimal/loss of response to prior imatinib:* 26% (8/31), i.e. OS = 74% *Good response to prior imatinib:* 5% (2/38), i.e. i.e. OS = 95% <u>Advanced phases</u> *Disease progressed from CP whilst on imatinib:* 45% (19/42), i.e. OS = 55%	NR	Results only reported as HR and OR compared with a historical cohort of patient who underwent SCT without previous imatinib treatment	Included: Second-line (post-imatinib failure)	**OS** of the CP cohort (N=72) was not reported in the submission; however mortality by response to imatinib were recorded. Large trial in comparison with the rest of comparator studies.

		Patients in advanced phases with no prior response to imatinib: 35% (6/17), i.e. OS = 65%				
Saussele (2010)[13] Median follow-up: 26 months (range 1-50) for CP, and 24 months (range 0-50) for advanced phase.	N= 65 (CP 37 , AP 3, BP 25; 11 of advanced patients achieved second and 1 patient achieved third CP before SCT), (mean age=38; 57% male in CP and 79% in AP & BP). Received SCT at: CP: • 2nd-line: 32 patients • 3rd-line or 4th-line: 5 patients AP and BP: • 2nd-line: 22 patients • 3rd-line or 4th-line: 6 patients • 22 patients treated with chemotherapy	**OS:** Estimated: CP (N=37) • 3 years: 94.1% (95% CI 83.8–99.4%) AP and BP combined (N=28) • 3 years: 58.8% (95% CI 38.6-77.5%)	**CMR** CP(N=37) 89% AP and BP combined (N=28) 93%	**GVHD** CP(N=37) Grade 3–4: 19% Chronic: 36% AP and BP combined (N=28) Grade 3–4: 35% Chronic: 21%	Included: Multiple lines.	Results for CP reported (N=37).
Schleuning (2010)[14]* Median follow-up: 19 months.	N=56 (first CP 21, second or higher CP 20, AP or BP 15) Had nilotinib and/or dasatinib (had not received first-line imatinib) prior to SCT.	**OS** Estimated: First CP(N=21) • 2 years: 85%. AP,CP, BP combined (N=56) Estimated non relapse mortality at 2 years: 33%	NR	NR	Included: Multiple lines.	Only abstract with limited information available. Small numbers of patients in first CP phase (N=21).

		and relapse incidence 15%.				
Weisser (2007)[15]	N=30 (second or higher CP; 10 and 20 patients had history of BP and AP respectively) (median age =51, 60% male) Received SCT at: • 2nd-line: after imatinib (imatinib given after IFN failure)	**OS** Estimated: <u>Second or higher CP</u> • 3 years: <35% BCR-ABL positive nuclei (N=13, 11 censored, median survival not reached): 81%; ≥35% BCR-ABL positive nuclei (N=17, 6 censored, median survival 101 days): 28%[a] **Mortality** at 1 year: 30%	<u>Second or higher CP</u> Cytogenetical relapse in 20%	**GVHD** <u>Second or higher CP(N=30)</u> Grade 3–4: 40%	Excluded: Mixed phases.	Although all patients are in the same phase, (second or higher CP), OS data are reported separately for patients with <35% and ≥35% BCR-ABL positive nuclei in bone marrow. Small study.

Abbreviations: AP = accelerated phase, BP = blast phase, CMR = Complete molecular response, CP = chronic phase, GVHD = Graft versus host disease, N = number of participants, NR = not reported, OS = overall survival

* Abstract presented at the Annual Meeting of ASH (2010-2011); no full publication is available for these sources, hence the data presented is limited to that present in the abstract

a Results estimated from figures

4.3.1 Hydroxycarbamide

Only two studies, Ibrahim (2011) and Kantarjian (2007) reported using HU in a refractory setting (Table 35).[3, 4] Ibrahim (2011)[4] used data from an interferon-failure sub-population in The UK Medical Research Council CML-III randomised trial of interferon alpha versus chemotherapy in CP CML patients.[38] In the Allan (1995) RCT,[38] 293 patients received interferon alpha and 294 patients received chemotherapy (with busulphan or hydroxyurea) treatment. In addition, all patients received a course of chemotherapy for tumour reduction as an induction treatment, and some patients also received chemotherapy while on interferon alpha. There were 278 Philadelphia positive CP CML patients in both the interferon alpha, and the no interferon alpha arm. The actual survival rates at 5 years for Philadelphia positive CP CML patients were, 36% (SD 3.8), and 54% (SD 3.7) for no interferon alpha and interferon alpha arms respectively. Ibrahim (2011)[4] reported data on 246 patients who failed interferon therapy (in the interferon alpha arm). However, of these, only 117 actually received HU; 122 remained on interferon alpha till disease progression and 7 received busulfan. The estimated 7 years overall survival for the interferon-failure sub-population was 34.4%. It may be that these results include a small proportion of Philadelphia negative CP CML patients. Pfizer did not consider this population in the submission because patients did not receive any TKI prior to HU treatment.

Kantarjian (2007)[3] is a retrospective study of 420 CML patients, who received first line imatinib treatment. One hundred and four patients were identified with imatinib failure in CP CML. The post-imatinib failure treatment was either SCT (8 patients), dasatinib/nilotinib (35 patients) or other treatment (61 patients). Out of the 61 patients receiving other treatment, only 12 received HU; remaining treatments included tipifarnib, lonafarnib, cytarabine, homohorringtonine, decitabine, homoharringtonine, interferon alpha and others. The estimated 2 and 3 years OS for CP CML patients receiving "other" treatment was 77% and 70% respectively. Based on Hoyle (2011) report,[17] the submission used the estimated OS from the "other" treatment group in their model. Hoyle (2011)[17] assumed that survival when taking HU is the same as that of the "other" treatment arm for imatinib resistant patients. However, they also acknowledged that based on this assumption, the OS estimates for HU following TKI failure are uncertain.

4.3.2 Allogeneic stem cell transplantation

Eight studies[3, 6, 8-10, 12, 13, 15] and four conference abstracts[5, 7, 11, 14] reported on SCT in a refractory setting. Table 35 summarises results of all comparator studies.

4.3.3 Interferon alpha

Considering the highly unlikely usage of interferon (other than as a bridge to SCT, interferon alpha therapy is hardly used in England and Wales) and of the lack of suitable data, we did not consider clinical data on interferon alpha further here.

4.3.4 Quality assessment

Similarly to the quality appraisal of Study 200, comparator studies were assessed according to the Chambers (2009) criteria.[16] We have already emphasised the weakness of using a single arm study design as the only source for clinical evidence. We have also highlighted the further difficulties arising from comparing results from different single arms studies. Finding suitable comparator studies is very challenging, not least in terms of potential differences in the populations studied, the variable completeness of follow-up, publication bias, and lack of blinding throughout the literature.

Thirteen comparator studies[3-15] were identified. However, four of these are available only as conference abstracts,[5, 7, 11, 14] thus only limited information on quality assessment is available. Earlier in this section we commented on some of the weaknesses (Table 35) of the comparator studies, thus only our assessment of the Chambers (2009) criteria[16] is included in Table 36.

Table 36. Quality assessment of comparator non-RCTs identified by the systematic review

Study	Comparator	Eligibility criteria adequately reported?	Study population representative of a normal population?	An appropriate measure of variability reported?	Loss to follow-up reported or explained?	At least 90% included at baseline followed-up?	Were patients recruited prospectively?	Were patients recruited consecutively?	Did the study report relevant prognostic factors?	Pfizer Quality score	PenTAG comment
Benedicte (2010)[5]	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Bornhäuser (2006)[6]	SCT	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Poor	OK
Holroyd (2010)[7]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Ibrahim (2011)[4]	HU	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Jabbour (2006)[9]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Jabbour (2007)[8]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Jabbour (2011)[10]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Kantarjian (2007)[3]	SCT, HU	Yes	Yes	Yes	Yes	No[b]	No	Yes	Yes	Poor	OK
Markiewicz (2011)[11]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK
Oehler (2007)[12]	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK
Saussele (2010)[13]	SCT	Yes	Yes	Yes	Yes	Yes[c]	Yes	Yes	Yes	Good	OK
Schleuning	SCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Poor	OK

(2010)[14]											
Weisser (2007)[15]	SCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	OK

a >50% of patients (n=32) were at high risk for transplant-related deaths (Gratwold scores of 5–7)

b Of the 574 patients analysed, the outcome of 127 could not be retrieved in detail in relation to subsequent therapies or survival. The next analysis concentrated only on patients in whom imatinib therapy was discontinued for either clear cut resistance or recurrence (n=374) or for imatinib. toxicities (n=46)

c Follow-up was reported in the 84 patients who underwent transplantation

(Source: Pfizer submission, adapted from Table B83, p216)

4.4 Conclusions of the clinical effectiveness section

Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI. Bosutinib was also found to have an acceptable safety profile across all phases of the disease. Adverse events were restricted primarily to gastrointestinal toxicities (Table 4, p26).

The main two weaknesses of the clinical effectiveness evidence are, that Study 200 is a non-randomised single arm trial, and that while the licence is intended for treatment of adult patients with Ph^+ CML previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, the clinical evidence for bosutinib is taken entirely from Study 200, in which the great majority of patients were suited to either imatinib, nilotinib or dasatinib. Secondly, the clinical effectiveness evidence for the comparator treatments is very poor. Any comparison between Study 200 and comparator studies is highly prone to bias. In addition, OS data from Study 200 for CP patients is very immature.

Other, minor weaknesses of Study 200 are that approximately 40% of patients had previously taken IFN, while IFN is a very rare CML treatment in England and Wales, the fact that all patients had previously been treated with imatinib while the current first line treatment is nilotinib, the discrepancy between the duration of imatinib treatment reported in Study 200 and in IRIS trial, and the fact that only one participant with nilotinib intolerance was recruited in third line CP CML subpopulation.

On the other hand, the strength of the submitted evidence is that Study 200 is a large, multi-centre, consecutively recruited trial, with patients representative of population expected the in clinical practice in England and Wales (based on ECOG scores).

5 COST-EFFECTIVENESS

5.1 Manufacturer's review of cost-effectiveness evidence

5.1.1 Objective

The objective of the manufacturer's cost-effectiveness review was to identify cost-effectiveness studies in CML patients previously treated by one or more TKIs. It was assumed this population would include and be representative of the indicated population (patients for whom imatinib, nilotinib and dasatinib would be inappropriate).

We believe the objective of the cost-effectiveness review was appropriate for identifying existing answers to the decision problem, but note that by excluding studies of first-line TKIs possible sources of economic evidence to inform the *de novo* analysis could be missed.

5.1.2 Search strategy

Pfizer conducted two sets of searches to locate cost-effectiveness studies for this submission.

The first search (Pfizer submission, Section 10.10, p218) took terms for CML or Philadelphia Chromosome combined with methodological limits to economics/cost studies (see Pfizer submission, Section 10.10.4, p218 for full search strategy). These searches were run 2nd October 2012 and were performed in the databases listed in Table 37.

Table 37. Electronic databases searched by Pfizer for cost-effectiveness review (run from database inception; Source: Pfizer submission, Section 10.10, p218)

Database	Searched via
Ovid MEDLINE®	Ovid
EMBASE	Ovid
MEDLINE® In-Progress	Ovid
EconLit	Ovid
NHS EED	Cochrane Library and Centre for Reviews and Dissemination
Cochrane Library	Ovid

Pfizer state that search results were limited to Dasatinib, Nilotinib, Imatinib, Bosutinib, Stem-Cell, Hydroxycarbamide, Interferon, or Standard Care (Pfizer submission, Section 10.10.4, p220). It is not clear from the submission how this was achieved.

Pfizer additionally searched proceedings of selected conferences (Table 38) in February 2013 and NICE HTAs. Pfizer report that horizon scans were performed using the Google search engine (Pfizer submission, Section 10.10.5, p221).

Table 38. Conferences searched by Pfizer (Source: Pfizer submission, Section 10.10.5, p221)

Conference
International Society for Pharmacoeconomics and Outcomes (ISPOR)
International Congress on Leukemia Lymphoma Myeloma (ICLLM)
ESMA[a]
American Society of Clinical Oncology (ASCO)
American Society of Hematology (ASH)

a We were unable to identify this conference, but we believe, as does our clinical expert, Dr Rudin, that it probably refers to ESMO (European Society of Medical Oncology)

5.1.2.1 Update searches

In clarification, Pfizer confirmed they had updated the submission searches from 2nd October 2012 to April 2013. We are happy to accept these update searches in place of the horizon scanning.

5.1.2.2 ERG comment on search strategy

The searches performed were appropriate to the task.

5.1.3 Inclusion and exclusion criteria used in the study selection

Inclusion and exclusion criteria in the cost-effectiveness review are shown in Table 39. By excluding studies of first-line TKIs and excluding cost- (without assessment of effectiveness) it is possible that studies capable of informing the *de novo* model would be missed, but we note in Section 5.2.9.1 (p127) that an additional search was conducted in which the study type criteria were dropped. We believe the inclusion and exclusion criteria were appropriate to the objective of the cost-effectiveness review.

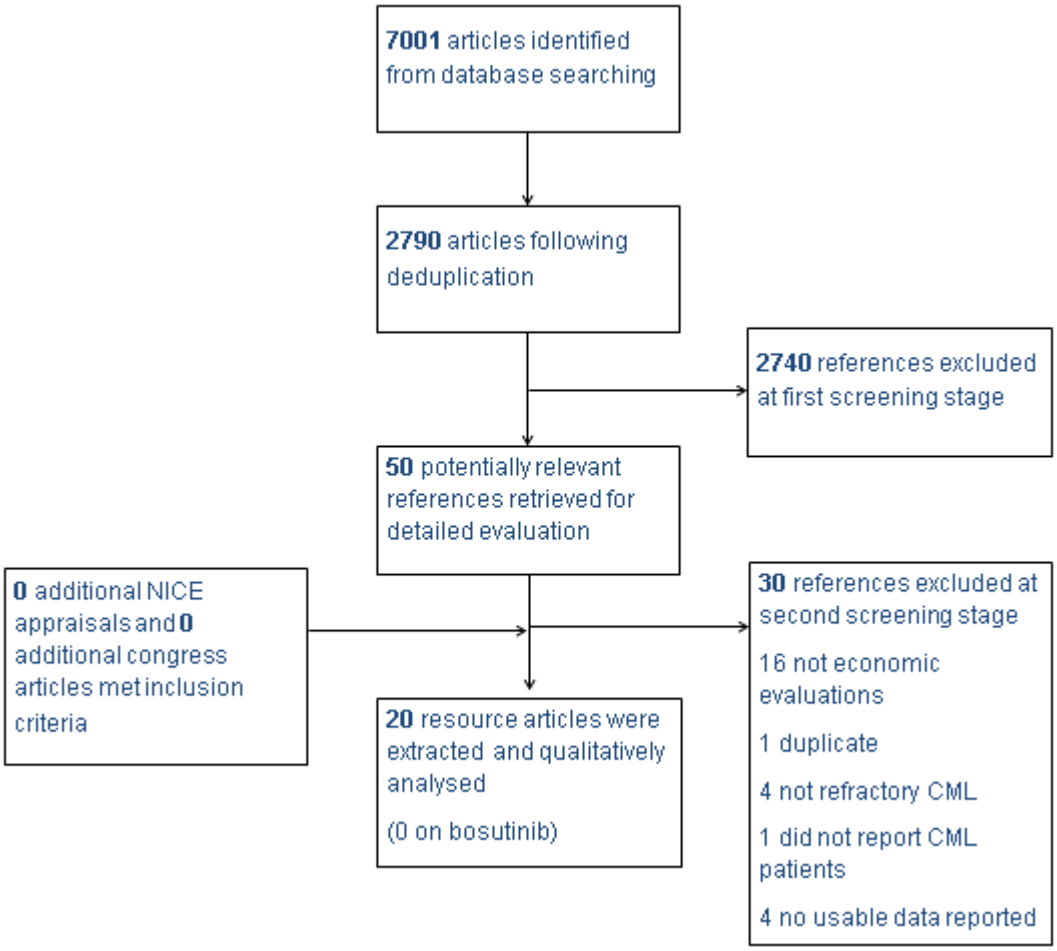
Table 39. Inclusion and exclusion criteria for systematic review of economic evidence

Category	Include	Exclude
Population	Adult patients with refractory CP, AP or BP Ph^+ CML (treated with at least one prior TKI)	Studies that did not report adult patients Studies that did not report patients with refractory Ph^+ CML
Intervention	Include but not limited to bosutinib, dasatinib, nilotinib and imatinib	
Comparators	Hydroxycarbamide, interferon, SCT, best supportive care, dasatinib, nilotinib, imatinib	
Outcomes	Incremental costs and QALYs Any other measure of effectiveness reported together with costs	
Study type	Full economic evaluation (including cost-consequence, cost-minimisation, cost-effectiveness, cost-utility, cost-benefit) comparing two or more interventions	
Publication type		Letters, editorials, reviews of economic articles (although reference lists of these would be hand searched)
Other	Reported in sufficient detail to assess methodological quality and extract data and results	

5.1.4 Results

Figure 9 shows the study flow diagram for the cost-effectiveness review. Searching identified 7,001 articles, which corresponded to 2,790 articles following de-duplication. Fifty articles were retrieved for detailed evaluation, of which 20 were included and 30 were excluded from the final set of studies for extraction and quality assessment. Details of the excluded studies were not given, and the reasons for exclusion are given for at most 26 of the 30 articles. We would have preferred to have access to the set of articles excluded after full paper retrieval but this was not provided by Pfizer.

Figure 9. Study flow diagram for systematic review of economic evidence



(Source: Pfizer submission, Section 7.1.1, p107)

The key included studies were Hoyle and colleagues (2011),[39] Rogers and colleagues (2012)[2] and Loveman and colleagues (2012),[40] which are all publications based on TA241 (Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance). These studies are most relevant to the decision problem as they study refractory CML in adults in the UK treated by TKIs. These studies also included details of submissions by Novartis and Bristol-Myers Squibb on the cost-effectiveness of nilotinib and dasatinib.

No studies were identified which investigated the cost-effectiveness of bosutinib in refractory CML.

5.1.5 Conclusions and ERG critique

Pfizer did not identify any economic evaluations of bosutinib in refractory CML. As such no conclusions were drawn from the systematic review regarding the decision problem. An additional

review was conducted by Pfizer (see Section 5.2.9.1, p127) to identify inputs for the *de novo* model, which relaxed inclusion criteria.

We believe the review of cost-effectiveness evidence was appropriate and accept that there are no economic evaluations of bosutinib in refractory CML.

5.2 Summary of the manufacturer's submitted evaluation

5.2.1 History of submission

Table 40 details the history of the Pfizer model submission. This report references the latest version of the model and report (received 22/04/2013).

Table 40. History of Pfizer model submission

Date	Detail
14/03/2013	PenTAG receive Pfizer model from NICE
19/04/2013–22/04/2013	PenTAG receive updated Pfizer model and supplementary report with corrections to errors highlighted by PenTAG in questions for clarification[a]

a PenTAG identified that the hazard ratio for OS in bosutinib CP patients was not implemented correctly. When Pfizer corrected the error the CP model base case ICER for bosutinib decreased from [redacted] per QALY to [redacted] per QALY.

5.2.2 Model structure

The submission includes three cohort models (for patients starting in CP, AP and BP). In each model bosutinib is compared with hydroxycarbamide, interferon (CP model only) and SCT. The models are described as "semi-Markov models" but there are no transition probabilities as would be expected from a Markov model.[41, 42] The membership of each state is calculated in a manner similar to that which would be expected in an area-under-the-curve model.

Cycles in the models last one month and a half-cycle correction was not applied.

Bosutinib patients receive bosutinib until they discontinue treatment due to intolerance or resistance, progress to a later disease stage (AP or BP for those in CP, BP for those in AP, not applicable for those in BP), or die. Bosutinib patients receive hydroxycarbamide following bosutinib discontinuation until death (even in the case of further disease progression).

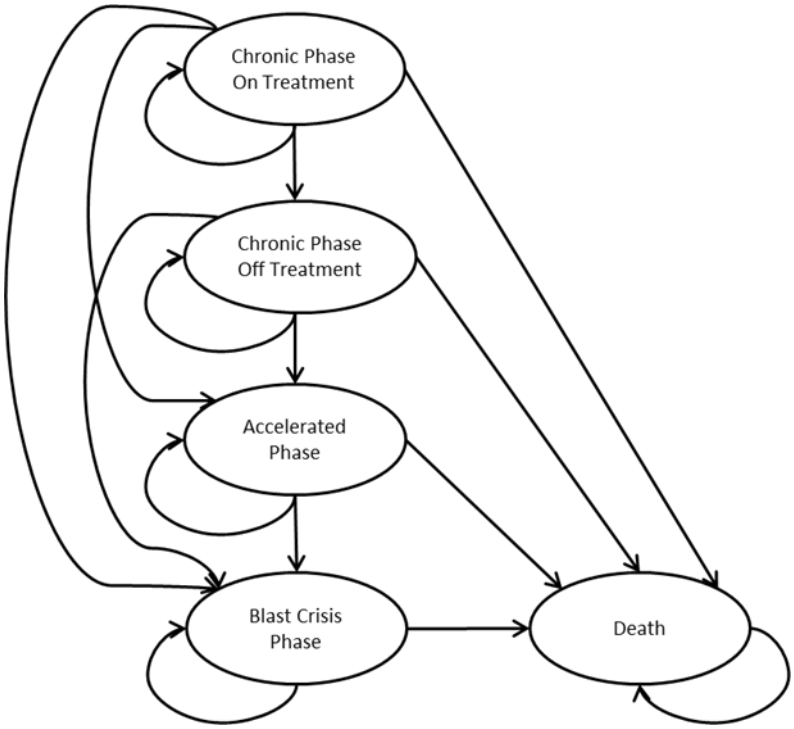
Hydroxycarbamide patients receive hydroxycarbamide regardless of disease progression until death.

Interferon patients receive interferon until they discontinue treatment (similarly to bosutinib patients), progress to a later disease stage (AP or BP), or die. Interferon patients receive hydroxycarbamide following bosutinib discontinuation until death (even in the case of further disease progression).

SCT patients receive SCT and are thereafter regarded as cured in the base case analysis and so do not progress to later disease stages and do not receive drug treatment after SCT.

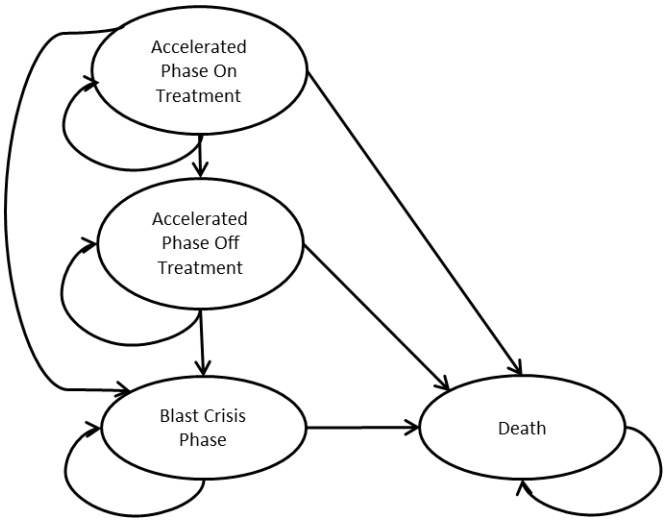
The models are structured similarly, with time on and off treatment in the initial phase, later disease phases (if applicable) and death. Figure 10 shows the CP model structure, Figure 11 shows the AP model structure and Figure 12 shows the BP model structure.

Figure 10. Chronic phase (CP) model structure



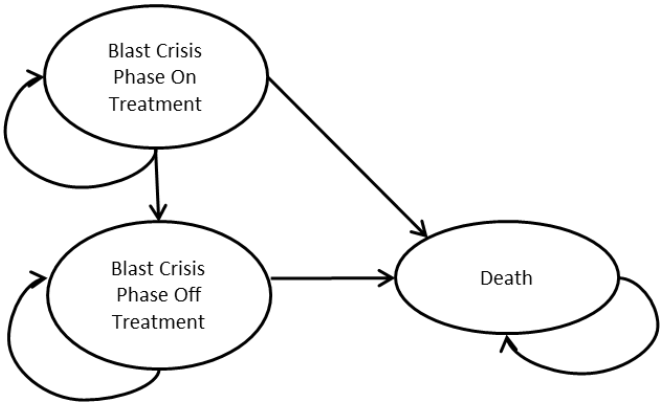
(Source: Pfizer submission, Section 7.2.2, p109)

Figure 11. Accelerated phase (AP) model structure



(Source: Pfizer submission, Section 7.2.2, p110)

Figure 12. Blast phase (BP) model structure



(Source: Pfizer submission, Section 7.2.2, p110)

5.2.2.1 State membership in the CP model

The proportion of the cohort in each state in the CP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)
2. The proportion in the Blast Crisis Phase state is set so that patients spend 6 months in the blast crisis phase
3. The proportion in the Accelerated Phase state is set so that patients spend 10 months in the accelerated phase

4. The proportion in the Chronic Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive or the proportion in the Blast Crisis Phase and Accelerated Phase states
5. The remainder of the population is in the Chronic Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Chronic Phase Off Treatment state is always zero.

Patients receiving a stem cell transplant are assumed to be cured and hence do not progress to the accelerated and blast crisis phases. Therefore the proportions in the Blast Crisis Phase, Accelerated Phase and Chronic Phase Off Treatment states are zero and the proportion in the Chronic Phase On Treatment state is set equal to the relevant overall survival curve.

5.2.2.2 State membership in the AP model

The proportion of the cohort in each state in the AP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)
2. The proportion in the Blast Crisis Phase state is set so that patients spend 6 months in the blast crisis phase
3. The proportion in the Accelerated Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive or the proportion in the Blast Crisis Phase state
4. The remainder of the population is in the Accelerated Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Accelerated Phase Off Treatment state is always zero.

Patients receiving a stem cell transplant are assumed to be cured and hence do not progress to the blast crisis phase. Therefore the proportions in the Blast Crisis Phase and Accelerated Phase Off Treatment states are zero and the proportion in the Accelerated Phase On Treatment state is set equal to the relevant overall survival curve.

5.2.2.3 State membership in the BP model

The proportion of the cohort in each state in the BP model was calculated as follows:

1. The total proportion alive is set to match the selected overall survival curve (as defined in Section 5.2.6.1, p118)

2. The proportion in the Blast Crisis Phase On Treatment state is set to match the selected time on treatment curve (as defined in Section 5.2.6.2, p122), except it is capped so as not to affect the total proportion alive
3. The remainder of the population is in the Blast Crisis Phase Off Treatment state

Patients receiving hydroxycarbamide do not discontinue treatment, so the proportion in the Blast Crisis Phase Off Treatment state is always zero. Patients receiving a stem cell transplant are assumed to be cured; therefore the proportion in the Blast Crisis Phase Off Treatment state is always zero.

5.2.3 Population

Bosutinib is indicated for patients with Ph^+ CML in the chronic, accelerated or blast phase who have failed one or more TKIs and for whom imatinib, nilotinib and dasatinib are considered inappropriate.

Pfizer estimate that each year, 80 of the 631 annual CML cases in England and Wales will be eligible to receive bosutinib, and of these 12 (15%) will be eligible to receive it second-line (following imatinib failure), 19 (24%) will be eligible to receive it third-line (following failure of imatinib and nilotinib), and 49 (61%) will be eligible to receive it fourth-line (Pfizer submission, Section 8.1, pp188-189).

Pfizer suggest that the third-line chronic phase cohort in Study 200 is most representative of the intended population, and hence this forms the basis of the population in the CP model and for many other parameters in the CP model.

All patients in the CP model were assumed to start treatment at age 54 years, which was the mean baseline age in the third-line CP cohort of Study 200 (Pfizer submission, Section 7.3.2, p124). All patients in the AP and BP models were assumed to start treatment aged 50 and 47 years respectively, which were the mean baseline ages in the AP and BP cohorts of Study 200 (Pfizer submission, Section 7.3.2, p124).

Pfizer assumed equal proportions of males and females in the patient population.

No assumptions were made in the model about previous treatments, although Study 200 evaluated patients who received imatinib first-line, followed by nilotinib and/or dasatinib. Some patients in Study 200 had previous interferon use (52% of third-line CP cohort, 50% of AP cohort and 30% of BP cohort) and some patients had previously received stem cell transplants (8% of third-line CP cohort, 9% of AP cohort and 6% of BP cohort).

There were no subgroups in any of the models.

5.2.4 Intervention and comparators

The intervention is bosutinib given until any of the following occur:

- progression to later phase CML,
- patient has/develops resistance to bosutinib,
- patient no longer tolerates bosutinib, or
- patient dies.

Following bosutinib discontinuation patients receive hydroxycarbamide until death.

The comparator treatments are:

- Hydroxycarbamide (patients receive until death)
- Interferon alpha (patients may discontinue treatment and then receive hydroxycarbamide until death)
- Allogeneic stem cell transplant (one-off treatment followed by medical management)

Interferon alpha is only considered as a comparator in the CP model because effectiveness estimates were not available for interferon alpha in the advanced and blast phases.

5.2.5 Perspective, time horizon and discounting

The Pfizer submission adopts the perspective of the NHS. Costs of drug acquisition, drug administration, medical management, adverse events and death are included. Impacts on costs outside the NHS budget (e.g., Personal Social Services) were not included as they were not expected to be affected significantly. Wider societal costs are not included. Health benefits are only included from the patient population being treated. Wider societal benefits are not included.

The time horizon is 50 years. As the patients start aged 47–54 years, this means the time horizon is to age 97–104 years.

Costs and QALYs are discounted at 3.5% per annum.[43] Life years are not discounted.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Overall survival

Overall survival (OS) is one of the most clinically relevant measures of treatment effectiveness and is also a key driver of cost-effectiveness.

Pfizer used results from Study 200 to inform the OS of bosutinib and estimated OS of hydroxycarbamide, interferon and SCT from published literature. Table 41 shows the methods which were used to calculate OS in the CP, AP and BP models, both in the base case and in a number of scenario analyses.

Overall survival of bosutinib is extrapolated in all three models, but most significantly in the CP model. Due to study protocol the OS after two years is biased (since patients are only followed up for two years after treatment discontinuation) and hence OS is only available from Study 200 up to two years. In the CP-3L cohort OS at two years (calculated by the Kaplan-Meier method) was 84%, so significant extrapolation takes place in the model. In the AP cohort OS at two years was 65.6%, again requiring significant extrapolation. In the BP cohort OS at two years was 35.4%, with median OS of 11.1 months, so some extrapolation was still necessary, but not to the same extent as for the CP and AP models.

Table 41. Methods used to calculate overall survival (OS) in Pfizer submission base case and scenario analyses

Model	Treatment	Base case OS	Scenario analysis OS
CP	Bosutinib	MCyR surrogate relationship based on Jabbour and colleagues (2009)[44] (see p119)	MCyR surrogate with different hazard ratio for OS Exponential distribution fitted to third line CP cohort from Study 200 "Cumulative survival approach" (see p121)
	Hydroxycarbamide	Exponential distribution with mean OS = 3.5 years following Kantarjian (2007)[3]	Exponential distribution with different mean OS
	Interferon	Exponential distribution with mean OS = 3.6 years following Loveman (2012)[40]	*None*
	SCT	Exponential distribution fitted to Jabbour (2011)[10]	Weibull distribution fitted to Jabbour (2011)[10] Exponential distribution fitted to Oehler (2007)[12]
AP	Bosutinib	Exponential distribution fitted to AP cohort OS in Study 200	Extreme value distribution fitted to AP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 16 months to match length of time spent in AP and BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Jabbour (2011)[10]
BP	Bosutinib	Exponential distribution fitted to OS in Study 200	Weibull distribution fitted to BP cohort OS in Study 200
	Hydroxycarbamide	Exponential distribution with mean OS = 6 months to match length of time spent in BP in CP model	*None*
	SCT	Exponential distribution fitted to Oehler (2007)[12]	Exponential distribution fitted to Saussele (2010)[13]

MCyR surrogate overall survival

Overall survival for bosutinib patients in the CP model was estimated using a MCyR surrogate approach. This approach was not used for OS for bosutinib patients in the AP and BP models as sufficiently mature OS data was available from Study 200 to fit parametric curves. A very similar MCyR approach has been used in a previous assessment, TA241,[2] which investigated nilotinib, dasatinib and high-dose imatinib for treatment of Ph^+ imatinib-resistant or imatinib-intolerant CML patients.

Following Rogers and colleagues (2012)[2] Pfizer assume a hazard ratio of overall mortality of 0.370 for patients achieving a MCyR versus those not achieving a MCyR. Pfizer assumed that the same hazard ratio would apply for patients achieving a MCyR using bosutinib as bosutinib is a TKI with a similar mode of action to imatinib.

Pfizer first extracted individual patient OS data from Jabbour and colleagues (2009),[44] which investigates the effectiveness of high-dose imatinib in patients after cytogenetic failure on standard-dose imatinib. Pfizer then fitted an exponential curve to the OS data using the maximum likelihood method. This curve, adjusted for general mortality, was then used as the basis for fitting a new curve with two components: survival for responders and survival for non-responders. These two components were both exponential curves with scale factors set such that the hazard ratio between matched 0.370. It was then assumed that the MCyR rate in Jabbour and colleagues (2009)[44] would be 41.7%, so that the overall survival in Jabbour would be equal to 41.7% × (OS for MCyR) + (100% − 41.7%) × (OS for no MCyR). The exponential parameters were chosen to achieve the best fit to the adjusted exponential curve fitted to the Jabbour OS data.

Finally OS for bosutinib was estimated by using the MCyR rate of 38.9%, which corresponds to the best cumulative response at a minimum follow up of 12 months for the entire 3rd-line population (not the post-hoc unmet clinical need population), i.e., 38.9% is the proportion of patients achieving a MCyR at any time or maintaining a MCyR present at baseline, with all patients followed up for at least 12 months (median follow-up 28.5 months).

Fitting parametric distributions to overall survival data

For bosutinib patients in the AP and BP models exponential distributions were fitted to individual patient data from the relevant cohorts in Study 200. The entire AP and BP cohorts were used (i.e., no post-hoc "unmet need" subpopulation was considered, nor were cohorts divided into imatinib-failure patients and multiple TKI-failure patients), but analysis was restricted to the first two years, since the study protocol stated that patients would only be followed up for two years post-discontinuation. In addition an exponential distribution was fitted to the CP cohort for a scenario analysis. Pfizer do not state explicitly that maximum likelihood methodology is used but it is very likely that this is the case.

For SCT patients in the CP model individual patient data was extracted from the relevant overall survival curve in Jabbour and colleagues (2011)[10] and an exponential distribution was fitted to this OS data. Again it is likely, but not explicitly stated, that the maximum likelihood methodology was used. The same methodology was used in the AP and BP models but fitted to OS data from Oehler and colleagues (2007).[12]

Choosing exponential distributions with desired mean overall survival

The method of moments was used to choose exponential distributions with desired mean OS for hydroxycarbamide in all three models and for interferon in the CP model. The method of moments involves simply setting the rate parameter λ to 1/(Mean OS).

Pfizer "cumulative survival approach"

Pfizer developed a "cumulative survival approach" for bosutinib overall survival in a scenario analysis of the CP model which they describe as similar to the cumulative survival approach used in TA251. Their approach involves estimating OS as PFS + 10 months in AP + 6 months in BP. We do not believe it is correct to describe this method as similar to the approach in TA251 as the cumulative survival approach in TA251 involved estimating OS as the sum of time spent on treatments, which is a different structural assumption.

Death due to non-CML mortality

Death due to non-CML mortality was originally calculated as follows for all treatments in the CP, AP and BP models, except for bosutinib in the CP model (Pfizer submission, Section 7.3.2, p124):

> For all three models, for all comparators, background mortality was incorporated into the model, to ensure that parametric curve fits did not over predict survival as patients aged.
>
> Background mortality was applied in the model by subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200), and adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012). The starting age in the AP and BP models are 50 and 47 respectively, so these ages are used to adjust for background mortality.
>
> As this component of mortality increases over time, it has the effect of ensuring survival curves do not asymptote to 0, estimating survival beyond what can be expected in clinical practice, where patients are likely to experience co-morbidities and competing risks.

The method for incorporating non-CML mortality for bosutinib in the CP model was changed following clarifications from the manufacturer in which they corrected an error in calculating CML mortality from the MCyR surrogate relationship (p119). Rather than using the above method, CML mortality was estimated accounting for general mortality (see p119) and then general mortality is added to CML mortality in a manner similar to that used in TA241 and described by Rogers and colleagues (2012).[2]

5.2.6.2 Time on treatment

Time on treatment has clinical relevance because treatments can reduce or improve health related quality of life. It is also very relevant to cost-effectiveness because higher drug acquisition costs are incurred while patients are on bosutinib or interferon rather than hydroxycarbamide.

Bosutinib and interferon are both discontinued when disease progresses (or the patient dies), the patient does not tolerate them or the technology is not efficacious. Hydroxycarbamide is received until death and is not discontinued; therefore for hydroxycarbamide time on treatment is equal to overall survival. Stem cell transplant patients have a one-off procedure followed by medical management, with medical management continuing until death.

Time on bosutinib

Time on bosutinib is incorporated into the model by fitting a lognormal distribution to the individual patient data for discontinuation in Study 200 for the relevant cohort, i.e., in the CP model the CP-3L cohort is used (Figure 13), in the AP model the AP cohort is used (

Figure 14) and in the BP model the BP cohort is used (

Figure 15).

Figure 13. [redacted]

Figure 14. [redacted]

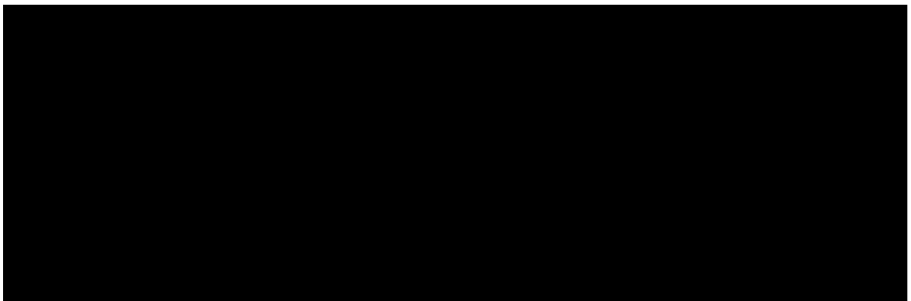


Figure 15. [redacted]

Time on interferon

Time on interferon is incorporated into the model using an exponential distribution, chosen such that the mean time on treatment (ignoring the effect of non-CML mortality) would be 0.5 years.[40] This estimate was not taken from any study, but on the basis of expert opinion.

5.2.7 Health related quality of life

5.2.7.1 Utilities in CP CML

For CP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. From patients on 1st-line imatinib in the IRIS RCT of imatinib vs. IFN. These values were reported in Reed and colleagues (2004),[45] and are estimated from a large sample of patients, using the EQ-5D, which is preferred in the NICE reference case. The mean utility is 0.85 at age 50. In TA251, we, PenTAG, applied this value to the utility for all 1st-line TKIs: imatinib, nilotinib and dasatinib in CP, given the lack of relevant high-quality utility data for these treatments, and based on clinical opinion and the similarity of the incidence of adverse events across treatments.
2. From patients in Study 200 of people on bosutinib. The weighted average utility for 3rd-line patients, mostly over the first two years of treatment, was [redacted] (p131 Pfizer submission). At baseline, [redacted] of 3rd-line CP patients completed the EQ-5D. The weighted average utility for 2nd-line patients also mostly over the first two years of treatment, was [redacted] (estimated by us from data on pp357-8 Pfizer submission). At baseline, [redacted] of 2nd-line CP patients completed the EQ-5D.

For their base case, Pfizer used the estimate from the IRIS trial.

Next, Pfizer found no relevant studies to estimate the utility for patients on HU in CP. They therefore assumed the same utility as for bosutinib. In TA251, we also found no relevant data for the utility for patients on HU in CP. We also set this value to equal the utility for the TKIs.

Next, Pfizer found two sources for utilities for patients after SCT in CP:

1. They correctly cite our TA251 analysis where we assumed a disutility vs. the general population of 0.041 for the 75% of patients in a "low risk" population and a disutility of 0.079 for the remaining 25% of patients in a "high risk" population. For details of our analysis, see our TA251 report.[17] In brief, the disutility of 0.079 was in respect of chronic graft-versus-host disease and was elicited from 12 US clinicians familiar with bone marrow transplantation. This therefore gave a mean utility at age 54 of 0.81 for patients in the "low risk" population and 0.76 for patients in the "high risk" population, giving a weighted mean of 0.80.
2. They cite utilities after SCT in CP of 0.60 from the BMS submission in TA241 and 0.81 from the Novartis submission in TA251 (p135 Pfizer submission). However, they give no further details on how these were estimated.

In their base case, Pfizer estimate a utility after SCT in CP of 0.71 at age 54.

Next, Pfizer assume a utility for patients on IFN in CP of 0.71, which they took from our analysis in TA241 (IFN was not a treatment in our TA251 analysis).

As in our TA251 analysis, all utilities are assumed to decrease gradually with age.

5.2.7.2 Utilities in AP CML

For AP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. 0.73 at age 54. We used this value in TA251 for treatment with HU (we did not model treatment with TKIs in AP). This value was originally reported in Dalziel and colleagues (2004).[46]
2. From patients in Study 200 of people on bosutinib. The weighted average utility, [redacted]. At baseline, [redacted] of AP patients completed the EQ-5D.

For their base case, Pfizer used the first value.

Next, Pfizer assumed the same value of 0.73 for patients on HU in AP.

Finally, for patients after SCT in AP, Pfizer assume a utility of 0.71 for patients age 54, the same as for patients after SCT in CP.

5.2.7.3 Utilities in BP CML

For AP CML, Pfizer claim that the most appropriate sources of utility data for patients on bosutinib are (Table 42, p126):

1. 0.52 at age 54. We used this value in TA251 for treatment with HU (we did not model treatment with TKIs in BP). This value was originally reported in Dalziel and colleagues (2004).[46]
2. From patients in Study 200 of people on bosutinib. The weighted average utility, [redacted], was [redacted] (p132 Pfizer submission), which is only slightly less than the averages for 3rd-line CP and AP in Study 200. At baseline, [redacted] of BP patients completed the EQ-5D.

For their base case, Pfizer used the first value.

Next, Pfizer assumed the same value of 0.52 for patients in BP on HU and after SCT.

Table 42. Comparison of utilities used in TA251, used by Pfizer and measured in Study 200

Phase	Treatment	TA251	Study 200	Pfizer
CP	**Bosutinib**	For TKIs[a], 0.84 age 54, declining with age.	[redacted] at age [redacted] for 3rd-line, [redacted] for 2nd-line[d]	0.85 age 54, declining with age
	HU	0.84 age 54, declining with age	n/a	0.85 age 54, declining with age
	SCT	0.80 age 54, declining with age [b]		0.71 age 54, declining with age
	IFN	0.71, independent of age 51[c]		0.71 age 54, declining with age
AP	**Bosutinib**	n/a	[redacted]	0.73 age 54, declining with age
	HU	0.73 (declining with age from age 78)	n/a	0.73 age 54, declining with age
	SCT	n/a		0.71 age 54, declining with age
BP	**Bosutinib**	n/a	[redacted]	0.52 age 54, declining with age
	HU	0.52 (independent of age)	n/a	
	SCT	n/a		

a Bosutinib not modelled in TA251
b See text for derivation.
c From TA241; not modelled in TA251
d [redacted] calculated by PenTAG from data on p358 Pfizer submission

5.2.8 Adverse events

Adverse events are included only for bosutinib and are assumed to incur costs but not affect quality of life in any way not already reflected by utility values as specified in Section 5.2.7 (p124). Adverse events are assumed to occur in the first cycle only.

Resource use and costs associated with adverse events are discussed in Section 5.2.9.6 (p130).

5.2.9 Resources and costs

Resource use and cost data were drawn from multiple sources. Resource use data were largely drawn from TA251[17] (which were in turn based on a survey by Oxford Outcomes on behalf of Bristol-Myers Squibb), with most costs derived from the Department of Health National Schedule of Reference Costs 2011-12 for NHS trusts and NHS foundation trusts.[47]

5.2.9.1 Resource use systematic review

Pfizer conducted a systematic review for relevant resource use and cost data. The search was performed in October/November 2012 and used the same search strategy, inclusion and exclusion criteria as in Section 5.1 (p108), but with the study type criteria broadened to include any study that reported cost or resource data from the UK.

Abstracts were assessed by two reviewers for full paper retrieval. Full papers were obtained and assessed by two reviewers. Data extraction was conducted by one reviewer and checked by a second party.

Pfizer felt that insufficient resource use data had been identified and so sought data from first-line studies. As a result they included resource use and cost data from TA251.[17] Pfizer state that first-line data are appropriate as resource use is expected to be driven primarily by phase of disease rather than line of treatment (Pfizer submission, Section 7.4.18, p141).

Figure 16 shows the flow diagram of articles in the systematic review, and Table 43 shows the included studies.

Figure 16. Study flow diagram for resource use systematic review

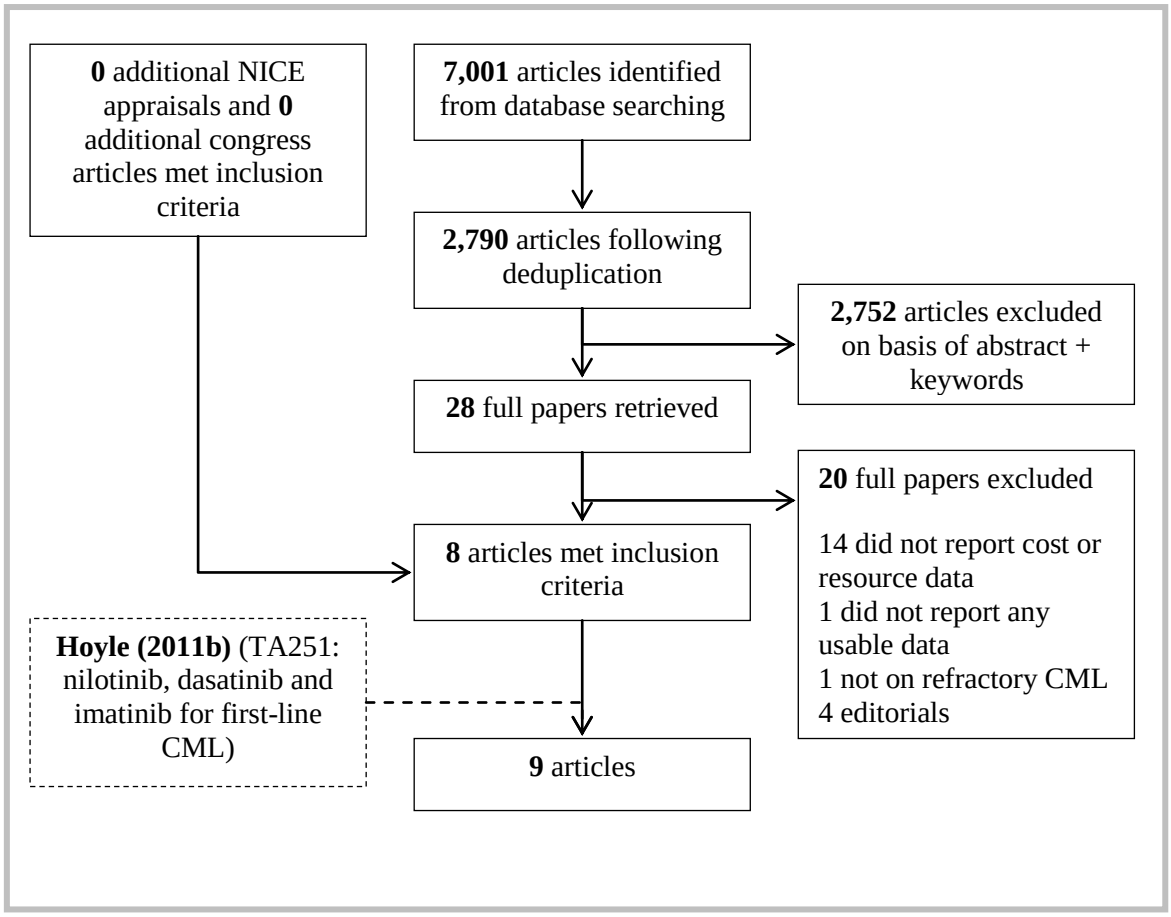


Table 43. Included studies in systematic review of resource use and cost data

Study	Resource use/cost included in Pfizer model base case	Notes
Hoyle (2011a)[39] Rogers (2012)[2] Loveman (2012)[40]	Interferon patients requiring assistance with injection Hydroxycarbamide and interferon dosing	TA241
Hoyle (2011b)[17]	Nurse-led outpatient appointments Consultant-led outpatient appointments Tests (various) Hospital inpatient bed days Hospital inpatient ICU days Adverse events	TA251
Darbà (2012)[48]	*None*	Not English language
Szabo (2009)[49]	*None*	Conference abstract
Taylor (2009a)[50]	*None*	Conference abstract
Taylor (2009b)[51]	*None*	Conference abstract
Warren (2004)[52]	*None*	

5.2.9.2 Drug acquisition

Drug acquisition costs per monthly model cycle were calculated by multiplying the expected dosage across the cycle by the drug cost per unit, to give monthly costs (costs per cycle) as shown in Table 44. Costs of stem cell transplant are discussed in Section 5.2.9.7 (p131).

Table 44. Costs per month of bosutinib, hydroxycarbamide and interferon

Intervention	Cost per month	Units per month	Source	Unit cost	Source
Bosutinib	£3,735.84	30.44	Recommended daily dose 500mg	£122.74	£3,436.67 for 28 tablet pack
Hydroxycarbamide	£12.75	121.75	Loveman (2012)[40]	£0.10	BNF 63[b]
Interferon	£1,296.03[a]	60.88	Rogers (2012)[2]	£21.29	BNF 63

a The Pfizer report states that the monthly cost of interferon including nurse assistance with injection for some patients is £648. We believe this assumes one unit daily, i.e., 30.44 units per month, and does not include the cost of nurse assistance. The Pfizer model assumes two injections per day.

b The Pfizer model cites the source as BNF 63 while the report cites the source as BNF 64

5.2.9.3 Drug administration

Pfizer assumed no drug administration costs for bosutinib and hydroxycarbamide. Pfizer assumed that 25% of interferon patients would require assistance with injection, following an assumption made by Rogers and colleagues (2012),[2] and that this would require a district nurse visit, each costing £39.[53]

The Pfizer model includes one nurse visit per cycle (i.e., per month) in drug administration costs for patients requiring assistance.

Stem cell transplant administration costs are discussed in Section 5.2.9.7 (p131).

5.2.9.4 Medical management, monitoring and tests

Pfizer included medical management costs as shown in Table 45 and a cost of palliative care before death (discussed in Section 5.2.9.5, p129). Medical management costs relating to stem cell transplant are discussed in Section 5.2.9.7 (p131).

Table 45. On-going medical management costs for patients on bosutinib, HU or IFN in Pfizer model

Item	Cost / month	Units / month[17]	Unit cost[47]
Chronic Phase			
Nurse-led outpatient appointment	£42	0.40	£106[a]
Consultant-led outpatient appointment	£111	0.90	£124[b]
Hospital inpatient ward day	£0	0.00	£322[c]
Hospital inpatient ward day	£0	0.00	£1,109[d]
Total	**£154**		
Accelerated Phase and Blast Crisis Phase			
Nurse-led outpatient appointment	£53	0.50	£106[a]
Consultant-led outpatient appointment	£161	1.30	£124[b]
Hospital inpatient ward day	£554	1.72	£322[c]
Hospital inpatient ward day	£111	0.10	£1,109[d]
Total	**£878**		

a Outpatient medical oncology - Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face
b Outpatient medical oncology - Consultant Led: Follow up Attendance Non-Admitted Face to Face
c Average of excess bed day – Non-elective inpatient - Malignant Disorders of Lymphatic or Haematological Systems, with/without CC
d Average of critical care unit costs – adult critical care (weighted by number of critical care periods)

Pfizer included costs of CML related tests (mostly bone marrow aspirations), separately for CP and for AP/BP, which were inflated from TA251[17] using the HCHS Pay and Prices index[53] to inflate from 2008/09 to 2011/12 prices. The resulting costs per cycle of tests in CP, AP and BP were £231, £377 and £377 respectively.

5.2.9.5 Palliative care

Pfizer used a cost of £6,004 for death based on a cost of £5,401 reported by Addicott and Dewar (2008)[54] and inflated from 2007/08 prices. The cost of £5,401 includes costs incurred in the acute and

community health sectors and is derived from 40 patients accessing a new programme of end of life choice.

5.2.9.6 Adverse events

Costs of adverse events were included for bosutinib but not for comparators. Pfizer state that this is in order to present a conservative estimate of the costs associated with bosutinib treatment. Frequencies of adverse events were estimated from the third-line CP cohort of Study 200 and included "treatment-emergent adverse events of grade 3 or 4 that occurred in 5% or more of the subpopulations contained within the third-line cohort of Study 200".

Table 46 shows the costs of adverse events for bosutinib in the Pfizer model, which are used for the CP model and also the AP and BP models. A one-off cost of £506.25 is assumed in the first cycle.

Table 46. Costs of adverse events for bosutinib in Pfizer model

AE	Proportion of patients (Study 200 CP-3L cohort, 28 March 2011 snapshot)	Cost per event	Cost source
Thrombocytopenia	25.4%	£503.99	TA251[17]
Neutropenia	14.4%	£506.13	
Anaemia	5.1%	£346.69	
Cardiac disorders	4.2%	£169.81	
Gastrointestinal disorders[a]	13.6%	£281.07	Erlotinib ERG report[55]
Hepatobiliary disorders	4.2%	£215.85	DH Reference costs 2011-12[47]
Infections and infestations	3.4%	£933.23	
Investigations	9.3%	£31.02	
Metabolism and nutrition disorders	3.4%	£1,576.37	
Musculoskeletal and connective tissue disorders	5.9%	£717.03	
Neoplasms benign, malignant and unspecified	3.4%	£1,570.14	
Nervous system disorders	4.2%	£1,091.02	
Respiratory, thoracic and mediastinal disorders[b]	2.5%	£32.10	TA251[17]
Skin and subcutaneous tissue disorders	1.7%	£138.76	Erlotinib ERG report[55]
Weighted average	**100%**	**£506.25**	

a Assumed to be diarrhoea
b Assumed to be pleural effusion

5.2.9.7 Stem cell transplant

Stem cell transplant costs were mainly drawn from the economic analysis performed for the NHS Blood and Transplant service[56] which estimated the upfront costs of SCT and the costs for three follow-up periods (1-6 months, 7-12 months and 13-24 months).

These costs were based on resource use in a Dutch cost study by van Agthoven and colleagues (2002)[57] into the costs of three forms of stem cell transplant for acute myeloid leukaemia and acute lymphoblastic leukaemia. The three forms were:

- BMT – Bone marrow transplant; stem cell graft harvested from the bone marrow of an HLA-identical sibling
- PBSCT – Peripheral blood stem cell transplant; stem cell graft harvested from the peripheral blood of an HLA-identical sibling
- MUD – Matched unrelated donor; stem cell graft from the bone marrow or peripheral blood of a voluntary matched unrelated donor

The study included direct medical costs for Personnel, Transplantation and Follow-up (two years), which importantly included outpatient clinic attendances and diagnostic tests during follow-up. The results of the study are shown in Table 47.

Table 47. Costs of stem cell transplant (1998 EUR, €) from van Agthoven and colleagues (2002)[57]

	BMT			**MUD**			**PBSCT**		
	Average cost per living patient	% alive	Average cost per transplant patient	Average cost per living patient	% alive	Average cost per transplant patient	Average cost per living patient	% alive	Average cost per transplant patient
Personnel	26,543		26,543	26,543		26,543	26,543		26,543
Transplantation	42,129	100	42,129	84,948	100	84,948	45,734	100	45,734
Follow-up phase 1 (1–6 months)	16,587	98	16,255	30,292	90	27,263	15,051	92	13,847
Follow-up phase 2 (7–12 months)	10,157	81	8,227	18,473	48	8,867	12,265	77	9,444
Follow-up phase 3 (13–24 months)	8,093	64	5,180	13,331	31	4,133	6,313	54	3,409
Total	**103,509**		**98,334**	**173,587**		**151,754**	**105,906**		**98,977**

In the economic analysis performed for the NHS Blood and Transplant service[56] unit costs were replaced with NHS costs (2009 prices) where possible, and where not possible were converted using the 1999 pound sterling / euro exchange rate and inflated at 3% per annum (Table 48).

Table 48. Costs of stem cell transplant (2009 GDP, £) from NHS Blood and Transplant service[56]

	Average cost per living patient	% alive	Weighted cost per transplant patient
Personnel	31,409	100	31,409
Transplantation	40,140	100	40,140
Follow-up phase 1 (1–6 months)	29,713	90	26,742
Follow-up phase 2 (7–12 months)	18,119	48	8,697
Follow-up phase 3 (13–24 months)	13,075	31	4,053
Total	**132,456**		**111,041**

The adaptation to NHS costs is not described in sufficient detail to be reproducible, but the researchers note that the weighted cost per transplant patient (£111k) is reassuringly close to the commissioning price (£101k).

Costs were then inflated by Pfizer using the HCHS Pay and Prices Index.[53]

Longer term follow-up was assumed to consist of 100 mg of ciclosporin twice daily. Costs per month used in Pfizer's model are presented in Table 49.

Table 49. Pfizer assumed costs associated with stem cell transplant

Item	Cost / month	Units / month	Unit cost
Initial treatment	£76,560	1	£76,560
Follow-up 1-6 months	£5,299	1	£5,299
Follow-up 7-12 months	£3,231	1	£3,231
Follow-up 13-24 months	£1,166	1	£1,166
Follow-up 25+ months	£140	60.88	£2.30

Patients receiving SCT in the blast crisis phase (i.e., SCT patients in the BP model) are assumed to receive two cycles of the FLAG-IDA chemotherapy regime before SCT, at a cost of £29,212. Table 50 gives a summary of costs for two cycles of the FLAG-IDA regime (further details available in Pfizer submission, Section 10.20, pp393-395).

Table 50. Summary of FLAG-IDA chemotherapy costs

Item	Item cost	Units	Unit cost
Drug acquisition			
Fludarabine	£1,471	10	£147.07
Cytarabine	£780	20	£39.00
Idarubicin	£1,048	12	£87.36
G-CSF	£1,922	Various	Various
Medical management			
Haematology tests	£3	1	£3.09
AML without CC: Elective inpatient stay	£4,866	1	£4,866
AML without CC: Elective excess bed day	£4,515	14	£322.34
Total (two cycles)	**£29,212**		

Abbreviations AML – acute myeloid leukaemia; CC – comorbidities and complications

5.2.9.8 Summary of costs

Table 51. Summary of costs per month in CP model

Intervention	Bosutinib	Hydroxy-carbamide	Interferon	SCT
Chronic Phase On Treatment				
Drug acquisition	£3,736	£13	£1,296	
Drug administration	£0	£0	£10	
Medical management	£154	£154	£154	£154
Tests	£231	£231	£231	£231
Adverse events	£506 first cycle only			
SCT costs				Month 0: £76,560 Months 1-6: £5,299 per month (p.m). Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£4,627** first cycle **£4,121** thereafter	**£398**	**£1,691**	Month 0: **£76,945** Months 1-6: **£5,684** p.m. Months 7-12: **£3,616** p.m. Months 13-24: **£1,551** p.m. Months 25+: **£525** p.m.
Chronic Phase Off Treatment				
Drug acquisition	£13		£13	
Drug administration	£0		£0	
Medical management	£154		£154	
Tests	£231		£231	
Total	**£398**		**£398**	
Accelerated & Blast Phases				
Drug acquisition	£13	£13	£13	
Drug administration	£0	£0	£0	
Medical management	£878	£878	£878	
Tests	£377	£377	£377	
Total	**£1,268**	**£1,268**	**£1,268**	
Death	**£6,004**	**£6,004**	**£6,004**	**£6,004**

Table 52. Summary of costs per month in AP model

Intervention	Bosutinib	Hydroxycarbamide	SCT
Accelerated Phase On Treatment			
Drug acquisition	**£3,736**	**£13**	
Drug administration	**£0**	**£0**	
Medical management	**£878**	**£878**	£878
Tests	**£377**	**£377**	£377
Adverse events	**£506 first cycle only**		
SCT costs			Month 0: £76,560 Months 1-6: £5,299 p.m. Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£5,498** first cycle **£4,991** thereafter	**£1,268**	Month 0: **£77,815** Months 1-6: **£6,554** p.m. Months 7-12: **£4,487** p.m. Months 13-24: **£2,421** p.m. Months 25+: **£1,396** p.m.
Accelerated Phase Off Treatment			
Drug acquisition	£13		
Drug administration	£0		
Medical management	**£878**		
Tests	**£377**		
Total	**£1,268**		
Blast Crisis Phase			
Drug acquisition	£13	£13	
Drug administration	£0	£0	
Medical management	**£878**	**£878**	
Tests	**£377**	**£377**	
Total	**£1,268**	**£1,268**	
Death	**£6,004**	**£6,004**	**£6,004**

Table 53. Summary of costs per month in BP model

Intervention	Bosutinib	Hydroxy-carbamide	SCT
Blast Crisis Phase On Treatment			
Drug acquisition	**£3,736**	**£13**	
Drug administration	**£0**	**£0**	
Medical management	**£878**	**£878**	£878
Tests	**£377**	**£377**	£377
Adverse events	**£506 first cycle only**		
SCT costs (including FLAG-IDA)			Month 0: £105,772 Months 1-6: £5,299 p.m. Months 7-12: £3,231 p.m. Months 13-24: £1,166 p.m. Months 25+: £140 p.m.
Total	**£5,498** first cycle **£4,991** thereafter	**£1,268**	Month 0: **£107,027** Months 1-6: **£6,554** p.m. Months 7-12: **£4,487** p.m. Months 13-24: **£2,421** p.m. Months 25+: **£1,396** p.m.
Blast Crisis Phase Off Treatment			
Drug acquisition	£13		
Drug administration	£0		
Medical management	**£878**		
Tests	**£377**		
Total	**£1,268**		
Death	**£6,004**	**£6,004**	**£6,004**

5.2.10 Cost-effectiveness results

This section presents the deterministic base case cost-effectiveness results.

Unless otherwise stated, positive Incremental cost-effectiveness ratios (ICERs) mean that the intervention is more costly and more effective than the comparator. Negative ICERs are not shown but instead it is stated whether the intervention "dominates" the comparator (is less costly and more effective) or is "dominated" by the comparator (is more costly and less effective).

Incremental net health benefits (INHBs) are also presented in units of QALYs. Incremental net health benefit is calculated as $INHB = \Delta QALYs - \Delta Costs/\lambda$ for a willingness-to-pay threshold λ. We present INHB at willingness-to-pay thresholds of £20,000 and £30,000 per QALY for all models, as well as INHB at willingness-to-pay threshold of £50,000 per QALY for the AP and BP models as Pfizer propose that bosutinib meets the end-of-life criteria in these patients. INHB are always shown relative to bosutinib, such that positive INHB for hydroxycarbamide (for example) means that hydroxycarbamide is cost-effective compared to bosutinib.

5.2.10.1 CP model deterministic results

Deterministic base case cost-effectiveness results from the CP model are shown in Table 54 (p138) and Figure 17 (p138). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 4.83 QALY (9.23 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted] (costs and QALYs discounted at 3.5% per annum, life years not discounted). The extra costs of bosutinib are mainly from drug acquisition, with smaller increases also due to additional medical management during the prolonged life expectancy. Interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib. Bosutinib is the most effective treatment, providing 3.56 QALYs more than the next most effective treatment, SCT.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000 and £30,000 per QALY are [redacted] and [redacted] QALYs respectively. At a willingness-to-pay threshold of £20,000 per QALY hydroxycarbamide gives the greatest expected net health benefit while at £30,000 per QALY bosutinib gives the greatest expected net health benefit.

Bosutinib patients spend longer in the chronic phase than other patients (11.54 years versus 2.58 for hydroxycarbamide, 2.67 for interferon and 6.60 for SCT) and also accrue more discounted QALYs in the chronic phase (6.77 QALYs versus 1.93 for hydroxycarbamide, 1.92 for interferon and 3.70 for SCT). Bosutinib patients also spend longer in the accelerated and blast phases than hydroxycarbamide and interferon patients (SCT patients are cured and do not progress to AP or BP), and accrue more discounted QALYs in the accelerated phase as a result, but not in the blast phase (due to greater discounting as BP is reached at a later time).

Bosutinib patients spend [redacted] life years in the CP off treatment state, in which they are treated with hydroxycarbamide.

[redacted]

Table 54. Deterministic CP model results

	Bosutinib	Hydroxycarbamide	Interferon	SCT
Life years (undiscounted)				
CP on treatment	[redacted]	2.58	0.54	6.60
CP off treatment	[redacted]	n/a	2.12	n/a
AP	0.73	0.51	0.52	n/a
BP	0.48	0.43	0.44	n/a
Total	**12.75**	**3.52**	**3.62**	**6.60**
Discounted QALYs				
CP on treatment	[redacted]	1.93	0.38	3.70
CP off treatment	[redacted]	n/a	1.53	n/a
AP	0.33	0.31	0.31	n/a
BP	0.16	0.19	0.19	n/a
Total	**7.26**	**2.43**	**2.42**	**3.70**
Discounted costs				
Technology cost	[redacted]	£490	£8,461	£141,132
Hydroxycarbamide following discontinuation	£1,053	n/a	£419	n/a
Monitoring	£24,372	£13,195	£13,386	£10,163
Tests	£27,315	£10,352	£10,583	£15,283
Palliative care	£4,174	£5,436	£5,419	£4,961
Adverse events	£506	n/a	n/a	n/a
Total	[redacted]	**£29,473**	**£38,268**	**£171,539**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified				
vs. hydroxycarbamide	[redacted]			
vs. interferon	[redacted]	Dominant		
vs. SCT	Dominant	111,511[a]	103,662[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)				
WTP £20,000/QALY	**n/a**	[redacted]	[redacted]	[redacted]
WTP £30,000/QALY	**n/a**	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 17. Cost-effectiveness plane in CP model, Pfizer base case

Note that (IFN, HU) and (Bosutinib, HU) denote that interferon and bosutinib are followed by hydroxycarbamide

5.2.10.2 AP model deterministic results

Deterministic base case cost-effectiveness results from the AP model are shown in Table 55 (p140) and

Figure 18 (p140). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 1.86 QALY (3.11 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted]. The extra costs of bosutinib are mainly drug acquisition and also due to additional medical management during the prolonged life expectancy. SCT is dominated by bosutinib as it is less effective and more costly. Bosutinib is the most effective intervention, providing a 0.80 QALY (1.45 life year) gain per patient over the next most effective intervention, SCT.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY are [redacted] QALYs respectively. At all three willingness-to-pay thresholds hydroxycarbamide therefore gives the greatest expected net benefit.

Bosutinib patients spend longer in the accelerated phase than patients receiving hydroxycarbamide and SCT (4.03 life years for bosutinib versus 1.02 life years for hydroxycarbamide and 3.02 life years for SCT), and accrue more discounted QALYs in the accelerated phase as well (2.56 QALYs for bosutinib versus 0.72 QALYs for hydroxycarbamide and 1.96 QALYs for SCT). Bosutinib patients spend slightly longer in the blast crisis phase than do hydroxycarbamide patients (0.45 versus 0.35 life

years; SCT patients do not transform to BP), and also accrue slightly more discounted QALYs in BP (0.20 versus 0.18).

Bosutinib patients spend [redacted] life years in the AP off treatment state, in which they are treated with hydroxycarbamide.

[redacted]

Table 55. Deterministic AP model results

	Bosutinib	Hydroxycarbamide	SCT
Life years (undiscounted)			
AP on treatment	[redacted]	1.02	3.02
AP off treatment	[redacted]	n/a	n/a
BP	0.45	0.35	n/a
Total	**4.48**	**1.37**	**3.02**
Discounted QALYs			
AP on treatment	[redacted]	0.72	1.96
AP off treatment	[redacted]	n/a	n/a
BP	0.20	0.18	n/a
Total	**2.76**	**0.90**	**1.96**
Discounted costs			
Technology cost	[redacted]	£204	£130,528
Hydroxycarbamide following discontinuation	£297	n/a	n/a
Monitoring	£41,726	£14,032	£29,414
Tests	£17,916	£6,025	£12,630
Palliative care	£5,280	£5,817	£5,520
Adverse events	£506	n/a	n/a
Total	[redacted]	**£26,078**	**£178,093**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified			
vs. hydroxycarbamide	[redacted]		
vs. SCT	Dominant	142,982[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)			
WTP £20,000/QALY	**n/a**	[redacted]	[redacted]
WTP £30,000/QALY	**n/a**	[redacted]	[redacted]
WTP £50,000/QALY	**n/a**	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 18. Cost-effectiveness plane in AP model, Pfizer base case

5.2.10.3 BP model deterministic results

Deterministic base case cost-effectiveness results from the BP model are shown in Table 56 (p142) and

Figure 19 (p142). The base case ICER for bosutinib versus hydroxycarbamide is [redacted] per QALY, with bosutinib providing an expected 0.60 QALY (1.23 life year) gain per patient over hydroxycarbamide at an extra cost of [redacted]. The extra costs of bosutinib are drug acquisition and additional medical management during the prolonged life expectancy. SCT is more costly than bosutinib but more effective. The ICER for SCT versus bosutinib is [redacted] per QALY. SCT is the most effective intervention, providing a 0.40 QALY (0.87 life year) gain per patient over the next most effective intervention, bosutinib.

The INHBs of hydroxycarbamide versus bosutinib at willingness-to-pay thresholds of £20,000, £30,000 and £50,000 per QALY are [redacted] QALYs respectively. The INHBs of SCT versus bosutinib at the same thresholds are [redacted] QALYs respectively.

Across all three willingness-to-pay thresholds hydroxycarbamide therefore gives the greatest expected net benefit.

Bosutinib patients spend [redacted] life years in the BP off treatment state, in which they are treated with hydroxycarbamide.

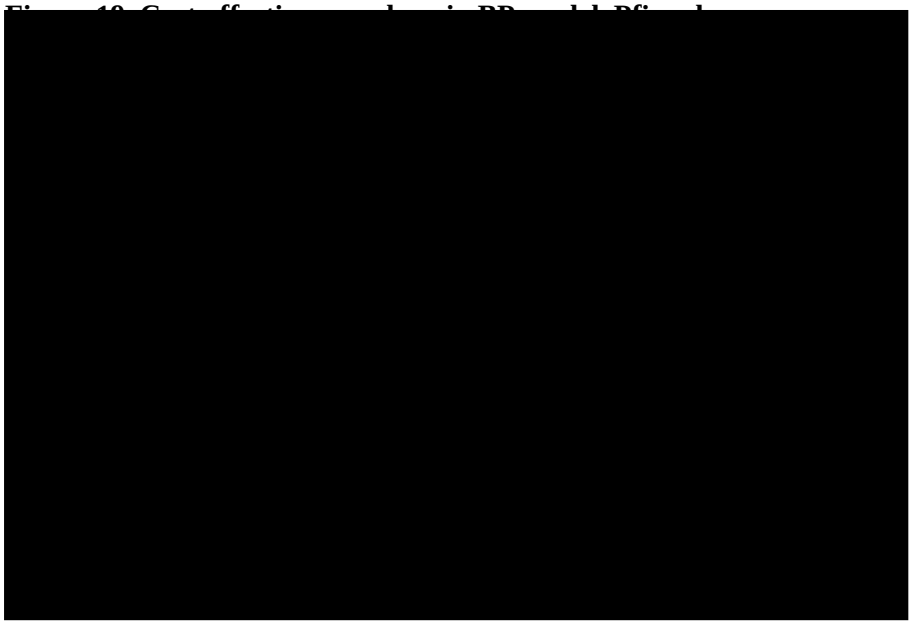
[redacted]

Table 56. Deterministic BP model results

	Bosutinib	Hydroxycarbamide	SCT
Life years (undiscounted)			
BP on treatment	[redacted]	0.54	2.64
BP off treatment	[redacted]	n/a	n/a
Total	**1.77**	**0.54**	**2.64**
Discounted QALYs			
BP on treatment	[redacted]	0.28	1.28
BP off treatment	[redacted]	n/a	n/a
Total	**0.88**	**0.28**	**1.28**
Discounted costs			
Technology cost	[redacted]	£82	£157,759
Hydroxycarbamide following discontinuation	£169	n/a	n/a
Monitoring	£17,935	£5,681	£26,011
Tests	£7,701	£2,439	£11,169
Palliative care	£5,743	£5,967	£5,586
Adverse events	£506	n/a	n/a
Total	[redacted]	**£14,170**	**£200,526**
ICERs (£/QALY) – positive ICER means intervention is more costly and more effective than comparator unless otherwise specified			
vs. hydroxycarbamide	[redacted]		
vs. SCT	[redacted]	186,265[a]	
Incremental Net Health Benefit vs. bosutinib (calculated by PenTAG)			
WTP £20,000/QALY	**0.0**	[redacted]	[redacted]
WTP £30,000/QALY	**0.0**	[redacted]	[redacted]
WTP £50,000/QALY	**0.0**	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator

Figure 19: Cost-effectiveness scatterplot in PBS model: Pfizer



5.2.11 Sensitivity analyses

5.2.11.1 One-way sensitivity analyses

Extensive one-way sensitivity analyses were not performed as Pfizer believed structural uncertainties were greater than parameter uncertainties. Scenario analyses were performed instead (see Section 5.2.11.3, p146).

5.2.11.2 Probabilistic sensitivity analysis

Pfizer conducted a probabilistic sensitivity analysis but cautioned that it could not capture all the uncertainty in the decision problems addressed by the economic models due to several sources of structural uncertainty.

Pfizer did not record the parameter values associated with probabilistic outputs and therefore no value of information analyses could be conducted.

CP model PSA

Table 57 gives a comparison of the key CP model deterministic and probabilistic results. The deterministic and mean probabilistic results are very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented graphically in the Pfizer report).

Further results are presented in Appendix R.

Table 57. Comparison of key CP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	Interferon	SCT
Deterministic results				
Total discounted QALYs	7.26	2.43	2.42	3.70
Total discounted costs	[redacted]	£29,473	£38,268	£171,539
ICER vs. hydroxycarbamide	[redacted]			
ICER vs. interferon	[redacted]	Dominant		
ICER vs. SCT	Dominant	111,511[a]	103,662[a]	
Probabilistic results				
Total discounted QALYs	7.15	2.43	2.39	3.84
Total discounted costs	[redacted]	£29,389	£36,091	£173,948
ICER vs. hydroxycarbamide	[redacted]			
ICER vs. interferon	[redacted]	Dominant		
ICER vs. SCT	Dominant	102,524[a]	104,118[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report

AP model PSA

Table 58 gives a comparison of the key AP model deterministic and probabilistic results. Deterministic results and mean probabilistic results were very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY, £30,000/QALY and £50,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented in the Pfizer report).

Further results are presented in Appendix R.

Table 58. Comparison of key AP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	SCT
Deterministic results			
Total discounted QALYs	2.76	0.90	1.96
Total discounted costs	[redacted]	£26,078	£178,093
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	Dominant	142,982[a]	
Probabilistic results			
Total discounted QALYs	2.75	0.91	1.95
Total discounted costs	[redacted]	£26,095	£175,420
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	Dominant	143,454[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	100.0%	0.0%
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £50,000/QALY[b]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report

BP model PSA

Table 59 gives a comparison of the key BP model deterministic and probabilistic results.

Deterministic results and mean probabilistic results were very similar.

The probabilities that bosutinib is cost-effective at willingness-to-pay thresholds of £20,000/QALY, £30,000/QALY and £50,000/QALY are [redacted] respectively (based on a separate PSA run to the results presented in the Pfizer report).

Further results are presented in Appendix R.

Table 59. Comparison of key BP model deterministic and probabilistic results

	Bosutinib	Hydroxycarbamide	SCT
Deterministic results			
Total discounted QALYs	0.88	0.28	1.28
Total discounted costs	[redacted]	£14,170	£200,526
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	[redacted]	186,265[a]	
Probabilistic results			
Total discounted QALYs	0.89	0.32	1.29
Total discounted costs	[redacted]	£15,262	£201,228
ICER vs. hydroxycarbamide	[redacted]		
ICER vs. SCT	[redacted]	192,016[a]	
Probability intervention is cost-effective at WTP £20,000/QALY[b]	[redacted]	100.0%	0.0%
Probability intervention is cost-effective at WTP £30,000/QALY[b]	[redacted]	[redacted]	[redacted]
Probability intervention is cost-effective at WTP £50,000/QALY[b]	[redacted]	[redacted]	[redacted]

a Intervention is less costly and less effective than comparator
b Based on a separate PSA run to results presented in Pfizer report
c Note that in the Pfizer submission this was reported as [redacted]/QALY

5.2.11.3 Scenario analyses

Pfizer conducted a number of scenario analyses for each of the models. Some of these are parameter changes and would normally be considered one-way sensitivity analyses, while others are structural changes to the model. Here, we simply report the results of the analyses. Later (Section 5.3, p159), we comment on the appropriateness of the analyses.

[redacted]. Note that shading does not indicate whether bosutinib is more or less costly or more or less effective than the comparator.

Table 60. Shading used to denote cost-effectiveness of bosutinib

White background	[redacted]
Grey background	[redacted]
Black background	

CP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 61 (p148). In most scenarios interferon is dominated by hydroxycarbamide and SCT is dominated by bosutinib. Where this is not the case additional results are presented. Further details of scenario analyses can be found in the Pfizer submission, Section 10.22, pp467-476.

In most analyses interferon is dominated by hydroxycarbamide, which Pfizer state is in keeping with clinical practice. When bosutinib is compared to hydroxycarbamide, bosutinib is always more expensive, and more effective, with ICERs ranging from [redacted] per QALY. There were four scenarios where the ICER of bosutinib versus hydroxycarbamide was substantially reduced:

- Patient population set to second line for bosutinib
- Hydroxycarbamide overall survival set to two years
- Resource use from TA241 is assumed
- Hazard ratio for survival in MCyR surrogate method of 0.876 used

Pfizer suggest that resource use from TA241 may be more appropriate than resource use from TA251 (the base case) because TA241 and this decision problem involve patients who have failed imatinib treatment.

In most analyses bosutinib dominates SCT. When the time on bosutinib treatment is calculated using a similar method to TA241 SCT becomes cheaper than bosutinib but also less effective, with an ICER of [redacted] per QALY. When the cost per month in CP post-discontinuation is increased to £1,040 for bosutinib, SCT becomes cheaper than bosutinib but also less effective, with an ICER of [redacted] per QALY.

Table 61. Scenario analyses applied to CP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	Dominant
Patient population				
Bosutinib patient population	CP-3L from Study 200	CP-3L post-hoc "unmet need" subpopulation	[redacted]	Dominant
		CP-2L population	[redacted]	Dominant
		CP post-hoc "unmet need" subpopulation	[redacted]	Dominant
Cohort starting age	54 years (mean age in CP-3L Study 200)	49 years (−10%)	[redacted]	Dominant
		59 years (+10%)	[redacted]	Dominant
Overall survival				
Bosutinib overall survival	MCyR using hazard ratio for survival of 0.37[2]	MCyR using hazard ratio for survival of 0.156 (lower bound of 95% CI)	[redacted]	Dominant
		MCyR using hazard ratio for survival of 0.876 (upper bound of 95% CI)	[redacted]	Dominant
		Exponential curve fitted to CP-3L OS	[redacted]	Dominant
		"Cumulative survival approach" (OS = PFS + 10 months AP + 6 months BP)	[redacted]	Dominant
SCT overall survival	Exponential curve fitted to Jabbour (2011)[10]	Weibull curve fitted to Jabbour (2011)[10]	Unchanged	Dominant
		Exponential curve fitted to Oehler (2007)[12]	Unchanged	Dominant
Hydroxycarba-mide overall survival	Mean OS = 42 months	Mean OS = 38 months (see Pfizer submission, Section 10.22, pp469-470 for justification)	[redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		Mean OS = 24 months (lower bound of plausible range in Rogers 2012)[2]	[redacted] bosutinib vs. interferon:[a] [redacted]	Unchanged
		Mean OS = 78 months (upper bound of plausible range in Rogers 2012)[2]	[redacted]	Unchanged
Transformation to AP and BP				
Time in blast phase	6 months	13 months[2]	[redacted]	Dominant
		3 months	[redacted]	Dominant
Transformation following SCT	Patients cannot transform to AP and BP, but remain in CP	Patients transform to AP and BP for 10 and 6 months respectively before death	[redacted]	Dominant
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to CP-3L cohort of Study 200	Loglogistic curve	[redacted]	Dominant
		Time on treatment equal to PFS minus discontinuation due to AEs[2]	[redacted]	[redacted]
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	Dominant
Costs				
Resource use	Medical management from TA251[17]	Medical management from TA241	[redacted]	Dominant
Cost of CP off treatment health state	Patients receive hydroxycarba-mide, costing £12.75 per month	Patients receive further treatment post-discontinuation in CP (e.g., other TKIs or SCT) costing £1,040 per month (similar to TA241)	[redacted]	[redacted]
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP & BP £2,536/month (doubled)[c]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		AP only doubled	[redacted]	Dominant
		BP only doubled	[redacted]	Dominant
Cost of death	£6,004	£569[17]	[redacted]	Dominant
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarba-mide arm only	[redacted]	Dominant
		Additional cost of £100/month in all arms wherever patients receive hydroxycarba-mide	[redacted]	Dominant
Utility values				
Source of utility for CP patients on bosutinib or hydr-oxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility at screening for CP-3L cohort in Study 200 used for all patients in CP on bosutinib and hydroxy-carbamide	[redacted]	Not reported
		Utility at screening for CP-3L cohort in Study 200 used for patients in CP on bosutinib only	[redacted]	Dominant
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251	Unchanged	Dominant
Interferon on-treatment utility value	Decrement to HRQL from interferon treatment	No decrement to HRQL from interferon treatment	Unchanged [redacted]bosutinib vs. interferon:[a] [redacted]	Unchanged
Utility values varying by age	Utility values adjusted to account for patient aging	No adjustment for aging	[redacted]	Dominant
Model settings				
Time horizon	50 years	2 years	[redacted]	Dominant
		5 years	[redacted]	Dominant
		10 years	[redacted]	Dominant
		25 years	[redacted]	Dominant

a In these scenarios interferon is not dominated by hydroxycarbamide
b In these scenarios SCT is cheaper than bosutinib
c Analysis conducted by PenTAG

AP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 62 (p152). In most scenarios (including the base case) bosutinib dominated SCT (i.e., bosutinib was cheaper and more effective than SCT). The ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] to [redacted] per QALY (ignoring scenario analyses where the time horizon is shortened). The ICERs for SCT versus hydroxycarbamide ranged from £98,279 to £195,626 per QALY (again, ignoring scenario analyses where the time horizon is shortened).

Notable scenarios in terms of impact on ICERs included:

- Increasing the time spent in BP to 13 months (as used in Rogers and colleagues 2012[2]) increases the ICERs of both bosutinib and SCT versus hydroxycarbamide to [redacted] and £195,626 per QALY respectively.
- Setting the time on bosutinib treatment equal to PFS from Study 200 results in bosutinib becoming more expensive than SCT. In this scenario the ICER of SCT versus hydroxycarbamide is unchanged at £142,982 per QALY and the ICER of bosutinib versus hydroxycarbamide is [redacted] per QALY. The ICER of bosutinib versus SCT is [redacted] per QALY but SCT would be deemed extended dominated by hydroxycarbamide and bosutinib and hence SCT would not be viewed as a proper comparator.
- Using medical management costs from TA241 instead of TA251 results in an ICER for bosutinib versus hydroxycarbamide of [redacted] per QALY.
- Doubling the cost per cycle of AP results in an increased ICER for bosutinib versus hydroxycarbamide of [redacted] per QALY.

Further details of scenario analyses can be found in the Pfizer submission, Section 10.23, pp477-483.

Table 62. Scenario analyses applied to AP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	Dominant
Patient population				
Cohort starting age	50 years (mean age in Study 200 AP cohort)	45 years (−10%)	[redacted]	Dominant
		55 years (+10%)	[redacted]	Dominant
Overall survival				
Bosutinib overall survival	Exponential curve fitted to Study 200 AP cohort OS	Extreme value curve fitted to Study 200 AP cohort OS (15 Feb 2012 snapshot)	[redacted]	Dominant
Stem cell transplant overall survival	Exponential curve fitted to AP cohort in Oehler (2007)[12]	Weibull curve fitted to AP cohort in Oehler (2007)[12]	Unchanged	Dominant
		Exponential curve fitted to AP cohort in Jabbour (2011)[10]	Unchanged	Dominant
Time spent in BP				
Time spent in blast phase	6 months	13 months[2]	[redacted]	Dominant
		3 months	[redacted]	Dominant
Transformation following SCT				
Transformation following SCT	Patients cannot transform to BP, but remain in AP	Patients transform to BP 6 months before death	[redacted]	Dominant
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200 AP cohort	Time on treatment equal to PFS from Study 200 (AP to BP)[a]	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 AP cohort	[redacted]	Dominant
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	Dominant
Costs				
Resource use	Medical management in TA251	Medical management in TA241	[redacted]	Dominant

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP and BP £2,536 (doubled)[b]	[redacted]	Dominant
		AP only doubled[c]	[redacted]	Dominant
		BP only doubled	[redacted]	Dominant
Cost of death	£6,004	£569[17]	[redacted]	Dominant
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	Dominant
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	Dominant
Utility values				
Source of utility for AP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for AP and BP cohorts from Study 200 used for all patients in AP and BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	Not reported
		Utility for AP in Study 200 only used for AP patients on bosutinib in the model (remainder as per base-case)	[redacted]	Dominant
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251[17]	Unchanged	Dominant
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	Dominant
Model settings				
Time horizon	50 years	2 years	[redacted]	Dominant
		5 years	[redacted]	Dominant
		10 years	[redacted]	Dominant

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
		25 years	[redacted]	Dominant

a In these scenarios SCT was cheaper than bosutinib
b Analysis conducted by PenTAG
c Pfizer reported an ICER of £136,703/QALY for SCT vs. hydroxycarbamide, PenTAG calculated a different ICER of £168,310/QALY

BP model scenario analyses

Pfizer conducted a number of scenario analyses which are summarised in Table 63 (p155). In all scenarios SCT is more effective and more costly than bosutinib, which is in turn more costly and more effective than hydroxycarbamide. The ICERs for bosutinib versus hydroxycarbamide ranged from [redacted] per QALY. The scenarios in which the ICER was lowest (i.e., in which bosutinib was most cost-effective) were:

- Utility values from Study 200 used for bosutinib (± hydroxycarbamide) patients (instead of IRIS trial utilities)
- Extreme value distribution used for bosutinib OS instead of exponential distribution

The scenarios in which the ICER for bosutinib versus hydroxycarbamide was highest were:

- Time spent in BP set to 13 months
- Time on treatment equal to PFS from Study 200
- Cost of BP health state doubled

The ICER for SCT versus bosutinib varied from [redacted] per QALY.

Further details of scenario analyses can be found in the Pfizer submission, Section 10.24, pp483-489.

Table 63. Scenario analyses applied to BP model

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Base case			[redacted]	[redacted]
Patient population				
Cohort starting age	47 years (mean age in Study 200 BP cohort)	42 years (−10%)	[redacted]	[redacted]
		52 years (+10%)	[redacted]	[redacted]
Overall survival				
Bosutinib overall survival	Exponential curve fitted to Study 200 BP cohort OS	OS estimated by fitting 2nd best fitting curve (Weibull) to BP cohort from Study 200	[redacted]	[redacted]
Stem cell transplant overall survival	Exponential curve fitted to BP cohort in Oehler (2007)[12]	Weibull curve fitted to BP cohort in Oehler (2007)[12]	[redacted] Unchanged	[redacted]
		Exponential curve fitted to "advanced phase" cohort in Saussele (2010)[13]	[redacted] Unchanged	[redacted]
Time spent in BP				
Time spent in blast phase	6 months	13 months[2]	[redacted]	Unchanged
		3 months	[redacted]	Unchanged
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200 BP cohort	Time on treatment equal to PFS from Study 200	[redacted]	[redacted]
		Loglogistic curve fitted to discontinuation data from Study 200 BP cohort	[redacted]	[redacted]
Dosing				
Bosutinib dose	Licensed dose (500 mg once daily)	Dosing in Study 200	[redacted]	[redacted]
Costs				
Resource use	Medical management in TA251	Medical management in TA241	[redacted]	[redacted]
Cost of BP health state	BP £1,268/month	BP £2,536 (doubled)[b]	[redacted]	[redacted]
Cost of death	£6,004	£569[17]	[redacted]	[redacted]

Parameter	Base case	Scenario analysis	ICER bosutinib vs. hydroxy-carbamide	ICER bosutinib vs. SCT
Cost of best supportive care	Best supportive care = hydroxy-carbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	Unchanged (reported as [redacted] in Pfizer report)
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	[redacted] (reported as [redacted] in Pfizer report)
Cost of SCT	All patients incur cost of FLAG-IDA at £29,212	FLAG-IDA cost removed	Unchanged	[redacted]
Utility values				
Source of utility for BP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for BP cohort from Study 200 used for all patients in BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	Not reported
		Utility for BP in Study 200 only used for BP patients on bosutinib in the model (remainder as per base-case)	[redacted]	[redacted]
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251[17]	Unchanged	[redacted]
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	[redacted]
Model settings				
Time horizon	50 years	2 years	[redacted]	[redacted]
		5 years	[redacted]	[redacted]
		10 years	[redacted]	[redacted]
		25 years	[redacted]	[redacted]

a A wiring error was discovered in Pfizer's model meaning that the log-logistic curve for AP patients was used instead of the curve for BP patients. This gave an original erroneous ICER of [redacted] per QALY.

5.2.12 Model validation and face validity check

Pfizer describe the following model validation and face validity checks (Pfizer submission, Section 7.8.1, p185).

Model design

At the design stage of the model, it was presented to a leading clinician currently treating CML patients in the UK (October 2012), in order to ensure the model has face validity, and matched clinical practice. The key issues around the economic modelling such as time horizon, comparators, survival analysis, adverse events, and utility measures were discussed with other experts using at an advisory meeting in December 2012.

The subsequent model design and shell were then presented to a senior UK economist (and former member of the NICE appraisal committee), whose comments were then incorporated. After this the full economic model was developed, and a first draft of the submission document produced.

Model accuracy and calculations

A number of steps were taken to validate the technical accuracy of the model and submission.

Firstly, estimates of time on treatment and overall survival from the final model were checked against values calculated in a separate spreadsheet – results were the same.

Secondly, extensive one-way sensitivity analyses were conducted on all model inputs and results were reviewed to ensure that changes in cost and effectiveness measures were consistent with expectations.

Thirdly, random checks were made on model inputs compared with source data.

As a last step in the model validation process, the model was reviewed by a senior health economist not involved with the project, using the Drummond checklist, as well as a proprietary internal checklist from BresMed (who developed the model). Following this review a report was produced, with discussions held and changes made to the model and documented accordingly

Finally, in terms of internal validity, as discussed in Section 7.2.2 [of Pfizer submission] the survival functions used to generate estimates of time on treatment and overall survival for bosutinib, hydroxycarbamide and stem cell transplant are very close to those obtained based on the empirical (Kaplan-Meier) survival distributions (see Section 7.3.1 [of Pfizer submission]), and results seen in published NICE technology appraisals (TA241, TA251).

External review

Following the development of the model, the model and submission were reviewed by an independent UK economist not thus far involved with the project. This economist works in a department of a leading centre for health economics in the UK, and part of an Evidence Review Group. The economist reviewed the submission, highlighting areas for improvement and clarification, as well as any assumptions they did not agree with. Following this review, further changes were made (as well as amendments made to answers questions they raised), ahead of submission to NICE.

5.3 Critique of manufacturer's submitted evidence

5.3.1 Checking wiring of Pfizer's model

We checked the wiring of Pfizer's model in the following three ways:

- We built an independent, simplified version of Pfizer's model. This model did not use discrete model cycles. Instead, QALYs and costs were estimated by applying unit costs and utilities to the undiscounted life year estimates for each treatment in each arm in Pfizer's model. The results of the simplified model (e.g. total discounted costs and QALYs, ICERs) were similar to those from Pfizer's model. For example, the ICER for bosutinib vs. HU in CP was estimated as [redacted] vs. [redacted] from Pfizer's model. This provides strong evidence that there are no serious wiring errors in Pfizer's model in addition to the error we found in the original version of the model.
- We checked the key formulae in Pfizer's model.
- We checked that the model outputs were correct when input parameters were set to extreme values.

5.3.2 NICE reference case checklist

NICE reference case[43] requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	P	Population changed to reflect revised indication from the EMA for bosutinib. Population limited to include only patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	P	Does not include SCT following bosutinib (see Section 5.3.6, p162)
Perspective on costs	NHS and PSS	Y	See Section 5.3.7.1, p164
Perspective on outcomes	All health effects on individuals	Y	
Type of economic evaluation	Cost-effectiveness analysis	Y	
Synthesis of evidence on outcomes	Based on a systematic review	Y	
Measure of health benefits	QALYs	Y	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Y	*For bosutinib, hydroxycarbamide and interferon:* RCT of imatinib vs. combination of IFN-α and cytarabine. *For SCT:* Submissions to TA241 from Bristol-Myers Squibb and Novartis.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Y	
Discount rate	3.5% p.a. for costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	

Y – Yes; N – No; U – Unclear; P – Partially

5.3.3 Critical appraisal frameworks

Table 64. Critical appraisal checklist from Drummond and colleagues (1997)[58]

Item	Critical appraisal	Reviewer comment
Is there a well-defined question?	Y	
Is there a clear description of alternatives (i.e., who did what to whom, where and how often)?	Y	
Has the correct patient group / population of interest been clearly stated?	Y	
Is the correct comparator used?	P	Believe more appropriate to include SCT following bosutinib failure (see Section 5.3.6, p162)
Is the study type reasonable?	Y	
Is the perspective of the analysis clearly stated?	P	See Section 5.3.7.1, p164
Is the perspective employed appropriate?	Y	
Is effectiveness of the intervention established?	P	No evidence from RCT for specified population. Non-randomised evidence suggests bosutinib is capable of achieving cytogenetic response in some patients but no mature data on overall survival.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	Y	
Are the costs and consequences consistent with the perspective employed?	P	See Section 5.3.7.1, p164
Is differential timing considered?	Y	Discount rates for costs and QALYs 3.5% in line with NICE reference case
Is incremental analysis performed?	Y	
Is sensitivity analysis undertaken and presented clearly?	Y	

Y – Yes; N – No; U – Unclear; P – Partially

5.3.4 Model structure

The model structure chosen by Pfizer for bosutinib is very similar to the structure we, PenTAG, used in TA241[2] and importantly includes chronic phase states both on and off treatment and accelerated and blast crisis phase states. We believe the model structure is appropriate for the treatment sequence bosutinib followed by hydroxycarbamide, although in Section 5.3.6 (p162) we discuss how appropriate the selected treatment sequences are.

We also believe the model structure is appropriate for hydroxycarbamide and interferon.

The model structure for SCT is effectively a two state model with two states, alive and dead. SCT is assumed to be curative and therefore not followed by treatments expected in the event of SCT failure, i.e., TKI, hydroxycarbamide.

We believe the cycle length of one month is appropriate for the CP model. A shorter cycle length may have been marginally more appropriate for the AP model and would probably have been more appropriate for the BP model, however we doubt this would significantly impact on cost-effectiveness and changing the cycle length would require a great deal of work.

5.3.5 Population

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used as 2nd-line. However, as we say in Section 2.2.2 (p45), we believe that bosutinib will be used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis assumes 3rd-line use of bosutinib, and we consider the cost-effectiveness of bosutinib for use as 2nd-line in an important scenario analysis.

5.3.6 Intervention and comparators

As stated in Section 5.2.4, p117, Pfizer consider the following treatment sequences in the CP model:

- (Bosutinib, HU)
- HU
- SCT
- (IFN, HU)

The focus of our critique is on the first three sequences, as we understand that IFN is now virtually never used for CML in England & Wales due to poor quality of life.

For the AP and BP models, Pfizer consider the same treatment sequences with the exception of (IFN, HU), because they say that appropriate clinical effectiveness evidence is lacking.

Pfizer seem unsure whether HU or SCT is the main comparator for bosutinib. They say: "*It has been noted by clinicians that hydroxycarbamide is rarely, if ever used in CML patients and therefore SCT may be a more appropriate comparator*" (Pfizer submission, p104). This is later contradicted: "*No data was found on the uptake of SCT versus hydroxycarbamide (BSC) in the patient population under consideration in this license. Clinical experts have estimated that only 30% of this population would be eligible for SCT given the strict eligibility criteria and availability of donors, it is assumed that the rest will receive hydroxycarbamide*" (Pfizer submission, p190).

Our clinical expert, Dr Rudin, agrees with the second statement. We imagine that the actual proportion of patients who have a SCT may be less than 30% because this is a major operation which we assume some patients will not wish undergo. Furthermore, Pfizer later say "*Nonetheless, SCT remains the only 'cure' for CML and bosutinib is not expected to replace SCT for the minority of patients who are eligible to receive a SCT and who have a match*." (Pfizer submission, p192).

For all these reasons, we believe that HU is clearly the most important comparator treatment.

Pfizer assume that after patients become resistant or intolerant to bosutinib (as either 2nd-, 3rd- or 4th-line), they are then treated with HU until death. We agree that this is reasonable for those patients who are unsuitable for SCT or for those who are suitable for, but do not want SCT. However, our understanding is that patients who are suitable for and want a SCT may either proceed directly to transplant, or may try bosutinib first, and then when they become resistant or intolerant to bosutinib, they will likely then try SCT. Given that patients are predicted to take 3rd-line bosutinib for only about [redacted], we understand that if a patient is eligible for SCT before bosutinib treatment, they are very likely still to be eligible for SCT only [redacted] later. Indeed, Pfizer acknowledge this: "*However, in practice the impact of introducing another effective TKI option may result in a reduction in the numbers of SCT since patients or clinicians may prefer to try another TKI before or instead of SCT given the considerable cost, morbidity and mortality impact associated with SCT*" (Pfizer submission, p192).

In summary, we assume the following comparators for CP:

- (Bosutinib, HU)
- (Bosutinib, SCT) (only for those eligible for SCT)
- HU
- SCT (only for those eligible for SCT)
- (IFN, HU)

In other words, for those patients unsuited to SCT, the relevant comparators are:

- (Bosutinib, HU)
- HU
- (IFN, HU)

And for those suited to SCT, the main comparators are:

- (Bosutinib, SCT)
- SCT

But for completeness, we also model the following comparators:

- (Bosutinib, HU)
- HU
- (IFN, HU)

For AP and BP, we believe exactly the same arguments apply as for CP, except we do not model (IFN, HU).

In theory, it would be possible to additionally model the treatment sequence (IFN, SCT). However, we do not do this because IFN is rarely used now in England & Wales.

5.3.7 Perspective, time horizon and discounting

5.3.7.1 Perspective

Pfizer state (Section 5, p37) that a NHS/PSS perspective for costs is adopted in line with the NICE reference case, and this is reiterated on p39. In Section 7.2.6, p114, however it is stated that only NHS costs are included as "In this disease area there are not expected to be significant impacts on costs outside the NHS budget".

We believe that certain costs included in the economic analysis include costs incurred by PSS rather than NICE, e.g., the cost of palliative care prior to death is taken from Addicott and Dewar (2008)[54] and just over half of the cost is incurred in the community sector.

We do not believe that significant PSS costs have been excluded from the analysis and are therefore satisfied that the perspective adopted is appropriate, although reported inconsistently.

5.3.7.2 Time horizon

We are satisfied that a time horizon of 50 years is sufficient to account for all costs and benefits relevant to the decision problem.

5.3.7.3 Discounting

Discounting is applied at 3.5% per annum as per the NICE reference case.[43] We note that the discount factor is calculated on the basis of integer years from commencing treatment rather than months, which we feel would have been more appropriate and technically simple to implement. This however did not significantly impact on cost-effectiveness so we are satisfied that discounting is appropriate.

5.3.8 Treatment effectiveness and extrapolation

5.3.8.1 Overall survival (OS)

For the CP model, Pfizer's methods of estimating OS are not consistent across the four comparator treatments. OS for the bosutinib arm is estimated using a surrogate relationship using MCyR measured at minimum follow-up of 12 months in Study 200. This relationship was estimated as explained in Section 5.2.6.1 (p119). OS for the comparators: HU, SCT and IFN is estimated either by extrapolation directly from single arm trials (HU and SCT), or expert opinion (IFN) (Section 5.2.6.1, p118).

We believe that there are serious problems with Pfizer's methods of estimating OS for the four treatments because they involve numerous assumptions, for many of which there is little supporting evidence. Instead, we suggest that there is a superior method of estimating OS for all comparator treatments, which we describe as the Cumulative Survival method, not just in the CP model, but also in the AP and BP models. This is explained in detail in Section 6.1, p190.

Key assumptions underlying Pfizer's method of estimating OS for all comparators in CP are given in Table 65 below. All assumptions are important.

Table 65. Assumptions underlying Pfizer's methods of estimating OS for treatments in CP

Assumption	Description	Evidence to support
1. Lack of randomisation	Given that clinical effectiveness evidence is not randomised across treatments, we assume that estimated clinical effectiveness is similar to that which would be observed in a randomised trial of all treatments. This requires that many factors are similar across the single arm studies, e.g. patient baseline characteristics, medical management.	None given
2. Inconsistency in methods of estimated OS by treatment	OS is estimated using different methods across treatments: by a surrogate MCyR relationship for bosutinib and by extrapolating OS for HU, SCT and IFN. Assume that the MCyR surrogate relationship yields similar OS as extrapolation of mature OS for bosutinib	Very little
3. MCyR in model should refer to unmet need population	The MCyR value of 38.9% used to estimate OS for bosutinib in CP is taken from the whole population of Study 200. Pfizer report the corresponding MCyR value for the unmet need population as 43%. They say it is appropriate to use MCyR from the whole population because this is similar to the unmet need value. However, MCyR for the unmet need population is based on a sample of only 21 patients.	Some evidence, but limited due to small sample.
4. Validity of MCyR surrogate relationship:	The MCyR surrogate relationship is crucially dependent on MCyR and OS observed in a trial of patients on high-	Jabbour (2009)[44]

subsequent treatments	dose imatinib.[44] In particular, for the surrogate relationship to apply to bosutinib, Pfizer assume that all patients in Jabbour (2009) received only HU after high-dose imatinib, as they assume that all patients received HU after bosutinib. Furthermore, as explained in Section 5.3.6, p162, we believe it is appropriate to consider the treatment sequence (bosutinib, HU) for some patients and (bosutinib, SCT) for others.	
5. Validity of MCyR surrogate relationship: OS a function of MCyR only	Pfizer assume that OS is purely a function of MCyR. In particular OS is assumed independent of the duration and depth of response, and independent of treatment. In particular, the MCyR surrogate relationship is based on patients taking high-dose imatinib. However, Pfizer apply the relationship to MCyR achieved for patients taking bosutinib.	Unknown
6.Validity of MCyR surrogate relationship: unmet need population	The MCyR surrogate relationship estimated from Jabbour (2009)[44] is for patients who are both suited and unsuited to TKIs. However, Pfizer apply the relationship only to patients unsuited to TKIs.	Very little
7. 2nd-line OS from Jabbour (2009) appropriate for estimating OS for 3rd-line bosutinib	The MCyR surrogate relationship calibrates OS for 3rd-line using in CP for bosutinib to OS from Jabbour (2009)[44], but this is for a 2nd-line line population (after imatinib). OS for bosutinib is therefore probably over-estimated.	None

Pfizer claim that bosutinib OS estimated by MCyR is similar to that obtained by extrapolating bosutinib OS from Study 200 (Pfizer clarifications, Figure 7, p28; see also Appendix V). They then say that this validates their estimated bosutinib OS. However, we consider that the extrapolated OS is likely to be misleading for the following four reasons:

1. OS for bosutinib in CP is extremely immature, with approximately 85% patients still alive at 2 years. Any extrapolation of such immature OS data means that the estimated mean OS is extremely uncertain.
2. Whilst we require OS for bosutinib for patients unsuited to TKIs, most patients in Study 200 were suitable for TKIs. However, Pfizer estimate OS for bosutinib by extrapolating OS from Study 200.
3. Pfizer's model assumes that all patients in the bosutinib arm subsequently receive HU. However, Pfizer do not tell us the nature of subsequent treatments in Study 200. Given that the bosutinib OS data relates mostly to people who are suited to TKIs in Study 200, and not to those patients unsuited to TKIs (as required), these patients may have been treated with TKIs after bosutinib treatment. If so, this would likely lead to an over-estimate of OS for the bosutinib arm, as such subsequent TKIs are likely to extend OS.

4. As Pfizer acknowledge, OS for bosutinib in Study 200 may be over-estimated because of selective censoring of patients. In particular, patients who discontinued treatment with bosutinib had to be followed up for survival for only 2 years, whereas all patients still on bosutinib were followed up whilst on bosutinib (Pfizer submission, p119).

In the current HTA, we believe that Pfizer's methods for estimating OS for treatments in CP result in the highly implausible result that the mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm and the time on 4th-line HU in the (IFN, HU) arm ([redacted] vs. 2.6 vs. 2.1 years respectively) (shown in Figure 20 below). We believe, and clinical expert advice has agreed, that this is unreasonable. Furthermore, this assumption acts dramatically in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU and (Bosutinib, HU) vs. (IFN, HU), because the price of HU is negligible. In Section 6.1, p190, we show how we correct for this under the Cumulative Survival method.

Figure 20.

[redacted]

Pfizer's surrogate relationship between MCyR and OS is very similar to the relationship that we, PenTAG, derived for TA241, to estimate OS for 2nd-line high-dose imatinib, nilotinib, dasatinib and IFN after imatinib failure for patients starting in CP CML. We believe that it was more appropriate to use the MCyR relationship in TA241 than in the current appraisal because fewer Assumptions were required in TA241. Specifically, although Assumptions 1, 4 and 5 above were required, Assumptions 2, 3, 6 and 7 were not. In particular, the crucial Assumption 2, was not required, i.e. the same method (MCyR) was used to estimate OS for all treatments. Nonetheless, with hindsight and with the experience of two previous HTAs in CML, we believe that it would have been useful to have

performed the Cumulative Survival method, at least as a sensitivity analysis, if not as the base case analysis.

By contrast, OS for bosutinib for the AP and BP models is not estimated using a MCyR relationship. Instead, it is extrapolated directly from OS from Study 200. Therefore, for the AP and BP models, the methods of estimating OS for the three treatments: bosutinib, HU and SCT are consistent. Furthermore, Assumptions 2–7 (Table 65, p165) are not required. However, we identify the following six criticisms with Pfizer's method of estimating OS for all treatments in the AP model:

1. Importantly, Assumption 1 still applies, i.e. randomisation is still lacking between comparator treatments.
2. OS for bosutinib in the AP model is very immature, with 65% of patients still alive at maximum follow up (Pfizer submission, p122). The means that the estimated mean OS in the bosutinib arm is highly uncertain.
3. Whilst we require OS for bosutinib for patients unsuited to TKIs, most patients in Study 200 were suitable for TKIs. However, Pfizer estimate OS for bosutinib by extrapolating OS from Study 200.
4. In their model, Pfizer assume that all patients receive HU after bosutinib failure. However, Pfizer do not state the nature of treatments after bosutinib failure in Study 200. Given that most patients in Study 200 were suited to TKIs, some patients may have had other TKIs after bosutinib failure, and this would likely increase their OS and hence lead to an over-estimate of OS for bosutinib for patients unsuited to TKIs.
5. As stated above when discussing CP, as Pfizer acknowledge, OS for bosutinib in Study 200 may be over-estimated because of selective censoring of patients.
6. In the AP model, as in the CP model, Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 1.0 years respectively) (Figure 21). As in CP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 21.

[redacted]

Similarly, in the BP model, the six criticisms for AP above also apply, although Criticism 2 is less of a problem between OS for bosutinib for BP (35% alive at maximum follow-up of 2 years) is more mature than for AP (65% alive). Criticism 6 again applies. Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 0.5 years respectively) (Figure 22). As in CP and AP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 22.

[redacted]

Under the Cumulative Survival method, we again correct for these imbalances, in an analogous way as for CP CML, described in Section 6.1 (p190).

Estimation of OS for bosutinib in CP using MCyR surrogate relationship

In addition to our belief that the use of a MCyR surrogate relationship to estimate OS for bosutinib patients in CP is inappropriate (as stated above), we also note some issues with the methodology used by Pfizer, although these do not significantly impact cost-effectiveness (see Appendix S).

Briefly, rather than fitting to data from Jabbour and colleagues (2009),[44] Pfizer instead fitted to an exponential curve fitted to the study. Pfizer also assumed a lower MCyR rate from Jabbour and colleagues (2009)[44] to the rate used in TA241.[2] Pfizer also use an inappropriate formula to calculate the monthly probability of death from non-CML causes. None of these shortcomings were judged significant enough to warrant changing Pfizer's base case and our objections to Pfizer's methodology as described above (p165) still stand.

Non-CML mortality

We identified a number of shortcomings with Pfizer's method of incorporating non-CML mortality but did not judge that these were significant enough to warrant significant changes to the model. See Appendix S for further details.

5.3.8.2 OS for HU in CP

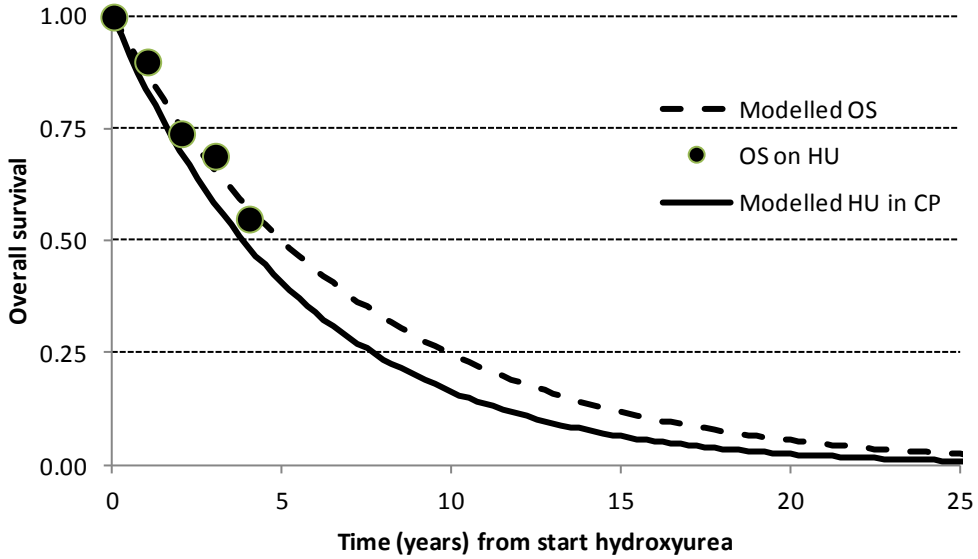
As stated in Section 5.2.6.1, p118, Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] Pfizer say that this study was used for the same purpose in TA241 and TA251 (Pfizer submission, p121). We agree that we, PenTAG, and Novartis, the manufacturer of nilotinib and imatinib used this study for this purpose in TA251. Furthermore, Novartis used this study for this purpose in TA241 (Novartis TA241 submission, p36). Our review of the literature at the time of TA251 suggested that this study was most appropriate for estimating OS for HU in CP.

This study enrolled patients in the USA from 1999 to 2005 who had failed on imatinib. Most (89%) were resistant to imatinib, but some (11%) were intolerant. For patients starting in CP, 8 subsequently received treatment with SCT, 35 with dasatinib/nilotinib and 61 'other' treatments. Of the 'other' treatment group, only 12 of the 61 patients received HU. The remaining patients received regimens including tipifarnib, ionafarnib, decitabine, cytarabine, homoharringtonine and IFN. The median age was 54 years, coincidentally and appropriately the same age as assumed in Pfizer's current model.

We also agree with Pfizer when they say that OS in the CP "other" treatment cohort was 77% at 2 years and 70% at 3 years (p94 Pfizer submission).

We agree with Pfizer when they state that an exponential curve was fitted to OS for CP HU in TA251 (Pfizer submission, p121). However, we disagree when they claim that the resulting mean OS was 3.5 years (Pfizer submission, p121). Instead, Novartis assumed a mean time on HU in CP (not OS) of 3.5 years (Novartis response document, 18th Oct 2011). Using Pfizer's estimated mean times in AP of 10 months and BP of 6 months, gives an estimated OS for HU of 3.5 + 0.8 + 0.5 = 4.8 years. Furthermore, we, PenTAG, estimated a mean OS for HU of 7.0 years (Hoyle and colleagues (2011),[17] p164). Below (Figure 23), we reproduce our exponential fit to the empirical data from Kantarjian and colleagues (2007)[3], taken from our TA251 Assessment report.[17]

Figure 23. PenTAG TA251 fit to CP HU OS data from Kantarjian and colleagues (2007)[3]



(Source: PenTAG TA251 submission,[17] Figure 29, p165)

From this figure, we can see clearly that Pfizer's estimate of OS on HU in CP of 3.5 years is far lower than indicated from Kantarjian and colleagues (2007).[3]

Clearly, the quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available to inform this parameter. We further note that clinical experts who advised Novartis in TA241 suggested that it was reasonable to assume that OS for HU is the same as OS for the "other" treatment group given the lack of available relevant data on HU in this setting (p164[17]).

Pfizer state that OS for HU in CP from Kantarjian and colleagues (2007)[3] should be viewed as an upper bound for the purposes of the current appraisal, given that the data from this study is for 2nd-line CML, whereas Pfizer's base case analysis is for 3rd-line, and we might expect OS to be lower for 3rd-line HU compared to 2nd-line HU. We agree that this is true for a 3rd-line analysis. However, as

stated in Section 5.3.5, p162, there is uncertainty as to whether bosutinib would be more likely to be used 2nd- or 3rd-line in England & Wales were it approved by NICE. If it is more likely to be used 2nd-line, then OS from Kantarjian and colleagues (2007)[3] is then appropriate.

Interestingly, our estimated mean OS of 7.0 years for HU in CP from TA251 is similar to Pfizer's base case estimate of [redacted] years for the mean survival on HU after bosutinib. Whilst this observation could be seen to corroborate our estimate of 7.0 years, we caution that we disagree with the derivation of Pfizer's estimate (Section 5.3.8.1, p165).

We adjust Pfizer's model to allow for a mean OS in the HU arm in CP of 7.0 years by changing the mean OS for HU, parameter "hu_cp_os" (cell E38 in worksheet "Efficacy") from 42 to 85 months. Note that we do not set this to 7.0 × 12 = 84 months, because Pfizer apply additional mortality due to background causes. Here, we do not change the mean times on HU after bosutinib or IFN failure. The ICERs are then as shown in Table 67 below. As explained above, we believe that the key comparison is (Bosutinib, HU) vs. HU, indicated in bold.

[redacted]

Note that shading does not indicate whether bosutinib is more or less costly or more or less effective than the comparator.

Table 66. Shading used to denote cost-effectiveness of bosutinib

Table 67. Pfizer's base case ICERs for CP CML adjusted for mean time in HU arm

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
Mean OS in HU arm increased from 3.5 to 7.0 years	[redacted]	Unchanged	Unchanged

5.3.8.3 OS for SCT in CP

Pfizer performed a literature review for studies that report OS after SCT. The results of this review suggest that relevant data for patients in CP is sparse. This is unfortunate since the cost-effectiveness of the comparison (bosutinib, HU) vs. SCT is strongly influenced by this parameter. There is substantial uncertainty in mean OS after SCT in CP because:

- OS for SCT is very immature, with maximum follow-up of 2 or 3 years, at which time at least 70% of patients are still alive. By contrast, mean OS is several years.
- This assessment concerns patients unsuited to TKIs other than bosutinib. However, all trial data refers to patients both suited and unsuited to TKIs.
- All trials of SCT have very small patient populations, in particular, all less than 100 patients.

As stated in Section 5.2.6.1, p118, Pfizer's base case estimate of OS after SCT for patients in CP was based on data from Jabbour and colleagues (2011).[10] Pfizer state that they chose this study "*because it was a full publication (rather than abstract), included the most comparable patient population (majority were third line) and presented OS curves.*" (Pfizer submission, p121) We agree with Pfizer that the Jabbour and colleagues (2011) patient population is mostly appropriate for the current HTA, given that patients were resistant to a TKI.[10] We further agree that most patients were 3rd-line, having previously received two TKIs. However, the sample size is extremely small, with only 16 CP patients (see Figure 3B of Jabbour and colleagues (2011)[10]) contributing to the estimates of OS, which is reflected in a very wide 95% confidence interval in the estimated 2-year OS of 72% (49%–96%). Also, the median age of 44 in this study is rather lower than that 54 years assumed in Pfizer's CP model.

Pfizer say that they digitised the OS data from Jabbour and colleagues (2011)[10] and then reconstructed the underlying patient level data. The exponential function fitted the patient level data best. Pfizer's fit to the Kaplan-Meier OS data from Jabbour and colleagues (2011)[10] appears reasonable. For example, the Kaplan-Meier estimate at 2 years of 72% is close to the 74% in the model.

Pfizer state (Pfizer submission, p121): "*The only other full-publication that reported OS in a format that was useable for our economic evaluation was Oehler 2007, but this was in a second-line population only and therefore deemed to be less relevant. Nonetheless, this is considered in a sensitivity analysis.*" In Oehler and colleagues (2007),[12] 145 patients in the US who received imatinib before allogeneic hematopoietic cell transplantation was retrospectively compared to 231 historical cohort patients who did not receive imatinib. Henceforth, we consider only the patients who previously received imatinib, as this is relevant to the current appraisal. As in Jabbour and colleagues (2011),[10] the median age (40 years) was lower than the starting age of 54 in Pfizer's CP model.

However, the sample size of 72 patients that informed the estimate of OS was far greater than the tiny sample of 16 patients in Jabbour and colleagues (2011).[10]

OS for CP patients was estimated as 78% at 3 years in Oehler and colleagues (2007).[12] Pfizer states that this study is less relevant than Jabbour and colleagues (2011)[10] because it concerns 2nd-line treatment, whereas Jabbour and colleagues (2011)[10] is mostly for 3rd-line treatment. However, as stated in Section 5.3.5, p162, we believe that bosutinib may be used for 2nd-line treatment and hence it is relevant to estimate OS for SCT in 2nd-line.

In addition, two further studies that report OS after SCT for patients starting in CP CML satisfy Pfizer's inclusion criteria (Pfizer submission, p90): Saussele and colleagues (2010)[13] and Schleuning and colleagues (2010).[14]

All patients in the study by Saussele and colleagues (2010)[13] had previously been treated with imatinib. Of the 37 CP patients, most, 32, were 2nd-line (after imatinib), and 5 were 3rd or 4th-line. The median age at transplantation was 37. OS at 3 years after SCT was 94.1% (95% CI 83.8–99.4%) in the 37 CP patients.

The retrospective registry study of Schleuning and colleagues (2010)[14] is published in abstract form only. All patients had been treated with nilotinib and/or dasatinib. Twenty-one patients were in CP and 20 patients in second or higher CP at the time of transplant. OS at 2 years was greater than 85% for the 15 patients in first CP.

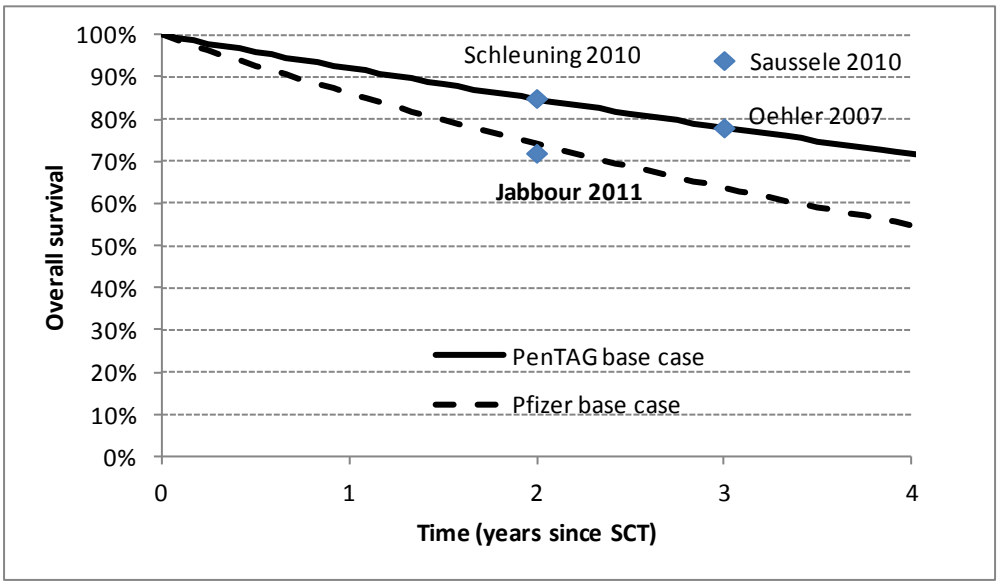
Whilst we acknowledge that there is no obviously superior source of data to estimate OS for SCT in CP, we believe that it is more appropriate to use the data from Oehler and colleagues (2007)[12] in preference to data from Jabbour and colleagues (2011),[10] which is Pfizer's preference, because:

- The sample size of 72 patients in Oehler and colleagues (2007)[12] that informs the estimate of OS is far greater than the tiny sample of 16 patients in Jabbour and colleagues (2011).[10]
- Whilst there is debate about the most appropriate line of treatment, we believe that it is reasonable to use the mostly 2nd-line data from Oehler and colleagues (2007)[12] as opposed to the mostly 3rd-line data from Jabbour and colleagues (2011).[10]
- The OS data from Oehler and colleagues (2007)[12] is clearly more consistent with that from Schleuning and colleagues (2010)[14] and Saussele and colleagues (2010)[13] (see Figure 24)

In summary, the PenTAG base case uses OS data from Oehler and colleagues (2007).[12]

In Figure 24, we can see clearly that Pfizer's base case estimate of OS after SCT in CP, shown by the dotted line, and which based on data from Jabbour and colleagues (2011),[10] is at the lower extreme of the data available, whereas our estimate of OS is more central (continuous line).

Figure 24. OS after SCT in CP



In Pfizer's model, we change the log(scale) parameter of the exponential distribution, cell E4 in worksheet "SCT parametric curves" from 1.897 to 2.491. The mean OS after SCT in CP then increases substantially, from 6.6 to 11.6 years. We notice that Pfizer estimate the log(scale) parameter of the exponential distribution using data from Oehler and colleagues (2007)[12] as 1.915, which is substantially different to our estimate of 2.491. However, it is impossible for us to reconstruct their analysis which led to this estimate. We do however note that the KM OS curve that Pfizer present on p381 appears inconsistent with the Kaplan-Meier curve shown in Figure 1A of Oehler and colleagues (2007).[12] In particular, Pfizer's figure shows OS at 3 years of approximately 0.72, whereas the figure from Oehler and colleagues (2007) is 0.78.[12]

The impact of our revised estimate of OS for SCT in CP on cost-effectiveness is given in Table 68 below. Note that while (Bosutinib, HU) continues to dominate SCT, the incremental costs and QALYs do change, as shown in Table 69.

Table 68. Pfizer's base case ICERs for CP CML adjusted for PenTAG preferred OS SCT

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
Mean OS in SCT arm increased from 6.6 to 11.6 years	Unchanged	Dominant	Unchanged

Table 69. Effect of PenTAG preferred OS on incremental outcomes, (Bosutinib, HU) vs. SCT

	Incremental discounted costs	Incremental discounted QALYs	INHB at WTP £20,000/QALY	INHB at WTP £30,000/QALY
Pfizer base case	[redacted]	+3.56	[redacted]	[redacted]
Mean OS of SCT increased to 11.6 years	[redacted]	+1.54	[redacted]	[redacted]

5.3.8.4 Time on treatment

The cost-effectiveness of bosutinib treatment sequences is very sensitive to the time on bosutinib treatment in all CML phase models. As stated in Section 5.2.6.2, p122, Pfizer estimate the time on bosutinib for all CML phases from Study 200. For 3rd-line CP CML, Pfizer fitted a log-normal distribution to the time on bosutinib treatment, and this appears reasonable. They estimate the mean time on 3rd-line bosutinib as [redacted] years. Fortunately, time on 3rd-line bosutinib data in Study 200 is rather mature, and so little extrapolation is required. However, this data is for the whole 3rd-line population in Study 200, whereas we are concerned with patients unsuited to TKIs. This therefore adds some uncertainty to the estimated time on bosutinib treatment.

Given that we believe that bosutinib may be used 2nd-line at least as often as 3rd-line, we asked Pfizer to provide Kaplan-Meier data for time on 2nd-line CP bosutinib. They agree, see Figure 25 below.

Figure 25. [redacted]

(a) Imatinib resistant (b) Imatinib intolerant

(Source: Pfizer clarifications, p35)

Later, we show that we estimate the mean time on 2nd-line bosutinib as approximately [redacted] years, far longer than the [redacted] years for 3rd-line treatment. This is a key parameter in our estimation of the cost-effectiveness of bosutinib treatment sequences in 2nd-line (Section 6.3.1, p214).

Our clinical advisor, Dr Rudin, believes that patients may often remain on bosutinib for the entire duration of CP in clinical practice. This would be in contrast to Study 200, where it appears that patients typically stopped bosutinib treatment well before progression to AP or BP. We consider this scenario in a sensitivity analysis (Section 6.3.1, p214).

Now turning to bosutinib use in AP, the time on bosutinib treatment is also rather mature, with approximately [redacted] of patients still on bosutinib at maximum follow-up (

Figure 14, p122). Therefore, little extrapolation is required. Pfizer again fitted a log-normal distribution to the time on bosutinib treatment, and this appears reasonable. They estimate the mean time on bosutinib in AP as [redacted] years.

The time on bosutinib treatment in BP is almost completely run off (

Figure 15, p123). Pfizer again fitted a log-normal distribution to the time on treatment, and this appears reasonable. They estimate the mean time on bosutinib in BP as [redacted] years.

Pfizer assume that HU is taken until death, which is appropriate.

As stated in Section 5.2.6.2, p123, Pfizer estimate the mean time on IFN was estimated as 0.5 years, on clinical advice. We believe this is a reasonable assumption.

5.3.9 Health related quality of life

Relevant sources for utility data, and Pfizer's base case utilities are given in Table 42, p126. First we note that there is uncertainty due to the fact that all sources of utilities were taken from patients who are both suited and unsuited to TKIs other than bosutinib, whereas we are interested in values appropriate for patients who are unsuited to TKIs.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 (Table 42, p126). In addition, they assume a utility for IFN in CP of 0.71, which is the same as our assumption in TA241. Their only departure from our previous assumptions is their estimate of the utility after SCT in CP, where they assume 0.71, versus our TA251 estimate of 0.80.

Importantly, Pfizer prefer the utilities that we have used previously to those from their Study 200. They justify this decision as follows (Pfizer submission, p137):

"*Whilst values taken directly from the intervention clinical trial is often more appropriate, the values in previous appraisals are from the IRIS study. This study collected arrange of utilities, in a large cohort of patients, including the utility of patients who progressed to AP and BP whilst not on active*

treatment. These utilities, though vital for modelling, are not available from Study 200. In addition the use of the IRIS values provides consistency with previous technology appraisals."

We agree that it is generally preferable to take utilities directly from the clinical trial of the intervention in question, in this case Study 200. Furthermore, the only source of utilities for bosutinib is Study 200 (IRIS gives utilities for imatinib), and this Study used the EQ-5D, which is preferred by NICE, and Study 200 is in the appropriate lines of treatment (2nd and 3rd-line vs. 1st-line in IRIS). But in this case, we are satisfied with Pfizer's decision because:

- Pfizer's utility of 0.85 for bosutinib in CP is only slightly higher than the Study 200 value of [redacted] for 3rd-line treatment. Furthermore, the Study 200 mean utility for 2nd-line [redacted] Pfizer's estimate of 0.85. As stated in Section 5.3.5, p162, the most relevant line of treatment for this appraisal is uncertain.
- Ideally, we would like a trial-based estimate of the utility of patients on bosutinib over the entire duration of treatment (i.e. approximately 3 years for 3rd-line). However, utility measurements were heavily biased towards the start of bosutinib treatment. Therefore, this arguably limits the usefulness of the utilities from Study 200.
- The estimated utility of 0.85 for CP imatinib is based on a much larger study than Study 200.
- The mean utility from Study 200 for AP of [redacted] is the same as for 3rd-line CP. However, it is well know that quality of life is lower in AP. Therefore, arguably the Study 200 AP estimated utility lacks face validity.

We do not agree with Pfizer's justification of consistency with previous technology appraisals.

However, given that there is a reasonable argument to use utilities from Study 200, we perform the following sensitivity analysis:

- Utility bosutinib = [redacted] at age 54 (Study 200 value),
- Utility HU = Utility bosutinib = [redacted], and
- SCT, IFN unchanged from Pfizer base case.

Next, as stated above, Pfizer's only departure from our previous assumptions is their estimate of the utility after SCT in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Having inspected the source of our estimate, we believe that there is insufficient evidence to have a clear preference for our 0.80, and Pfizer's estimate is not unreasonable. Therefore, we accept Pfizer's base case estimate of 0.71, but we perform the following sensitivity analysis:

- Utility SCT = 0.80 at age 0.54 (increased from Pfizer base case 0.71),

- Utility bosutinib, HU, IFN = unchanged from Pfizer base case.

5.3.10 Adverse events

We are satisfied that using adverse event data from Study 200 is appropriate to the decision problem.

5.3.11 Resource use and costs

5.3.11.1 Resource use systematic review

Pfizer's systematic review of resource use and costs did not include first-line CML, but Pfizer include TA251[17] on the basis that they did not get sufficient data in their systematic review. It would have been more appropriate to conduct another systematic review but we are satisfied that TA251 should include the most relevant UK resource use and costs for first-line CML.

5.3.11.2 Drug acquisition

Pfizer have provided us with the acquisition cost of bosutinib (Table 44, p128) of £3,735.84 per month, or approximately £123 per day. We assume that this is indeed the price that the NHS would pay. In their base case analysis, Pfizer assume that all patients receive the licensed dose of bosutinib of 500mg per day, i.e. a dose intensity of 100%, in all CML phases. However, patients may increase the dose up to 600mg per day, or reduce the dose to 400mg or 300mg daily (Pfizer submission, p472), or may have dose interruptions. In short, we investigated Pfizer's assumption of a dose intensity of 100%, and we found it to be appropriate given the available data. The details are as follows.

Pfizer appropriately investigated the observed dose adjustments in Study 200. Specifically, they allowed for the proportion of Study 200 patients that received increased or decreased doses. As the duration of time at the new dose and time to new dose is not reported, they assumed that all patients received the adjusted dose for the entire duration of treatment with bosutinib. Given this, they estimated the mean daily cost for 3rd-line CP as [redacted] (Pfizer submission, p473), for AP as [redacted], and BP [redacted] and we agree with their calculations. Given that these costs are virtually identical to the mean cost assuming no dose adjustments, Pfizer assumed a dose intensity of 100% for all phases of CML.

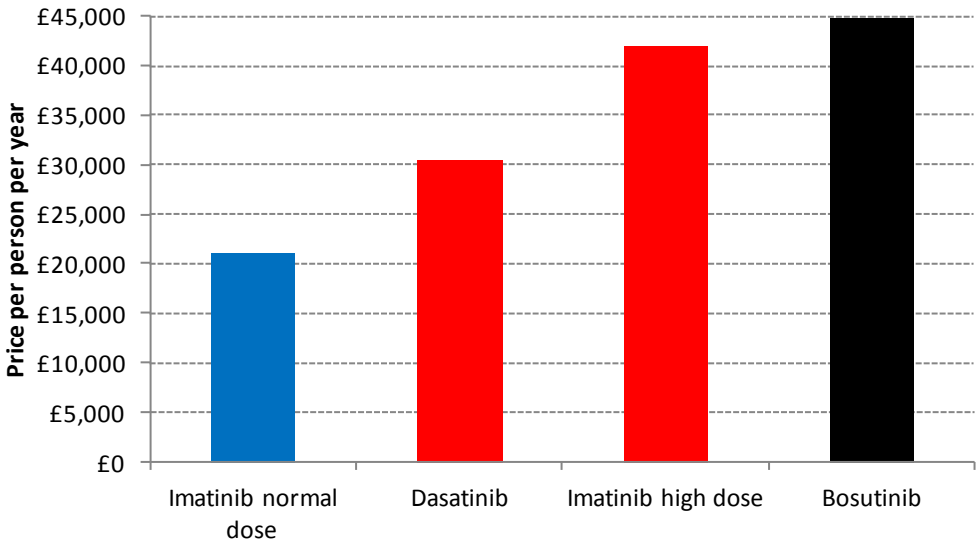
However, Pfizer's dose intensity calculation ignores (a) the possibility that people changed dose more than once and (b) treatment interruptions. Indeed, treatment interruptions are indicated for non-haematological adverse reactions (Pfizer submission, Table A1, p21), and some patients did have treatment with bosutinib interrupted due to adverse events (Pfizer submission, p359). We asked Pfizer to provide an indication of the mean time that patients were not receiving bosutinib due to dose interruptions. In response, they stated that in CP, approximately [redacted] of patients had at least one interruption of bosutinib treatment, and that for these patients, the mean total interruption period was

approximately [redacted]. The effect of modelling this is that the cost-effectiveness of bosutinib treatment sequences improves, but only incrementally. Specifically, the effect is to reduce the mean per patient cost in the bosutinib arms by approximately [redacted] × £44,830 / 12 = [redacted], where the annual acquisition cost of bosutinib is £44,830. Pfizer's base case ICER of (bosutinib, HU) vs. HU then improves very slightly, but still remains at [redacted] per QALY after rounding. The improvement in the ICERs for (bosutinib, HU) vs. HU in AP and BP are also slight. Given this, and given that the dose intensity of bosutinib whilst patients are actually taking the drug is slightly greater than 100%, we agree with Pfizer's assumption of a dose intensity of bosutinib of 100% for all phases of CML.

Given that bosutinib is given in packs of 28 tablets, there is scope for wastage. However, we estimate that if we allow for a plausible amount of wastage at the time the patient stops taking bosutinib, the ICERs for the bosutinib treatment sequences worsen only incrementally for all CML phases. Therefore, henceforth, we ignore wastage of bosutinib.

Figure 26 below shows the prices per person per year of TKI drugs for CML that have been assessed by NICE in the past and the price of bosutinib in this assessment. We are unable to cite the Patient Access price of nilotinib for reasons of confidentiality. Normal dose imatinib (blue shading) and nilotinib were recommended by NICE in TA251 and TA241 for 1st- and 2nd-line use. TKIs not recommended by NICE (red shading) are dasatinib for 1st- and 2nd-line use (TA251 and TA241) and high-dose imatinib for 2nd-line use (TA241). The price per patient per year is greatest for bosutinib (£44,830). The prices of the other TKIs are: normal dose imatinib = £20,994, dasatinib = £30,498, high dose imatinib = £41,989.

Figure 26. Prices of TKI drugs for CML assessed by NICE



Next, we are satisfied with Pfizer's estimation of the cost of HU as £12.75 per month (Table 44, p128). It is important to note that HU is extremely cheap.

We are also satisfied with Pfizer's estimation of the cost of IFN of £1,296 per month (Table 44, p128). We do however caution that the price that hospitals pay for IFN may be substantially lower due to discounted purchasing. However, we have no high quality evidence to support this claim, and so we accept Pfizer base case assumption. Furthermore, the cost-effectiveness of bosutinib versus IFN is rather insensitive to this parameter because Pfizer assume that IFN is taken for only about 0.5 years, far shorter than bosutinib, at about [redacted] years.

5.3.11.3 Stem cell transplant

As explained in Section 5.2.9.7, p131, Pfizer assume the cost of a SCT operation of £76,560, which was based on a 2010 NHS Blood and Transplant costing study,[56], which in turn was taken from van Agthoven and colleagues (2002).[57] In short, we are satisfied that the source of this cost and the cost itself are reasonable.

Pfizer also assume in the BP model that all patients receiving SCT first receive two cycles of FLAG-IDA chemotherapy. All patients are assumed to survive these cycles of chemotherapy and go on to incur SCT costs. The cost of FLAG-IDA was estimated based on Pastore and colleagues (2003),[59] in which 6.5% of patients died while undergoing one cycle of FLAG-IDA, which would suggest not all BP patients would go on to receive SCT. We investigated this and while the ICER for SCT versus bosutinib decreased it was not judged to have a significant impact.

5.3.11.4 Adverse events

Pfizer's assumptions regarding adverse events (i.e., adverse events incur costs but do not affect HRQL and are incurred in the first cycle) are broadly consistent with previous assessments of TKIs for CML. The PenTAG assessment in TA241[2] did not include costs for adverse events as these were expected to be low and could lend spurious accuracy. In previous assessments, adverse events have been used to estimate discontinuation rates, but this is not necessary in this assessment, as fairly mature discontinuation data is available from Study 200.

We note that the cost of adverse events in the AP and BP models are assumed to be the same as in the CP model. This is unrealistic as Table B29 of Pfizer's submission (Section 6.9.2, pp84-85) shows higher rates of adverse events for AP and BP patients than CP patients (Table B27, pp81-82). Using the same methodology as was used for CP to estimate a cost for AP and BP (combined) produced a value of £1,011 compared to the cost in CP of £506, i.e., the cost doubled. This however did not have a significant impact on cost-effectiveness.

We believe that adverse events are unlikely to have a significant impact on cost-effectiveness and are therefore satisfied by Pfizer's methodology.

5.3.11.5 Drug administration

Drug administration costs are incurred for interferon. We found an error in the calculation of the drug administration costs (see Appendix S) but it did not significantly impact cost-effectiveness.

5.3.11.6 Medical management, monitoring and tests

First, as explained in Section 5.2.9.7, p131, Pfizer assume the following follow-up costs after SCT: monthly costs for months 1–6 of £5,299, monthly costs for months 7–12 of £3,231 and monthly costs for months 13–24 of £1,166. In months 25 onwards, patients are assumed to receive 100mg of ciclosporin twice daily, giving a monthly cost of £140 (Pfizer submission, p145). As explained in Section 5.2.9.7, p131, these costs are taken from a NHS Blood and Transplant costing study,[56]. The underlying resource use for this study was taken from van Agthoven and colleagues (2002).[57] In short, we are satisfied that the source of these costs and the costs themselves are reasonable.

Pfizer's assumptions for medical management, monitoring and testing are given in Section 5.2.9.4, p129. These assumptions were based on those that we used originally in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey of 6 UK-based CML clinicians. However, Pfizer seem unaware that in TA251, our assumptions for medical management, monitoring and testing were challenged by Novartis, the manufacturer of nilotinib. In particular, in their response to our Assessment Report for TA251, Novartis submitted a response document, dated 18th October 2011, in which they stated that we over-estimated the frequencies of some resource use items. In response, we amended some of our assumptions for resource use in CP CML, as shown in Table 70.

Table 70. Selected resource use assumptions for CP CML

	Treatment	Nurse visits / month	Haematologist visits / month	Bone marrow aspirations / month
Pfizer current HTA	Bosutinib	0.4	0.9	0.3
	HU, IFN	0.4	0.9	0.3
	SCT	0.4	0.9	0.3
PenTAG TA251	Imatinib, dasatinib, nilotinib	0	0.33	0
	HU	0	0.72	0
	SCT	0	0	0
PenTAG current HTA	Bosutinib	0	0.33 per month, plus 2 at t = 0	0
	HU, IFN	0	0.72	0
	SCT	0	Many visits in months 0–24 included in ongoing costs from van Agthoven (2002)[57] 0.31 visits per month for month 24 onwards	0

Appendix U gives the full text of our response to Novartis' criticism of our original resource use assumptions in TA251. The NICE appraisal committee for TA251 were satisfied with our revised assumptions.

In April 2013, we asked our clinical expert, Claudius Rudin, to comment on our revised TA251 assumptions. His view of resource use whilst patients take TKIs is unchanged. However, as shown in Table 70 above, whilst patients are taking bosutinib, we now additionally include two haematologist visits at time zero. As stated in Appendix U, Dr Rudin believes that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly, i.e., there would be two more visits in the first three months than in subsequent three month periods. In TA251, we ignored the costs of the visits at 2, week 4, month 2 and month 4, because that appraisal was for 1st-line use of TKIs, and these costs cancelled between treatments almost exactly. In the current appraisal, we cost for these visits because a TKI, bosutinib, is used in just one treatment arm, and hence these costs do not cancel out in the other arms, HU and SCT. Also, we assume that all patients remain on bosutinib treatment, given that Pfizer's model predicts that [redacted] of patients are still on bosutinib treatment at 4 months.

Dr Rudin is still satisfied with our assumptions for patients whilst taking HU. Further, he believes that these are also appropriate for treatment whilst on IFN.

In TA251, we assumed no nurse visits, haematologist visits or bone marrow aspirations for patients after SCT. Dr Rudin agrees with the assumptions of no nurse visits or bone marrow aspirations, but disagrees with our assumption for frequency of haematologist visits after SCT. Specifically, he suggests that there are many such appointments in the first 100 days after SCT: twice a week after discharge at approximately day 28 until approximately day 60, then weekly until day 100, then monthly for the first year and if all goes well approximately every second month in the 2nd year, gradually extending to yearly after the 4th or 5th year. He advised that there would be much more frequent consultant-led clinic appointments, every 2 months if there is chronic graft versus host disease (cGvHD). Further, he agrees with the assumption that we and Novartis used in TA251 that 54% of patients get cGvHD after SCT.

We note that the follow-up costs assumed by Pfizer after SCT reflect a similar number of haematologist visits in the first 2 years as suggested by Dr Rudin. Specifically, in the period 0–6 months after transplant, patients visited an outpatient clinic an average of approximately 20 times, from 6–12 months after transplant, approximately 11 times, and from 12–24 months, approximately 10 times.[57] Therefore, on the basis of the suggested frequency of haematologist visits from Dr Rudin and the additional costs assumed by Pfizer after SCT, we first assume no haematologist visits in the first 2 years in addition to those already costs from the monthly follow up costs above. Second, we assume that all patients incur a background 0.31 visits per month from month 24 onwards, which is a weighted average of 0.50 per month for patients with cGvHD and the long term 0.08 per month for patients without cGvHD, with the weight being 54% of patients with cGvHD.

Note that whilst our estimate of consultant appointments in TA251 was incorrect, the cost-effectiveness of the 1st-line TKIs in this appraisal would have changed only marginally given the assumptions we now use in the current HTA. This is because SCT treatment was modelled as a downstream treatment in TA251, and costs of SCT largely cancelled between treatment arms. This is not the case in the current appraisal because SCT is one of the initial treatments.

As shown in Table 70 above, we assume no bone marrow aspirations. In TA251, we originally allowed for 0.3 bone marrow aspirations per month for all treatments. This constituted 94% of our estimated costs for tests of £216 per month. Pfizer's estimated cost for tests of £231 was based on the £216 per inflated to 2011/12 prices. Given that bone marrow aspirations constituted almost all test costs, in the current HTA, we assume zero test costs for all treatments.

When we alter Pfizer's model to reflect our preferred resource use assumptions shown in Table 70 above (see Appendix W for details), the cost-effectiveness of bosutinib improves versus hydroxycarbamide: Pfizer's ICER decreases from [redacted] per QALY. The costs of

bosutinib and SCT both decrease, although the costs of bosutinib decrease farther; as a result bosutinib continues to dominate SCT (Table 71).

Table 71. Pfizer's base case ICERs for CP CML adjusted for resource use assumptions preferred by PenTAG

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
PenTAG resource use assumptions in Table 49, p184.	[redacted]	Dominant	[redacted]

5.3.12 Cost-effectiveness results

We are satisfied that the results presented by Pfizer match those from the model supplied.

5.3.13 Sensitivity analyses

5.3.13.1 One-way sensitivity analyses

Pfizer conduct a number of one-way sensitivity analyses but by no means on all parameters. Tornado diagrams are not provided. Pfizer group their one-way sensitivity analyses along with explorations of structural uncertainty in Section 5.2.11.3, p146.

5.3.13.2 Probabilistic sensitivity analysis

We agree with Pfizer that probabilistic sensitivity analyses are not particularly useful as they do not account for the significant structural uncertainties in the decision problems, and we have therefore not critiqued the probabilistic sensitivity analyses in detail.

5.3.13.3 Scenario analyses

2nd-line use of bosutinib in CP patients

Pfizer's base case analysis assumes that bosutinib is used 3rd-line, but we feel it is likely that bosutinib will be used 2nd-line rather than 3rd-line due to the approval of nilotinib for 1st-line use, clinical opinion suggesting that imatinib is unlikely to be used in patients resistant to imatinib, and dasatinib not being approved 1st-line or post imatinib failure. Therefore as an important scenario analysis, we estimate the cost-effectiveness of bosutinib for 2nd-line CP. Pfizer did conduct a scenario analysis in which the 2nd-line cohort was used as the model population, however we do not believe that Pfizer's sensitivity analysis is appropriate as it includes only a change in the MCyR rate and does not include a change in the length of time patients spend on treatment – this biases the results in favour of cost-effectiveness of bosutinib.

We conduct our own scenario analysis based on treatment discontinuation curves provided by Pfizer in response to questions of clarification (Figure 25, p176) and on the MCyR rate for 2nd-line patients published in Cortes and colleagues (2011), in which the cumulative MCyR rate at a minimum follow-up of 12 months (median follow-up 24.2 months) was 140/266 = 52.6%.[24]

We estimated from Figure 25 (p176) that median time on 2nd-line bosutinib treatment would be [redacted] years for imatinib resistant patients and [redacted] years for imatinib intolerant patients. As there were 200 imatinib resistant patients versus 88 imatinib intolerant patients we estimated the median time on 2nd-line bosutinib treatment as (200 × [redacted] + 88 × [redacted]) / 288 = [redacted] years.

For simplicity, we then assumed an accelerated failure time model, i.e., the time to bosutinib treatment discontinuation for 2nd-line patients would be as for 3rd-line patients, but with time rescaled. This is achieved simply by adjusting the scale parameter μ of the log-normal distribution. The mean and median times on treatment are both scaled by the same factor. The median time on treatment from Study 200 in the 3rd-line CP cohort was 8.6 months = 0.72 years (15 February 2012 snapshot; Pfizer submission, Section 6.8.5, p72). We therefore estimated that the appropriate scaling factor was [redacted]/0.72 = [redacted].

To achieve the required [redacted] scaling of mean time on treatment we took mean time on treatment for 3rd-line patients from the model as [redacted] years and adjusted μ using Solver such that the mean time on 2nd-line treatment from the model was equal to [redacted] years when OS was adjusted using the MCyR rate of 52.6%, giving μ = [redacted].

Under this scenario analysis (and with no other alterations to the Pfizer model) we find that bosutinib is more costly and more effective than SCT and that the cost-effectiveness of bosutinib has worsened generally (see Table 72).

Table 72. Pfizer's base case ICERs for CP CML adjusted for 2nd-line patients

Intervention	**(Bosutinib, HU) vs.**		
Comparator	*HU*	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
2nd-line CP cohort	[redacted]	[redacted]	[redacted]

It should be cautioned that, due to lack of evidence, no adjustments were made to survival or time on treatment for hydroxycarbamide and SCT to reflect the choice of a 2nd-line cohort (although the

estimate of effectiveness of hydroxycarbamide is already taken from a 2nd-line study), nor was the age adjusted for any patients.

Pfizer's "cumulative survival approach" to bosutinib OS in CP model

Pfizer present results of a "cumulative survival approach" in Table B64, Section 7.5.9, p160, and in Table B151, Section 10.22, p469. We believe this is a flawed analysis and that the methodology – while described as similar to an approach in TA251 – is not to be confused with the cumulative survival method we present in Section 6.1 (p190). Further discussion of this can be found in Section 6.1.4 (p202).

Bosutinib OS in BP model

We identified that there was a formula error in the scenario analysis where bosutinib OS in the BP model is based on fitting a Weibull distribution to Study 200 OS individual patient data. We corrected the formula error and re-fitted the Weibull distribution. The ICER for bosutinib versus hydroxycarbamide in this scenario increased from [redacted] per QALY.

5.4 Cost-effectiveness conclusions

No previous cost-effectiveness evaluations of bosutinib in refractory CML were identified in Pfizer's systematic review. The *de novo* economic evaluation submitted by Pfizer contains ICERs significantly lower than those calculated by PenTAG (see Section 6, p190), in which the following items were adjusted:

- The method of estimation of OS for all comparators using our "cumulative survival method"
- Mean overall survival on HU (CP model only)
- Mean overall survival after SCT (CP model only)
- Medical management resource use (CP model only)

The cumulative survival method also allows an estimation of the cost-effectiveness of bosutinib followed by SCT, which we believe is a relevant treatment sequence for patients able to receive SCT.

The cumulative survival method had the greatest impact on cost-effectiveness, with the additional items not affecting the cost-effectiveness of the PenTAG base case significantly (although some do affect the Pfizer base case significantly).

Table 73. Comparison of Pfizer and PenTAG base case ICERs

	Pfizer ICERs		**PenTAG ICERs**	
	(Bosutinib, HU) vs. HU	(Bosutinib, SCT) vs. SCT	(Bosutinib, HU) vs. HU	(Bosutinib, SCT) vs. SCT
CP model	[redacted]	n/a	[redacted]	[redacted]
AP model	[redacted]	n/a	[redacted]	[redacted]
BP model	[redacted]	n/a	[redacted]	[redacted]

n/a as not estimated by Pfizer

Although there is significant uncertainty regarding the effectiveness of HU and SCT and regarding which TKIs will be attempted before bosutinib, the PenTAG base case is fairly robust to these uncertainties as it is primarily driven by the drug acquisition cost of bosutinib.

6 ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Cumulative survival method

As explained in Section 5.3.8.1, p165 above, we believe that there are major problems with the methods Pfizer have used to estimate OS for all comparator treatments, especially for the CP model, but also for the AP and BP models. This leads to the implausible prediction that the mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm and the time on 4th-line HU in the (IFN, HU) arm for the CP, AP and BP models. Also as explained in Section 5.3.8.1, p165, in our base case, we have used a different method, the Cumulative Survival method, of estimating OS for all treatments in all model phases.

The Cumulative Survival method was used by us, PenTAG, in our base case analysis in TA251, of the cost-effectiveness of imatinib, nilotinib and dasatinib for 1st-line CML. In a sensitivity analysis, we estimated OS separately using a surrogate relationship based on CCyR and on MMR (major molecular response). In this appraisal, the method was also used by Novartis, the manufacturer of nilotinib. By contrast, Bristol-Myers Squibb, the manufacturer of dasatinib, estimated OS for all treatments using a surrogate relationship based on CCyR. In this appraisal, our base case analysis was accepted by the NICE Appraisal Committee as most appropriate.

6.1.1 Cumulative survival method CP

We first discuss the Cumulative Survival method applied to treatment starting in CP CML.

The motivation for performing the method in the CP is as follows. Pfizer estimate that the on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in arm and the time on 4th-line HU in the (IFN, HU) arm (versus 2.6 versus 2.1 years respectively) (

Figure 27). We believe, and clinical expert advice has agreed, that this is unreasonable. Furthermore, this assumption acts dramatically in favour of the cost-effectiveness of (Bosutinib, HU) versus HU and (Bosutinib, HU) versus (IFN, HU), because the price of HU is negligible.

Figure 27.

Under the Cumulative Survival method, we correct for this imbalance.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (IFN, HU) arm, the mean time, cost and QALY whilst on 3rd-line IFN treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

Clearly, not all patients in the (Bosutinib, HU) arm will survive to start 4th-line HU treatment. The key assumption of the Cumulative Survival method is that, in the (Bosutinib, HU) arm, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. None of Assumptions 1–7 (Table 65, p165), which are necessary for Pfizer's methods of estimating OS, are required.

Equivalently, we assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equals that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib. We believe that the life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib is probably an upper bound, as discussed in Section 6.1.4 (p202).

Similarly, in the (IFN, HU) arm, the life expectancy of those patients who start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm.

Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

In the next sections, we estimate the total life years, costs and QALYs for the (Bosutinib, HU), (IFN, HU) and (Bosutinib, SCT) treatment arms.

6.1.1.1 Cumulative survival method CP time on treatment

We denote T as the mean per patient undiscounted time. This is split in to four parts, corresponding to 3rd-line CP, 4th-line CP, AP and BP. Here, without loss of generality, we assume that all patients start 3rd-line treatment for CML. The notation of these time components is given in Table 74 below.

Table 74. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in CP.

	(Bosutinib, HU)	**HU**	**SCT**	**(IFN, HU)**	**(Bosutinib, SCT)**
3rd-line CP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{IFN,HU}}^{IFN\ 3}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line CP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{IFN,HU}}^{HU\ 4}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$
AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{AP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$		$\mathrm{T}_{\mathrm{IFN,HU}}^{AP}$	
BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$		$\mathrm{T}_{\mathrm{IFN,HU}}^{BP}$	

Then under the Cumulative Survival method, the component times are calculated as shown in Table 75, where S_{BOS} denotes the probability that a patient is still alive when he/she stops treatment with bosutinib, i.e. the probability that a patient in the (Bosutinib, HU) arm starts 4th-line HU treatment, which equals the probability that a patient in the (Bosutinib, SCT) arm starts 4th-line SCT treatment. S_{IFN} represents the analogous quantity for IFN.

Table 75. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in CP

	(Bosutinib, HU)	HU	SCT	(IFN, HU)	(Bosutinib, SCT)
3rd-line CP	unchanged	unchanged	unchanged	unchanged	unchanged
4th-line CP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{AP}}$	
BP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			$S_{\mathrm{IFN}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$	

Unfortunately, S_{BOS} and S_{IFN} are not calculated in Pfizer's model. However, we estimate upper bounds for these quantities, 95.5% and 99.8% respectively, by assuming that the only mortality whilst patients are on bosutinib or IFN treatment is due to background causes. These estimates are based on Pfizer's base case estimates of time on 3rd-line bosutinib and 3rd-line IFN. These upper bounds in turn yield lower bounds for the ICERs of (Bosutinib, HU) versus HU and versus (IFN, HU).

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm and 4th-line HU in the (IFN, HU) arm are very similar (2.5 vs. 2.6 vs. 2.6 years respectively) (Figure 28). The mean time on HU in the (Bosutinib, HU) arm is slightly lower because not all patients (95.5%) reach HU treatment, whereas all patients start treatment in the HU arm and nearly all patients (99.8%) in the (IFN, HU) arm start HU treatment.

In addition, the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are very similar (6.3 vs. 6.6 years respectively) (Figure 28). Similarly, the time is slightly lower in the (Bosutinib, SCT) arm, again because only 95.5% reach SCT treatment.

Figure 28.

6.1.1.2 Cumulative survival method CP total costs and QALYs

Next, we denote C as the mean per patient discounted total costs. Then, as for T, this variable is split in to four parts, corresponding to 3rd-line CP, 4th-line CP, AP and BP, using exactly the same notation as for T, shown in Table 76, where d_{BOS} denotes the mean discount factor at the time of cessation of bosutinib treatment across all patients. Technically, this is the integral over all time of the probability density function of the bosutinib discontinuation function at time t multiplied by the discount factor at time t. d_{IFN} represents the analogous quantity for IFN.

d_{BOS} and d_{IFN} can be calculated directly from Pfizer's model and equal 93.0% and 99.4% respectively. These quantities are also based on Pfizer's base case estimates of time on 3rd-line bosutinib and 3rd-line IFN. They also assume a discount rate of 3.5% p.a.

Then under the cumulative survival method, the component costs are calculated as shown in Table 76.

Table 76. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in CP

	(Bosutinib, HU)	**HU**	**SCT**	**(IFN, HU)**	**(Bosutinib, SCT)**
3rd-line CP	unchanged	unchanged	unchanged	unchanged	unchanged
4th-line CP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{HU}}$	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{SCT}}$
AP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{AP}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{AP}}$	
BP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{BP}}$			$S_{\mathrm{IFN}}d_{\mathrm{IFN}}\mathrm{C}_{\mathrm{HU}}^{\mathrm{BP}}$	

The component QALYs are calculated in exactly the same way.

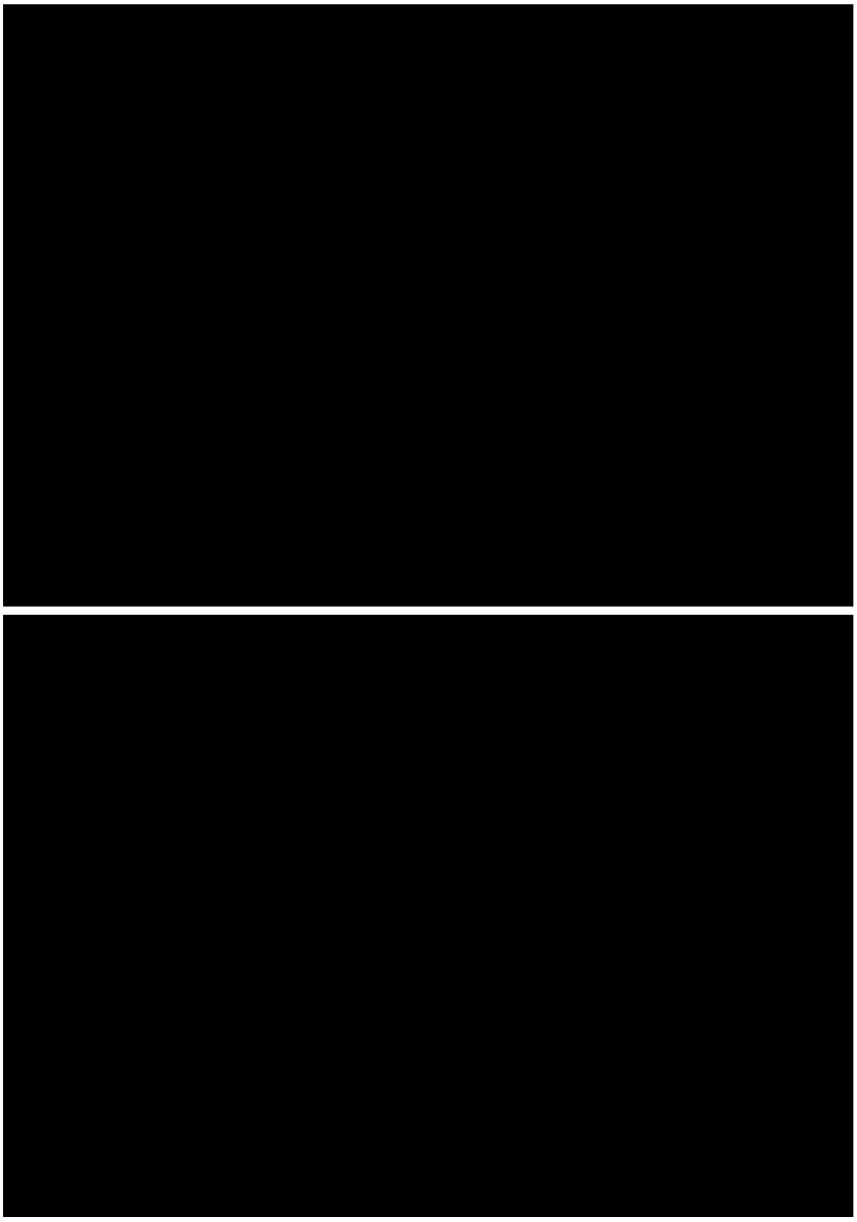
The ICERs are then as shown in Table 77 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT, indicated by bold font.

Table 77. PenTAG ICERs under the Cumulative Survival method for CP

Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

n/a as not estimated by Pfizer

Figure 29.



Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) and (IFN, HU) arms survive to start 4th-line HU treatment, i.e. $S_{\mathrm{BOS}} = S_{\mathrm{IFN}}$ = 100%, and
- no discounting of costs and QALYs, i.e. $d_{\mathrm{BOS}} = d_{\mathrm{IFN}}$ = 100%,

then the ICER for (Bosutinib, HU) versus HU is [redacted] per QALY and (Bosutinib, HU) versus (IFN, HU) is [redacted] per QALY. These ICERs only then depend on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm and IFN treatment in the (IFN, HU) arm. In other words, we ignore all costs and QALYs on HU treatment and in AP and BP in all arms, in particular ignoring all costs and QALYs in the entire HU arm.

Similarly, the ICER for (Bosutinib, SCT) versus SCT is [redacted] per QALY and then depends only on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, SCT) arm, i.e. ignoring all costs and QALYs in the entire SCT arm.

6.1.2 Cumulative survival method AP

We now discuss the Cumulative Survival method applied to treatment starting in AP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 1.0 years respectively) (Figure 30). As in CP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 30.

[redacted]

Under the Cumulative Survival method, we again correct for this imbalance, in an analogous way as for CP CML, described above. The details are given in Appendix T. The key assumptions are that the life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equals that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib, and in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm are very similar (1.01 vs. 1.02 years respectively) (Figure 31). The mean time on HU in the (Bosutinib, HU) arm is slightly lower because not all patients (98.9%) reach HU treatment, whereas all patients start treatment in the HU arm.

In addition, the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are very similar (2.99 vs. 3.02 years respectively) (Figure 31). Similarly, the time is slightly lower in the (Bosutinib, SCT) arm, again because only 98.9% reach SCT treatment.

Figure 31.

The ICERs are then as shown in Table 78 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT, indicated in bold.

Table 78. PenTAG ICERs under the Cumulative Survival method for AP CML

Intervention	(Bosutinib, HU) vs.	(Bosutinib, SCT) vs.

Comparator	***HU***	*SCT*	*HU*	***SCT***
Pfizer base case	[redacted]	Dominant	**n/a**	
Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]

n/a as not estimated by Pfizer

Figure 32.

[redacted]

Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) arm survival to start 4th-line HU treatment, i.e. S_{BOS} =100%, and
- no discounting of costs and QALYs, i.e. d_{BOS} = 100%,

then the ICERs for (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT are both [redacted] per QALY. This ICER only then depends on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm. In other words, we ignore all costs and QALYs on HU and SCT treatments in all arms, in particular ignoring all costs and QALYs in the entire HU and SCT arms.

6.1.3 Cumulative survival method BP

We now discuss the Cumulative Survival method applied to treatment starting in BP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

Pfizer estimate that the mean time on 4th-line HU in the (Bosutinib, HU) arm is greater than the mean time on 3rd-line HU in the HU arm ([redacted] vs. 0.54 years respectively) (Figure 33). As in CP and AP, we believe that this is unreasonable. Again, this assumption acts in favour of the cost-effectiveness of (Bosutinib, HU) vs. HU, because the price of HU is negligible.

Figure 33.

[redacted]

Under the Cumulative Survival method, we again correct for this imbalance, in an analogous way as for CP and AP CML. The details are given in Appendix T. The key assumptions are that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib, and in

the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

Now, the mean times on 4th-line HU in the (Bosutinib, HU) arm, 3rd-line HU in the HU arm are virtually identical (0.54 vs. 0.54 years respectively) (Figure 34), and the mean times on 4th-line SCT in the (Bosutinib, SCT) arm, and 3rd-line SCT in the SCT arm are virtually identical (2.64 vs. 2.64 years respectively) (Figure 34).

Figure 34.

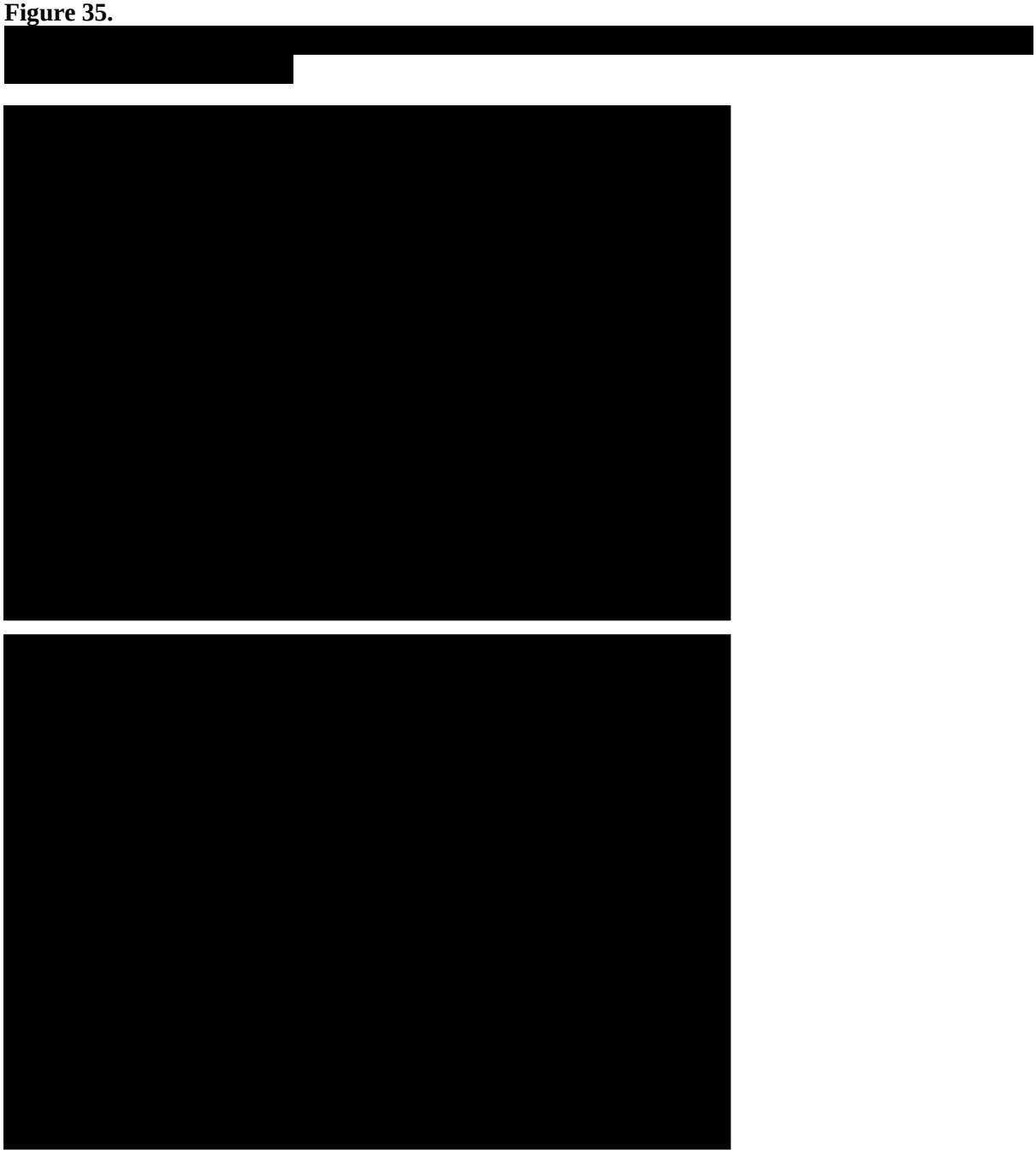
The ICERs are then as shown in Table 79 below. As explained above, we believe that the key comparisons are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT, indicated in bold.

Table 79. PenTAG ICERs under the Cumulative Survival method for BP CML

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
Pfizer base case			n/a	
Cumulative survival method				

n/a as not estimated by Pfizer
a (Bosutinib, HU) cheaper and less effective than SCT

Figure 35.



Notice that if we were to assume:

- that all patients in the (Bosutinib, HU) arm survival to start 4th-line HU treatment, i.e. $S_{\mathrm{BOS}} = 100\%$, and
- no discounting of costs and QALYs, i.e. $d_{\mathrm{BOS}} = 100\%$,

then the ICERs for (Bosutinib, HU) vs. HU and (Bosutinib, SCT) vs. SCT are both [redacted] per QALY. This ICER only then depends on the total mean costs and QALYs on bosutinib treatment in the (Bosutinib, HU) arm. In other words, we ignore all costs and QALYs on HU and SCT treatments in all arms, in particular ignoring all costs and QALYs in the entire HU and SCT arms.

6.1.4 Cumulative survival method discussion

We believe that the method to estimate OS for all treatments should be simple and parsimonious for the following reasons:

- Evidence for OS for all comparators is from single arm trials.
- The quality of evidence for OS for patients having failed a TKI for all comparators is poor.
- Worse still, there is no OS evidence whatsoever specifically for patients unsuited to TKIs for HU, SCT and IFN, and only limited evidence for bosutinib.

Pfizer's method for estimating OS involves numerous assumptions (Table 65, p165), for which there is little or no evidence. Furthermore, their results appear implausible. By contrast, the Cumulative Survival method requires just a single assumption and gives far more plausible estimates for the times on treatment. Therefore, we believe that the Cumulative Survival method should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The Cumulative Survival method additionally has the attractive property that the ICERs for the key comparisons of (bosutinib, HU) vs. HU and (bosutinib, SCT) vs. SCT depend almost exclusively on the costs and QALYs per unit time whilst patients are on bosutinib treatment. This leads to the following attractive predictions about the ICERs for the key comparisons of (bosutinib, HU) vs. HU and (bosutinib, SCT) vs. SCT under the Cumulative Survival method, none of which apply under Pfizer's method.

- They are very insensitive to the estimated mean time on HU and SCT. This is attractive because these quantities are highly uncertain due to the lack of quality clinical evidence.
- They are largely independent of line of treatment of bosutinib, as they are influenced heavily by the costs and QALYs on bosutinib per unit time, not over the entire duration of bosutinib treatment.
- They are insensitive to whether the clinical evidence relates just to those patients unsuited to TKIs or to all patients after imatinib failure.
- They are insensitive to the nature of subsequent treatments in the trials that inform OS for all comparator treatments.

Pfizer briefly mention a sensitivity analysis which they dub the "Cumulative survival approach" (p160 & p469) in which they estimate OS for bosutinib as PFS plus 10 months in AP and 6 months in BP. We agree with Pfizer that their "Cumulative survival approach" is "similar to the cumulative survival approach in TA251" (Pfizer submission, p469). We believe it is similar in that OS for bosutinib is not estimated by a surrogate approach, but instead is estimated as the sum of times in various health states. Nonetheless, their method is importantly different to the method we describe as the "Cumulative Survival" method for two main reasons. First, it is based on PFS, not on time on bosutinib treatment. Pfizer assume that OS is estimated as PFS plus time on AP plus time on BP. As we discussed in TA241, we disagree, because of the definition of progression. In Study 200, progression can indeed be due to progression to AP or BP, but also due to other events such as doubling of white blood cell count over at least 1 month with a second count >20 x 109/L confirmed at least 1 week later, loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss, loss of MCyR with an increase of ≥30% in Ph+ metaphases (p346 Pfizer submission). Therefore, we believe that Pfizer underestimate OS under their method. Second, Pfizer apply their "Cumulative survival approach" only to the bosutinib arm, not to the comparator arms. Therefore, the crucial Assumption 1 (Table 65, p165) remains, i.e. inconsistency in the method of estimating OS across comparators.

The Cumulative Survival method in the form we have just described is not mentioned by Pfizer in the current HTA. We find this puzzling, given that it was the accepted base case model structure in TA251 and given that Pfizer contrast their current analysis with the analyses from TA251 in great details in almost every other area, including choice of utilities, resource use and surrogate survival relationship.

If anything, the Cumulative survival method may slightly over-estimate OS in the bosutinib arm, and therefore is favourable to the cost-effectiveness of bosutinib, for three reasons.

First, the method assumes that the mean time on HU after bosutinib is approximately equal to the mean time on HU (without bosutinib). In other words, that the life expectancy on HU does not decrease at a later line of treatment. Conversely, life expectancy generally decreases with line of treatment.

Second, our estimate of S_{BOS}, the probability that a patient is still alive when he/she stops treatment with bosutinib, i.e. the probability that a patient in the (Bosutinib, HU) arm starts 4th-line HU treatment, which equals the probability that a patient in the (Bosutinib, SCT) arm starts 4th-line SCT treatment, is an upper bound since we assume that the only cause of mortality whilst patients are on bosutinib is background mortality, i.e. unrelated to CML. In reality, mortality is likely to be greater. In particular, an evidence-based estimate of the upper bound of S_{BOS} is 94.9%, which we derive as

follows. In the 3rd-line CP cohort of Study 200, by the 15th February 2012 snapshot, there had been 23 deaths overall, of which 6 occurred during bosutinib treatment or within 30 days of last dose, and 17 died more than 30 days after discontinuation of bosutinib (p83 Pfizer submission). Given that there were 118 3rd-line CP patients, if we assume that all patients were off bosutinib treatment at the data snapshot, this gives an upper bound of 100% − 6 / 118 = 94.9%. This is an upper bound because some patients were still taking bosutinib at the data cut off.

Third, the method does not allow for the fact that background mortality for patients starting 4th-line HU or SCT is slightly greater than for patients starting 3rd-line HU or SCT, reflecting an average time of [redacted] years on 3rd-line bosutinib in CP. However, we ignore this because exploratory calculations suggest that correcting this inaccuracy increases the ICER of bosutinib only very marginally.

Furthermore, we also do not allow for the fact that total QALYs on 4th-line HU will be slightly lower than on 3rd-line HU because utilities are assumed to reduce slightly with age. However, we ignore this for the same reason.

6.2 Derivation of PenTAG base case

In this section we present derivations of the PenTAG base cases in the CP, AP and BP models. The impacts of the individual components of our base case on cost-effectiveness are shown, as well as selected combinations of components and finally the base case which is composed of all components.

We also show more detailed results of the PenTAG base case and comparisons of the Pfizer and PenTAG base cases in the cost-effectiveness plane.

Unless otherwise stated, all ICERs lie in the first (NE) quadrant (i.e., the intervention is more costly and more effective than the comparator). We believe that the comparisons that are most relevant to the decision problem are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT. These ICERs are therefore highlighted in bold.

6.2.1 Derivation of PenTAG CP base case

Table 80 shows the derivation of the PenTAG base case in the CP model. Unless otherwise stated, IFN is dominated by HU.

Table 80. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
	Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
	Pfizer base case	[redacted]	Dominant	[redacted]	n/a		
1[b]	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2	Medical management costs revised	[redacted]	Dominant	[redacted]	n/a		
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	[redacted]	Dominant	[redacted]	n/a		
4	Mean OS of SCT increased from 6.6 to 11.6 years	[redacted]	Dominant	[redacted]	n/a		
1+2[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+3[b]		[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
1+4[b]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+3+4		[redacted]	Dominant	[redacted]	n/a		
1+2+3+4[b]	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT
b Interferon is more costly and more effective than hydroxycarbamide

c Interferon is less costly and less effective than hydroxycarbamide

Our base case ICERs for (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT are [redacted] and [redacted] per QALY respectively. The cumulative survival method is the principal cause of the increase in the ICER for (Bosutinib, HU) versus HU from [redacted] per QALY, as individually it results in an ICER of [redacted] per QALY. The change in medical management costs improves the cost-effectiveness of bosutinib both when applied to Pfizer's base case and also as a component of the PenTAG base case. Increases in the overall survival for HU and SCT patients results in a significant worsening in the cost-effectiveness of bosutinib according to Pfizer's model but the change is less pronounced with the cumulative survival method as these OS gains are passed on to bosutinib patients also. Figure 36 shows the mean time on each treatment for each treatment arm in the PenTAG base case. Note that while SCT is now predicted to provide more life years than (Bosutinib, HU) (11.6 versus [redacted]), it is not predicted to provide more QALYs (5.7 versus [redacted]), although as stated before we believe the appropriate comparisons are (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT.

Figure 36. [redacted]

[redacted]

The general effect of bosutinib in the PenTAG base case is to increase total QALYs by between [redacted] and [redacted] and increase discounted costs by around £100,000, as is shown in Figure 37. Comparisons of the cost-effectiveness planes in the Pfizer and PenTAG bases are shown in

Figure 38, in which it can be seen that HU and SCT become significantly more effective and marginally less costly. (Bosutinib, HU) by contrast becomes less effective and less costly. Further details are shown in Table 81.

Figure 37.

Figure 38.

Table 81. Life years, QALYs and costs in PenTAG CP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	(IFN, HU)	SCT
Life years (undiscounted)					
CP on treatment	[redacted]	[redacted]	5.87	0.54	11.59
CP off treatment	5.61	11.06	n/a	5.86	n/a
AP	0.62	n/a	0.65	0.65	n/a
BP	0.45	n/a	0.47	0.47	n/a
Total	[redacted]	[redacted]	**6.99**	**7.52**	**11.59**
Discounted QALYs					
CP on treatment	[redacted]	[redacted]	3.94	0.38	5.72
CP off treatment	3.50	5.08	n/a	3.90	n/a
AP	0.31	n/a	0.35	0.35	n/a
BP	0.16	n/a	0.18	0.18	n/a
Total	[redacted]	[redacted]	**4.47**	**4.82**	**5.72**
Discounted costs					
CP on treatment	[redacted]	[redacted]	£5,970	£9,038	£151,863
CP off treatment	£5,302	£134,862	n/a	£5,919	n/a
AP	£6,981	n/a	£7,861	£7,794	n/a
BP	£5,102	n/a	£5,745	£5,696	n/a
Palliative care	£4,356	£3,842	£4,905	£4,863	£4,326
Adverse events	£506	£506	n/a	n/a	n/a
Total	[redacted]	[redacted]	**£24,482**	**£33,311**	**£156,189**

6.2.2 Derivation of PenTAG AP base case

Table 82 shows the derivation of the PenTAG AP base case.

Table 82. Derivation of PenTAG base case AP CML

	Intervention	(Bosutinib, HU) vs.		(Bosutinib, SCT) vs.	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	Dominant	n/a	
1	Cumulative survival method	[redacted]	Dominant	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	Dominant	[redacted]	[redacted]

[redacted]

The PenTAG AP base case is composed simply of the cumulative survival method. The effect of this change is to introduce the (Bosutinib, SCT) arm and to worsen slightly the cost-effectiveness of

(Bosutinib, HU) versus HU, with the ICER increasing from [redacted] per QALY. The ICER of (Bosutinib, SCT) versus SCT is estimated at [redacted] per QALY.

Figure 39 shows the mean time on each treatment in the PenTAG AP base case. It can be seen that the time spent on HU in AP in the (Bosutinib, HU) arm is similar to the time spent in AP in the HU arm, and likewise for SCT in the (Bosutinib, SCT) arm.

Figure 39.

[redacted]

Figure 40 shows the cost-effectiveness plane for the PenTAG AP base case. In this instance, bosutinib adds [redacted] QALYs and [redacted].

Figure 41 shows a comparison of the Pfizer and PenTAG base case cost-effectiveness planes, showing that the PenTAG base case reduces the effectiveness and cost of bosutinib and introduces the (Bosutinib, SCT) arm. Further details are shown in Table 83.

Figure 40.

[redacted]

Figure 41. [redacted]

[redacted]

Table 83. Life years, QALYs and costs in PenTAG AP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	SCT
Life years (undiscounted)				
AP on treatment	[redacted]	[redacted]	1.02	3.02
AP off treatment	1.01	2.99	n/a	n/a
BP	0.35	n/a	0.35	n/a
Total	[redacted]	[redacted]	**1.37**	**3.02**
Discounted QALYs				
AP on treatment	[redacted]	[redacted]	0.72	1.96
AP off treatment	0.68	1.83	n/a	n/a
BP	0.16	n/a	0.18	n/a
Total	[redacted]	[redacted]	**0.90**	**1.96**
Discounted costs				
AP on treatment	[redacted]	[redacted]	£15,117	£172,572
AP off treatment	£14,129	£161,294	n/a	n/a
BP	£4,808	n/a	£5,144	n/a
Palliative care	£5,437	£5,160	£5,817	£5,520
Adverse events	£506	£506	n/a	n/a
Total	[redacted]	[redacted]	**£26,078**	**£178,093**

6.2.3 Derivation of PenTAG BP base case

Table 84 shows the derivation of the PenTAG BP base case. In both the Pfizer base case and PenTAG base case (Bosutinib, HU) is less costly and less effective than SCT.

Table 84. Derivation of PenTAG base case BP CML

	Intervention	(Bosutinib, HU) vs.		(Bosutinib, SCT) vs.	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	[redacted]	[redacted]	n/a	
1	Cumulative survival method	[redacted]	[redacted]	[redacted]	[redacted]
1	**PenTAG base case**	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

As in the AP model, the only change is the introduction of the cumulative survival method. This results in the additional intervention arm (Bosutinib, SCT). The PenTAG base case ICERs for (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT are [redacted] and [redacted] per QALY

respectively. The ICER for (Bosutinib, HU) versus HU is increased from [redacted] per QALY in the Pfizer model because costs and QALYs are reduced in this arm but QALYs are more heavily reduced.

The mean time on each treatment for each treatment arm in the PenTAG BP base case is shown in Figure 42, which demonstrates that bosutinib provides an extra [redacted] life years.

Figure 42.

[redacted]

The PenTAG base case cost-effectiveness plane is shown in Figure 43, and demonstrates that bosutinib provides an extra [redacted] QALYs for an extra cost of around [redacted]. The SCT arms give approximately [redacted] extra QALY at an extra cost of approximately [redacted].

Figure 44 shows a comparison of the Pfizer and PenTAG BP base cases in the cost-effectiveness plane and demonstrate that the PenTAG base case introduces the (Bosutinib, SCT) arm and reduces the costs and QALYs of the (Bosutinib, HU) arm. Further details are shown in Table 85.

Figure 43.

Figure 44.

Table 85. Life years, QALYs and costs in PenTAG BP base case

	(Bosutinib, HU)	(Bosutinib, SCT)	HU	SCT
Life years (undiscounted)				
BP on treatment	[redacted]	[redacted]	0.54	2.64
BP off treatment	0.54	2.64	n/a	n/a
Total	[redacted]	[redacted]	**0.54**	**2.64**
Discounted QALYs				
BP on treatment	[redacted]	[redacted]	0.28	1.28
BP off treatment	0.28	1.27	n/a	n/a
Total	[redacted]	[redacted]	**0.28**	**1.28**
Discounted costs				
BP on treatment	[redacted]	[redacted]	£8,203	£194,940
BP off treatment	£8,117	£192,892	n/a	n/a
Palliative care	£5,904	£5,528	£5,967	£5,586
Adverse events	£506	£506	n/a	n/a
Total	[redacted]	[redacted]	**£14,170**	**£200,526**

6.3 Key sensitivity analyses applied to PenTAG and Pfizer base cases

In this section we select scenario analyses which we regard as key analyses either as explorations of potentially valid alternative base cases or of uncertainty in key parameters.

6.3.1 Key sensitivity analyses CP

We conducted a number of scenario analyses on both the Pfizer base case and the PenTAG base case (see Table 86 and Table 87). Some of these were performed because they were potentially valid as base cases (e.g., 2nd-line cohort, utilities from Study 200) while others were to explore the effect of uncertainty in key parameters.

When applied to the PenTAG base case, none of the sensitivity analyses have a significant impact on the relevant ICERs of (Bosutinib, HU) versus HU and (Bosutinib, SCT) versus SCT; in all scenarios, (Bosutinib, HU) is not cost-effective versus HU at cost-effectiveness thresholds of £20,000 or £30,000 per QALY, and likewise for (Bosutinib, SCT) versus SCT.

When applied to the Pfizer base case, some of the sensitivity analyses have a significant impact on the ICER of (Bosutinib, HU) versus HU. In particular, if bosutinib is used in a 2nd-line cohort we predict an ICER of [redacted] per QALY using Pfizer's base case; if bosutinib is received until transformation to AP (as might be the case if bosutinib is the last available TKI for a patient) we predict an ICER of [redacted] per QALY. In these two scenarios, it is also worth noting that (Bosutinib, HU) is no longer

cost-effective versus SCT, although we feel that a more appropriate comparison is (Bosutinib, SCT) vs. SCT.

Table 86. Important scenario analyses applied to PenTAG base case for CP model

Intervention	**(Bosutinib, HU) vs.**			**(Bosutinib, SCT) vs.**		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	[redacted]	[redacted]	[redacted]	[redacted]	**n/c**	[redacted]
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	[redacted]	[redacted]	[redacted]
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
SCT utility set to TA251 utility	**n/c**	[redacted]	n/c	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

a (Bosutinib, HU) is less costly and less effective than SCT

Table 87. Important scenario analyses applied to Pfizer base case CP model

Intervention	**(Bosutinib, HU) vs.**		
Comparator	***HU***	*SCT*	*IFN*
Pfizer base case	[redacted]	Dominant	[redacted]
2nd-line CML cohort from Study 200	[redacted]	[redacted]	[redacted]
Mean OS HU decreased from 3.5 to 1.8 years (−50%)	[redacted]	n/c	n/c
Mean OS HU increased from 3.5 to 5.2 years (+50%)	[redacted]	n/c	n/c
Mean OS for SCT decreased from 6.6 to 3.3 years (−50%)	**n/c**	[redacted]	n/c
Mean OS for SCT increased from 6.6 to 9.9 years (+50%)	**n/c**	Dominant	n/c
On bosutinib treatment until transformation to AP	[redacted]	[redacted]	[redacted]
Bosutinib and HU utility set to Study 200 utility	[redacted]	n/c	[redacted]
SCT utility set to TA251 utility	**n/c**	Dominant	n/c

n/c – Not changed from base case
Shading as in Table 86

6.3.2 Key sensitivity analyses AP

We performed two sensitivity analyses on both the PenTAG and Pfizer base cases. In the first analysis, we increased the overall survival of HU from 1.37 to [redacted] years to match the time spent in AP off bosutinib treatment in the (Bosutinib, HU) arm. In the second analysis, we used utilities from Study 200. In both the PenTAG and Pfizer base cases, these sensitivity analyses did not significantly impact on the ICERs. Using Study 200 utilities improves cost-effectiveness as the HRQL under bosutinib is improved, but the ICERs remain well above the £20,000, £30,000 and £50,000 per QALY thresholds, at [redacted] per QALY in the PenTAG and Pfizer models respectively.

Table 88. Important scenario analyses applied to PenTAG base case for AP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]
HU OS = Time in Bosutinib AP Off Treatment [redacted]	[redacted]	n/c	[redacted]	[redacted]
Study 200 utilities	[redacted]	Dominant	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 89. Important scenario analyses applied to Pfizer base case for AP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	Dominant
HU OS = Time in Bosutinib AP Off Treatment [redacted]	[redacted]	n/c
Study 200 utilities	[redacted]	Dominant

n/c – Not changed from base case
Shading as in Table 88

6.3.3 Key sensitivity analyses BP

We performed similar sensitivity analyses in the BP model as in the AP model. We found that increasing the OS of HU to match the time spent off bosutinib in the (Bosutinib, HU) arm significantly worsened cost-effectiveness in the Pfizer model but had very little effect in the PenTAG model, as expected. Use of Study 200 utilities improved cost-effectiveness, but the ICER of (Bosutinib, HU) versus HU remained high, at [redacted] per QALY in the PenTAG and Pfizer models respectively. (Bosutinib, HU) was consistently less costly and less effective than SCT, except when the Pfizer base case was adjusted for Study 200 utilities.

Table 90. Important scenario analyses applied to PenTAG base case for BP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	[redacted]	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study 200 utilities	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 91. Important scenario analyses applied to Pfizer base case for BP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	n/c
Study 200 utilities	[redacted]	Dominated

n/c – Not changed from base case

[redacted]

7 END OF LIFE

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML.

We agree that there is clearly no case for CP CML because life expectancy under the comparator treatments of HU and SCT are far greater than the threshold of 2 years.

We believe that bosutinib does not meet the End of Life criteria in any phase of CML, as demonstrated in Table 92 and Table 93 below.

Table 92. End of Life criteria for bosutinib in AP

Criterion	Pfizer comments	PenTAG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Pfizer claim life expectancy is approx. 1.3 years (p103 Pfizer submission)	In summary, it seems likely that the life expectancy for patients on an appropriate comparator treatment is close to the threshold of 24 months, as follows: First, we believe that the relevant comparator for most people is HU rather than SCT. Pfizer estimate life expectancy under HU as 1.4 years and after SCT as 3.0 years. We have no alternative value for SCT. We believe that the estimate of 1.4 years for HU is based on weak evidence. Also, Pfizer estimate a mean time on HU after bosutinib of [redacted] years.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pfizer claim extension to life expectancy is approx. 1.7 years (p103 Pfizer submission)	We believe that this criterion is probably satisfied. We understand that Pfizer's base case claims extension to life of 3.1 years for (Bosutinib, HU) vs. HU and 1.5 years vs. SCT. Under our Cumulative Survival method, the extension to life is 2.3 years.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Pfizer claim patient population < 8 p.a. (p103 Pfizer submission)	We believe that this criterion is clearly satisfied. Pfizer's estimate is not unreasonable.
The estimates of the extension to life are robust and can be shown or reasonably inferred from	No discussion	We believe that this criterion is not satisfied for the numerous reasons given in Section 5.3.8.1, p165.

either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)		For example, estimates of OS are not randomised, the method of estimation of OS is not consistent across treatments, OS is estimated from very small sample sizes, and largely from people suited to TKIs (whereas they should be for people unsuited to TKIs), OS data is immature.
The assumptions used in the reference case economic modelling are plausible, objective and robust.	No discussion in relation to End of Life	This criterion is difficult to evaluate. Most assumptions for the AP model are plausible, but not robust.
Overall qualification for End of Life	**Yes**	**No**

Table 93. End of Life criteria for bosutinib in BP

Criterion	Pfizer comments	PenTAG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Pfizer claim life expectancy is approx. 0.5 years (p103 Pfizer submission)	In summary, it seems likely that this criterion is satisfied, as follows: First, we believe that the relevant comparator for most people is HU rather than SCT. Pfizer estimate life expectancy under HU as 0.5 years and after SCT as 2.6 years. We have no alternative value for SCT. We believe that the estimate of 0.5 years for HU is based on weak evidence. Also, Pfizer estimate a mean time on HU after bosutinib of [redacted] years
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pfizer claim extension to life expectancy is approx. 1.2 years (p103 Pfizer submission)	We believe that this criterion is probably satisfied. Pfizer's base case extension to life is 1.2 years for (Bosutinib, HU) vs. HU (the most relevant comparator), but (Bosutinib, HU) reduces life expectancy vs. SCT. Under our Cumulative Survival method, the extension to life is 0.6 years.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in	Pfizer claim patient population < 8 p.a. (p103 Pfizer submission)	We believe that this criterion is clearly satisfied. Pfizer's estimate is not unreasonable.

England.		
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	No discussion	We believe that this criterion is not satisfied for the same reasons given for AP (Table 92).
The assumptions used in the reference case economic modelling are plausible, objective and robust.	No discussion in relation to End of Life	This criterion is difficult to evaluate. Most assumptions for the BP model are plausible, but not robust.
Overall qualification for End of Life	**Yes**	**No**

8 IMPLICATIONS FOR RESEARCH

Research in to the following would be welcome:

- The EMA's marketing authorisation is conditional on the following trial to be conducted, with final clinical study report due 30th September 2018[29]:

  "a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options."

  We agree that this would improve our understanding of bosutinib in the unmet need population.
- However, better still would be a randomised trial of bosutinib versus the comparators HU or SCT in the unmet need population.
- More mature OS data for bosutinib in all phases, specifically for patients in the patient population appropriate to this appraisal, i.e., those after TKIs failure, unsuited to imatinib, nilotinib and dasatinib. This would allow us to test our default assumption under the Cumulative Survival method that bosutinib does not affect mortality once it is discontinued. We assume that this will be recorded from Study 200. However, a larger patient population would be welcome from the single-arm trial recommended by the EMA.
- High quality estimate of OS on HU in all phases of CML for 2nd-line patients, and also for patients in the population appropriate to this appraisal, ideally from the randomised trial we recommend above, would be useful for modelling the cost-effectiveness of bosutinib (or other new TKIs in the future) versus HU. But we understand that this data may not be collected due to ethical reasons, as HU is not a potent treatment for CML.
- Similarly for OS after SCT in CP.
- Utilities for patients after SCT.

REFERENCES

1. Cortes J, Kantarjian H, Kim DW, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib: 36-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.

2. Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:1-410.

3. Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer 2007;109:1556-60.

4. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. Haematologica 2011;96:1779-82.

5. Benedicte D, Emmanuel B, Nicole R, et al. Impact of prior second-generation tyrosine kinase inhibitors on the outcome of hematopoietic stem cell transplantation for chronic myeloid leukemia In 52nd Annual Meeting of the American Society of Hematology, 2010.

6. Bornhauser M, Kroger N, Schwerdtfeger R, et al. Allogeneic haematopoietic cell transplantation for chronic myelogenous leukaemia in the era of imatinib: a retrospective multicentre study. Eur J Haematol 2006;76:9-17.

7. Holroyd A, Philips E, Szydlo R, et al. Response to tyrosine kinase inhibitor therapy in patients undergoing allogeneic hematopoietic stem cell transplantation for advanced phase chronic myeloid leukemia, In 52nd Annual Meeting of the American Society of Hematology, 2010, 2010.

8. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. Cancer 2007;110:340-4.

9. Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after Bcr-Abl kinase mutation-related imatinib failure. Blood 2006;108:1421-3.

10. Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-7.

11. Markiewicz M, Dzierzak-Mietla M, Wisniewska-Piaty K, et al. The favorable results of allo-HSCT in TKI-resistant CML, In 53rd Annual Meeting of the American Society of Hematology, In 53rd Annual Meeting of the American Society of Hematology, 2011, 2011.

12. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-9.

13. Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-5.

14. Schleuning M, Scholten M, van Bienzen A, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia after prior treatment with nilotinib or dasatinib, In 52nd Annual Meeting of the American Society of Hematology, 2010.

15. Weisser M, Schleuning M, Haferlach C, et al. Allogeneic stem-cell transplantation provides excellent results in advanced stage chronic myeloid leukemia with major cytogenetic response to pre-transplant imatinib therapy. Leuk Lymphoma 2007;48:295-301.

16. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol 2009;62:1253-1260 e4.

17. Hoyle M, Pavey T, Ciani O, et al. Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. National Institute for Health and Clinical Excellence (NICE): Peninsula Technology Assessment Group (PenTAG), University of Exeter 2011.

18. Bhamidipati PK, Kantarjian H, Cortes J, et al. Management of imatinib-resistant patients with chronic myeloid leukemia. Ther Adv Hematol 2013;4:103-17.

19. Haematological Malignancy Research Network. Chronic myelogenous leukaemia http://www.hmrn.org/Statistics/Cancer_Info.aspx?id=1 (last accessed 13 May 2013), 2013.

20. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.

21. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-8.

22. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011;118:686-92.

23. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol 2009;27:469-71.

24. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.

25. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403-12.

26. Trask PC, Cella D, Besson N, et al. Health-related quality of life of bosutinib (SKI-606) in imatinib-resistant or imatinib-intolerant chronic phase chronic myeloid leukemia. Leuk Res 2012;36:438-42.

27. Pfizer. Study 200 Clinical Study Report.

28. Khoury HJ, Gambacorti-Passerini C, Kantarjian H, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Failure with Imatinib Plus Dasatinib and/or

Nilotinib: 24-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.

29. European Medicines Agency. Assessment report: bosulif, 2013.

30. Trask PC, Cella D, Powell C, et al. Health-related quality of life in chronic myeloid leukemia. Leuk Res 2013;37:9-13.

31. Dalziel K, Round A, Stein K, et al. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess 2005;9:iii-iv, 1-146.

32. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:iii-x, 1-173.

33. Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions (Available from www.cochrane-handbook.org): The Cochrane Collaboration, 2011.

34. Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Healthcare, 2009.

35. Porcher R, Desseaux K. What inference for two-stage phase II trials? BMC Med Res Methodol 2012;12:117.

36. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.

37. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP, 2011.

38. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. Lancet 1995;345:1392-7.

39. Hoyle M, Rogers G, Moxham T, et al. Cost-effectiveness of dasatinib and nilotinib for imatinib-resistant or -intolerant chronic phase chronic myeloid leukemia. Value Health 2011;14:1057-67.

40. Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:iii-xiii, 1-137.

41. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press, 2006.

42. Hawkins N, Sculpher M, Epstein D. Cost-effectiveness analysis of treatments for chronic disease: using R to incorporate time dependency of treatment response. Med Decis Making 2005;25:511-9.

43. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. Process and methods guides, 2013.

44. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. Blood 2009;113:2154-60.

45. Reed SD, Anstrom KJ, Ludmer JA, et al. Cost-effectiveness of imatinib versus interferon-alpha plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2004;101:2574-83.

46. Dalziel K, Round A, Stein K, et al. Effectiveness and cost-effectiveness of imatinib for first-line treatment of

chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. Health Technol Assess 2004;8:iii, 1-120.

47. Department of Health. Reference costs 2011-12 (available from: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012), 2012.

48. Darbà J, Kaskens L. Análisis coste-efectividad de dasatinib frente a imatinib a dosis alta en el tratamiento de la leucemia mieloide crónica en pacientes resistentes a dosis estándar de imatinib. PharmacoEconomics Spanish Research Articles 2012;9:63-71.

49. Szabo SM, Davis C, Sidhu S, et al. Characterizing resource use and treatment costs for chronic myelogenous leukemia (CML) in the UK (UK). Value Health 2009;12:A268.

50. Taylor M, Saxby R, Davis C. Using short-term response to predict long-term outcomes in patients with imatinib-resistent or imatinib-intolerant chronic myeloid leukaemia. Value Health 2009;12:A50.

51. Taylor MJ, Saxby RC, Davis C. An Economic Evaluation of Dasatinib for the Treatment of Imatinib-Resistant Patients with Chronic Myelogenous Leukaemia. ASH Annual Meeting Abstracts 2009;114:A4535.

52. Warren E, Ward S, Gordois A, et al. Cost-utility analysis of imatinib mesylate for the treatment of chronic myelogenous leukemia in the chronic phase. Clin Ther 2004;26:1924-33.

53. Curtis L. Unit Costs of Health and Social Care 2012: Personal Social Services Research Unit, 2012.

54. Addicott R, Dewar S. Improving choice at end of life: a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice programme in Lincolnshire. London: King's Fund, 2008.

55. Bagust A, Boland A, Dundar Y, et al. Erlotinib for the treatment of relapsed non-small-cell lung cancer: Liverpool Reviews and Implementation Group, 2006.

56. NHS Blood and Transplant. The future of unrelated donor stem cell transplantation in the UK (report of the UK Stem Cells Strategic Forum), 2010.

57. van Agthoven M, Groot MT, Verdonck LF, et al. Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow Transplant 2002;30:243-51.

58. Drummond MF. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1997.

59. Pastore D, Specchia G, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed acute myeloid leukemia: single-center experience. Ann Hematol 2003;82:231-5.

9 APPENDICES

9.1 Appendix A: Incident population for bosutinib treatment in England & Wales

The following table is reproduced from Table C1, p188 of Pfizer's submission.

Table C1: Estimated annual, incident population for bosutinib treatment in England and Wales

Population	Estimated incidence	Assumption	Reference
Cases of chronic myeloid leukaemia in England and Wales	631	596 people in England and 35 people in Wales diagnosed with CML in 2010. Assuming that incidence has been stable since 2010.	Office of National Statistics Cancer Statistics Registrations, England, 2010 Welsh Cancer Intelligence and Surveillance Unit, Annual Publication No. SA12/01
People with Ph+ CML and treated with a 1st-line TKI (imatinib)	599	95% of those diagnosed with CML are Ph+. All diagnosed patients are treated with a 1st-line TKI (imatinib).	Goldman, 2009 Assumption
People for whom 1st-line imatinib treatment is unsuccessful and are treated with a 2nd-line TKI	234	39% of 1st-line patients discontinued imatinib (excluding those who discontinued due to mortality or receipt of a SCT) and all are treated with a 2nd-line TKI (usually nilotinib)	Deininger, 2009 Assumption
2nd-line patients for whom current 2nd-line TKIs are inappropriate options and therefore **eligible for bosutinib at 2nd-line**	12	5% of imatinib-resistant patients from Study 200 may have been unsuitable for treatment with nilotinib and dasatinib at 2nd-line, due to the presence of mutations conferring resistance or co-morbidities	Draft EPAR
Patients for whom 2nd-line TKI treatment is unsuccessful and are treated with a 3rd-line TKI	107	48% of 2nd-line patients discontinued nilotinib due to lack of efficacy (progression) or intolerance (adverse events) and treated with a 3rd-line TKI	Kantarjian (2011)
3rd-line patients whom the remaining TKI is not an appropriate option and therefore **eligible for bosutinib at 3rd-line**	19	18% of third-line patients from Study 200 may have been unsuitable for treatment with nilotinib or dasatinib at third-line (depending on previous treatment), due to the presence of mutations conferring resistance or co-morbidities, and therefore may be eligible for bosutinib at 3rd-line.	Draft EPAR
Patients for whom all currently available TKIs have been unsuccessful at 3rd-line and are therefore **eligible for bosutinib at 4th-line**	49	56% of 3rd-line patients (nilotinib and dasatinib) discontinue treatment excluding those discontinued due to mortality or receipt of a SCT) and have therefore exhausted all TKI options currently available.	Garg (2009)
Total incident population eligible to receive bosutinib under its proposed licensed indication	**80**	**80 patients per year may be eligible for bosutinib.**	

9.2 Appendix B: Pfizer search strategy

Embase 1974 to January 18th 2013: accessed January 21st 2013

# ▲	Searches	Results
1	exp chronic myeloid leukemia/	28150
2	exp myeloid leukemia/	94931
3	chronic.mp. or exp CHRONIC DISEASE/	1137090
4	2 and 3	37637
5	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	36017
6	1 or 4 or 5	40870
7	imatinib.mp. or exp IMATINIB/	25210
8	(gleevec or glivec).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	7043
9	(STI-571 or STI571 or CGP-57148B or CGP57148B).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3450
10	imatinib mes?late.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3959
11	7 or 8 or 9 or 10	25381
12	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1825148
13	11 and 12	8632
14	((second or third or fourth) adj2 line).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18247
15	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	20661

16	exp hydroxycarbamide/	18838
17	exp stem cell transplantation/	73805
18	(HSCT or SCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	16373
19	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	80164
20	(best adj2 support*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2980
21	BSC.mp.	1903
22	exp alpha interferon/	42290
23	("roferon-a" or "intron-a").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4127
24	(interferon adj2 alpha).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	58762
25	exp bosutinib/	768
26	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	785
27	13 or 14	26479
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	164462
29	exp Meta Analysis/	68526
30	((meta adj analy$) or metaanalys$).tw.	64279
31	(systematic adj (review$1 or overview$1)).tw.	49775
32	or/29-31	126912
33	cancerlit.ab.	667
34	cochrane.ab.	29194
35	embase.ab.	26182

36	(psychlit or psyclit).ab.	960
37	(psychinfo or psycinfo).ab.	6477
38	(cinahl or cinhal).ab.	8859
39	science citation index.ab.	1924
40	bids.ab.	426
41	or/33-40	44645
42	reference lists.ab.	8707
43	bibliograph$.ab.	13958
44	hand-search$.ab.	4023
45	manual search$.ab.	2311
46	relevant journals.ab.	733
47	or/42-46	26833
48	data extraction.ab.	10705
49	selection criteria.ab.	19538
50	48 or 49	28886
51	review.pt.	1927821
52	50 and 51	17160
53	letter.pt.	810639
54	editorial.pt.	423694
55	animal/	1814965
56	human/	14033665
57	55 not (55 and 56)	1358614
58	or/53-54,57	2579283

59	32 or 41 or 47 or 52	158341
60	59 not 58	152465
61	Clinical trial/	880466
62	Randomized controlled trial/	338298
63	Randomization/	60597
64	Single blind procedure/	16904
65	Double blind procedure/	115252
66	Crossover procedure/	36027
67	Placebo/	224651
68	Randomi?ed controlled trial$.tw.	83038
69	Rct.tw.	10825
70	Random allocation.tw.	1244
71	Randomly allocated.tw.	18468
72	Allocated randomly.tw.	1879
73	(allocated adj2 random).tw.	797
74	Single blind$.tw.	13248
75	Double blind$.tw.	140106
76	((treble or triple) adj blind$).tw.	322
77	Placebo$.tw.	189572
78	Prospective study/	223692
79	or/61-78	1323025
80	Case study/	18387
81	Case report.tw.	246829

82	Abstract report/ or letter/	874710
83	or/80-82	1135017
84	79 not 83	1286701
85	Clinical study/	89188
86	Case control study/	73451
87	Family study/	9857
88	Longitudinal study/	57858
89	Retrospective study/	305071
90	Prospective study/	223692
91	Randomized controlled trials/	25395
92	90 not 91	222997
93	Cohort analysis/	138791
94	(Cohort adj (study or studies)).mp.	93662
95	(Case control adj (study or studies)).tw.	66302
96	(follow up adj (study or studies)).tw.	43659
97	(observational adj (study or studies)).tw.	50576
98	(epidemiologic$ adj (study or studies)).tw.	70019
99	(cross sectional adj (study or studies)).tw.	68258
100	or/85-89,92-99	1060706
101	60 or 84 or 100	2135162
102	6 and 27 and 28 and 101	634

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: accessed January 21st 2013

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	14336
2	exp Leukemia, Myeloid/	73716
3	exp Chronic Disease/ or chronic.mp.	866224
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	22855
5	2 and 3	21552
6	1 or 4 or 5	26689
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9340
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1329087
9	7 and 8	3386
10	((second or third or fourth) adj2 line).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	12295
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9716
12	exp Hydroxycarbamide/	6966
13	exp Hematopoietic Stem Cell Transplantation/	24548
14	(HSCT or SCT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	9314
15	(stem adj2 cell adj2 transplant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	52708
16	("roferon-a" or "intron-a").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease	602

	supplementary concept, unique identifier]	
17	(interferon adj2 alpha).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	34862
18	exp Interferon-alpha/	22848
19	(best adj2 support*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1940
20	BSC.mp.	1393
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	159
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	101858
23	9 or 10	15527
24	Randomized controlled trials as Topic/	82308
25	Randomized controlled trial/	337940
26	Random allocation/	75868
27	Double blind method/	117051
28	Single blind method/	16860
29	Clinical trial/	472870
30	exp Clinical Trials as Topic/	259509
31	or/24-30	838537
32	(clinic$ adj trial$1).tw.	186641
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	118891
34	Placebos/	31156
35	Placebo$.tw.	144503
36	Randomly allocated.tw.	14961

37	(allocated adj2 random).tw.	690
38	or/32-37	374411
39	31 or 38	967127
40	Case report.tw.	185707
41	Letter/	775875
42	Historical article/	288376
43	Review of reported cases.pt.	0
44	Review, multicase.pt.	0
45	or/40-44	1239238
46	39 not 45	940466
47	Epidemiologic studies/	5506
48	exp case control studies/	577770
49	exp cohort studies/	1213923
50	Case control.tw.	66232
51	(cohort adj (study or studies)).tw.	68832
52	Cohort analy$.tw.	3047
53	(Follow up adj (study or studies)).tw.	34614
54	(observational adj (study or studies)).tw.	35931
55	Longitudinal.tw.	121664
56	Retrospective.tw.	236529
57	Cross sectional.tw.	139952
58	Cross-sectional studies/	148552
59	or/47-58	1671329

60	Meta-Analysis as Topic/	12349
61	meta analy$.tw.	47037
62	metaanaly$.tw.	1193
63	Meta-Analysis/	36590
64	(systematic adj (review$1 or overview$1)).tw.	39507
65	exp Review Literature as Topic/	6473
66	or/60-65	95085
67	cochrane.ab.	22972
68	embase.ab.	20860
69	(psychlit or psyclit).ab.	844
70	(psychinfo or psycinfo).ab.	8116
71	(cinahl or cinhal).ab.	7677
72	science citation index.ab.	1607
73	bids.ab.	331
74	cancerlit.ab.	546
75	or/67-74	38173
76	reference list$.ab.	7893
77	bibliograph$.ab.	10357
78	hand-search$.ab.	3325
79	relevant journals.ab.	572
80	manual search$.ab.	1965
81	or/76-80	21577
82	selection criteria.ab.	16585

83	data extraction.ab.	8165
84	82 or 83	23449
85	Review/	1735402
86	84 and 85	15340
87	Comment/	518398
88	Letter/	775875
89	Editorial/	318524
90	animal/	4993336
91	human/	12521330
92	90 not (90 and 91)	3656512
93	or/87-89,92	4819761
94	66 or 75 or 81 or 86	121442
95	94 not 93	113116
96	46 or 59 or 95	2475570
97	6 and 22 and 23 and 96	198

EBM Reviews - Cochrane Central Register of Controlled Trials December 2012, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2012, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2012, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2012: accessed January 21st 2012

# ▲	Searches	Results
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ ?	243
2	exp Leukemia, Myeloid/ ?	1243

3	exp Chronic Disease/ or chronic.mp. ?	55159
4	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	663
5	2 and 3 ?	322
6	1 or 4 or 5 ?	711
7	(imatinib or gleevec or glivec or STI-571 or STI571 or CGP-57148B or CGP57148B or imatinib mes?late).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	398
8	(refractory or intoleran* or failure* or resistan*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	66651
9	7 and 8 ?	119
10	((second or third or fourth) adj2 line).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	1784
11	(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	602
12	exp Hydroxycarbamide/ ?	289
13	exp Hematopoietic Stem Cell Transplantation/ ?	779
14	(HSCT or SCT).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	538
15	(stem adj2 cell adj2 transplant*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	2329
16	("roferon-a" or "intron-a").mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	258
17	(interferon adj2 alpha).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	4044

18	exp Interferon-alpha/ ?	2264
19	(best adj2 support*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	437
20	BSC.mp. ?	175
21	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] ?	3
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ?	7700
23	9 or 10 ?	1896
24	6 and 22 and 23 ?	26

(Source: Pfizer submission, Appendix 2, p201)

9.3 Appendix C: Quality assessment tool

Chambers criteria for quality assessment of non-RCTs

Criteria used for quality assessment
1 Were selection/eligibility criteria adequately reported?
2 Was the selected population representative of that seen in normal practice?
3 Was an appropriate measure of variability reported?
4 Was loss to follow-up reported or explained?
5 Were at least 90% of those included at baseline followed-up?
6 Were patients recruited prospectively?
7 Were patients recruited consecutively?
8 Did the study report relevant prognostic factors?

Using the above criteria, a study's quality could be scored as good, satisfactory or poor; good, if the answer is 'yes' to all of criteria 1 to 8; satisfactory, if the answer is 'yes' to criteria 2 and 4-7; poor, if the answer is not 'yes' to one or more of the criteria listed for 'satisfactory'

(Source: Pfizer submission, Appendix 7, p215)

9.4 Appendix D: Eligibility criteria for Study 200

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Signed and dated informed consent prior to any protocol-specific screening procedures • Cytogenetic- or PCR- based diagnosis of any phase of Ph^+ CML or Ph^+ ALL whose disease was resistant to full-dose imatinib (≥600 mg) or was intolerant of any dose of imatinib (please see Appendix 10.14 for definitions of resistance/intolerance) • Adequate duration of prior imatinib therapy • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for CP patients and 0, 1 or 2 for advanced phase leukaemia patients • No antiproliferative or antileukaemia treatment within 7 days of the first dose of bosutinib (except hydroxycarbamide and anagrelide) • At least three months post allogeneic stem cell transplantation • Recovery to grade 0/1, or to baseline, from any toxicities of prior anticancer treatment (excluding alopecia) • Able to take daily oral capsules or tablets reliably • Adequate bone marrow function (for imatinib-resistant patients in chronic phase only) o Absolute neutrophil count (ANC) >1000/mm3 (>1 x109/L) o Platelets ≥100,000/mm3 (≥100 x 109/L) and absence of any platelet transfusions during the preceding 14 days • Adequate hepatic function o AST/ALT ≤2.5 x ULN or ≤5 x ULN if attributable to liver involvement of leukaemia o Total bilirubin ≤1.5 x ULN • Adequate renal function o Creatine ≤1.5 x ULN • Willingness to use reliable birth control (if applicable) throughout the study and 30 days after the last dose • Documented normal INR if not on oral anticoagulant therapy, or if on oral anticoagulant therapy, consistent target INR ≤3 **<u>Additional inclusion criteria specific to Study 200 populations</u>** <u>Third-line CP CML population</u> • Imatinib-resistant or imatinib-intolerant CP	• Ph negative leukaemia or Bcr-Abl negative leukaemia • Overt leptomeningeal leukaemia (free of CNS involvement for <2 months) • Extramedullary disease only • GVHD (treated or untreated) within 60 days of study start • Documented history of the T315I Bcr-Abl mutation (this criterion added as of 10th June 2008 based on lack of efficacy in this group) • Pregnant or breastfeeding • Major surgery within 14 days or radiotherapy within 7 days before the first dose of bosutinib (recovery from any previous surgery should have been completed before day 1) • History of clinically significant or uncontrolled cardiac disease including: o history of or active congestive heart failure o uncontrolled angina or hypertension within 3 months o myocardial infarction within 12 months o clinically significant ventricular arrhythmia o diagnosed or suspected congenital or acquired prolonged QT syndrome o unexplained syncope o history of prolonged corrected QT interval (QTc) • Prolonged QTc (>0.45 seconds, average of triplicate readings at screening) • Concomitant use of or need for medications known to prolong the QT interval • Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval • Recent (within 30 days of study entry) or ongoing clinically significant gastrointestinal disorder • Evidence of serious active infection, or significant medical or psychiatric illness • Known seropositivity to human immunodeficiency virus or current acute or chronic hepatitis B or hepatitis C (antigen positive), cirrhosis or clinically significant abnormal laboratory findings that would, in the investigator's judgement, make the patient inappropriate for this study

Ph+ CML also previously treated with dasatinib and/or nilotinib, to which the patient developed resistance or intolerance <u>Advanced phase CML population</u> • Advanced phase Ph+ CML previously treated with 1 or more TKIs (imatinib only or imatinib and dasatinib and/or nilotinib)	
<u>Second-line CP CML patient population</u>	
• Imatinib-resistant or imatinib-intolerant CP Ph^+ CML • QTc interval <470 msec at screening	

(Source: Pfizer submission, Table B6, p53 and Appendix 15, p 349)

9.5 Appendix E: Outcome definitions used in Study 200

Outcome	Description/details
Cytogenetic Response	At least 20 metaphases were required for post-baseline assessment. If fewer than 20 metaphases were available, fluorescence in situ hybridisation (FISH) analysis of bone marrow aspirate for the presence of Bcr-Abl fusion protein could be used, provided ≥200 cells were analysed. Cytogenetics were performed within 14 days of registration and every 3 months thereafter. After 2 years, assessments were performed every 6 months. For CP patients, disease status was assessed at baseline and every 12 weeks during the first 2 years of treatment, every 24 weeks thereafter, and at the time of treatment completion. For advanced phase patients, cytogenetic assessments were performed monthly until week 12, or until the patient's status returned to chronic phase (whichever came first) and at week 24
Major cytogenetic response (MCyR)	0%—35% Ph^+ metaphases (0%—35% positive cells by FISH) MCyR = CCyR + PCyR
Complete cytogenetic response (CCyR)	0% Ph^+ metaphases (<1% positive cells by FISH)
Partial cytogenetic response (PCyR)	1%—35% Ph^+ metaphases (1%—35% positive cells by FISH)
Minor Cytogenetic Response (MiCyR)	36%—65% Ph^+ metaphases (36%—65% positive cells by FISH)
Minimal Cytogenetic Response	66%—95% (66%—95% positive cells by FISH)
No Cytogenetic Response	>95% positive cell (>95% positive cells by FISH)
Haematological Response	Haematological responses were based upon peripheral blood assessments (complete blood count, including 5-part differential, platelet count, absolute neutrophil count), bone marrow assessments (differential, clonal evolution) and clinical assessments of extramedullary disease. Peripheral blood assessments were performed at screening, weeks 1, 2, 3, 4, 8, 12, every 12 weeks during the first 2 years of treatment, every 24 weeks beginning with the third year of treatment and at the final visit
Complete haematological response (CHR)	For a patient to be deemed to possess a CHR, they must have fulfilled all of the following haematological criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in blood • White blood cell count (WBC) ≤ institutional ULN • Platelets <450 x 10^9/L • <20% basophils in blood • No extramedullary involvement (including hepato- or

Outcome	Description/details
	splenomegaly) • Platelets ≥100 x 10^9/L (only applicable to advanced phase) • Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (only applicable to advanced phase) • ≤5% bone marrow blasts (only applicable to advanced phase)
Overall haematological response (OHR)	A patient was defined as having an OHR if they met the criteria for any one of: CHR, no evidence of leukaemia (NEL) or return to chronic phase (RCP). <u>CHR</u> See above for criteria <u>NEL</u> A patient was defined as having NEL if they met all of the following criteria: • No peripheral blood blasts or promyelocytes • Myelocytes and metamyelocytes <5% in the blood • WBC ≤ institutional ULN • 450 x 10^9/L> platelets ≥20 x 10^9/L • ANC ≥0.5 x 10^9/L • <20% basophils in blood • No extramedullary involvement • ≤5% bone marrow blasts (only applicable to advanced phase) <u>RCP</u> To be defined as having achieved RCP, a patient had to meet all of the below criteria, with the exception of patients with CP CML who were not required to have post-baseline bone marrow samples taken. Disappearance of features defining accelerated and blast phases, but still in chronic phase as noted by: • <15% blasts in both peripheral blood and bone marrow • <30% blasts and promyelocytes in both peripheral blood and bone marrow • <20% basophils in both peripheral blood and bone marrow • No extramedullary involvement other than liver/spleen
Major haematological response (MHR)	A patient was defined as having a MHR if they met the criteria for either a CHR or NEL (see above)
Molecular Response	Assessed with non-nested RT-PCR for the BcrAbl transcript performed at a central laboratory (Quest Diagnostics) monthly for the first 3 months, every 3 months through 2 years and every 6 months thereafter
Major molecular response (MMR)	≥ 3 log reduction from standardised baseline (baseline based upon the PCR data of 120 previously untreated CML patients) in ratio of Bcr-Abl to Abl transcripts
Complete molecular response (CMR)	Undetectable Bcr-Abl transcript, with a PCR sensitivity of ≥5 log
Progression-free survival (PFS)	Within Study 200, PFS was calculated as the time from start of bosutinib therapy to disease progression (as assessed by an investigator), treatment discontinuation due to death or death within 30 days of the last dose. For patients who were

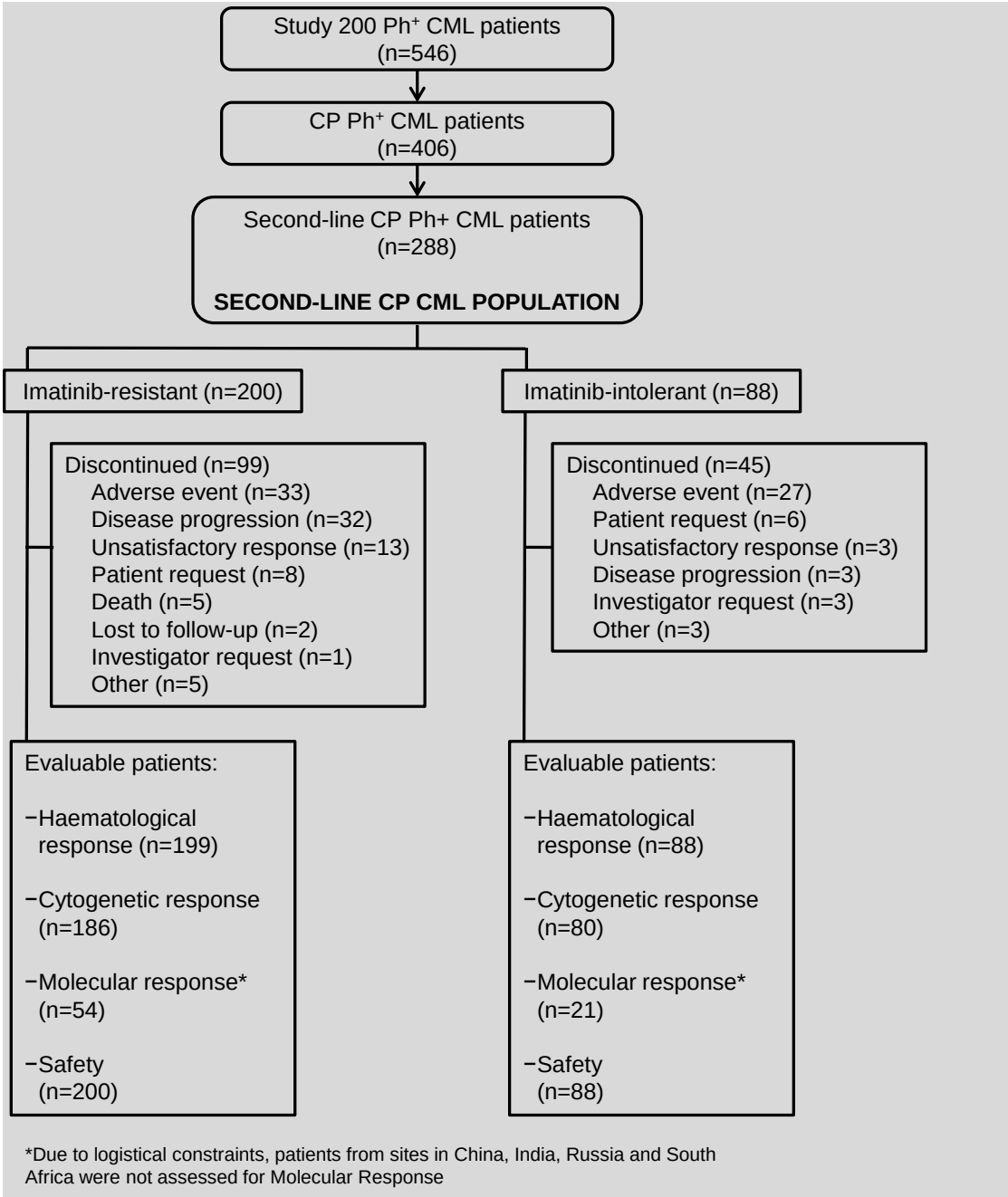
Outcome	Description/details
	last known to be alive and without progression, censoring was performed using the last date at which the patient was known to be progression free. Progression was defined by possession of any of the following criteria: • Entry in CP and clear progression to AP within the first 4 weeks of therapy (early progressor). To be considered a progressor to AP, a patient must have had an absolute increase of at least 10% in the count(s) qualifying the patient for accelerated phase • Evolution from initial CP, or from CP to which the patient returned, to AP or BP (evolution had to be measured on at least 2 consecutive assessments, at least 1 week apart) • Doubling of white blood cell count over at least 1 month with a second count >20 x 10^9/L confirmed at least 1 week later • Loss of confirmed CHR which was subsequently confirmed by a haematological assessment at least 2 weeks after the initial finding of loss • Loss of MCyR with an increase of ≥30% in Ph^+ metaphases
Overall survival (OS)	Overall survival was taken as the interval from the date of the first dose of bosutinib to the date of death, due to any cause. Patients who were not recorded as dead at the end of the study were censored at the last date at which they were known to be alive. The Study 200 protocol only required patients who discontinued treatment to be followed up for 24 months. It should therefore be noted that overall survival is truncated at 24 months for these patients and that this may bias the analysis with regards to this outcome
AP/BP Transformation Rate	Patients were considered to have undergone transformation if they experienced an evolution of disease from CP at study entry to AP or BP, or from AP at study entry to BP. This measure of transformation had to be present on 2 consecutive post-baseline assessments at least 1 week apart. In cases where the last haematological assessment did not confirm AP or BP status, then treatment discontinuation due to disease progression and death, or death within 30 days of last dose was considered a confirmation of transformation
FACT-Leu	The FACT-Leu is a 44-item, self-reported, reliable and valid assessment of health-related quality-of-life in patients with leukaemia. The FACT-Leu measures leukaemia specific health related quality of life and consists of 4 domains (27 items): • Physical well being (PWB) • Social well being (SWB) • Emotional well being (EWB) • Functional well being (FWB) The FACT-leu also measures a leukaemia subscale (LEUS) of additional concerns (17 items)

Outcome	Description/details
EQ-5D	EQ-5D is a patient-reported outcome which was obtained at screening, weeks 4, 8 and 12, every 12 weeks thereafter and at the end of treatment visit in countries where appropriate translations were available. EQ-5D assessments were also administered at the time of disease progression, grade 3 or 4 toxicitiy or at the time of early withdrawal. EQ-5D is a 5-item validated assessment of patient utility, consisting of: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Where each item takes an integral value from 1 (“no problems”) to 3 (“extreme problems”). The scores on these 5 items are summarised to create a single summary score. Since the questions may be answered differently in different countries/regions, for example due to different societal perspectives or customs, different weightings or tarrifs may be applied to the summary score. Study 200 EQ-5D data presented in this submission uses the UK summary score, such that the evidence is most relevant to the patient population covered in this submission i.e.patients in England and Wales. In addition, the EQ-5D has a general health visual anaolog scale (VAS): scores range from 0 to 100, where 0 is equivalent to the worst imaginable health state and 100 is equivalent to the best imaginable health state.
Adverse events (AEs)	Incidence and severity of AEs were reported at each study visit through 30 days after the last dose of bosutinib. Graded by use of the National Cancer Institute Common Terminology for Adverse Events Version 3.0[127]
Grade 3/4 adverse event	Unique clinical descriptions dictate the grading of each AE, but generally grade 3/4 AEs are considered severe (grade 3) or life-threatening or disabling (grade 4)

(Source: Pfizer submission, Appendix 14, p344)

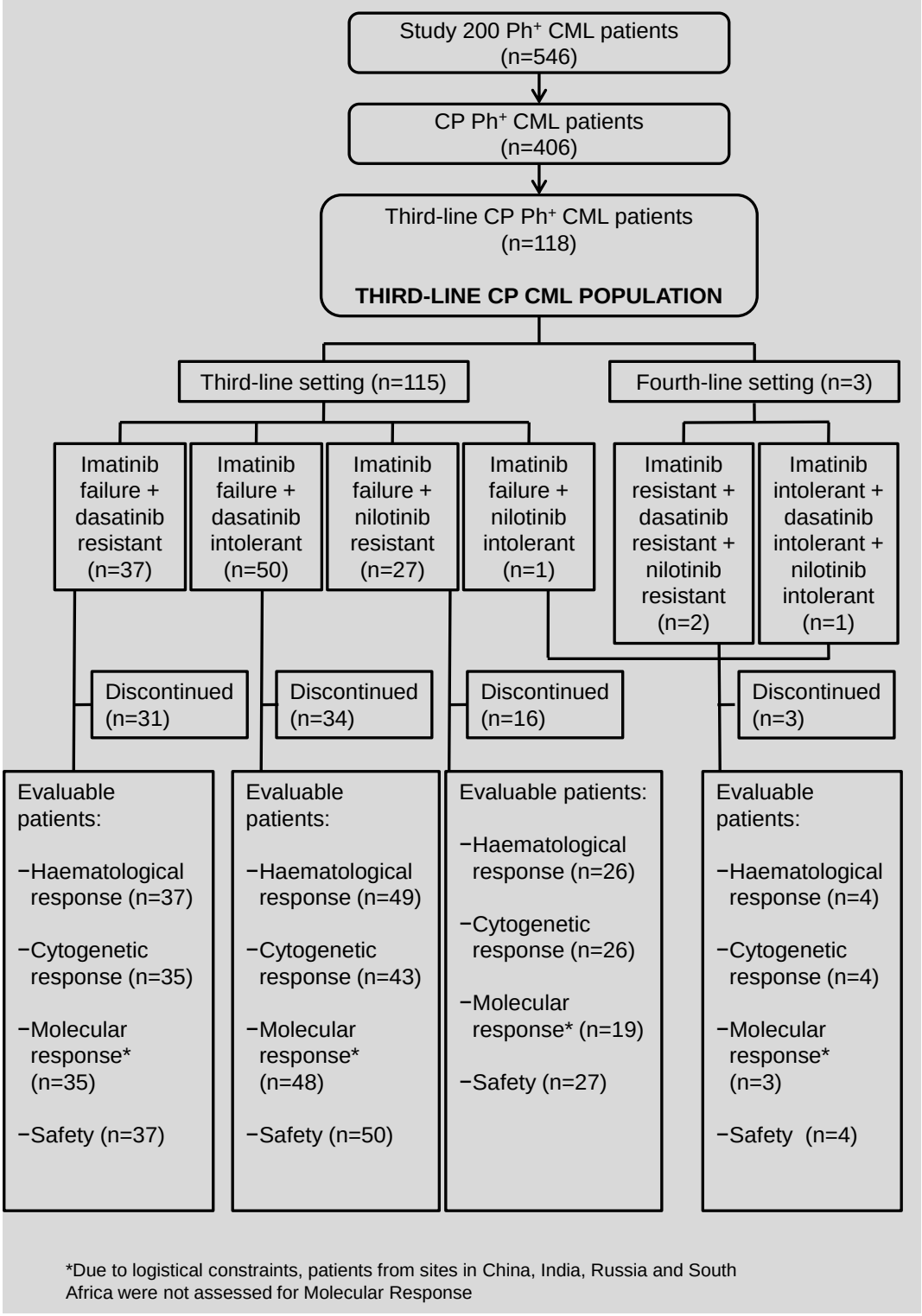
9.6 Appendix F: Participant flow diagrams

9.6.1 Participant flow for the second-line CP-CML population



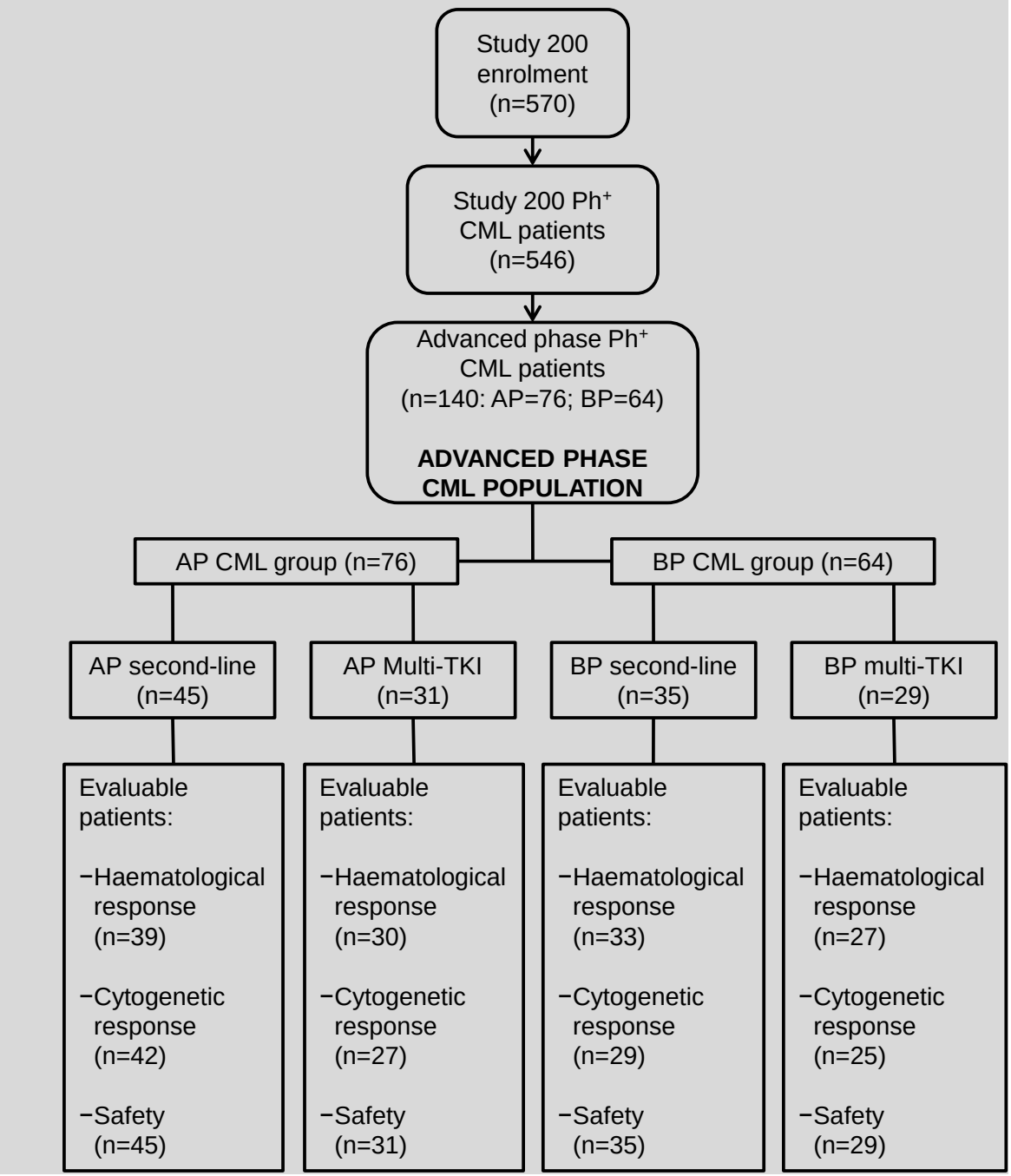
(Source: Pfizer submission, Figure B57, p352)

9.6.2 Participant flow for the third-line CP-CML population



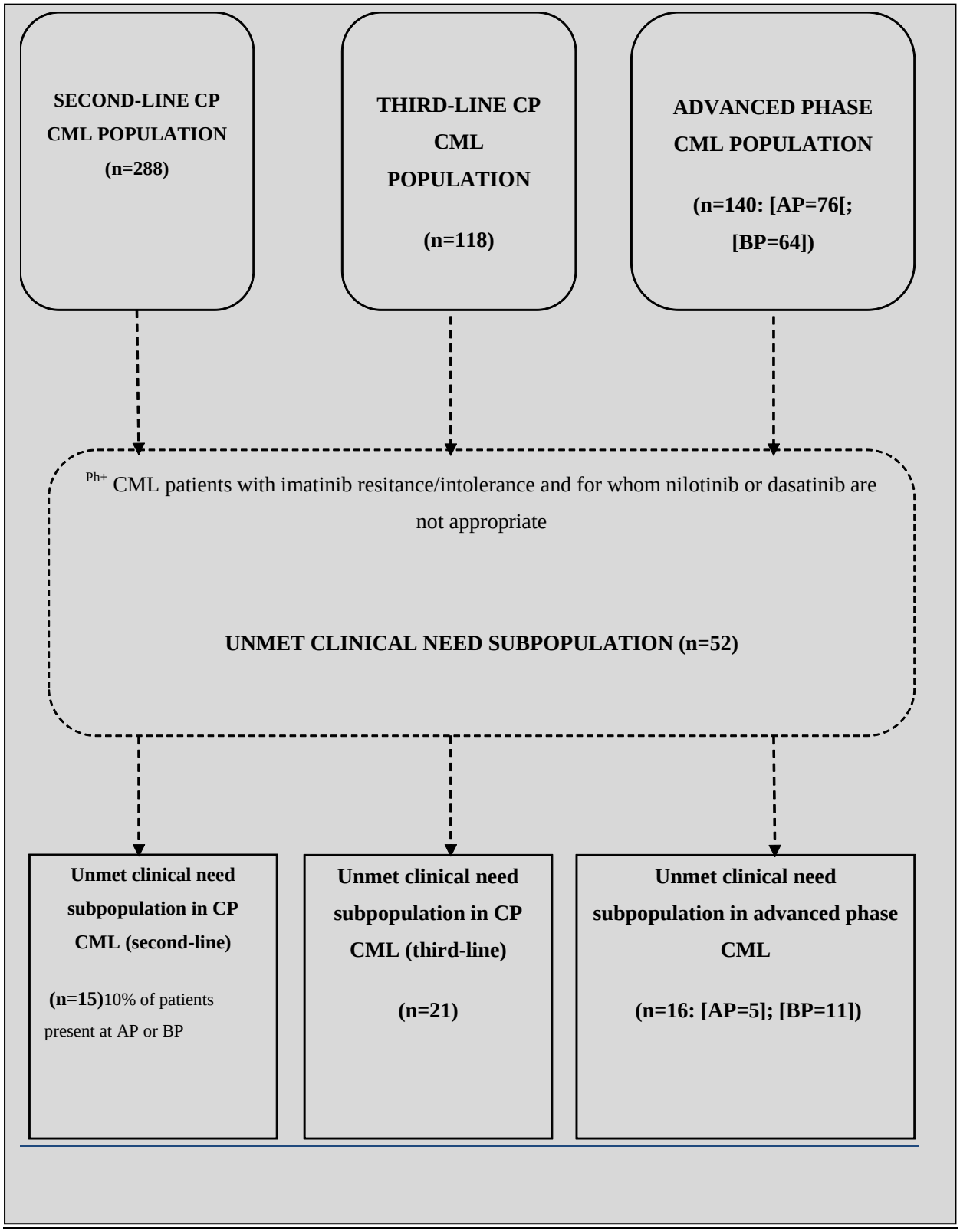
(Source: Pfizer submission, Figure B3, p60)

9.6.3 Participant flow for the advanced phases CML population



(Source: Pfizer submission, Figure B4, p61)

9.6.4 Participant flow for the unmet clinical need subpopulation



(Source: Pfizer submission, Figure B59, p362)

9.7 Appendix G: Unmet clinical need population eligibility; summary of mutations and medical conditions defining inappropriateness of nilotinib and dasatinib

	Nilotinib	**Dasatinib**
Mutation	Y253 E255 F359	F317 E255
Medical history or evidence of prior TKI intolerance	Coronary artery occlusion, coronary arterial stent insertion, arterial occlusive disease, coronary artery disease, arteriosclerosis, glucose tolerance impairment, coronary angioplasty, coronary artery bypass, hyperglycaemia, hypertriglyceridaemia, diabetes, pancreatitis	Pleural effusion, blood pressure increase, interstitial lung disease, chronic obstructive pulmonary disease, bronchitis chronic, pulmonary hypertension, pulmonary fibrosis, pulmonary oedema, emphysema, hypertension (Grade 3 or 4), cardiomyopathy, cardiac failure, ventricular failure, ventricular dysfunction, myocardial infarction., myocardial ischaemia, respiratory disorder

(Source: Pfizer submission, Table B109, p360)

9.8 Appendix H: Proportion of patients with T315I mutation at baseline

	N of patients assessed for mutations at baseline	**N of patients assessed with a T315I mutation at baseline**
CP2L	212/288 (74.6%)	9/212 (4.2%)
CP3L	83/118 (70.3%)	7/83 (8.4%)
Advanced phase	117/140 (83.6%)	15/117 (12.8%)

(Source: Pfizer response to clarification question A2)

9.9 Appendix I: Sample size calculations for Study 200

9.9.1 Sample size calculations for the second-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients resistant to imatinib and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a MCyR rate at 24 Weeks of 0.33 is of interest. Taking the interesting and uninteresting rates for MCyR rate at 24 Weeks to be p1=0.33 and p0=0.23, respectively, it was desired to test the null hypothesis of H0: p≤0.23 against the 1-sided alternative H1: p>0.23 Power calculation The hypothesis test was performed with a type I error rate of 0.05 and 80% power at p=0.33 Sample size calculation The design of the primary cohort incorporated a 4-stage group sequential design , requiring a maximum sample size of 167 evaluable patients, with a sample size of 82 expected under the null hypothesis, and a sample size of 115 expected when the true MCyR rate was p=0.33. Statistical analyses The test statistic, standardized using the empirical variance estimate, was assessed for efficacy at an overall 1-sided significance level of 0.05, and assessed for futility at an overall 1-sided significance level of 0.20. The decisions concerning stopping for efficacy or futility were based on the error spending functions at the actual number of enrolled patients at the interim analyses.
CP CML patients intolerant to imatinb and unexposed to other TKIs	Primary hypothesis Published dasatinib data have suggested that a 73% MCyR rate at 24 Weeks was of interest. Taking the interesting and uninteresting MCyR rates at 24 Weeks to be p1=0.73 and p0=0.56, respectively, the null hypothesis H0: p ≤p0 was tested against the alternative H1: p≥p1. Sample size calculation The optimum Simon 2-stage design for alpha=0.05, beta=0.20, required a maximum of n=55 patients with 16 in the first stage. If the response rate was no greater than 9/16=0.56 at stage 1, consideration was given to early termination. The expected sample size under the null was 31.5 and probability of early termination under the null was 0.60.

(Source: Pfizer submission, Table B102, p351)

9.9.2 Sample size calculations for the third-line CP CML population

TKI exposure history	Statistical analysis details
CP CML patients previously treated with imatinib and who were resistant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.30 and p0=0.10 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=29 patients with 10 in the first stage. If the response rate was no greater than 1/10 at stage 1, consideration was given to early termination. The expected sample size under the null was 15.0 and probability of early termination under the null was 0.74.
CP CML patients previously treated with imatinib and who were intolerant to dasatinib	Primary hypothesis Interesting and uninteresting 24-Week MCyR rates were taken to be p1=0.37 and p0=0.17 based on clinical estimates, given there was no approved therapy in this indication. Sample size calculation The optimum Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=35 patients with 12 in the first stage. If the response rate was no greater than 2/12=0.17 at stage 1, consideration was given to early termination. The expected sample size under the null was 19.7 and probability of early termination under the null was 0.67.
CP CML patients previously treated with imatinib who were resistant to nilotinib	Sample size calculation This cohort was sized using the same statistical considerations as in the dasatinib-resistant cohort, yielding a sample size of n=29 and an identical Simon 2-stage design. . Patients previously treated with imatinib who were either nilotinib intolerant or treated with both nilotinib and dasatinib were described. No testing was planned for this group.

(Source: Pfizer submission, Table B10, p58)

9.9.3 Sample size calculations for the advanced phase CML population

TKI exposure history	Statistical analysis details
Imatinib-resistant/intolerant CML patients in AP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.61 and p0=0.43 based on published nilotinib and dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=49 patients with 42 in the first stage. If the response rate was no greater than 22/42 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 42.6 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant patients in BP, unexposed to other TKIs	Primary hypothesis Interesting and uninteresting 48 Week OHR rates were taken to be p1=0.48 and p0=0.30 based on published dasatinib data. Sample size calculation The minimax Simon 2-stage for alpha=0.05, beta=0.20, required a maximum of n=45 patients with 41 in the first stage. If the response rate was no greater than 16/41 at stage 1, consideration was given to early termination. The expected sample size under the null hypothesis was 41.3 and probability of early termination under the null hypothesis was 0.92.
Imatinib-resistant/intolerant CML patients, exposed to other TKIs	Both AP and BP patient populations fitting this description were analysed descriptively.

(Source: Pfizer submission, Table B11, p59)

9.10 Appendix J: Number of planned and enrolled patients

Subject Group Study Cohort	Planned	Expected Evaluable	Enrolled
Chronic Phase Second-line (Prior Imatinib)			
Imatinib Resistant	186	167	200
Imatinib Intolerant	61	55	88
Chronic Phase Third line (Prior Imatinib + ≥1 Additional TKI)			
IM + NI-Intolerant or IM + D and NI	Descriptively analysed – no testing planned		4
IM + D-Resistant	32	29	37
IM + D-Intolerant	39	35	50
IM + NI-Resistant	32	29	27
Advanced Leukaemia (≥1 Prior TKI)[a]			
AP CML – 2nd Line	55	49	45
BP CML – 2nd Line	50	45	35
AP/BP – Multi-TKI	Descriptively analysed – no testing planned		60

Abbreviations: AP=accelerated phase, BP=blast phase, CML=chronic myelogenous leukaemia, D=dasatinib, IM=imatinib, NA=not applicable, NI=nilotinib, Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukaemia, TKI=tyrosine kinase inhibitor

All subjects in the advanced leukaemia group received imatinib; some subjects also received at least 1 additional TKI. Date of Snapshot: 28MAR11

(Source: Pfizer response to clarification questions A4)

9.11 Appendix K: Baseline characteristics for Study 200

9.11.1 Second-line CP CML

Characteristic	Imatinib-resistant (n=200)	Imatinib-intolerant (n=88)	Total
Age, y			
Median	51.0	54.5	53.0
Range	18-86	23-91	18-91
Sex, n (%)			
Female	84 (42%)	50 (57%)	134 (47%)
Male	116 (58%)	38 (43%)	154 (53%)
Haematological analysis, 10^9/L			
White blood cell count			
Median	6.7	5.9	6.5
Range	2.1-151	2.1-160.7	2.1-151
Platelet count			
Median	261.5	202.5	237.5
Range	47-2436	48-2251	47-2436
Duration of disease, y			
Median	4.0	2.8	3.6
Range	0.1-15.1	0.1-13.6	0.1-15.1
Treatment history			
No. of previous therapies*, n (%)			
1	131 (66%)	65 (74%)	196 (68%)
2	69 (35%)	23 (26%)	92 (32%)
Previous IFN	69 (35%)	23 (26%)	92 (32%)
Previous SCT	6 (3%)	2 (2%)	8 (3%)
Features of imatinib treatment			
Duration of previous imatinib treatment, y			
Median	2.6	1.5	2.2
Range	0.4-8.8	<0.1-8.3	<0.1-8.8
Previous CHR with imatinib, n (%)	164 (82%)	55 (63%)	219 (76%)
Reason for stopping imatinib, n (%)			
Adverse event (intolerance)†	1 (1%)	86 (98%)	87 (33%)
Disease progression	163 (92%)	1 (1%)	164 (62%)
Regimen completed	7 (4%)	0 (0%)	8 (3%)
Other	7 (4%)	1 (1%)	7 (3%)
Missing‡	22	0	22
1 or more Bcr-Abl mutations detected§	57/83 (69%)	8/32 (25%)	65/115 (57%)

*Includes previous tyrosine kinase inhibitor therapies. Percentages may not total 100% because of rounding
†Patients simultaneously meeting the protocol definitions for imatinib resistance and imatinib intolerance are categorized as having imatinib resistance
‡The reason for stopping imatinib was not reported
§Total of 83 imatinib-resistant and 32 imatinib-intolerant patients assessed for mutation status at baseline
(Source: Pfizer submission, Table B101, p350)

9.11.2 Third-line CP CML

Characteristic	IM + DAS resistant (n=37)	IM + DAS intolerant (n=50)	IM + NI resistant (n=27)	IM + DAS ± NI (n=4)*	Total (n=118)
Median age, y (range)	54.0 (23-69)	58.0 (25-79)	52.0 (20-73)	54.5 (31-62)	56.0 (20-79)
Sex, n (%)					
Female	23 (62)	27 (54)	13 (48)	2 (50)	65 (55)
Male	14 (38)	23 (46)	14 (52)	2 (50)	53 (45)
Race, n (%)					
White	27 (73)	38 (76)	17 (63)	3 (75)	85 (72)
Asian	4 (11)	9 (18)	3 (11)	0	16 (14)
Other	6 (16)	3 (6)	7 (26)	1 (25)	17 (14)
Median duration of CML disease, y (range)	7.5 (1.2-17.6)	5.6 (0.6-18.3)	5.9 (1.2-16.3)	11.7 (2.2-11.9)	6.7 (0.6-18.3)
ECOG Performance Status, n (%)†					
0	28 (76)	31 (62)	25 (93)	2 (50)	86 (74)
1	9 (24)	18 (36)	2 (7)	2 (50)	31 (26)
Median duration of prior therapy, (range)					
Imatinib, years	2.6 (0.02-6.4)	3.3 (0.1-6.6)	2.5 (0.7-5.9)	3.0 (1.4-6.4)	2.7 (0.02-6.6)
Dasatinib, months	18.3 (1.7-47.9)	17.3 (1.1-35.7)	0	4.1 (1.3-6.9)	17.7 (1.1-47.9)
Nilotinib, months	0	0	12.7 (1.7-38.9)	5.4 (0.8-6.1)	9.2 (0.8-38.9)
Additional prior therapies, n (%)					
Interferon	25 (68)	24 (48)	10 (37)	2 (50)	61 (52)
SCT	2 (5)	5 (10)	0	2 (50)	9 (8)

IM = Imatinib; DAS = Dasatinib; NI = Nilotinib; ECOG = Eastern Cooperative Oncology Group
*Includes 3 patients who previously received all 3 inhibitors (2 DAS + NI resistant; 1 DAS + NI intolerant) and 1 patient with NI intolerance
†ECOG Performance Status at baseline was missing for 1 patient with DAS intolerance
(Source: Pfizer submission, Table B7, p54)

9.11.3 Advanced phase CML

Characteristic	**AP IM only (n=45)**	**AP Multi TKI (n=31)**	**AP Total (n=76)**	**BP IM only (n=35)**	**BP Multi TKI (n=29)**	**BP Total (n=64)**
Age, y						
Median	47.00	56.00	50. 50	37.00	53.00	48.50
Range	18.00-73.00	21.00-83.00	18.00-83.00	19.00-75.00	22.00-82.00	19.00-82.00
Sex, n (%)						
Female	21 (47)	13 (42)	34 (45)	11 (31)	12 (41)	23 (36)
Male	24 (53)	18 (58)	42 (55)	24 (69)	17 (59)	41 (64)
Race, n (%)						
Asian	15 (33)	5 (16)	20 (26)	12 (34)	2 (7)	14 (22)
Black	3 (7)	2 (6)	5 (7)	5 (14)	6 (21)	11 (17)

Characteristic	AP IM only (n=45)	AP Multi TKI (n=31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Other*	3 (7)	2 (6)	5 (7)	0	1 (3)	1 (2)
White	24 (53)	22 (71)	46 (61)	18 (51)	20 (69)	38 (59)
Duration of CML						
N	41	29	70	34	29	63
Median	3.85	8.25	5.06	1.75	5.75	3.08
Range	1.11-22.06	1.5 - 19.22	1.11-22.06	0.35 - 5.56	1.05 - 14.46	0.35-14.46
ECOG Performance Status, n (%)						
0	26 (58)	15 (48)	41 (54)	16 (46)	6 (21)	22 (34)
1	18 (40)	15 (48)	33 (43)	10 (29)	18 (62)	28 (44)
2	1 (2)	1 (3)	2 (3)	9 (26)	5 (17)	14 (22)
Number of prior therapies						
1	29 (64)	0	29 (38)	30 (86)	0	30 (47)
2	16 (36)	6 (19)	22 (29)	5 (14)	11 (38)	16 (25)
3	0	19 (61)	19 (25)	0	16 (55)	16 (25)
4	0	6 (19)	6 (8)	0	2 (7)	2 (3)
Prior interferon therapy						
No	29 (64)	9 (29)	38 (50)	30 (86)	15 (52)	45 (70)
Yes	16 (36)	22 (71)	38 (50)	5 (14)	14 (48)	19 (30)
Prior imatinib†						
Yes	45 (100)	31 (100)	76 (100)	35 (100)	29 (100)	64 (100)
Prior dasatinib†						
No	45 (100)	6 (19)	51 (67)	35 (100)	6 (21)	41 (64)
Yes	0	25 (81)	25 (33)	0	23 (79)	23 (36)
Prior nilotinib†						
No	45 (100)	16 (52)	61 (80)	35 (100)	17 (59)	52 (81)
Yes	0	15 (48)	15 (20)	0	12 (41)	12 (19)
Prior stem cell transplant						
No	41 (91)	28 (90)	69 (91)	34 (97)	26 (90)	60 (94)
Yes	4 (9)	3 (10)	7 (9)	1 (3)	3 (10)	4 (6)
Reasons for stopping imatinib						
Adverse event (intolerance)	3 (7)	6 (19)	9 (12)	5 (14)	7 (24)	12 (19)
Disease progression/ Inadequate response	41 (91)	24 (77)	65 (86)	30 (86)	22 (76)	52 (81)
Other‡	0	1 (3)	1 (1)	0	0	0
Regimen completed	1 (2)	0	1 (1)	0	0	0

IM only= only prior TKI exposure is to imatinib; Multi TKI = Multiple TKI exposure
*Race Other: Afghan (1), Hispanic (7), Turkish (1)
†If a patient received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the patient is only counted once for the respective treatment
‡Other reason for discontinuing imatinib: Unknown
(Source: Adapted from Pfizer submission, Table B8, p55 and Pfizer response to clarification questions A3)

9.12 Appendix L: Response by baseline mutation status, Study 200

9.12.1 Response by baseline mutation status in the second-line CP evaluable population (15 May 2012 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)	
		CHR	MCyR
No mutation	132	119/132 (90)	70/120 (58)
≥1 mutation	78	65/77 (84)	44/77 (57)
≥2 mutations	11	8/11 (73)	3/10 (30)
Most common individual mutations[b]			
T315I[c,d]	9	2/9 (22)	2/9 (22)
M351T	9	9/9 (100)	8/9 (89)
F359V[d]	9	8/9 (89)	4/9 (44)
G250E	6	5/6 (83)	3/5 (60)
M244V	6	6/6 (100)	3/6 (50)
L248V	5	5/5 (100)	3/5 (60)
F317L[c]	4	4/4 (100)	3/4 (75)
E255K[d]	3	0/2	2/3 (67)
Y253H[d]	2	2/2 (100)	2/2 (100)
E255V[d]	2	2/2 (100)	1/2 (50)
F311I	2	2/2 (100)	1/2 (50)
F311L	2	2/2 (100)	2/2 (100)
E355G	2	2/2 (100)	1/2 (50)
H396P	2	2/2 (100)	2/2 (100)
H396R	2	1/2 (50)	0/2

[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint
[b] Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
(Source: Pfizer submission, Table B105, p356)

9.12.2 Response by baseline mutation status in the third-line CP CML population

	17 May 2011 snapshot			15 February 2012 snapshot		
Bcr-Abl mutation status	**n**	**Cumulative response, n/n evaluable[a] (%)**		**n**	**Cumulative response, n/n evaluable[a] (%)**	
		CHR	**MCyR**		**CHR**	**MCyR**
No mutation	44	34/44 (77)	15/43 (35)	46	35/45 (78)	18/45 (40)
≥1 mutation	39	26/39 (67)	11/35 (31)	40	26/39 (67)	14/37 (38)
≥2 mutations	9	3/9 (33)	2/9 (22)	9	3/9 (33)	2/9 (22)
Most common individual mutations[b]						
F317L[c]	8	4/8 (50)	1/7 (14)	8	4/8 (50)	1/7 (14)
T315I[c,d]	7	2/7 (29)	0/6	7	2/7 (29)	1/7 (14)[e]
G250E	6	3/6 (50)	0/5	6	3/6 (50)	0/5
Y253H[d]	6	5/6 (83)	4/6 (67)	6	5/6 (83)	5/6 (83)
M244V	3	3/3 (100)	2/3 (67)	3	3/3 (100)	2/3 (67)
F359V[d]	2	0/2	1/2 (50)	3	1/3 (33)	2/3 (67)
V299L[c]	2	1/2 (50)	0/2	2	1/2 (50)	0/2
F359C[d]	2	2/2 (100)	1/2 (50)	2	1/1 (100)	1/2 (50)
F359I	2	2/2 (100)	2/2 (100)	2	2/2 (100)	2/2 (100)

[a]Evaluable patient had received ≥1 bosutinib dose and had a valid baseline disease assessment for the corresponding endpoint
[b]Includes all mutations reported for ≥2 patients assessed at baseline
[c]Mutations that confer clinical resistance to dasatinib
[d]Mutations that confer clinical resistance to nilotinib
[e]The patient with the T315I mutation at baseline who responded with a MCyR had a PCyR at baseline that was maintained at Week 12 allowing the patient to be counted as a responder. The patient discontinued treatment due to an AE around Week 24 and did not have any further cytogenetic assessments

(Source: Pfizer submission, Table B19, p71)

9.12.3 Response by baseline mutation status in the advanced phase CML population (17 May 2011 snapshot)

Bcr-Abl mutation status	n	Cumulative response, n/n evaluable[a] (%)		
		CHR	OHR	MCyR
No mutation	52	19/49 (38.8)	23/49 (46.9)	16/43 (37.2)
≥1 mutation	65	10/59 (16.9)	21/59 (35.6)	13/55 (23.6)
Most common individual mutations[b]				
T315I[c,d]	15	0/13	1/13 (7.69)	1/13 (7.69)
F317L[c]	9	0/9	2/9 (22.2)	0/6
G250E	7	4/6 (66.7)	4/6 (66.7)	2/7 (28.6)
Y253H[d]	7	1/7 (14.3)	2/7 (28.6)	2/7 (28.6)
E255V[d]	5	0/4	0/4	1/3 (33.3)
M351T	5	2/5 (40.0)	3/5 (60.0)	1/4 (25.0)
E255K[d]	4	0/4	1/4 (25.0)	1/3 (33.3)
M244V	3	1/2 (50.0)	2/2 (100)	1/2 (50.0)
F359I	2	0/2	1/2 (50.0)	1/2 (50.0)
F359V[d]	2	0/2	1/2 (50.0)	0/2
F486S	2	1/2 (50.0)	1/2 (50.0)	2/2 (100)

[a]The evaluable population includes patients who had a valid baseline disease assessment
[b]Includes all mutations reported for ≥2 patients assessed at baseline
(Source: Pfizer submission, Table B26, p77)

9.13 Appendix M: Cytogenetic response rates, Study 200

9.13.1 Cytogenetic response rates for the second-line CP CML population

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]
Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.
(Source: Pfizer response to clarification questions A7)

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
(Source: Pfizer response to clarification questions A7)

9.13.2 Cytogenetic response rates for the third-line CP CML population

	12 months minimum follow-up 28 Mar 2011 Snapshot			24 months minimum follow up-15 February 2012 Snapshot		
Cohort	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**	**n[a]**	**MCyR N (%) (95% CI)**	**CCyR N (%) (95% CI)**
Post-hoc analysis: patients who attained a response or maintained a response present at BL[c]						
IM + D resistant	35	12 (34.3) (19.1, 52.2)	6 (17.1) (6.6, 33.7)	36	12 (33.3) (18.6, 51.0)	7 (19.4) (8.2, 36.0)
IM + D intolerant	43	19 (44.2) (29.1, 60.1)	18 (41.9) (27.0, 57.9)	44	21 (47.7) (32.5, 63.3)	19 (43.2) (28.4, 59.0)
IM + NI resistant	26	9 (34.6) (17.2, 55.7)	7 (26.9) (11.6, 47.8)	26	10 (38.5) (20.2, 59.4)	7 (26.9) (11.6, 47.8)
IM + (NI + D) or IM + NI intolerant*	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)	4	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)
Total	**108**	**42 (38.9) (29.7, 48.8)**	**33 (30.6) (22.1, 40.2)**	**110[d]**	**45 (40.9) (31.6, 50.7)**	**35 (31.8) (23.3, 41.4)**

Abbreviations: CI=confidence interval; CCyR= complete cytogenetic response; D=dasatinib; IM=imatinib; MCyR=major cytogenetic response; n=number of patients; NI=nilotinib; BL = baseline
*Includes 3 patients who previously received all 3 inhibitors and 1 patient with NI intolerance
[a]Evaluable patients had a baseline disease assessment
[c]Note: Percentages are based on number of patients in each analysis. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with MCYR at baseline who were allowed to maintain best response post-baseline.
[d]Includes Patients 200-060-001446 and 200-075-001612. Patient 200-075-001612 had a valid baseline cytogenetic assessment in 15FEB2012 but not 28MAR2011

(Source: Pfizer submission, adapted Table B13, p54)

9.13.3 Cytogenetic response rates for the advanced phase population

Cytogenetic response rates for the advanced phase CML population (28 Mar 2011 snapshot)

Cytogenetic response, n (%)	Accelerated phase			Blast phase		
	Second-line (n=42)	Multi-TKI (n=27)	Total (n=69)	Second-line (n=29)	Multi-TKI (n=25)	Total (n=54)
MCyR	20 (47.6)	4 (14.8)	24 (34.8)	13 (44.8)	3 (12.0)	16 (29.6)
CCyR	14 (33.3)	3 (11.1)	17 (24.6)	9 (31.0)	2 (8.0)	11 (20.4)
PCyR	6 (14.3)	1 (3.7)	7 (10.1)	4 (13.8)	1 (4.0)	5 (9.3)

(Source: Pfizer submission, Table B23, p75)

9.14 Appendix N: Haematological response rates, Study 200

9.14.1 CHR rates for the second-line CP CML population

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 28 March 2011 snapshot

Response, n (%) [95% CI]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Median follow-up (range), mo	31.79 (0.61 to 66.0)	30.54 (0.61-66.0)	35.05 (0.68-58.04)
Cytogenetic Response			
Evaluable[a]	266	186	80
MCyR	142 (53.4) [47.2,59.5]	103 (55.4) [47.9,62.7]	39 (48.8) [37.4,60.2]
CCyR	114 (42.9) [36.8, 49.0]	80 (43.0) [35.8,50.5]	34 (42.5) [31.5,54.1]
Haematological Response			
Evaluable[a]	287	199	88
CHR	244 (85.0) [80.4, 88.9]	170 (85.4) [79.8,90.0]	74 (84.1) [74.8,91.0]
Molecular Response			
Evaluable[b]	200	132	68
MMR	69 (34.5)[a] [27.9,41.5]	45 (34.1) [26.1,42.8]	24 (35.3) [24.1,47.8]
CMR	55 (27.5)[a] [21.4,34.2]	33 (25.0) [17.9,33.3]	22 (32.4) [21.5,44.8]

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
[b]From the total 288 subjects, this analysis excluded 88 subjects from China, India, Russia, and South Africa, where molecular assessment was not performed due to logistical constraints.
(Source: Pfizer response to clarification questions A7)

Response rates for second line CP CML total population, imatinib resistant and intolerant populations, 15 May 2012 snapshot

Response, n (%) [95% CI]	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Median follow-up (range), mo	41.7 (0.6-78.5)	41.8 (0.6-78.5)	39.5 (0.7-73.9
Cytogenetic Response			
Evaluable[a]	264	182	82
MCyR	155 (59) [53,65]	106 (58) [51,66]	49 (60) [48,70]
CCyR	130 (49) [43,55]	88 (48) [41,56]	42 (51) [40,62]
Haematological Response			
Evaluable[a]	285	194	91
CHR	244 (86) [81,90]	167 (86) [80,91]	77 (85) [76,91]
Molecular Response			
Evaluable[a]			
MMR	N/A	N/A	N/A
CMR	N/A	N/A	N/A

CI = confidence interval; IM-R = imatinib resistant; IM-I = imatinib intolerant
[a]Evaluable patients had received ≥1 bosutinib dose and had a valid baseline assessment for the corresponding endpoint.
(Source: Pfizer response to clarification questions A7)

9.14.2 CHR rates for the third-line CP CML population

Cohort	28 Mar 2011 Snapshot n	28 Mar 2011 Snapshot CHR N (%) (95% CI)	15 February 2012 Snapshot n	15 February 2012 Snapshot CHR N (%) (95% CI)
CHR including subjects with CHR at baseline[a,b]				
IM + (NI + D) or IM + NI Intolerant	4	3 (75.0) (19.4, 99.4)	4	3 (75.0) (19.4, 99.4)
IM + D Resistant	37	23 (62.2) (44.8, 77.5)	37	23 (62.2) (44.8, 77.5)
IM + D Intolerant	49	39 (79.6) (65.7, 89.8)	49	39 (79.6) (65.7, 89.8)
IM + NI Resistant	26	20 (76.9) (56.4, 91.0)	25	19 (76.0) (54.9, 90.6)
Total	**116**	**85 (73.3) (64.3, 81.1)**	**115[c]**	**84 (73.0) (64.0, 80.9)**

Abbreviations: CHR=major hematologic response; CI=confidence interval; D=dasatinib; IM=imatinib; n=number of patients; NI=nilotinib.
[a]Analysis includes patients who have a valid baseline hematologic measurement.
[b]Subjects with CHR at baseline are eligible for response post-baseline. In order to be considered a responder patient should have better post-baseline assessment than the baseline except for patients with CHR at baseline who were allowed to maintain best response post-baseline.
[c]Analysis includes Patient 200-060-001446 but excludes Patients 200-093-002244 and 200-093-002246 due to missing baseline hematologic assessment in 15 February 2012

(Source: Pfizer submission, Table B14, p65)

9.14.3 CHR rates for the advanced phase CML population (28 Mar 2011 snapshot)

Haematological response, n (%) [95% CI]	Accelerated phase			Blast phase		
	Second-line (n=39)	Multi-TKI (n=30)	Total (n=69)	Second-line (n=33)	Multi-TKI (n=27)	Total (n=60)
OHR	25 (64.1) [47.2-78.8]	13 (43.3) [25.5-62.6]	38 (55.1) [42.6-67.1]	12 (36.4) [20.4-54.9]	5 (18.5) [6.3-38.1]	17 (28.3) [17.5-41.4]
MHR	21 (53.9) [37.2-69.9]	11 (36.7) [19.9-56.1]	32 (46.4) [34.3-58.8]	8 (24.2) [11.1-42.3]	3 (11.1) [2.4-29.2]	11 (18.3) [9.5-30.4]
CHR	16 (41.0) [25.6-57.9]	8 (26.7) [12.3-45.9]	24 (34.8) [23.7-47.2]	8 (24.2) [11.1-42.3]	1 (3.7) [0.1-19.0]	9 (15.0) [7.1-26.6]

(Source: Pfizer submission, Table B22, p75)

9.15 Appendix O: Overall survival, Study 200

9.15.1 OS second-line CP CML population

Kaplan-Meier Estimate of Overall Survival Chronic Phase Second-line All-treated Population, 28 March 2011 snapshot

OS, K-M estimates, % (95%CI)	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Year 1	96.8 (94.0,98.3)	95.9 (92.0,97.9)	98.8 (92.0,99.8)
Year 2	90.6 (86.5,93.5)	87.6 (82.1,91.5)	97.6 (90.9,99.4)

(Source: Pfizer response to clarification questions A7)

9.15.2 OS third-line CP CML population

K-M estimate of OS in third-line CP all-treated population

	28 March 2011 Snapshot			15 February 2012 Snapshot		
Cohort	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**	**n**	**K-M Estimate At Year 1 (95% CI)**	**K-M Estimate At Year 2 (95% CI)**
IM + (NI + D) or IM + NI Intolerant	4	N/A	N/A	4	N/A	N/A
IM + D Resistant	37	82.8 (65.6, 91.9)	75.2 (56.1, 86.9)	38	83.6 (67.0, 92.3)	77.4 (59.7, 88.0)
IM + D Intolerant	50	93.9 (82.3, 98.0)	85.4 (71,7, 92.8)	50	93.9 (82.3, 98.0)	85.4 (71.7, 92.8)
IM + NI Resistant	27	96.3 (76.5, 99.5)	91.7 (70.5, 97.9)	27	96.3 (76.5, 99.5)	92.4 (73.0, 98.1)
Total	**118**	**91.2 (84.3, 95.2)**	**82.9 (74.1, 88.9)**	**119**	**91.4 (84.6, 95.3)**	**84.0 (75.8, 89.6)**

Abbreviations: CI=confidence interval; D=dasatinib; IM=imatinib; K-M=Kaplan-Meier; N/A=not applicable; n=number of patients; NI=nilotinib.
a. The sample size is too small to suggest accurate estimates.
Note: One year is assumed to have 12 months.

(Source: Pfizer submission, Table B18, p70)

9.16 Appendix P: Efficacy and safety studies

Protocol number	Study design	Treatment groups	No of subjects	Demographics	Duration of treatment
Phase I/II Study 200 (NCT00261846; 3160A4-200).	Phase 1/2 open-label 2-part study in subjects with Ph+ leukemia. Part 1: dose escalation. Part 2: efficacy study at the selected Phase 2 dose. To determine safety, tolerability, MTD, PK, PD, and efficacy in subjects with chronic phase and advanced phase Ph+ leukaemias. To explore pharmacogenomic effects.	Parts 1 and 2: bosutinib 100-mg capsules or 100-mg tablets Part 1: Dose levels studied were 400, 500, and 600 mg Part 2: selected dose=500 mg.	Randomised: 571 Treated: 570 - 18 in Part 1 - 553 in Part 2		QD until disease progression, unacceptable toxicity, or withdrawal of consent.
		CP CML Second line	288	Sex: 135F/153M Mean Age (min/max): 52 (18/91) years Race, % W/B/A/O: 64/5/19/12	
		CP CML Third line	118	Sex: 65F/53M Mean Age (min/max): 54 (20/79) years Race, % W/B/A/O: 72/3/11/14	
		Advanced phase Ph+ leukaemias (AP and BP CML; Ph+ ALL)	164	Sex: 69F/95M Mean Age (min/max): 50 (18/84) years Race, % W/B/A/O: 63/11/13/13	
Phase III Study 3000 (NCT00574873; 3160A4-3000)	Phase 3 randomised open-label trial. 1/ to compare the efficacy (rate of CCyR at 1 year) of bosutinib vs imatinib in subjects with chronic phase (CP) CML. 2/ to compare MMR at 1 year, duration of CCyR, CHR, and MMR, time to transformation to	Bosutinib 500 mg QD (100-mg tablets).	Randomised: 250 Treated: 248	Sex: 101F/149M Mean Age (min/max): 47 (19/91) years Race, % W/B/A/O: 64.5/1.0/24.15/ 10.4	QD until completion of 8 years or early discontinuation due to treatment failure, unacceptable toxicity, death, or withdrawal of consent
		matinib 400 mg QD (100-mg and/or 400-mg tablets).	Randomised: 252 Treated: 251	Sex: 117F/135M Mean Age (min/max): 46 (18/89) years Race, % W/B/A/O: 65/1/23/11	

	AP and BP; to assess the population PK; to assess the comparative safety of bosutinib vs imatinib.		Total: Randomised: 502 Treated: 499	Sex: 218F/284M Mean Age (min/max): 47 (18/91) years Race, % W/B/A/O: 65/1/24/10	
Phase I/II in Japanese subjects (NCT00811070; 3160A4-2203)	Phase 1/2 open-label, continuous daily dose administration, 2-part study in subjects with Ph+ leukaemia. To determine safety, tolerability, MTD, PK, PD, and efficacy of bosutinib in Japanese subjects with Ph+ leukaemias.	Part 1: bosutinib capsules (100 mg). Part 2: bosutinib tablet (100 mg). Part 1: Starting dose of 400 mg (up to max. 600 mg). Part 2: MTD=500 mg. Continuous oral dose administration from Day 1 onwards.	Part 1 Treated: 17 Part 2 Treated: 35	Sex: 20F /32M Mean Age (min/max): 54 (78/20) years Race, %: A: 100	QD until disease progression, unacceptable toxicity, or withdrawal of consent.

Note: Table information taken from Bosulif EMA assessment report,[29] study status is as of 15 Nov 2010. A=Asian; AP=Accelerated phase; B = Black; BA =Bioavailability; BE = Bioequivalence; BID = Twice daily; BMI=Body mass index; BP = Blast phase; CCyR=Complete cytogenetic response; CHR=Complete haematologic response; CML=Chronic myelogenous leukaemia; CP=chronic phase; CYP3A=Cytochrome P450 isoenzyme 3A; DB = Double-blind; ER=estrogen receptor; erbB2=epidermal growth factor receptor 2; F = Female; FR=fast release; HRQoL=health-related quality of life; M = Male; MBC=metastatic breast cancer; MMR=Major molecular response; MTD = Maximum tolerated dose; No = Number; O=other; ORR= objective response rate; OS= overall survival; PC = Placebo-controlled; PD = Pharmacodynamic; PG = Parallel-group; PgR=progesterone receptor; Ph+ = Philadelphia chromosome positive; PK = Pharmacokinetic; PFS=progression-free survival; QD=once a day; SR=low-release; TR=target release; vs = versus; "+" = Positive (for receptors);"-" = Negative (for receptors); W = White.

9.17 Appendix Q: Treatment discontinuation and adverse effects, Study 200

9.17.1 Second-line CP CML population

Treatment discontinuation in the second-line CP CML population, 28 March 2011 snapshot

Reason for discontinued treatment[a]	Total population (N=288)	IM-R population (N=200)	IM-I population (N=88)
Discontinued treatment, n (%)	159 (55.2)	108 (54.0)	51 (58.0)
AE	64 (22.2)	33 (16.5)	31 (35.2)
Disease progression	41 (14.2)	35 (17.5)	6 (6.8)
Lack of efficacy	21 (7.3)	17 (8.5)	4 (4.5)
Patient request	18 (6.3)	11 (5.5)	7 (8.0)
Death	5 (1.7)	5 (2.5)	0
Investigator Request	1 (0.3)	1 (0.5)	0
Lost to follow-up	2 (0.7)	2 (1.0)	0
Other[b]	7 (2.4)	4 (2.0)	3 (3.4)

(a) Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
(b) Other: For imatinib resistant: no CCyR at Week 48 (1 subject), non-compliance (1 subject), T315I mutation (1 subject), no CCyR, investigator/subject request, loss of CCyR, and increasing transcript levels (1 subject); For imatinib intolerant: transplant (2 subjects), non-compliance (1 subject).

(Source: Pfizer response to clarification questions A7)

Treatment discontinuation in the second-line CP CML population, 15 May 2012 snapshot

Reason for discontinued treatment	Total population (N=286)	IM-R population (N=195)	IM-I population (N=91)
Discontinued treatment, n (%)	166 (58)	109 (56)	57 (63)
AE	66 (23)	30 (15)	36 (40)
Disease progression	41 (14)	35 (18)	6 (7)
Lack of efficacy	24 (8)	19 (10)	5 (6)
Patient request	17 (6)	11 (6)	6 (7)
Death	6 (2)	6 (3)	0
Investigator Request	2 (1)	2 (1)	0
Lost to follow-up	2 (1)	2 (1)	0
Other	8 (3)	4 (2)	4 (4)

(Source: Pfizer response to clarification questions A7)

Rates of most common (≥20%) adverse events in the second-line CP CML population

AE[a], n (%)	IM-R (n=195)		IM-I (n=91)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhoea	165 (85)	18 (9)	79 (87)	10 (11)
Nausea	83 (43)	1 (1)	47 (52)	3 (3)
Rash	63 (32)	16 (8)	40 (44)	11 (12)
Vomiting	70 (36)	3 (2)	35 (39)	8 (9)
Pyrexia	57 (29)	1 (1)	16 (18)	1 (1)
Fatigue	47 (24)	1 (1)	23 (25)	2 (2)
Abdominal pain	46 (24)	2 (1)	24 (26)	2 (2)
Cough	44 (23)	0	17 (19)	0
Elevated ALT	41(21)	14 (7)	22 (24)	8 (9)
Upper abdominal pain	40 (21)	1 (1)	17 (19)	0
Elevated AST	36 (19)	7 (4)	19 (21)	5 (6)
Headache	34 (17)	0	18 (20)	0

IM-R = imatinib-resistant; IM-I = imatinib-intolerant; ALT = alanine aminotransferase; AST = aspartate aminotransferase

(Source: Pfizer submission, Table B108, p 359)

9.17.2 Third-line CP CML population

Rates of TEAEs (all grades) occurring in ≥10% and of TEAEs (grade 3/4) occurring in ≥5% of the third-line CP CML population

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
Any adverse event	118 (100)	74 (62.7)
Blood and lymphatic system disorders	58 (49.2)	35 (29.7)
Thrombocytopaenia	41 (34.7)	30 (25.4)
Neutropaenia	21 (17.8)	17 (14.4)
Anaemia	18 (15.3)	6 (5.1)
Cardiac disorders	13 (11.0)	5 (4.2)
Eye disorders	14 (11.9)	-
Gastrointestinal disorders	111 (94.1)	16 (13.6)
Diarrhoea	98 (83.1)	10 (8.5)
Nausea	56 (47.5)	-
Vomiting	46 (39.0)	-
Abdominal pain	23 (19.5)	-
Abdominal pain upper	20 (16.9)	-
Constipation	15 (12.7)	-
General disorders and administration site conditions	59 (50.0)	-
Fatigue	28 (23.7)	-
Pyrexia	18 (15.3)	-
Oedema peripheral	12 (10.2)	-
Hepatobiliary disorders	-	5 (4.2)
Infections and infestations	46 (39.0)	4 (3.4)
Injury, poisoning and procedural complications	15 (12.7)	-
Investigations	45 (38.1)	11 (9.3)
Alanine aminotransferase increased	18 (15.3)	8 (6.8)
Lipase increased	-	4 (3.4)
Aspartate aminotransferase increased	-	3 (2.5)
Metabolism and nutrition disorders	38 (32.2)	4 (3.4)
Decreased appetite	14 (11.9)	-
Musculoskeletal and connective tissue	50 (42.4)	7 (5.9)

AE[a], n (%)	All grades (≥10% incidence) (n=118)[1]	Grade 3/4 (≥5% incidence) (n=118)[2]
disorders		
Arthralgia	17 (14.4)	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	-	4 (3.4)
Nervous system disorders	43 (36.4)	5 (4.2)
Headache	30 (25.4)	-
Dizziness	15 (12.7)	-
Psychiatric disorders	13 (11.0)	-
Respiratory, thoracic and mediastinal disorders	47 (39.8)	5 (4.2)
Cough	20 (16.9)	-
Pleural effusion	12 (10.2)	-
Skin and subcutaneous tissue disorders	59 (50.0)	8 (6.8)
Rash	34 (28.8)	5 (4.2)
Pruritus	17 (14.4)	-
Vascular disorders	12 (10.2)	-

[a]Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA)
[1]For 'All grades' adverse events, the incidence threshold of ≥10% was applied to the entire third-line CP CML population (n=118)
[1]For 'All grades' adverse events, only adverse events occurring in ≥10% of the entire third-line CP cohort (n=118)
[2] For grade 3/4 adverse events, adverse events occurring in ≥5% of any of the constituent subpopulations

(Source: Pfizer submission, Table B27, p 81)

Number (%) of Subjects Reporting ≥10% TEAEs (CP3L Safety Population) (15 Feb 2012 snapshot)

System Organ Class a Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	4 (100)	38 (100)	50 (100)	27 (100)	119 (100)
Blood and lymphatic system disorders	2 (50.0)	20 (52.6)	23 (46.0)	14 (51.9)	59 (49.6)
Thrombocytopenia	2 (50.0)	9 (23.7)	18 (36.0)	12 (44.4)	41 (34.5)
Neutropenia	1 (25.0)	8 (21.1)	7 (14.0)	7 (25.9)	23 (19.3)
Anaemia	1 (25.0)	7 (18.4)	7 (14.0)	6 (22.2)	21 (17.6)
Leukopenia	0	4 (10.5)	0	0	4 (3.4)
Cardiac disorders	0	4 (10.5)	10 (20.0)	2 (7.4)	16 (13.4)
Ear and labyrinth disorders	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Eye disorders	2 (50.0)	5 (13.2)	8 (16.0)	3 (11.1)	18 (15.1)
Eye oedema	1 (25.0)	0	0	0	1 (0.8)
Scleral haemorrhage	1 (25.0)	0	0	0	1 (0.8)
Gastrointestinal disorders	4 (100)	37 (97.4)	47 (94.0)	24 (88.9)	112 (94.1)
Diarrhoea	4 (100)	30 (78.9)	41 (82.0)	23 (85.2)	98 (82.4)
Nausea	2 (50.0)	21 (55.3)	22 (44.0)	13 (48.1)	58 (48.7)
Vomiting	0	15 (39.5)	24 (48.0)	8 (29.6)	47 (39.5)
Abdominal pain	0	6 (15.8)	12 (24.0)	6 (22.2)	24 (20.2)
Abdominal pain upper	0	8 (21.1)	8 (16.0)	4 (14.8)	20 (16.8)
Constipation	2 (50.0)	4 (10.5)	6 (12.0)	3 (11.1)	15 (12.6)
Dyspepsia	0	7 (18.4)	4 (8.0)	1 (3.7)	12 (10.1)
Flatulence	0	4 (10.5)	2 (4.0)	2 (7.4)	8 (6.7)
Toothache	1 (25.0)	2 (5.3)	2 (4.0)	0	5 (4.2)
Haemorrhoids	0	1 (2.6)	0	3 (11.1)	4 (3.4)
Gingival pain	1 (25.0)	2 (5.3)	0	0	3 (2.5)
Gastrointestinal sounds abnormal	1 (25.0)	0	1 (2.0)	0	2 (1.7)
General disorders and administration site conditions	3 (75.0)	19 (50.0)	28 (56.0)	10 (37.0)	60 (50.4)
Fatigue	3 (75.0)	8 (21.1)	14 (28.0)	3 (11.1)	28 (23.5)
Pyrexia	1 (25.0)	6 (15.8)	7 (14.0)	4 (14.8)	18 (15.1)
Oedema peripheral	1 (25.0)	1 (2.6)	5 (10.0)	4 (14.8)	11 (9.2)
Asthenia	1 (25.0)	1 (2.6)	2 (4.0)	4 (14.8)	8 (6.7)
Pain	2 (50.0)	1 (2.6)	2 (4.0)	1 (3.7)	6 (5.0)
Chest pain	1 (25.0)	0	3 (6.0)	0	4 (3.4)
Temperature intolerance	1 (25.0)	0	0	0	1 (0.8)
Hepatobiliary disorders	1 (25.0)	0	3 (6.0)	2 (7.4)	6 (5.0)
Hyperbilirubinaemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Immune system disorders	0	5 (13.2)	2 (4.0)	3 (11.1)	10 (8.4)
Infections and infestations	3 (75.0)	15 (39.5)	20 (40.0)	11 (40.7)	49 (41.2)
Nasopharyngitis	1 (25.0)	2 (5.3)	5 (10.0)	4 (14.8)	12 (10.1)

Influenza	0	4 (10.5)	3 (6.0)	3 (11.1)	10 (8.4)
Upper respiratory tract infection	2 (50.0)	2 (5.3)	5 (10.0)	0	9 (7.6)
Lower respiratory tract infection	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Respiratory tract infection viral	0	0	0	3 (11.1)	3 (2.5)
Pharyngitis	1 (25.0)	1 (2.6)	0	0	2 (1.7)
Wound infection	1 (25.0)	0	0	0	1 (0.8)
Injury, poisoning and procedural complications	1 (25.0)	6 (15.8)	8 (16.0)	0	15 (12.6)
Procedural pain	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Investigations	2 (50.0)	15 (39.5)	18 (36.0)	12 (44.4)	47 (39.5)
Alanine aminotransferase increased	1 (25.0)	7 (18.4)	5 (10.0)	6 (22.2)	19 (16.0)
Blood creatinine increased	0	4 (10.5)	4 (8.0)	3 (11.1)	11 (9.2)
Aspartate aminotransferase increased	0	2 (5.3)	3 (6.0)	5 (18.5)	10 (8.4)
Blood alkaline phosphatase increased	0	2 (5.3)	0	3 (11.1)	5 (4.2)
White blood cells urine positive	1 (25.0)	0	0	0	1 (0.8)
Metabolism and nutrition disorders	2 (50.0)	9 (23.7)	18 (36.0)	9 (33.3)	38 (31.9)
Decreased appetite	0	3 (7.9)	6 (12.0)	4 (14.8)	13 (10.9)
Hyperuricaemia	1 (25.0)	1 (2.6)	4 (8.0)	0	6 (5.0)
Hyperkalaemia	0	0	1 (2.0)	3 (11.1)	4 (3.4)
Hypophosphataemia	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal and connective tissue disorders	3 (75.0)	17 (44.7)	21 (42.0)	9 (33.3)	50 (42.0)
Arthralgia	0	5 (13.2)	9 (18.0)	4 (14.8)	18 (15.1)
Back pain	1 (25.0)	5 (13.2)	4 (8.0)	3 (11.1)	13 (10.9)
Bone pain	0	5 (13.2)	3 (6.0)	1 (3.7)	9 (7.6)
Pain in extremity	0	1 (2.6)	5 (10.0)	3 (11.1)	9 (7.6)
Musculoskeletal pain	0	4 (10.5)	1 (2.0)	1 (3.7)	6 (5.0)
Joint swelling	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Musculoskeletal stiffness	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Nervous system disorders	1 (25.0)	12 (31.6)	21 (42.0)	14 (51.9)	48 (40.3)
Headache	1 (25.0)	9 (23.7)	13 (26.0)	8 (29.6)	31 (26.1)
Dizziness	1 (25.0)	5 (13.2)	8 (16.0)	3 (11.1)	17 (14.3)
Dysgeusia	1 (25.0)	0	1 (2.0)	1 (3.7)	3 (2.5)
Paraesthesia	1 (25.0)	0	2 (4.0)	0	3 (2.5)
Neuropathy peripheral	1 (25.0)	0	1 (2.0)	0	2 (1.7)
Sensory disturbance	1 (25.0)	0	0	0	1 (0.8)
Psychiatric disorders	1 (25.0)	2 (5.3)	9 (18.0)	1 (3.7)	13 (10.9)
Insomnia	1 (25.0)	2 (5.3)	4 (8.0)	1 (3.7)	8 (6.7)
Renal and urinary disorders	0	5 (13.2)	4 (8.0)	5 (18.5)	14 (11.8)
Reproductive system and breast disorders	0	2 (5.3)	2 (4.0)	4 (14.8)	8 (6.7)
Respiratory, thoracic and mediastinal disorders	2 (50.0)	13 (34.2)	26 (52.0)	8 (29.6)	49 (41.2)
Cough	1 (25.0)	5 (13.2)	11 (22.0)	4 (14.8)	21 (17.6)
Pleural effusion	0	2 (5.3)	11 (22.0)	1 (3.7)	14 (11.8)
Dyspnoea	0	1 (2.6)	10 (20.0)	1 (3.7)	12 (10.1)
Oropharyngeal pain	1 (25.0)	3 (7.9)	3 (6.0)	2 (7.4)	9 (7.6)
Dyspnoea exertional	1 (25.0)	1 (2.6)	3 (6.0)	0	5 (4.2)

Productive cough	0	0	5 (10.0)	0	5 (4.2)
Skin and subcutaneous tissue disorders	1 (25.0)	22 (57.9)	28 (56.0)	12 (44.4)	63 (52.9)
Rash	1 (25.0)	9 (23.7)	19 (38.0)	3 (11.1)	32 (26.9)
Pruritus	0	10 (26.3)	7 (14.0)	2 (7.4)	19 (16.0)
Dry skin	0	1 (2.6)	2 (4.0)	3 (11.1)	6 (5.0)
Alopecia	1 (25.0)	1 (2.6)	2 (4.0)	0	4 (3.4)
Skin depigmentation	1 (25.0)	0	0	0	1 (0.8)
Vascular disorders	1 (25.0)	1 (2.6)	9 (18.0)	2 (7.4)	13 (10.9)
Hypertension	0	1 (2.6)	6 (12.0)	0	7 (5.9)
Flushing	1 (25.0)	0	0	0	1 (0.8)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

(Source: Pfizer response to clarification questions A5)

Number (%) of Subjects Reporting ≥5% TEAEs Grades 3 or 4 AEs Only (CP3L Safety Population) (Data snapshot 15 Feb 2012)

System Organ Class [a] Preferred Term	IM + NI +/or D n=4	IM + D Resistant n=38	IM + D Intolerant n=50	IM + NI Resistant n=27	Total n=119
Any Adverse Event	1 (25.0)	22 (57.9)	38 (76.0)	15 (55.6)	76 (63.9)
Blood and lymphatic system disorders	1 (25.0)	11 (28.9)	16 (32.0)	8 (29.6)	36 (30.3)
Thrombocytopenia	0	7 (18.4)	15 (30.0)	8 (29.6)	30 (25.2)
Neutropenia	1 (25.0)	5 (13.2)	7 (14.0)	4 (14.8)	17 (14.3)
Anaemia	0	2 (5.3)	4 (8.0)	1 (3.7)	7 (5.9)
Cardiac disorders	0	1 (2.6)	7 (14.0)	0	8 (6.7)
Gastrointestinal disorders	0	7 (18.4)	7 (14.0)	2 (7.4)	16 (13.4)
Diarrhoea	0	3 (7.9)	5 (10.0)	2 (7.4)	10 (8.4)
Hepatobiliary disorders	0	0	3 (6.0)	2 (7.4)	5 (4.2)
Infections and infestations	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Investigations	0	2 (5.3)	5 (10.0)	4 (14.8)	11 (9.2)
Alanine aminotransferase increased	0	1 (2.6)	3 (6.0)	4 (14.8)	8 (6.7)
Lipase increased	0	1 (2.6)	1 (2.0)	2 (7.4)	4 (3.4)
Aspartate aminotransferase increased	0	0	1 (2.0)	2 (7.4)	3 (2.5)
Metabolism and nutrition disorders	0	2 (5.3)	1 (2.0)	1 (3.7)	4 (3.4)
Musculoskeletal and connective tissue disorders	0	1 (2.6)	4 (8.0)	2 (7.4)	7 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (6.0)	1 (3.7)	4 (3.4)

Nervous system disorders	0	1 (2.6)	4 (8.0)	0	5 (4.2)
Headache	0	1 (2.6)	3 (6.0)	0	4 (3.4)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6)	5 (10.0)	0	6 (5.0)
Pleural effusion	0	0	3 (6.0)	0	3 (2.5)
Skin and subcutaneous tissue disorders	0	2 (5.3)	6 (12.0)	0	8 (6.7)
Rash	0	0	3 (6.0)	0	3 (2.5)

Date of Snapshot: 15FEB12
Abbreviations: IM- Imatinib, D- Dasatinib, NI- Nilotinib
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Descending Order of the Incidences is presented at the level of Preferred Term within each System Organ Class based on the
incidences under 'Total' column.
a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject
may report two or more different adverse events within the higher level category.

(Source: Pfizer response to clarification questions A5)

9.17.3 Advanced phase CML population

Summary of adverse events for the advanced phase CML population

Event	AP IM only (n=45)	AP Multi TKI (n-31)	AP Total (n=76)	BP IM only (n=35)	BP Multi TKI (n=29)	BP Total (n=64)
Any TEAE	45 (100)	31 (100)	76 (100)	34 (97.1)	29 (100)	63 (98.4)
TEAEs related to study drug	45 (100)	30 (96.8)	75 (98.7)	34 (97.1)	26 (89.7)	60 (93.8)
Grade 3 or 4 TEAEs	36 (80)	30 (96.8)	66 (86.8)	26 (74.3)	23 (79.3)	49 (76.6)
Grade 3 or 4 TEAEs related to study drug	25 (55.6)	22 (71)	47 (61.8)	19 (54.3)	15 (51.7)	34 (53.1)
SAEs	23 (51.1)	18 (58.1)	41 (53.9)	18 (51.4)	17 (58.6)	35 (54.7)
TEAEs leading to discontinuation	10 (22.2)	8 (25.8)	18 (23.7)	1 (2.9)	5 (17.2)	6 (9.4)
TEAEs leading to dose reduction	17 (37.8)	14 (45.2)	31 (40.8)	11 (31.4)	6 (20.7)	17 (26.6)
TEAEs leading to dose delay	23 (51.1)	21 (67.7)	44 (57.9)	17 (48.6)	11 (37.9)	28 (43.8)

(Source: Pfizer response to clarification questions A6)

Rates of most common (≥10%) treatment-emergent adverse events in the advanced phase CML population

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	76 (100)	45(100)	31(100)	63 (98.4)	34 (97.1)	29 (100)
Blood and lymphatic system disorders	56 (73.7)	32 (71.1)	24 (77.4)	35 (54.7)	19 (54.3)	16 (55.2)
Anaemia	32 (42.1)	15 (33.3)	17 (54.8)	18 (28.1)	10 (28.6)	8 (27.6)
Thrombocytopaenia	32 (42.1)	16 (35.6)	16 (51.6)	18 (28.1)	9 (25.7)	9 (31.0)
Neutropaenia	12 (15.8)	4 (8.9)	8 (25.8)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	3 (4.7)	3 (8.6) 0	0
Leukopenia	6 (7.9)	3 (6.7)	3 (9.7)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	6 (7.9)	4 (8.9)	2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Cardiac disorders	14 (18.4)	7 (15.6)	7 (22.6)	8 (12.5)	5 (14.3)	3 (10.3)
Eye disorders	15 (19.7)	7 (15.6)	8 (25.8)	8 (12.5)	6 (17.1)	2 (6.9)
Gastrointestinal disorders	72 (94.7)	42 (93.3)	30 (96.8)	53 (82.8)	28 (80.0)	25 (86.2)
Diarrhoea	65 (85.5)	38 (84.4)	27 (87.1)	42 (65.6)	23 (65.7)	19 (65.5)
Nausea	34 (44.7)	17 (37.8)	17 (54.8)	32 (50.0)	18 (51.4)	14 (48.3)
Vomiting	34 (44.7)	23 (51.1)	11 (35.5)	25 (39.1)	11 (31.4)	14 (48.3)
Abdominal pain	20 (26.3)	16 (35.6)	4 (12.9)	11 (17.2)	9 (25.7)	2 (6.9)
Abdominal pain upper	10 (13.2)	7 (15.6)	3 (9.7)	5 (7.8)	2 (5.7)	3 (10.3)
Constipation	13 (17.1)	8 (17.8)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
General disorders and administration site conditions	47 (61.8)	24 (53.3)	23 (74.2)	41 (64.1)	23 (65.7)	18 (62.1)
Pyrexia	28 (36.8)	16 (35.6)	12 (38.7)	22 (34.4)	16 (45.7)	6 (20.7)
Fatigue	15 (19.7)	3 (6.7)	12 (38.7)	12 (18.8)	5 (14.3)	7 (24.1)
Asthenia	10 (13.2)	6 (13.3)	4 (12.9)	4 (6.3)	4 (11.4)	0
General physical health deterioration	1 (1.3)	0	1 (3.2)	3 (4.7)	0	3 (10.3)
Oedema peripheral	3 (6.7)	4 (12.9)	7 (9.2)	0	4 (13.8)	4 (6.3)
Hepatobiliary disorders	5 (6.6)	3 (6.7)	2 (6.5)	4 (6.3)	4 (11.4)	0
Hyperbilirubinaemia	-	-	-	-	-	-
Infections and infestations	42 (55.3)	23 (51.1)	19 (61.3)	34 (53.1)	19 (54.3)	15 (51.7)
Pneumonia	8 (10.5)	4 (8.9)	4 (12.9)	10 (15.6)	4 (11.4)	6 (20.7)
Sepsis	-	-	-	-	-	-
Upper respiratory tract infection	8 (10.5)	6 (13.3)	2 (6.5)	2 (3.1)	1 (2.9)	1 (3.4)
Investigations	38 (50.0)	20 (44.4)	18 (58.1)	31 (48.4)	18 (51.4)	13 (44.8)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	10 (13.2)	5 (11.1)	5 (16.1)	4 (6.3)	4 (11.4)	0
Neutrophil count decreased	-	-	-	-	-	-
Aspartate aminotransferase increased	11 (14.5)	7 (15.6)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Lipase increased	-	-	-	-	-	-
Metabolism and nutrition disorders	27 (35.5)	17 (37.8)	10 (32.3)	22 (34.4)	11 (31.4)	11 (37.9)
Decreased appetite	6 (7.9)	4 (8.9)	2 (6.5)	12 (18.8)	5 (14.3)	7 (24.1)
Hypokalaemia	2 (2.6)	0	0 2 (6.5)	5 (7.8)	2 (5.7)	3 (10.3)
Hypophosphataemia	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders	26 (34.2)	18 (40.0)	8 (25.8)	24 (37.5)	13 (37.1)	11 (37.9)
Arthralgia	10 (13.2)	8 (17.8)	2 (6.5)	7 (10.9)	6 (17.1)	1 (3.4)
Pain in extremity	10 (13.2)	7 (15.6)	3 (9.7)	6 (9.4)	4 (11.4)	2 (6.9)
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	11 (14.5)	6 (13.3)	5 (16.1)	7 (10.9)	4 (11.4)	3 (10.3)
Blast crisis in myelogenous leukaemia	-	-	-	-	-	-
Nervous system disorders	24 (31.6)	14 (31.1)	10 (32.3)	26 (40.6)	16 (45.7)	10 (34.5)
Headache	12 (15.8)	9 (20.0)	3 (9.7)	13 (20.3)	9 (25.7)	4 (13.8)
Dizziness	8 (10.5)	4 (8.9)	4 (12.9)	9 (14.1)	6 (17.1)	3 (10.3)
Psychiatric disorders	16 (21.1)	6 (13.3)	10 (32.3)	11 (17.2)	6 (17.1)	5 (17.2)
Renal and urinary disorders	11 (14.5)	5 (11.1)	6 (19.4)	8 (12.5)	5 (14.3)	3 (10.3)
Renal failure acute	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	35 (46.1)	19 (42.2)	16 (51.6)	23 (35.9)	14 (40.0)	9 (31.0)
Dyspnoea	14 (18.4)	8 (17.8)	6 (19.4)	12 (18.8)	7 (20.0)	5 (17.2)
Cough	13 (28.9)	8 (25.8)	21 (27.6)	6 (17.1)	3 (10.3)	9 (14.1)
Oropharyngeal pain	8 (10.5)	4 (8.9)	4 (12.9)	2 (3.1)	1 (2.9)	1 (3.4)
Pleural effusion	9 (11.8)	5 (11.1)	4 (12.9)	4 (6.3)	2 (5.7)	2 (6.9)
Skin and subcutaneous tissue disorders	42 (55.3)	25 (55.6)	17 (54.8)	30 (46.9)	17 (48.6)	13 (44.8)
Rash	25 (32.9)	16 (35.6)	9 (29.0)	20 (31.3)	10 (28.6)	10 (34.5)
Vascular disorders	11 (14.5)	4 (8.9)	7 (22.6)	7 (10.9)	7 (20.0)	0
Hypertension	7 (9.2)	3 (6.7)	4 (12.9)	2 (3.1)	2 (5.7)	0

(Source: Pfizer response to clarification questions A6)

Rates of TEAEs (grade 3/4) occurring in ≥5% of the advanced phase populations

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Any adverse event	66 (86.8)	36 (80.0)	30 (96.8)	49 (76.7)	26 (74.3)	23 (79.3)
Blood and lymphatic system disorders	42 (55.3)	20 (44.4)	22 (71.0)	29 (45.3)	18 (51.4)	11 (37.9)
Anaemia	23 (30.3)	11 (24.4)	12 (38.7)	12 (18.8)	7 (20.0)	5 (17.2)
Thrombocytopaenia	25 (32.9)	11 (24.4)	14 (45.2)	17 (26.6)	9 (25.7)	8 (27.6)
Neutropaenia	11 (14.5)	4 (8.9)	7 (22.6)	13 (20.3)	9 (25.7)	4 (13.8)
Febrile neutropaenia	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Leukopenia	3 (3.9)	1 (2.2)	2 (6.5)	7 (10.9)	3 (8.6)	4 (13.8)
Leukocytosis	3 (3.9)	2 (4.4)	1 (3.2)	2 (3.1)	0	2 (6.9)
Cardiac disorders	5 (6.6)	3 (6.7)	2 (6.5)	3 (4.7)	1 (2.9)	2 (6.9)
Eye disorders	0	0	0	3 (4.7)	1 (2.9)	2 (6.9)
Gastrointestinal disorders	14 (18.4)	7 (15.6)	7 (22.6)	14 (21.9)	5 (14.3)	9 (31.0)
Diarrhoea	3 (3.9)	1 (2.2)	2 (6.5)	4 (6.3)	2 (5.7)	2 (6.9)
Nausea	-	-	-	-	-	-
Vomiting	3 (3.9)	1 (2.2)	2 (6.5)	2 (3.1)	0	2 (6.9)
Abdominal pain	1 (1.3)	1 (2.2)	0	2 (3.1)	2 (5.7)	0
Abdominal pain upper	-	-	-	-	-	-
Constipation	-	-	-	-	-	-
General disorders and administration site conditions	7 (9.2)	1 (2.2)	6 (19.4)	10 (15.6)	4 (11.4)	6 (20.7)
Pyrexia	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Fatigue	3 (3.9)	0	3 (9.7)	2 (3.1)	0	2 (6.9)
Asthenia	-	-	-	-	-	-
General physical health deterioration	0	0	0	2 (3.1)	0	2 (6.9)
Hepatobiliary disorders	2 (2.6)	1 (2.2)	1 (3.2)	3 (4.7)	3 (8.6)	0
Hyperbilirubinaemia	0	0	0	3 (4.7)	3 (8.6)	0
Infections and infestations	12 (15.8)	5 (11.1)	7 (22.6)	14 (21.9)	4 (11.4)	10 (34.5)
Pneumonia	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	1 (2.9)	3 (10.3)
Sepsis	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9) 0	1 (2.9) 0
Upper respiratory tract infection	-	-	-	-	-	-
Investigations	14 (18.4)	8 (17.8)	6 (19.4)	11 (17.2)	5 (14.3)	6 (20.7)
Platelet count decreased	5 (6.6)	4 (8.9)	1 (3.2)	5 (7.8)	2 (5.7)	3 (10.3)
Alanine aminotransferase increased	6 (7.9)	3 (6.7)	3 (9.7)	1 (1.6)	1 (2.9)	0
Neutrophil count decreased	1 (1.3)	1 (2.2)	0	0	0	0
Aspartate aminotransferase increased	4 (5.3)	3 (6.7)	1 (3.2)	0	0	0

AE, n (%)	AP Total (n=76)	AP IM only (N=45	AP multi-TKI (N=31)	BP Total (n=64)	BP IM only (N=35)	BP multi-TKI (N=29)
Lipase increased	1 (1.3)	0	1 (3.2)	2 (3.1)	2 (5.7)	0
Metabolism and nutrition disorders	9 (11.8)	4 (8.9)	5 (16.1)	7 (10.9)	3 (8.6)	4 (13.8)
Decreased appetite	-	-	-	-	-	-
Hypokalaemia	1 (1.3)	0	1 (3.2)	3 (4.7)	1 (2.9)	2 (6.9)
Hypophosphataemia	3 (3.9)	1 (2.2)	2 (6.5)	1 (1.6)	1 (2.9)	0
Musculoskeletal and connective tissue disorders	4 (5.3)	3 (6.7)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Arthralgia	-	-	-	-	-	-
Pain in extremity	-	-	-	-	-	-
Neoplasms, benign malignant and unspecified (incl. cysts and polyps)	7 (9.2)	3 (6.7)	4 (12.9)	4 (6.3)	3 (8.6)	1 (3.4)
Blast crisis in myelogenous leukaemia	2 (2.6)	0	0 2 (6.5)	1 (1.6)	1 (2.9)	0
Nervous system disorders	4 (5.3)	1 (2.2)	3 (9.7)	6 (9.4)	2 (5.7)	4 (13.8)
Headache	2 (2.6)	1 (2.2)	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Dizziness	-	-	-	-	-	-
Psychiatric disorders	1 (1.3)	0	1 (3.2)	2 (3.1)	0	2 (6.9)
Renal and urinary disorders	1 (1.3)	0	1 (3.2)	4 (6.3)	2 (5.7)	2 (6.9)
Renal failure acute	0	0	0	2 (3.1)	2 (5.7)	0
Respiratory, thoracic and mediastinal disorders	8 (10.5)	3 (6.7)	5 (16.1)	6 (9.4)	4 (11.4)	2 (6.9)
Dyspnoea	6 (7.9)	2 (4.4)	4 (12.9)	2 (3.1)	2 (5.7)	0
Cough	-	-	-	-	-	-
Pleural effusion	4 (5.3)	1 (2.2)	3 (9.7)	2 (3.1)	1 (2.9)	1 (3.4)
Skin and subcutaneous tissue disorders	3 (3.9)	3 (6.7)	0	5 (7.8)	2 (5.7)	3 (10.3)
Rash	3 (3.9)	3 (6.7)	0	2 (3.1)	1 (2.9)	1 (3.4)
Vascular disorders	5 (6.6)	1 (2.2)	4 (12.9)	1 (1.6)	1 (2.9)	0
Hypertension	4 (5.3)	1 (2.2)	3 (9.7)	1 (1.6)	1 (2.9)	0

(Source: Pfizer response to clarification questions A6)

9.17.4 Post-hoc analyses of patients with unmet clinical need

Incidence rates of adverse events by type for the unmet clinical need subpopulation

Event	CP (second-line) (n=15)	CP (third line) (n=21)	Total CP CML (n=36)	AP CML (n=5)	BP CML (n=11)	Total advanced phase CML (n=16)	Total subpopulation of unmet clinical need (n=52)
Any TEAE (N, %)	15 (100)	21 (100)	36 (100)	5 (100)	11 (100)	16 (100)	52 (100)
Grade 3 or 4 TEAEs (N, %)	11 (73.3)	12 (57.1)	23 (63.9)	5 (100)	8 (72.7)	13 (81.3)	36 (69.2)
TEAEs leading to discont. (N, %)	4 (26.7)	5 (23.8)	9 (25.0)	1 (20)	3 (27.3)	4 (25.0)	13 (25)
SAEs (N, %)	6 (40.0)	10 (47.6)	16 (44.4)	4 (80.0)	8 (72.7)	12 (75.0)	28 (53.8)

(Source: Pfizer submission, Table B110, p 365)

9.17.5 Study 3000, number (%) of subjects experiencing drug related treatment-emergent adverse events with an incidence of ≥5%

	Treatment		
System Organ Class Preferred Term	**Bosutinib N=248**	**Imatinib N=251**	**Total N=499**
ANY ADVERSE EVENT	227 (91.5)	218 (86.9)	445 (89.2)
Blood and lymphatic system disorders	94 (37.9)	118 (47.0)	212 (42.5)
Thrombocytopenia	65 (26.2)	67 (26.7)	132 (26.5)
Neutropenia	29 (11.7)	65 (25.9)	94 (18.8)
Anaemia	37 (14.9)	45 (17.9)	82 (16.4)
Leukopenia	21 (8.5)	50 (19.9)	71 (14.2)
Eye disorders	8 (3.2)	34 (13.5)	42 (8.4)
Eyelid oedema	2 (0.8)	18 (7.2)	20 (4.0)
Gastrointestinal disorders	181 (73.0)	106 (42.2)	287 (57.5)
Diarrhoea	163 (65.7)	45 (17.9)	208 (41.7)
Nausea	66 (26.6)	81 (32.3)	147 (29.5)
Vomiting	61 (24.6)	22 (8.8)	83 (16.6)
Abdominal pain upper	24 (9.7)	10 (4.0)	34 (6.8)
Abdominal pain	21 (8.5)	7 (2.8)	28 (5.6)
General disorders and administration site conditions	54 (21.8)	68 (27.1)	122 (24.4)
Fatigue	22 (8.9)	22 (8.8)	44 (8.8)
Oedema peripheral	4 (1.6)	21 (8.4)	25 (5.0)
Investigations	123 (49.6)	75 (29.9)	198 (39.7)
Alanine aminotransferase increased	73 (29.4)	14 (5.6)	87 (17.4)
Aspartate aminotransferase increased	59 (23.8)	12 (4.8)	71 (14.2)
Lipase increased	25 (10.1)	20 (8.0)	45 (9.0)
Blood creatine phosphokinase increased	10 (4.0)	22 (8.8)	32 (6.4)
Blood alkaline phosphatase increased	14 (5.6)	9 (3.6)	23 (4.6)
Gamma-glutamyltransferase increased	14(5.6)	1 (0.4)	15 (3.0)
Metabolism and nutrition disorders	39 (15.7)	43 (17.1)	82 (16.4)
Hypophosphataemia	12 (4.8)	25 (10.0)	37 (7.4)
Decreased appetite	19 (7.7)	3 (1.2)	22 (4.4)
Musculoskeletal and connective tissue disorders	19 (7.7)	80 (31.9)	99 (19.8)
Muscle spasms	1 (0.4)	44 (17.5)	45 (9.0)
Myalgia	6 (2.4)	21 (8.4)	27 (5.4)
Bone pain	2 (0.8)	16 (6.4)	18 (3.6)
Nervous system disorders	34 (13.7)	18 (7.2)	52 (10.4)
Headache	13 (5.2)	6 (2.4)	19 (3.8)
Skin and subcutaneous tissue disorders	80 (32.3)	69 (27.5)	149 (29.9)
Rash	45 (18.1)	28 (11.2)	73 (14.6)
Periorbital oedema	0	34 (13.5)	34 (6.8)
System organ class totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same system organ class. Date of snapshot: 31AUG2010			

(Source: Pfizer response to clarification questions A1)

9.18 Appendix R: Detailed results of probabilistic sensitivity analyses

This section details results of the probabilistic sensitivity analyses which were not felt important enough to include in the main report.

9.18.1 CP model results

Figure 45. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer clarification, Figure 9, p30)

Figure 46. Cost-effectiveness acceptability curve, all strategies (note dotted line is interferon)

(Source: Pfizer clarification, Figure 10, p30)

Figure 47. Pairwise comparison of hydroxycarbamide and bosutinib in PSA (incremental costs and QALYs of bosutinib versus hydroxycarbamide)

(Source: Pfizer clarification, Figure 11, p31)

9.18.2 AP model results

Figure 48. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer submission, Section 7.6.8, p171)

Figure 49. Cost-effectiveness acceptability curve, all strategies

(Source: Pfizer submission, Section 7.6.8, p171)

Figure 50. Pairwise comparison of hydroxycarbamide and bosutinib intervention

(Source: Pfizer submission, Section 7.6.8, p172)

9.18.3 BP model results

Figure 51. Scatterplot of probabilistic sensitivity analysis, all strategies

(Source: Pfizer submission, Section 7.7.8, p181)

Figure 52. Cost-effectiveness acceptability curve, all strategies

(Source: Pfizer submission, Section 7.7.8, p182)

Figure 53. Pairwise comparison of bosutinib versus hydroxycarbamide

(Source: Pfizer submission, Section 7.7.8, p182)

9.19 Appendix S: Shortcomings in Pfizer's analysis with minimal effect on cost-effectiveness

Here, we discuss three aspects of Pfizer's model with which we agree. We do not adjust the model for our base case analysis because, when corrected, the cost-effectiveness of bosutinib changes only incrementally.

9.19.1 Death from non-CML causes

We believe that death due to all-cause mortality (in fact, due to non-CML mortality) for bosutinib patients is not correctly incorporated in the Pfizer model. The Pfizer report states that all-cause mortality is incorporated using the following method (except for bosutinib in CP model):

1. Overall survival is initially estimated by extrapolating from trial data
2. Background mortality already incorporated in the overall survival from the MCyR surrogate method is removed by "subtracting the monthly probability of death for a patient aged 54 (the mean age of the third-line CP cohort in Study 200)"
3. Age-appropriate background mortality is incorporated by "adding the monthly probability of death for a patient at the age of the cohort taken from the Office of National Statistics Interim Life Tables 2008-2010 (ONS, 2012)"

This contrasts with the method used by PenTAG in TA241[2] in which CML and non-CML mortality were jointly calibrated to OS in Jabbour and colleagues,[44] estimating non-CML mortality from UK Life Tables. We believe this is a more consistent method of estimating CML mortality and hence overall survival, but in reality neither method is ideal as both rely on accounting for the non-CML mortality that would be experienced by an average patient, rather than the average non-CML mortality that would have been experienced by the heterogeneous population described in Jabbour and colleagues.[44] As both methods are subject to the same criticism and the same methodology is applied across all interventions hence not introducing bias, we were content to accept the general methodology, with a few further considerations.

We do not believe that simple addition and subtraction of monthly probabilities of death from survival curves is logical. Instead we believe it is appropriate to estimate hazard rates and cumulative hazard functions, which may be added and subtracted, and then use the net cumulative hazard function to calculate overall survival, as follows:

1. Overall survival is initially estimated using the MCyR surrogate method, and denoted $S_{surrogate}(t)$
2. The cumulative hazard from the MCyR surrogate method is then $\Lambda_{surrogate}(t) = -\ln S_{surrogate}(t)$

3. The cumulative hazard experienced by a patient consistently feeling the force of non-CML mortality as experienced at age 54 is calculated as $\Lambda_{Non-CML|54}(t) = \lambda_{Non-CML|54} \times t$ where $\lambda_{Non-CML|54} = -\ln(1 - q_{54})$ where q_{54} is the probability of dying before age 55 if one is alive at age 54
4. The cumulative hazard experienced by a patient due to non-CML mortality as experienced at the appropriate age is calculated as $\Lambda_{Non-CML}(t_i) = \Lambda_{Non-CML}(t_{i-1}) - \ln\big(1 - q(x_{i-1})\big) \times (t_i - t_{i-1})$ where $q(x_{i-1})$ is the probability of dying before age $x_{i-1} + 1$ if one is alive at age x_{i-1} and x_0 is the starting age (54 years)
5. The net cumulative hazard is calculated as $\Lambda_{OS}(t) = \Lambda_{surrogate}(t) - \Lambda_{Non-CML|54}(t) + \Lambda_{Non-CML}(t)$
6. The overall survival is calculated as $S_{OS}(t) = \exp\{-\Lambda_{OS}(t)\}$

Furthermore, the Pfizer model does not appear to correctly implement the method described in the Pfizer report, as it calculates the monthly probability of death as $(1 + q_x)^{\frac{1}{12}} - 1$ rather than the correct calculation of $1 - (1 - q_x)^{\frac{1}{12}}$. This results in an underestimate of the monthly probability of death, particularly in older patients where q_x is greater. Note that this is in fact irrelevant as we do not consider that a simple correction to this monthly probability calculation would result in a correct and logical overall incorporation of non-CML mortality.

In addition we do not believe that the overall survival should be adjusted according to the mean age of the third-line CP cohort in study 200, since this study does not form the basis of the overall survival estimates, which instead come from Jabbour and colleagues.[44] The mean age of patients is not reported in Jabbour and colleagues, but the median age is reported as 54 years.[44] We also do not believe that simply adjusting according to any average age is ideal as the rate of non-CML mortality is nonlinearly related to age, but in the absence of any further data demonstrating the effect of age on overall survival within Jabbour and colleagues we believe it is a suitable approximation to adjust according to the median age.

Finally we note that in the Pfizer model the age used to adjust overall survival is 56 years rather than 54 years but this has a negligible impact.

We estimate that correct incorporation of non-CML mortality results in a 0.22 year decrease in mean OS for bosutinib from the Pfizer calculation. We felt this was unlikely to result in a significant impact on cost-effectiveness and it would require substantial changes to the model, so we have not pursued further.

9.19.2 Interferon drug administration resource use

Pfizer assume that 25% of interferon patients require assistance with injecting, following the assumption made in Rogers and colleagues (2012),[2] but the model includes only one district nurse visit per cycle for those patients requiring assistance. Rogers and colleagues by contrast assume one district nurse visit per day, which we believe is appropriate. The drug administration cost for interferon per cycle is therefore equal to 25% × £39 × 30.4 = £296.77 (compared to an original cost of £9.75).

Correcting this error results in a change in the Pfizer base case CP model ICER of bosutinib versus interferon from [redacted] per QALY, although interferon continues to be dominated by hydroxycarbamide. ICERs of bosutinib versus hydroxycarbamide and SCT in the CP model are unchanged, as are ICERs in the AP and BP model. As this results in only a small change in the ICER of bosutinib versus interferon (which is not the main comparison in the decision problem as interferon is dominated by hydroxycarbamide which is more reflective of clinical practice) we do not correct this in the base case.

9.19.3 Estimation of OS for bosutinib in CP using MCyR surrogate relationship

As described in Section 5.2.6.1 (p118) Pfizer fit a single curve (denoted curve A in this section) to OS from Jabbour and colleagues (2009)[44] before fitting a weighted combination of curves (denoted curve B in this section) to an adjusted version of curve A (A'). While we are satisfied that curve A is fitted appropriately, we note that Pfizer then use equal weighting across the curve when fitting curve B to curve A', which is particularly inappropriate when the underlying OS data is immature (maximum follow-up 7.7 years) and curve A' is extrapolated for 50 years. We note however that curve B is closely fitted to A' for the first 20 years, and hence although we do not agree with the methodology we do not believe a materially different estimate of cost-effectiveness would be obtained through a more appropriate methodology.

Pfizer assumed that 35/84 = 41.7% of patients in Jabbour and colleagues (2009)[44] achieved or maintained a MCyR, whereas in TA241 it was decided that the appropriate figure was 37/84 = 44.0%.[2] Substituting this value and re-calibrating as described in the Pfizer clarifications we calculated the CP model ICER of bosutinib versus hydroxycarbamide increased marginally from [redacted] per QALY.

Pfizer's model additionally had some logical errors:

- Curve A was adjusted to curve A' by adding and subtracting monthly mortality probabilities from a survival distribution, which is not logical. The more appropriate method is very

similar to the method employed to incorporate CML and non-CML mortality as conducted by Pfizer.

- Monthly probabilities of dying from non-CML causes were incorrectly estimated from annual probabilities taken from life tables. The correct formula is $q_{monthly} = 1 - \left(1 - q_{yearly}\right)^{1/12}$ while Pfizer used $q_{monthly} = \left(1 + q_{yearly}\right)^{1/12} - 1$ which underestimates non-CML mortality.
- Different methods were now used to incorporate non-CML mortality for bosutinib and for the comparators. This inconsistency could introduce bias.

We conducted an exploratory analysis where we corrected all the logical errors, including changing the method to incorporate non-CML mortality for hydroxycarbamide to match the method used for bosutinib. The resulting ICER for bosutinib versus hydroxycarbamide was [redacted] per QALY (up marginally from [redacted] per QALY). We also investigated the joint effect of changing the MCyR rate and correcting the logical errors and obtained an ICER of [redacted] per QALY. We did not feel this was a sufficiently important change in the ICER to warrant changing the base case for the analysis.

9.20 Appendix T: Cumulative survival method for AP and BP models

9.20.1 Cumulative survival method AP

Here, we discuss the Cumulative Survival method applied to treatment starting in AP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

We assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib.

Similarly, in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

We estimate the total life years, costs and QALYs for the (Bosutinib, HU), and (Bosutinib, SCT) treatment arms.

The notation of the time components is given in Table 94 below.

Table 94. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in AP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line AP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$
BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BP}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$		

Then under the Cumulative Survival method, the component times are calculated as shown in Table 95, where S_{BOS} and d_{BOS} have the analogous meanings as described in Section 6.1.1 (p190).

Table 95. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in AP

	(Bosutinib, HU)	HU	SCT	(Bosutinib, SCT)
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
BP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			

From Pfizer's model, we estimate an upper bound for S_{BOS} as 98.9% by assuming that the only mortality whilst patients are on bosutinib treatment is due to background causes. This estimate is based on Pfizer's base case estimates of time on 3rd-line bosutinib.

d_{BOS} = 94.5% from Pfizer's model, based on Pfizer's base case estimate of time on 3rd-line bosutinib and a discount rate of 3.5% p.a.

Under the cumulative survival method, the component costs are calculated as shown in Table 96.

Table 96. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in AP

	(Bosutinib, HU)	HU	SCT	(Bosutinib, SCT)
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$
BP	$S_{\mathrm{BOS}}d_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{BP}}$			

The component QALYs are calculated in exactly the same way.

9.20.2 Cumulative survival method BP

Here, we discuss the Cumulative Survival method applied to treatment starting in BP CML.

Without loss of generality, we again assume that all patients start on 3rd-line treatment.

First, the mean total life years, costs and QALYs are unchanged in the HU and SCT arms.

Next, in the (Bosutinib, HU) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged. Similarly, in the (Bosutinib, SCT) arm, the mean time, cost and QALYs whilst on 3rd-line bosutinib treatment are unchanged.

We assume that life expectancy for patients starting 4th-line HU treatment who have previously taken bosutinib equal that for patients starting 3rd-line HU treatment in patients who have not previously taken bosutinib.

Similarly, in the (Bosutinib, SCT) arm the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

We estimate the total life years, costs and QALYs for the (Bosutinib, HU), and (Bosutinib, SCT) treatment arms.

The notation of the time components is given in Table 97 below.

Table 97. Notation for mean per patient undiscounted time split by stage of disease and treatment arm starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{BOS\ 3}$	$\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$	$\mathrm{T}_{\mathrm{SCT}}$	$\mathrm{T}_{\mathrm{BOS,SCT}}^{BOS\ 3}$
4th-line BP	$\mathrm{T}_{\mathrm{BOS,HU}}^{HU\ 4}$	n/a		$\mathrm{T}_{\mathrm{BOS,SCT}}^{SCT\ 4}$

Then under the Cumulative Survival method, the component times are calculated as shown in Table 98, where S_{BOS} and d_{BOS} have the analogous meanings as described in Section 6.1.1 (p190).

Table 98. Mean per patient undiscounted times calculated under Cumulative Survival method for patients starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}}\mathrm{T}_{\mathrm{SCT}}$

From Pfizer's model, we estimate an upper bound for S_{BOS} as 99.9% by assuming that the only mortality whilst patients are on bosutinib treatment is due to background causes. This estimate is based on Pfizer's base case estimates of time on 3rd-line bosutinib.

d_{BOS} = 97.9% from Pfizer's model, based on Pfizer's base case estimate of time on 3rd-line bosutinib and a discount rate of 3.5% p.a.

Under the cumulative survival method, the component costs are calculated as shown in Table 99.

Table 99. Mean per patient discounted cost calculated under Cumulative Survival method for patients starting in BP

	(Bosutinib, HU)	**HU**	**SCT**	**(Bosutinib, SCT)**
3rd-line AP	unchanged	unchanged	unchanged	unchanged
4th-line AP	$S_{\mathrm{BOS}} d_{\mathrm{BOS}} \mathrm{T}_{\mathrm{HU}}^{\mathrm{HU}}$			$S_{\mathrm{BOS}} d_{\mathrm{BOS}} \mathrm{T}_{\mathrm{SCT}}$

The component QALYs are calculated in exactly the same way.

9.21 Appendix U: Correspondence from TA251 concerning medical management

The following text is reproduced from our document "Addendum to PenTAG report for TA251: Prepared and sent by PenTAG, 3rd November 2011".

Novartis correctly state that during chronic phase CML, alongside other monitoring test costs, we originally assumed a monthly frequency of:

0.4 visits with a nurse

0.9 visits with a haematologist/oncologist, and

0.3 bone marrow aspirations.

These figures were taken from the 2009 Oxford Outcomes survey of 6 UK-based CML clinicians (see p179 our report).

Novartis claim that this is an overestimate the frequency of outpatient visits. They claim that it is more reasonable to assume one visit per 3 to 6 months, based on current ELN guidelines. They also claim that we over-estimate the frequency of bone marrow aspirations.

We have presented Novartis' criticisms to our clinical advisor, and he agrees that we have over-estimated these quantities. He believes that it is more likely that NHS patients on a TKI would be seen at week 2, week 4, month 2, month 4 and then 3-monthly. Patients on hydroxyurea would be seen about every 6 weeks. Furthermore, patients would rarely be seen by a nurse (without a consultant). Our advisor claims that clinical practice for bone marrow aspiration varies from only a single test, to tests at month 0, 3, 6, 12, 18 and 24 or until CCyR, but not after 24 months.

Given this new information and current European treatment guidelines, we have calculated revised base case cost-effectiveness estimates assuming lower medical management costs during the chronic phase. The modelling for our revised estimates now assumes:

- one visit to a haematologist/oncologist every 3 months for patients on a TKI, i.e. 0.33 visits per month.
- one visit to a haematologist/oncologist every 6 weeks for patients hydroxyurea, i.e. 0.72 visits per month.
- no outpatient nurse visits.
- no bone marrow aspirations (given that some clinicians give no repeat tests and given that for those cases when repeat aspirations are given, costs would cancel to a large extent between treatment arms).

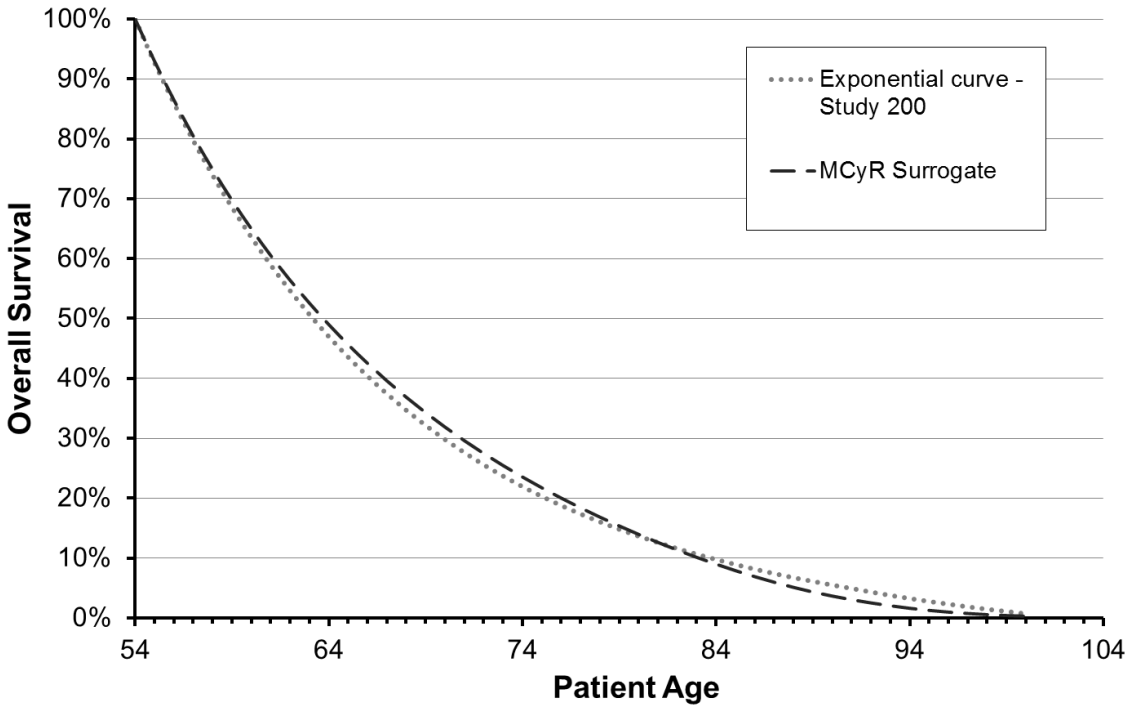
We can safely ignore the initial higher frequency of visits when patients start taking TKIs, as these costs effectively cancel out between treatment arms (because virtually all patients on 1st-line TKIs are still on treatment at 4 months). We leave all other assumptions for the costs of medical management unchanged (see p180 our report), although these contribute only marginally.

These new cost assumptions give a mean medical management cost of £169 per month per patient on TKIs in chronic phase and £317 per patient on HU in chronic phase.

9.22 Appendix V: Comparison of overall survival in CP model calculated by MCyR surrogate, Study 200 Kaplan-Meier and exponential fit

Pfizer state (Pfizer clarification, Figure 7, p28) that the overall survival (OS) obtained by the MCyR surrogate method was validated by comparing it to the exponential curve fitted to Study 200 CP-3L cohort OS, with the curves being very similar:

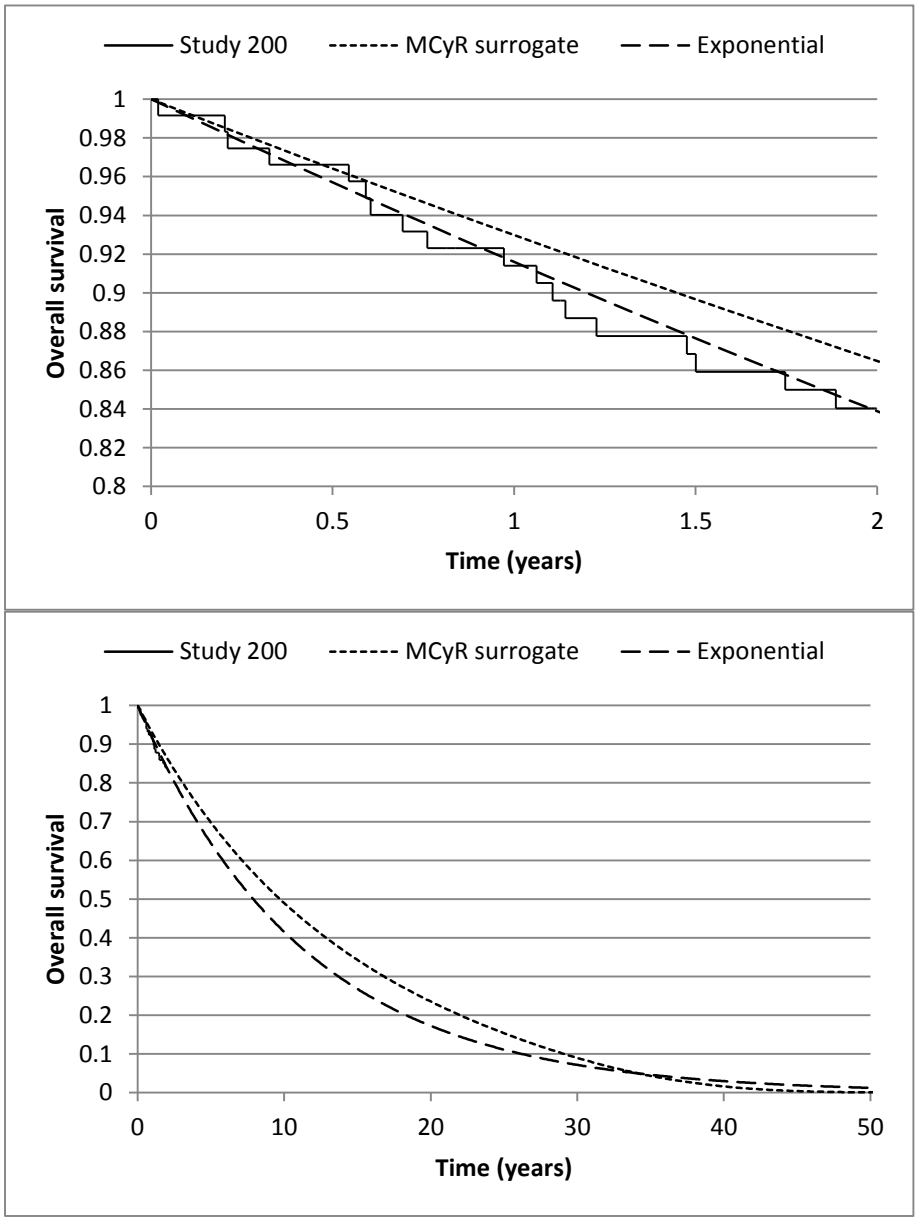
Figure 54. OS in CP model calculated by exponential curve and MCyR surrogate method



(Source: Pfizer clarifications, Figure 7, p28)

We believe this figure is not an accurate reflection of the exponential curve used in Pfizer's model. Figure 55 shows the actual OS in the CP model and demonstrates that the MCyR surrogate method is overestimating the OS.

Figure 55. Actual OS in CP model



Note that we do not accept that the Study 200 OS is good quality data for the purposes of estimating OS for patients on bosutinib in the unmet need population; indeed we identify a number of issues with the data (see Section 5.3.8.1, p165). This is presented only to demonstrate the shortcomings of the MCyR surrogate method (since we believe Study 200 OS is already likely to be biased upwards). As the MCyR surrogate method is a key component of Pfizer's CP base case we believe this is further reason to not accept Pfizer's base case estimate of OS for patients on bosutinib in CP.

9.23 Appendix W: Adjusting Pfizer's model for PenTAG preferred medical management resource use

Table 100. Changes to Pfizer's model to achieve PenTAG preferred medical management resource use

Worksheet	Cell(s)	Change

PF_Bosutinib	AG11	Change from
		`=ae_bosutinib_cost+AB11*c_cpt_bos`
		to
		`=ae_bosutinib_cost+AB11*c_cpt_bos+2*p_clin_onc`

Costs	C117	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$57`
		to
		`=1/3*p_clin_onc+$F$57`

	D117	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$59`
		to
		`=0.72*p_clin_onc+$F$59`

	C118, D118, D119	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55)+Parameters!$N$56+$F$59`
		to
		`=0.72*p_clin_onc+$F$59`

	C119	Change from
		`=SUMPRODUCT(Parameters!$N$37:$N$40, Parameters!$N$52:$N$55) + Parameters!$N$56 + $F$61 + (1-Parameters!$N$34)*Parameters!$N$33`
		to
		`=0.72*p_clin_onc+$F$61+(1-Parameters!$N$34)*Parameters!$N$33`

	C84, D84	Set to 0

PF_Interferon	BE11:BE610	Change from (row 11)
		`=SUM(Z11:AA11)*SUMPRODUCT( Parameters!$N$37:$N$40, Parameters!$N$52:$N$55) + AB11*SUMPRODUCT(Parameters!$N$42:$N$45, Parameters!$N$52:$N$55) + AC11*SUMPRODUCT(Parameters!$N$47:$N$50, Parameters!$N$52:$N$55)`
		to
		`=SUM(Z11:AA11)*0.72*p_clin_onc + AB11*SUMPRODUCT(Parameters!$N$42:$N$45, Parameters!$N$52:$N$55) + AC11*SUMPRODUCT(Parameters!$N$47:$N$50, Parameters!$N$52:$N$55)`

	BF11:BF610	Change from (row 11)

		`=SUM(Z11:AA11)*Parameters!$N$56 + SUM(AB11:AC11)*Parameters!$N$57`
		to
		`=SUM(AB11:AC11)*Parameters!$N$57`

PF_StemCellTransplant	AE11:AE610	Replace `c_sct_25` with `c_sct_25+(0.54*0.5+0.46*0.08)*p_clin_onc`

Bosutinib for previously treated chronic myeloid leukaemia STA: a single technology appraisal

PenTAG responses to factual inaccuracies identified in our report by Pfizer

31st May 2013
Updated 11th June (corrupted section references corrected and References reformatted for readability)

Commercial in confidence information is underlined and highlighted turquoise, e.g., [redacted].
Academic in confidence information is underlined and highlighted yellow, e.g., [redacted].

Issue 1 Clinical Effectiveness sub-population claim

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Within the bosutinib summary of safety section on page 26, the ERG report states the following: *"In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI."* Similarly, on page 106 in the "conclusions of the clinical effectiveness section" of the ERG report, the following is stated: *"Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI."*	Pfizer request that the underlined text be removed.	Pfizer disagree that the "clinical effectiveness appears to be mainly seen in patients with previous intolerance to TKI". As the ERG reference in Appendices M, N and O, there are good response rates in terms of cytogenetic responses, haematological responses, and overall survival respectively, in both the TKI intolerant and TKI resistant sub-groups within the 2nd and 3rd line Chronic Phase cohorts. In the most recent data snapshots MCyR rates were: - 62.2%, 76.0% and 79.6% for the IM + Das-R (n=37), IM + Nil-R (n=25), and IM + Das-I (n=49) sub-populations respectively - 58% (n=195) and 60% (n=91) for the IM-R and IM-I sub-populations respectively in 2nd line Chronic Phase	We were citing European Medicines Agency Assessment Report for Bosulif/bosutinib (EPAR), unfortunately during formatting the references were removed from the report. The reference was added to both sentences: *"In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI (EPAR)."* *"Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI (EPAR)."* We have highlighted this omission in our Errata document. References: EPAR, European Medicines Agency Assessment Report for Bosulif/bosutinib, CHMP, January 2013. http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002373/WC500141745.pdf

		Kaplan-Meier estimated survival at 2 years for the most recent data snapshot for the 3rd line CP sub-populations were: - 77.4%, 92.4% and 85.4% for the IM + Das-R (n=37), IM + Nil-R (n=27), and IM + Das-I (n=50) sub-populations respectively	

Issue 2 Population for bosutinib

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On pages 40, 45 and 47 the ERG describe the current management of CML and the likely positioning of bosutinib. Specifically the ERG assert that nilotinib is increasingly the 1st line choice in CML over imatinib and dasatinib is not routinely available (particularly after	Pfizer request that the ERG revise their assumption that most patients are now treated with nilotinib 1st line and that dasatinib is not used. In addition, we request that the ERG make clear that 2nd line use of bosutinib is expected to be rare and that 3rd and 4th	The description of the current management of CML patients and positioning of bosutinib is inaccurate for the following reasons: 1) The license clearly states that bosutinib is only for patients for whom imatinib, nilotinib and dasatinib are unsuitable. We re-iterate that it could be inappropriate to assume that difficulty in accessing a licensed treatment (dasatinib) is the same as being unsuitable for a treatment. 2) A market research survey of 45 UK clinicians treating CML, conducted in 2012 reported that 89% of their patients were treated with imatinib 1st line, compared to only 5% and 6% for dasatinib and nilotinib respectively (Pfizer data on file). This also aligns with CML guidelines, such as the 2009 ELN guidelines. 3) The ERG asserts that dasatinib is rarely used in the UK and therefore bosutinib would generally be used mostly at 2nd line after nilotinib. However, a significant proportion of the prevalent and incident population are using dasatinib at 1st line due to clinical trials such as SPIRIT 2. The trial recruited 810 patients between August 2008 and February 2013, comparing imatinib to dasatinib (1:1) at 1st line, with 172 sites across the UK participating (of	We consider this issue to be a matter of judgement, not a factual inaccuracy.

2014 and the termination of the CDF). Therefore, bosutinib is most likely to be used in 2nd and 3rd line.	line use is more likely.	which 136 recruited) (www.spirit-cml.org). 4) In addition, it is worth noting that generic versions of imatinib are expected to become available in 2016. According to Hoyle 2012: *"assuming a modest 25% price cut on patent expiry, the ICER for nilotinib vs. imatinib increases substantially, from £36,000 to £54,000 per QALY"* – this could significantly change the 1st and 2nd line recommendations and prescribing patterns. 5) As noted in our submission, [redacted] 6) Pfizer notes that there appears to be a rapid reappraisal of dasatinib ongoing as part of TA251, which creates uncertainty around the future availability of dasatinib within the NHS. In addition, dasatinib has been included on the new national CDF formulary in a 2nd/3rd line positioning. In summary, Pfizer believe that the use of bosutinib in a predominantly 3rd and 4th line positioning is consistent with the current and future prescribing trends in CML. Amendment of these assumptions will clarify the positioning of bosutinib and the relevance of the Study 200 3rd line cohort to the decision problem.	

Issue 3 Comparison of bosutinib vs imatinib at 1st line

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 48, paragraph 1 of the ERG report the following is stated: *"In this RCT, bosutinib failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib."*	Remove *"...was actually numerically superior..."* and insert the following: *"...was not statistically significant, but had a numerical advantage..."*	Numerical superiority is not a recognised statistical term, and superiority is a term applied to a statistically significant difference on an endpoint powered for superiority. Since the BELA trial did not find a statistically significant difference between bosutinib and imatinib at 24 months on the primary efficacy endpoint, it is statistically	We accept the proposed amendment. In our Errata document, we change the paragraph to: *"...was not statistically significant, but had a numerical advantage..."*

		inappropriate and potentially misleading to use the term 'superior' in the context of discussing these results. If the current text is retained it could mislead some readers to believe that imatinib is statistically superior to bosutinib in the first-line context, which is inaccurate.	

Issue 4 Error in the proportion of patients previously prescribed interferon

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 58, the ERG state that 32% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy.	Please amend this figure to 33%.	This figure is incorrectly reported by the ERG.	We accept the proposed amendment. This is recorded in our Errata document.

Issue 5 Median duration of prior imatinib treatment

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 59, 2nd paragraph of the ERG report, the following is stated: *"Pfizer report the median duration of previous imatinib in the 2nd-line bosutinib chronic phase population as 2.6 years for imatinib-resistant people and as 1.5 years for imatinib-intolerant*	Delete the text underlined and replace with the following paragraph: *"Although these durations are lower than the median of 8*	It is factually inaccurate to assume the imatinib failure population in study 200 is similar to the overall imatinib population in IRIS. All participants in study 200 had failed on imatinib prior to enrolment, and so they are more similar to the IRIS population who discontinued/failed treatment rather than the majority (55%) of trial participants who continued on imatinib treatment at 8 years (Deininger 2009).	We welcome this additional information. However, we consider this issue to be a matter of judgement, not a

people (Pfizer submission, p350). Similarly, they report the median duration of previous imatinib in the 3rd-line CP population as 2.7 years (Pfizer submission, p54). <u>However, these durations are much lower than the median of 8 years on 1st-line imatinib in the IRIS trial. We are unable to account for this large discrepancy. We believe that if patients in Study 200 were truly representative of people who fail on imatinib, their median duration of imatinib should be approximately 8 years."</u>	*years on 1st line imatinib in the IRIS trial, this may be expected given that this is an imatinib failure population and is comparable to prior imatinib use in other trials of TKIs used at 2nd and 3rd line."*	Furthermore, the duration of prior imatinib therapy observed in Study 200 is similar to that observed in other second line and third line trials of CML patients who have previously failed imatinib. For example, in 2nd line CP CML patients who received dasatinib or high dose imatinib after prior imatinib failure (Kantarjian 2009), 60% had a first line imatinib duration of 3 years or less, with 11% having had less than 1 year of first line imatinib treatment. In second line CP CML patients who received nilotinib after imatinib failure, median prior imatinib use was 2.7 years (Kantarjian 2011). In the third line setting, median prior imatinib use in CML patients in CP or advanced phase ranges from 1.75 to 3.9 years across studies (Quintas-Cardama 2007, Garg 2009, Giles 2010, Russo-Rossi 2012). Therefore patients who are resistant or intolerant to imatinib, like those enrolled in study 200, are likely to have far shorter median durations of imatinib therapy than patients who do not fail on imatinib, such as the majority in the IRIS trial. In correcting this error, the ERG report will remove a misleading assertion currently being made that study 200 is not representative of second line and third line imatinib failure patients observed in clinical practice in the UK.	factual inaccuracy.

Issue 6 Pre-defined vs Post-hoc definition of MCyR

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On p.71, paragraph one, the ERG state the following: *"As mentioned in Section 4.2.4*	Please delete the first set of underlined wording and change to the following: *"...were*	It is misleading when discussing the clinical results in the clinical section of the ERG report to assert that the pre-specified results were not used, as this implies that the manufacturer did	We describe our response in our Errata document.

(p67), the protocol pre-defined analyses considering patients with baseline MCyR or CCyR as non-responders were not used. The post-hoc analyses (when both achieved and maintained MCyR or CCyR are considered to be a response) were used."	*presented in the clinical section of the submission along with the post-hoc analyses".* Please add the following after the second set of underlined wording: *"…in the economic model."*	not present them in the submission when in fact they were presented in the clinical section of the submission. It is also worth noting that including patients who maintain either MCyR or CCyR is a well accepted additional analysis that provides treating clinicians with a more clinically relevant understanding of TKI efficacy in 2nd and later lines of therapy, and is widely presented in CML trials with TKIs. Adding in text that both pre-specified and post hoc analyses were presented in the clinical section, but that only the latter were used in the model clarifies what the manufacturer actually did in the submission.	

Issue 7 Pre-defined vs Post-hoc definition of CHR

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On p.73, paragraph one, the ERG state the following: Similarly to cytogenetic responses, not the protocol pre-defined analyses considering patients with baseline CHR as non-responders, but new analyses when both, achieved and maintained response, are considered to be a response, are discussed.	Please delete the underlined wording and change to the following: '*In contrast to cytogenetic responses, the protocol pre-defined haematological analyses considered responders to be subjects who maintained a response or had a better response than at baseline, and these*	It is factually misleading when discussing the clinical results in the clinical section of the ERG report to assert that the pre-specified haematological results were not used when in fact they were. Page 49 of the study 200 CSR, states that with regard to haematological response definitions: *'To be a responder, a subject had to maintain a response or have a better response than at baseline'*. This is in contrast to the cytogenetic response primary efficacy variable analysis where 'a subject had to attain a better post-baseline response than the status at baseline to be counted as a responder' (p.47). Haematological	This is corrected in our Errata document.

	were presented in the clinical and economic sections of the submission.'	responses therefore had a different pre-specified definition of response in comparison to cytogenetic response. The above text amendment should be made in order to avoid the misrepresentations that 1) the manufacturer failed to present the pre-specified haematological response results in the submission document when it fact it did so, and 2) the pre-specified definitions of cytogenetic and haematological responder in study 200 are identical, when in fact they were not.	

Issue 8 Overall survival associated with hydroxycarbamide/hydroxyurea (HU)

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 170 (and in the executive summary) the ERG report that: *"However, we disagree when they claim that the resulting mean OS was 3.5 years (Pfizer submission, p121). Instead, Novartis assumed a mean time on HU in CP (not OS) of 3.5 years (Novartis response document, 18th Oct 2011). Using Pfizer's estimated mean times in AP of 10 months and BP*	Pfizer request that the discussion of HU OS is amended to reflect what is published in Loveman 2012 and the NICE report of TA241, published in January 2012, both of which state that HU was associated with a mean OS of 3.5 years. Pfizer also request that the ERG acknowledge the potential relevance of this third-line OS estimate of HU given	On page 52 of Loveman (2012) the following is stated: *"Novartis estimated progression-free survival and overall survival for patients on hydroxycarbamide, by analysing clinical trial data for imatinib-resistant patients who were re-treated with nilotinib and then treated with hydroxycarbamide upon nilotinib failure. It should be noted that this is a different patient group from those treated with hydroxycarbamide as second line after imatinib resistance. In the absence of any more reliable data, we have used the data and assumptions from the Novartis submission model in our analyses."* The references supporting this assumption	First, we believe that Pfizer have not identified any factual inaccuracies in our report. We urge the NICE committee to read Section 5.3.8.2, p169 in our report concerning this matter, together with Pfizer's comments here. The NICE technology appraisal guidance for 241 cited by Pfizer, http://www.nice.org.uk/nicemedia/live/13645/57823/57823.pdf ; states that that SHTAC conducted new analyses using PenTAG's model for people with imatinib-

of 6 months, gives an estimated OS for HU of 3.5 + 0.8 + 0.5 = 4.8 years. Furthermore, we, PenTAG, estimated a mean OS for HU of 7.0 years"	that the third-line cohort of Study 200 is the base-case population in both the Pfizer and ERG analyses. Equally, the ERG should make clear that comparison to a second-line population potentially over-estimates the efficacy of HU compared to the third-line bosutinib cohort.	were not clear and so Pfizer contacted Professor Loveman about this issue on 14th December 2012 but unfortunately Professor Loveman was unable to provide any clarity on the source of this data. At this point, Pfizer incorrectly assumed that the source of the data was taken from Kantarjian 2007. Nonetheless, it appears that this estimate was accepted in the final report of TA241. Indeed, Novartis even suggested that the OS for HU should be modified to 3 years after the SHTAC amendments (see p. 29 and 36) and this modification appears to be partially accepted by the Committee in their consideration of the plausible ICERs for nilotinib vs HU (p. 37 - (http://www.nice.org.uk/nicemedia/live/13645/57823/57823.pdf). Pfizer agree that based on Kantarjian 2007, the OS of patients receiving non-TKI treatments including HU is around 7 years. However, Pfizer emphasise that this is a second-line population and suggest that the OS estimate described above, which appears to be for a third-line population, is a more appropriate comparator (or this figure could be adjusted as in the Pfizer sensitivity analyses). Pfizer believe that this amendment would ensure that Committee members are aware of prior assumptions relating to the OS associated with HU and are able to make informed decisions about the plausible estimates.	resistant CML, with minor modifications (p24); "Treatment with 1.5 years of hydroxycarbamide was associated with 3.5 years of overall survival" However, we have not seen any evidence from clinical trials to support this figure. We note that Pfizer now agree with us that based on Kantarjian 2007, the OS of patients receiving non-TKI treatments including HU is around 7 years. Concerning Pfizer's point about the relevance of this study (2nd-line) to the current appraisal for bosutinib, we repeat the following from p170-1 of our report; "*Pfizer state that OS for HU in CP from Kantarjian and colleagues (2007)[3] should be viewed as an upper bound for the purposes of the current appraisal, given that the data from this study is for 2nd-line CML, whereas Pfizer's base case analysis is for 3rd-line, and we might expect OS to be lower for 3rd-line HU compared to 2nd-line HU. We agree that this is true for a 3rd-line analysis. However, as stated in Section 5.3.5, p161, there is uncertainty as to whether bosutinib would be more likely to be used 2nd- or 3rd-line in England & Wales were it approved by NICE. If it is more likely to be used 2nd-line, then OS from Kantarjian and colleagues (2007)[3] is then appropriate*."

Issue 9 Overall survival associated with stem cell therapy (SCT)

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On pages 172 and 173, the ERG assert that Oehler 2007 is the more relevant study to use in the base-case estimates of SCT OS, given that the sample size is greater and that: *"...we believe that bosutinib may be used for 2nd-line treatment and hence it is relevant to estimate OS for SCT in 2nd-line."*	Given the likely population for bosutinib described in issue 1 above, Pfizer request that the ERG acknowledge that it is highly conservative to compare a 2nd line SCT population with a 3rd line bosutinib population. Pfizer also request that figure 24 on p. 124 is amended to reflect the considerable differences in the populations between these studies, which may explain the differential OS estimates.	In agreement with the population outlined in issue 1, the third-line cohort is used by the ERG in the base case of Study 200. Therefore, although Jabbour 2011 is a small study, Pfizer maintain that this is the most appropriate comparator as it is the only predominantly third-line SCT study. Both Oehler 2007 and Sauselle 2010 comprise of young patients who received imatinib for short durations (median 0.83 in Oehler 2007) and 100% and 8% were at second-line respectively. Schleuning (2010) is also not felt to be comparable to the Study 200 cohort as these patients had not received 1st line imatinib, and again consist of 2nd and 3rd line patients. Pfizer believe that this amendment would ensure that Committee members are fully aware of the assumptions relating to OS associated with SCT and are able to make informed decisions about the plausible estimates.	Once again, we believe that Pfizer have not identified any factual inaccuracies in our report. There are pros and cons of using each trials. Also, Pfizer claim that Jabbour 2011 is the only predominantly third-line SCT study. However, it is not clear whether the patients in Schleuning (2010) were predominantly 2nd- or 3rd-line, as we this publication says only that patients had been treated with "*nilotinib and/or dasatinib*". However, we think this is not the place for a full discussion of the relevance of the various clinical trials to the current appraisal. We urge the NICE committee to read Section 5.3.8.3, p171 in our report concerning this matter, together with Pfizer's comments here.

Issue 10 Appropriateness of the cumulative survival approach

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 190, the ERG state that: *"The key assumption of the Cumulative Survival method is that, in the (Bosutinib, HU) arm, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. None of Assumptions 1–7 (Table 65, p164), which are necessary for Pfizer's methods of estimating OS, are required."* Similarly, on page 201, the ERG state that: *"By contrast, the Cumulative Survival method requires just a single assumption and gives far more plausible estimates for the times on treatment."*	Pfizer request that the statements relating to assumptions for the cumulative survival approach are modified to reflect the additional key assumption that patients who stop bosutinib treatment (regardless of reason) immediately resume a hydroxycarbamide survival curve. Additionally, Pfizer request that the statement on page 202 is amended to reflect the fact that the ERG cannot be sure that the cumulative survival method over-estimates the bosutinib OS. Finally, Pfizer request that the ERG make clear the inconsistencies between this approach and that taken in TA241, on which recommendations were made about the use of TKIs in refractory CML.	Pfizer recognise that there is uncertainty around the estimation of OS for bosutinib, but feel that to assume an immediate resumption of a hydroxycarbamide survival curve (a key assumption not documented by the ERG) is highly pessimistic. We feel that the cumulative survival approach is unlikely to over-estimate the OS associated with bosutinib and hence cost-effectiveness, for the following reasons: 1. If we look at the population with the most mature OS data, blast phase patients; the OS predicted by fitting a curve to the data is 1.77 compared to [redacted] years predicted by the cumulative survival approach. A difference of around 7 months in OS in this advanced population would be highly significant to patients and there is no justification provided by the ERG as to this reduction in OS. 2. This approach is inconsistent with the previous refractory CML appraisal and if used, would potentially have changed the recommendations. According to Loveman (2012, table 41), the OS for dasatinib and nilotinib was 13.4 and 13.0 yrs respectively, with treatment durations of 3.1 and 2.4 yrs respectively. Had the cumulative survival approach been used in this appraisal, the new OS for dasatinib and nilotinib would have been only 10.1 and 9.4 years respectively (assuming 7 years OS for HU, as per the current ERG base-case). However, in TA241, it was assumed that the OS for	Once again, we believe that Pfizer have not identified any factual inaccuracies in our report. We have explained our Cumulative Survival method carefully both in a technical and non-technical style. We do not think our statement on p202 is factually inaccurate: "*If anything, the Cumulative survival method may slightly over-estimate OS in the bosutinib arm, and therefore is favourable to the cost-effectiveness of bosutinib, for three reasons*." This is because this is a matter of opinion, not a factual inaccuracy and because we do not say that "we are sure" that the method over-estimate OS in the bosutinib arm. Instead, we say that the method "*may slightly"* over-estimate OS in the bosutinib arm. On p166 of our report, we clearly state that we used a surrogate survival approach to estimate OS for the TKIs in TA241. Furthermore, we discuss this

Finally, on page 202, the ERG state that: *"If anything, the Cumulative survival method may slightly over-estimate OS in the bosutinib arm, and therefore is favourable to the cost-effectiveness of bosutinib, for three reasons."*		HU was in fact 3.5 years. The base-case ICER from SHTAC with PAS for nilotinib vs HU was £27K (HU OS 3.5 yrs, Nil TOT 6.5 yrs, Nil OS 13 years). As such, if HU OS was increased to 7 years and Nil OS reduced to 9 years in this analysis, to more closely represent the current ERG assumptions, it is highly likely the ICER would have been >£30K even with the PAS. 3. As noted by the ERG on page 60, the inclusion of patients with T315I and V229L mutations in Study 200 is likely to have resulted in under-estimated efficacy results and therefore an improved ICER would be expected. 4. As noted by the ERG on page 71, the response rates in the post-hoc analysis group are actually higher than those in the full group. Again, it is therefore possible that efficacy is under-estimated in the model, and an improved ICER may be expected.	choice in the light of the current appraisal. Pfizer now present 4 arguments to support their assertion that the cumulative survival approach is unlikely to over-estimate OS for bosutinib. First, we stress that our base case analysis does not allow for our belief that the Cumulative Survival method may slightly over-estimate OS in the bosutinib arm. Second, we believe that there are counter-arguments to points 1, 3 and 4 now raised by Pfizer, which are to be found in our report. Finally, we do not believe that it is appropriate here to discuss the impact of using the Cumulative Survival method to estimate the cost-effectiveness of TKIs from previous appraisals.

Issue 11 Comparison of acquisition costs

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On pages 179 and 180, the ERG describes the annual acquisition costs of the currently available TKIs (excluding nilotinib) compared to	Pfizer request that this comparison is removed.	Pfizer considers it is inappropriate to include a direct cost comparison to drugs that are not comparators for bosutinib in the scope of this appraisal. Any comparison of bosutinib to	Once again, this is not a factual inaccuracy.

bosutinib.		treatments not in the scope exceeds the agreed remit of the appraisal.	

Issue 12 Scenario analysis assuming treatment until progression

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On pages 176 and pages 231, the ERG discuss a sensitivity analysis that assumes patients stay on treatment until progression into AP or BP. On page 231, the ERG specifically state that: *"...if bosutinib is received until transformation to AP (as might be the case if bosutinib is the last available TKI for a patient)"*	Pfizer request that the ERG remove this highly conservative and potentially clinically inappropriate scenario analysis, for the reasons described to the right, or provide a more accurate description of the assumptions relating to this scenario. In addition, clarification is needed about how this scenario analysis is applied in the context of a cumulative survival approach, specifically how time pre-progression is derived for bosutinib.	Pfizer suggest that this is a clinically inappropriate scenario analysis for a number of reasons: 1. This contradicts the treatment durations taken from Study 200, which represents mature discontinuation data, with median durations reached in all cohorts. 2. It is reasonable to assume, and clinically plausible, that if all patients did stay on treatment until progression, there would be a corresponding increase in OS; particularly given that around 20% of patients discontinued Study 200 in the 3rd line cohort due to tolerability, rather than lack of efficacy. 3. Finally, if this approach is justified on the basis that 'bosutinib is the last available TKI', implying that even patients who lose response stay on treatment, this assumption should equally apply to currently available TKIs. Therefore, the appropriate cost comparator in this scenario would be a 'failed' TKI. This would have a significant impact on the ICER given the substantial differential in cost between TKIs and	Once again, this is not a factual inaccuracy. First, this is a scenario analysis, and is not part of our base case. Second, we performed this analysis on the advice of our clinical advisor and haematologist, Dr Rudin. We do, however, draw the committee's attention to Pfizer's 3rd point. We believe this issue is best discussed further by the Appraisal Committee. The implementation of this scenario analysis in the context of the cumulative survival method is as follows: 1. All times in treatment are held fixed 2. The cost of (Bosutinib, HU) CP Off Treatment (denoted $C_{BOS,HU}^{HU\,4}$) is scaled by a factor of [redacted] which is calculated as the ratio of the monthly cost of (Bosutinib, HU) CP On Treatment

		HU. This scenario analysis has a significant impact on the ICER in both the Pfizer and PenTAG analyses and therefore introduces significant uncertainty to the Committee. It is therefore vital to ensure the likelihood and validity of the scenario analysis is appropriately reflected in order to make a more informed decision.	(named c_cpt_bos in Pfizer's model) and the monthly cost of bosutinib CP Off Treatment (named c_cpd_bos in Pfizer's model) This requires an additional assumption that even though more time would be spent on bosutinib, there would be no corresponding benefit in terms of time pre-transformation to AP. The validity of this assumption was not explored by PenTAG as it is only a scenario analysis and not a part of the base case.

Issue 13 Cost-effectiveness planes drawn by the Evidence Review Group

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 194 (figure 29) and on page 197 (figure 32) the cost-effectiveness planes plotted by the ERG contain an inaccurate cost-effectiveness frontier.	Figures should be redrafted to only connect points on the frontier, in the case of Figure 29, hydroxycarbamide and bosutinib.	Although these figures do not affect the results of the model, the presentation is confusing, and suggests that Stem Cell Transplant lies on the cost-effectiveness frontier, when it is actually dominated by bosutinib treatment in two of the three scenarios (in Figure 35 it does lie on the cost-effectiveness frontier).	This is not an error. The dashed lines indicate the comparisons which are presented as relevant. There is no claim that these lines represent the cost-effectiveness frontier.

Issue 14 AP and BP sensitivity analysis on HU OS

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 215, the ERG describe a sensitivity analysis for the AP cohort in the PenTAG base-case, where HU OS is assumed to equal the time *"...we increased the overall survival of HU from 1.37 to [redacted] years to match the time spent in AP off bosutinib treatment in the (Bosutinib, HU) arm"* The same analysis is described on page 215 for the blast phase cohort.	Pfizer request the ERG to clarify how this scenario analysis works under a cumulative survival approach.	It is not clear how the OS for HU can be increased to [redacted] years under a cumulative survival approach, where the time in AP off bosutinib is assumed to be the same as HU in AP (i.e. 9 months). Although the impact of this scenario analysis on the ICER is small, Pfizer feel that clarification on this analysis would support greater understanding of how the uncertainty around HU OS impacts the cost-effectiveness of bosutinib.	The OS for HU is increased by adjusting the HU output from Pfizer's model. The resulting time in AP and BP in Pfizer's model are then fed into the cumulative survival approach as before. We describe this in more detail in our Errata document, as well as modifications to the analysis which are felt, on reflection, to be more appropriate.

Issue 15 End of life criteria

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 217, concerning the end of life criteria 1, the ERG state that: *"In summary, it seems likely that the life expectancy for patients*	Pfizer request that the ERG remove the statement underlined to the left.	This statement is not aligned with the ERG's previous critique of our approach to estimating OS in AP and could therefore cause confusion about whether	Once again, Pfizer have not identified any factual inaccuracies in our report. Without more details, it is difficult to respond to Pfizer's claim that "*This statement is not aligned with the ERG's previous critique of our approach to estimating*

on an appropriate comparator treatment is close to the threshold of 24 months... Also, Pfizer estimate a mean time on HU after bosutinib of [redacted]."		this criterion is met or not.	*OS in AP*". However, we assume that Pfizer are referring to our base case assumption of a mean OS in the HU arm in AP of 1.37 years. We state in our report that this parameter is uncertain. The important assumption in our base case analysis is to invoke the Cumulative Survival method, under which the cost-effectiveness of bosutinib is rather insensitive to the mean OS in the HU arm.

References

Deininger M, O'Brien SG, Guilhot F et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib, ASH 51, 2009. https://ash.confex.com/ash/2009/webprogram/Paper23968.html

EPAR, European Medicines Agency Assesment Report for Bosulif/bosutinib, CHMP, January 2013.http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002373/WC500141745.pdf

Garg RJ, Kantarjian H, O'Brien S, Quintás-Cardama A, Faderl S, Estrov Z,Cortes J. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood. 2009 Nov 12;114(20):4361-8.

Giles FJ, Abruzzese E, Rosti G, Kim DW, Bhatia R, Bosly A, Goldberg S, Kam GL, Jagasia M, Mendrek W, Fischer T, Facon T, Dünzinger U, Marin D, Mueller MC, Shou Y, Gallagher NJ, Larson RA, Mahon FX, Baccarani M, Cortes J, Kantarjian HM. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. Leukemia. 2010 Jul;24(7):1299-301.

Hoyle M et al. General Methodoogical issues in cost-effectiveness analysis inspired by the assessment of dasatinib, nilotinib and imatinib for 1st-line chronic myeloid leukaemia. Value in Health 2012 15: A277 – A575

Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-7.

Kantarjian H, Pasquini R, Lévy V,. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). Cancer. 2009 Sep 15;115(18):4136-47.

Kantarjian HM, Giles FJ, Bhalla KN. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood. 2011 Jan 27;117(4):1141-5.

Loveman E, Cooper K, Bryant J, et al. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: A systematic review and economic evaluation. Health Technology Assessment 2012;16:1-137.

NICE. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. Jan 2012. Available at: http://www.nice.org.uk/nicemedia/live/13645/57823/57823.pdf

Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-9.

Quintas-Cardama A, Kantarjian H, Jones D, Dasatinib (BMS-354825) is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib(AMN107) therapy failure. Blood. 2007 Jan 15;109(2):497-9.
Rossi AR, Breccia M, Abruzzese E. Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors. Haematologica 2013;98.
Schleuning M, Scholten M, van Biezen A, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia after prior treatment with nilotinib or dasatinib, In 52nd Annual Meeting of the American Society of Hematology, 2010.

Errata to PenTAG report for NICE

Bosutinib for previously treated chronic myeloid leukaemia STA: a single technology appraisal

31st May 2013

Updated 11th June 2013 (corrupted section references in Section 1 corrected and page breaks inserted to aid readability)

In this document, we describe errata identified in the light of the factual inaccuracies in our report uncovered by Pfizer.

None of these errors affects our base case ICERs for bosutinib.

Commercial in confidence information is underlined and highlighted turquoise, e.g., [redacted].
Academic in confidence information is underlined and highlighted yellow, e.g., [redacted].

1 RESPONSE TO ISSUE 1 (CLINICAL EFFECTIVENESS SUB-POPULATION CLAIM)

Pfizer described the following problem:

> Within the bosutinib summary of safety section on page 26, the ERG report states the following:
>
> *"In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI."*
>
> Similarly, on page 106 in the "conclusions of the clinical effectiveness section" of the ERG report, the following is stated:
>
> *"Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI."*

Pfizer requested that the underlined text be removed as they did not agree with the statements above.

We were citing European Medicines Agency Assessment Report for Bosulif/bosutinib (EPAR). Thus instead of removing the sentences, the reference for EPAR should be added:

"In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TK (EPAR)."

"Bosutinib was associated with good cytogenetic and haematological responses and overall survival (Table 2, p25), although due to cross-resistance between second generation TKI, clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI (EPAR)."

References:

EPAR, European Medicines Agency Assessment Report for Bosulif/bosutinib, CHMP, January 2013 (http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002373/WC500141745.pdf)

2 RESPONSE TO ISSUE 3 (COMPARISON OF BOSUTINIB VS. IMATINIB AT 1ST LINE)

Pfizer described the following problem:

On page 48, paragraph 1 of the ERG report the following is stated: *"In this RCT, bosutinib failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib."*

Pfizer highlighted the fact that numerical superiority does not imply statistical significance, and suggested the following change (underlined) which we accept:

"In this RCT, bosutinib failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib <u>was not statistically significant, but had a numerical advantage compared to</u> bosutinib."

3 RESPONSE TO ISSUE 4 (ERROR IN THE PROPORTION OF PATIENTS PREVIOUSLY PRESCRIBED INTERFERON)

Pfizer described the following problem:

On page 58, the ERG state that 32% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy.

Pfizer identified an error on page 58 of our report, first paragraph, in the following sentence (underlined):

"…In fact, 52% of 3rd-line CP patients and 32% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy..."

This should read:

"…In fact, 52% of 3rd-line CP patients and 33% of 2nd-line CP patients in Study 200 had previously had interferon alpha therapy…"

4 RESPONSE TO ISSUE 6 (PRE-DEFINED VS POST-HOC DEFINITION OF MCYR)

Pfizer described the following problem:

> On p.71, paragraph one, the ERG state the following:
>
> *"As mentioned in Section 4.2.4 (p67), the protocol pre-defined analyses considering patients with baseline MCyR or CCyR as non-responders were not used. The post-hoc analyses (when both achieved and maintained MCyR or CCyR are considered to be a response) were used."*

Pfizer request deleting the underlined wordings and requested to add that both pre-specified and post hoc analyses were presented in the clinical section, but that only the latter were used in the model (to clarify what the manufacturer did in the submission).

We reviewed the suggested amendments and since the mentioned paragraph refers to Section 4.2.4 (p67), and because of an error identified below (Issue 7), we amend paragraph 5 on page 67 instead. We delete the underlined wording:

"…The new analyses consider patients who maintained or achieved a cytogenetic or haematological response as responders. Using the two approaches, 32%, or 38.9% of third-line CP CML patients, achieved, or attained and achieved MCyR at 12 months minimum follow up respectively. The results of the post-hoc analyses, with higher response rates, when both achieved and maintained response are considered to be a response, were reported in Pfizer submission, and are used in the cost-effectiveness model…"

And add (underlined below): "…*While both the protocol pre-defined and the post hoc analyses were presented in the clinical section of the submission*…"

The corrected paragraph should read:

"…The new analyses consider patients who maintained or achieved a cytogenetic response as responders. Using the two approaches, 32%, or 38.9% of third-line CP CML patients, achieved, or attained and achieved MCyR at 12 months minimum follow up respectively. While both the protocol pre-defined and the post hoc analyses were presented in the clinical section of the submission, the results of the post-hoc analyses, with higher response rates, when both achieved and maintained response are considered to be a response, are used in the cost-effectiveness model…"

5 RESPONSE TO ISSUE 7 (PRE-DEFINED VS POST-HOC DEFINITION OF CHR)

Pfizer described the following problem:

On p.73, paragraph one, the ERG state the following*: Similarly to cytogenetic responses, not the protocol pre-defined analyses considering patients with baseline CHR as non-responders, but new analyses when both, achieved and maintained response, are considered to be a response, are discussed.*

Pfizer identified an error and requested deleting the underlined wordings.

We accept the proposed amendment and change the sentence to the following:

'…In contrast to cytogenetic responses, the protocol pre-defined haematological analyses considered responders to be subjects who maintained a response or had a better response than at baseline, and these were presented in the clinical and economic sections of the submission…'

6 RESPONSE TO ISSUE 14 (AP AND BP SENSITIVITY ANALYSIS ON HU OS)

Pfizer described the following problem:

> On page 215, the ERG describe a sensitivity analysis for the AP cohort in the PenTAG base-case, where HU OS is assumed to equal the time
>
> *"...we increased the overall survival of HU from 1.37 to [redacted] years to match the time spent in AP off bosutinib treatment in the (Bosutinib, HU) arm"*
>
> The same analysis is described on page 215 for the blast phase cohort.

Pfizer requested that PenTAG clarify how this sensitivity analysis was carried out using the cumulative survival approach.

The general principle when conducting these sensitivity analyses was to adjust Pfizer's model to achieve the desired HU OS and then feed the relevant times in AP and BP into the cumulative survival approach.

We describe this in more detail below, as well as modifications to the analysis which are felt, on reflection, to be more appropriate.

6.1 AP sensitivity analysis

Under the cumulative survival approach we made the following calculations:

1. We set cell E34 in sheet "Inputs-AP" equal to [redacted] months
2. This resulted in T_{HU}^{HU} (notation as in Table 94, Section 9.20.1, p293) increasing from 1.02 to [redacted] years, T_{HU}^{BP} Increasing from 0.35 to 0.38 years and OS for HU increasing from 1.37 to [redacted] years
3. The cumulative survival approach was calculated as before as specified in Table 95 (Section 9.20.1, p294)

Upon reflection PenTAG believe this sensitivity analysis was flawed for the following reasons:

1. The OS for HU should have been increased to match the total time spent off bosutinib treatment, i.e., AP off treatment *plus* BP (which is [redacted] years rather than [redacted] years)
2. Cell E34 can be set to a non-integer value which would have allowed the overall survival for HU to match the time off bosutinib treatment exactly

The analysis was conducted again to address these issues such that now the OS for HU is increased from 1.37 to [redacted] years as follows:

1. We set cell E34 in sheet "Inputs-AP" equal to [redacted] months (note that it was not necessary to set cell E34 to a non-integer value)
2. This resulted in T_{HU}^{HU} increasing from 1.02 to [redacted] years, T_{HU}^{BP} increasing from 0.35 to 0.40 years, and overall survival for HU increasing from 1.37 to [redacted] years
3. The cumulative survival approach was calculated as before as specified in Table 95 (Section 9.20.1, p294)

After reconducting this analysis, the corrected ICERs in the sensitivity analysis are shown in Table 1 and Table 2 (ICERs in bold are the comparisons deemed most relevant).

Table 1. Sensitivity analysis applied to PenTAG base case for AP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	Dominant	[redacted]	[redacted]
HU OS = Time in Bosutinib arm off treatment [redacted]	[redacted]	Dominant	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 2. Sensitivity analysis applied to Pfizer base case for AP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	Dominant
HU OS = Time in Bosutinib arm off treatment [redacted]	[redacted]	n/c

n/c – Not changed from base case
Shading as in Table 1

6.2 BP sensitivity analysis

Under the cumulative survival approach we made the following calculations:

1. We set cell N88 in sheet "Parameters" to [redacted] months
2. This resulted in T_{HU}^{HU} (which is also the OS for HU) increasing from 0.54 to [redacted] years
3. The cumulative survival approach was calculated as before as described in Table 98 (Section 9.20.2, p295)

This sensitivity analysis contains the same minor flaw that it assumed the need for cell N88 to take an integer value. In the CP and AP models N88 is effectively rounded down but in the BP model for HU it is allowed to be non-integer. Note that this analysis does not contain the significant flaw of the AP analysis where time in BP was not included.

The analysis was reconducted using a non-integer value for N88 to match the OS for HU to the time in BP off bosutinib treatment as follows:

1. Cell N88 in sheet "Parameters" was set to [redacted] months
2. This resulted in T_{HU}^{HU} (which is also the OS for HU) increasing from 0.54 to [redacted] years
3. The cumulative survival approach was calculated as before as described in Table 98 (Section 9.20.2, p295)

The corrected ICERs in the sensitivity analysis then are shown in Table 3 and Table 4 (ICERs in bold are the comparisons deemed most relevant).

Table 3. Sensitivity analysis applied to PenTAG base case for BP model

Intervention	**(Bosutinib, HU) vs.**		**(Bosutinib, SCT) vs.**	
Comparator	***HU***	*SCT*	*HU*	***SCT***
PenTAG base case	[redacted]	[redacted]	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n/c – Not changed from base case

[redacted]

Table 4. Sensitivity analysis applied to Pfizer base case for BP model

Intervention	**(Bosutinib, HU) vs.**	
Comparator	***HU***	*SCT*
Pfizer base case	[redacted]	[redacted]
HU OS = Time in Bosutinib BP Off Treatment [redacted]	[redacted]	n/c

n/c – Not changed from base case
Shading as in Table 3

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6 June 2013

Dear [redacted]

Patient Access Scheme proposal: bosutinib (Bosulif)

I am writing to confirm the Department of Health's position on the Patient Access Scheme (PAS) arrangements that have been proposed by Pfizer for bosutinib (Bosulif), which is being appraised by NICE for the treatment of adult patients with chronic myeloid leukaemia. The proposal is for a simple discount scheme, with the discount applied at the point of purchase or invoice.

I understand that Pfizer has proposed the simple discount PAS on the condition that the level of discount offered through the scheme should remain confidential and should not be published in final NICE guidance.

The Department is content for the PAS proposal to be considered in the relevant appraisal, with the level of discount remaining confidential.

NICE must, of course, be satisfied that sufficient information can be communicated to stakeholders to explain an appraisal recommendation. In this regard, what constitutes a sufficient level of transparency is a matter for the Institute to determine in developing its guidance. In addition, the NHS must have access to the discount price when final NICE guidance is made available, so Trusts and commissioners are able properly to account for the PAS.

Yours sincerely

[redacted],
Medicines, Pharmacy and Industry Group

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

The patient access scheme will apply to bosutinib (Bosulif®), which is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP) and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

3.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme aims to improve patient access and cost effectiveness of bosutinib when used in adult patients, with a high unmet clinical need, because they are unsuitable for treatment with all of the currently available TKIs (imatinib, nilotinib and dasatinib).

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme is a simple discount, which is conditional on the level of discount offered remaining confidential and not being published in NICE guidance. It is proposed that NHS Trust procurement entities that have entered into a contract with Pfizer, containing appropriate confidentiality provisions, will purchase bosutinib at a discount applied to the invoice at the point of purchase.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme will apply to the full licensed population, as described in Section 3.1.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent upon any criteria and is simply applied as a discount.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme will apply to all NHS patients for whom bosutinib is indicated and where the NHS procurement entities have entered into an agreement with appropriate confidentiality provisions with Pfizer.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

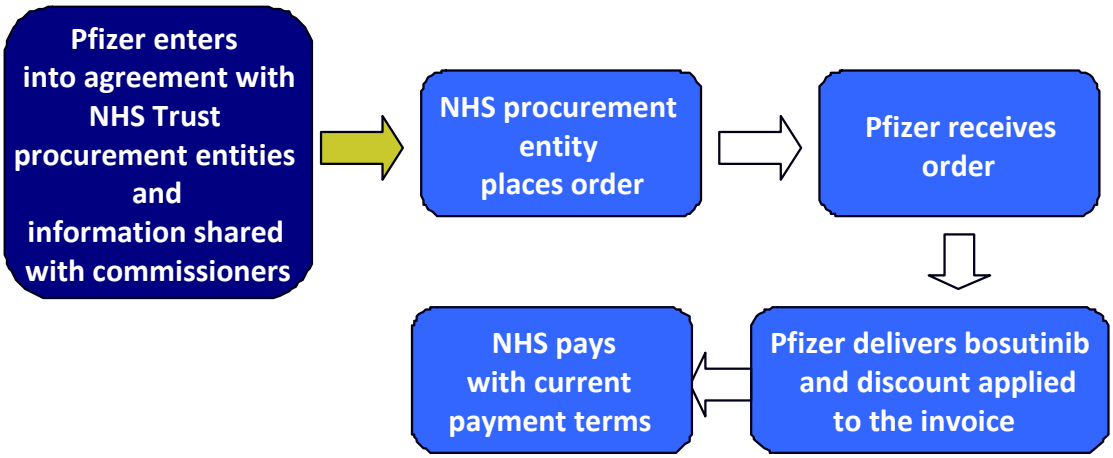
The discount will be applied at the point of invoice.The current list price for bosutinib 500mg/28 tablets pack is £3436.67 and for bosutinib 100mg/28 tablets pack is £859.17.

[redacted]. As noted above, these details are provided in confidence.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will be applied at the point of invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the scheme.

The proposed patient access scheme will be conditional upon:

(1) NICE positive guidance for bosutinib use in adult patients with chronic phase (CP), accelerated phase (AP) and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

(2) The relevant NHS procurement entity entering into a contract with Pfizer that contains appropriate confidentiality provisions; and will remain in place so long as NICE positive guidance exists for bosutinib review and subject to Department of Health agreement.

This PAS is conditional on the level of discount offered remaining confidential and not being published in NICE guidance.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme taking into account current legislation.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Not applicable.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been applied by reducing the current NHS list price of bosutinib.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The PAS is a simple discount and therefore does not impact the clinical effectiveness data used in the evidence synthesis or in the economic model.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The PAS is a simple discount introduced at the point of invoice and as a result will not be associated with operational or implementation costs.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 1 Base-case cost-effectiveness results CP – Without PAS

	Bosutinib	Hydroxycarbamide	SCT	Interferon
Intervention cost (£)	[redacted]	£490	£141,132	£8,461
Other costs (£)	[redacted]	£28,983	£30,407	£29,808
Total costs (£)	[redacted]	£29,473	£171,539	£38,268
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]
LYG	12.75	3.52	6.60	3.62
LYG difference	N/A	9.23	6.16	9.14
QALYs	7.26	2.43	3.70	2.42
QALY difference	N/A	4.83	3.56	4.84
ICER (£)	N/A	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 2 Base-case cost-effectiveness results CP – With PAS

	Bosutinib	Hydroxycarbamide	SCT	Interferon
Intervention cost (£)	£73,332	£490	£141,132	£8,461
Other costs (£)	£57,421	£28,983	£30,407	£29,808
Total costs (£)	£130,752	£29,473	£171,539	£38,268
Difference in total costs (£)	N/A	£101,279	-£40,787	£92,484
LYG	12.75	3.52	6.60	3.62
LYG difference	N/A	9.23	6.16	9.14
QALYs	7.26	2.43	3.70	2.42
QALY difference	N/A	4.83	3.56	4.84
ICER (£)	N/A	£20,972	Dominated	£19,105

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 3 Base-case cost-effectiveness results AP – Without PAS

	Bosutinib	Hydroxycarbamide	SCT
Intervention cost (£)	[redacted]	£204	£130,528
Other costs (£)	[redacted]	£25,874	£47,565
Total costs (£)	[redacted]	£26,078	£178,093
Difference in total costs (£)	N/A	[redacted]	[redacted]
LYG	4.48	1.37	3.02
LYG difference	N/A	3.11	1.46
QALYs	2.76	0.90	1.96
QALY difference	N/A	1.86	0.8
ICER (£) (vs Bosutinib)	N/A	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4 Base-case cost-effectiveness results AP – With PAS

	Bosutinib	Hydroxycarbamide	SCT
Intervention cost (£)	£60,511	£204	£130,528
Other costs (£)	£65,727	£25,874	£47,565
Total costs (£)	£126,237	£26,078	£178,093
Difference in total costs (£)	N/A	£100,159	-£51,855
LYG	4.48	1.37	0.00
LYG difference	N/A	3.11	3.02
QALYs	2.76	0.90	0.00
QALY difference	N/A	1.86	1.96
ICER (£) (vs bosutinib)	N/A	£53,789	Dominated

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5 Base-case cost-effectiveness results BP – Without PAS

	Bosutinib	Hydroxycarbamide	SCT
Intervention cost (£)	[redacted]	£82	£157,759
Other costs (£)	[redacted]	£14,088	£42,767
Total costs (£)	[redacted]	£14,170	£200,526
Difference in total costs (£)	N/A	[redacted]	[redacted]
LYG	1.77	0.54	2.64
LYG difference	N/A	1.23	-0.87
QALYs	0.88	0.28	1.28
QALY difference	N/A	0.6	-0.4
ICER (£) (vs bosutinib)	N/A	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio. * SCT is more expensive and more effective than bosutinib in the BP, ICER for SCT over bosutinib presented.

Table 6 Base-case cost-effectiveness results BP – With PAS

	Bosutinib	Hydroxycarbamide	SCT
Intervention cost (£)	£17,882	£82	£157,759
Other costs (£)	£32,054	£14,088	£42,767
Total costs (£)	£49,936	£14,170	£200,526
Difference in total costs (£)	N/A	£35,765	-£150,590
LYG	1.77	0.54	2.64
LYG difference	N/A	1.23	-0.87
QALYs	0.88	0.28	1.28
QALY difference	N/A	0.60	-0.40
ICER (£)	N/A	£59,191	£117,577*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio. * SCT is more expensive and more effective than bosutinib in the BP, ICER for SCT over bosutinib presented.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 7 Base-case incremental results – without PAS

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYGs	ICER (£) incremental (QALYs)
CP							
Hydroxycarbamide	£29,473	2.43	3.52				
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SCT	£171,539	3.70	6.60	[redacted]	[redacted]	[redacted]	[redacted]
AP							
Hydroxycarbamide	£26,078	0.90	1.37				
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SCT	£178,093	1.96	3.02	[redacted]	[redacted]	[redacted]	[redacted]
BP							
Hydroxycarbamide	£14,170	0.28	0.54				
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SCT	£200,526	1.28	2.64	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 8 Base-case incremental results – with PAS

Technologies	Total costs (£)	Total QALYs	Total LYs	Incremental costs (£)	Incremental QALY	Incremental LYG	ICER (£) incremental (QALYs)
CP							
Hydroxycarbamide	£29,473	2.43	3.52				
Interferon	£38,268	2.42	3.62	£8,795	-0.01	0.10	Dominated
Bosutinib	£130,752	7.26	12.75	£101,279	4.83	9.23	£20,972
SCT	£171,539	3.70	6.60	£40,787	-3.56	-6.16	Dominated
AP							
Hydroxycarbamide	£26,078	0.90	1.37				
Bosutinib	£126,237	2.76	4.48	£100,159	1.86	3.11	£53,789
SCT	£178,093	1.96	3.02	£51,855	-0.80	-1.45	Dominated
BP							
Hydroxycarbamide	£14,170	0.28	0.54				
Bosutinib	£49,936	0.88	1.77	£35,765	0.60	1.23	£59,191
SCT	£200,526	1.28	2.64	£150,590	0.40	0.87	£380,037

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

There are a number of uncertainties in the economic model for bosutinib. However, relatively few of these are parameter uncertainties, with the uncertainty relating to a structural assumption e.g. the appropriate utilities to use. Extensive sensitivity analyses are therefore presented in Section 4.11 below, including deterministic and scenario analyses.

Tornado diagrams are not presented, as the majority of important assumptions (approach used to overall survival, time on treatment assumptions, etc.) are not related to the value used, but the approach selected. A tornado diagram would be misleading, in omitting many of the more sensitive areas of the model.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 1 CP Scatter plot – Without PAS

Figure 2 CP Cost-effectiveness acceptability curve – Without PAS

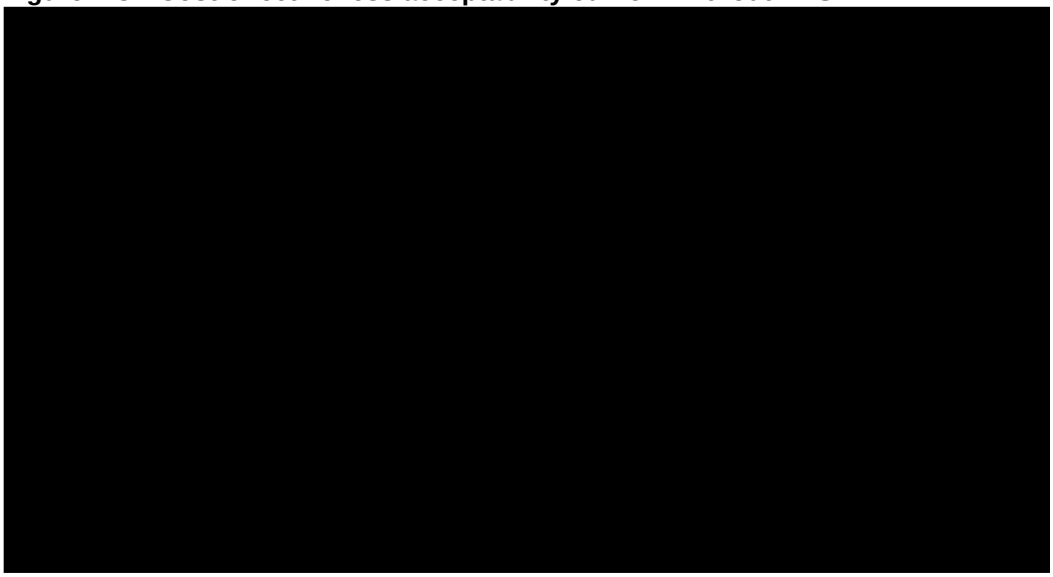


Figure 3 CP scatter plot – With PAS

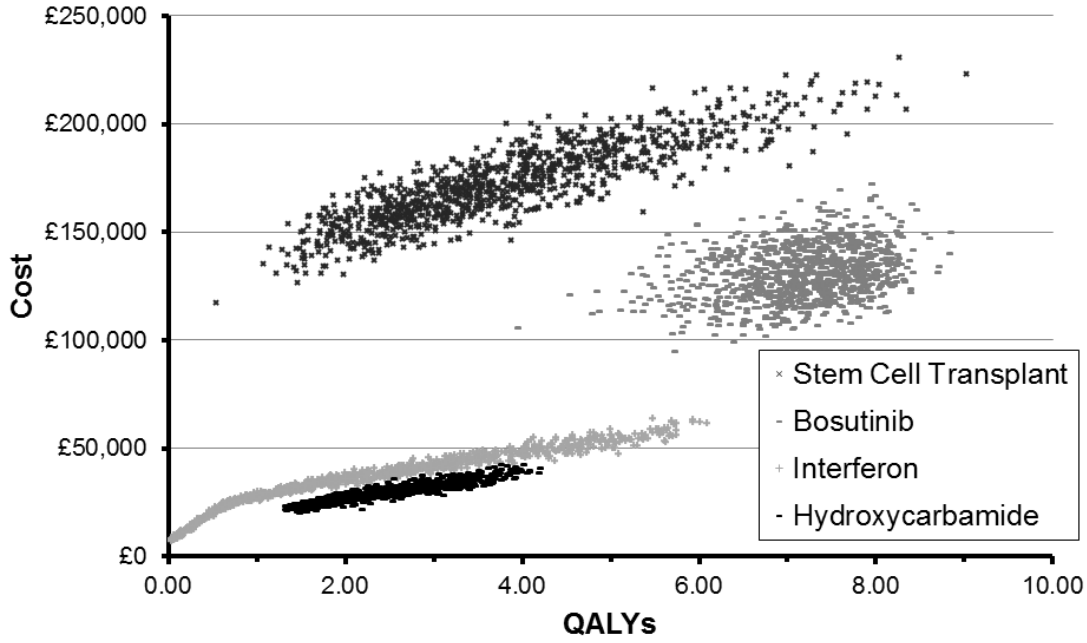


Figure 4 CP Cost-effectiveness acceptability curve – With PAS

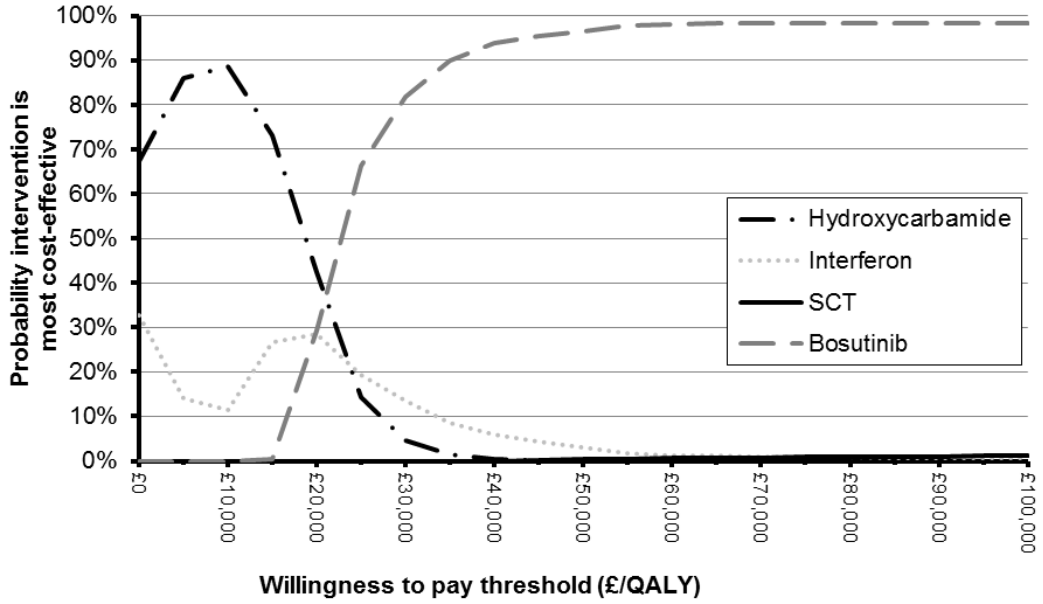


Figure 5 AP scatter plot – Without PAS

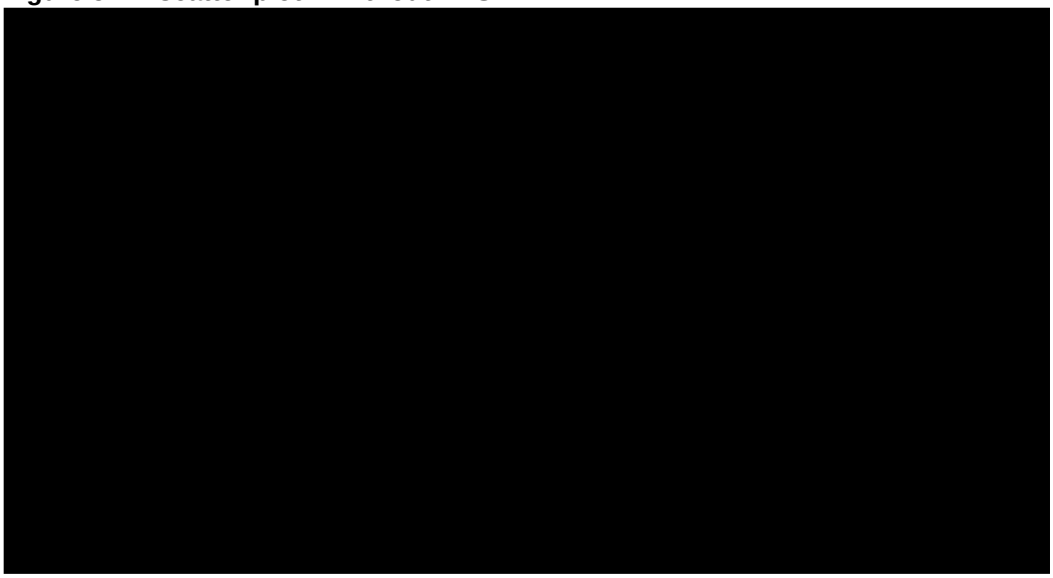


Figure 6 AP Cost-effectiveness acceptability curve – Without PAS

Figure 7 AP scatter plot – With PAS

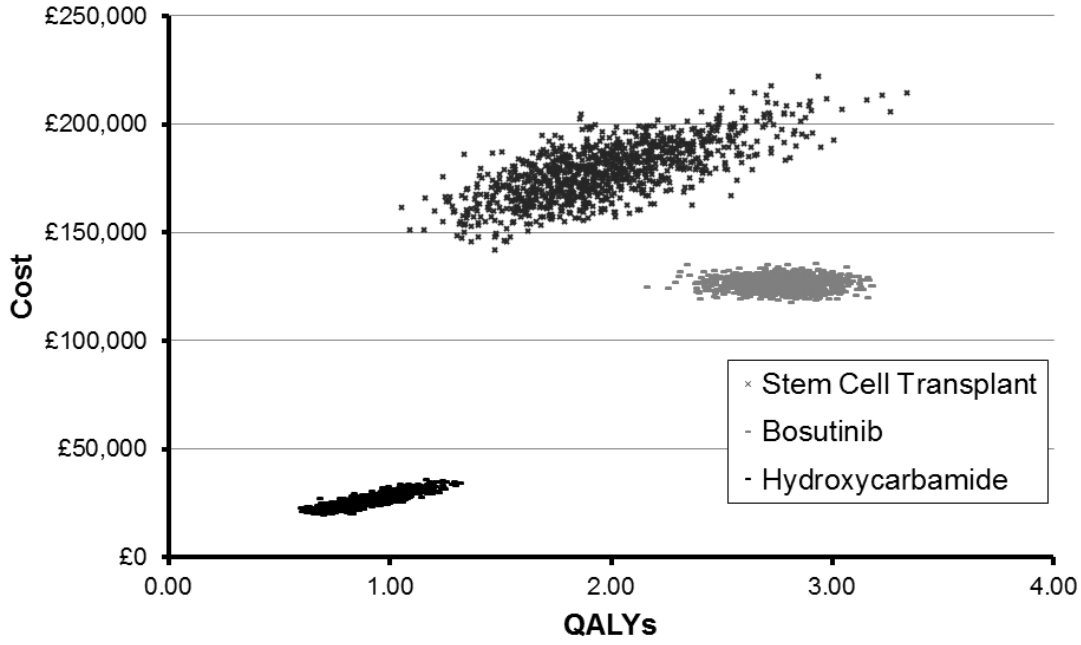


Figure 8 AP Cost-effectiveness acceptability curve – With PAS

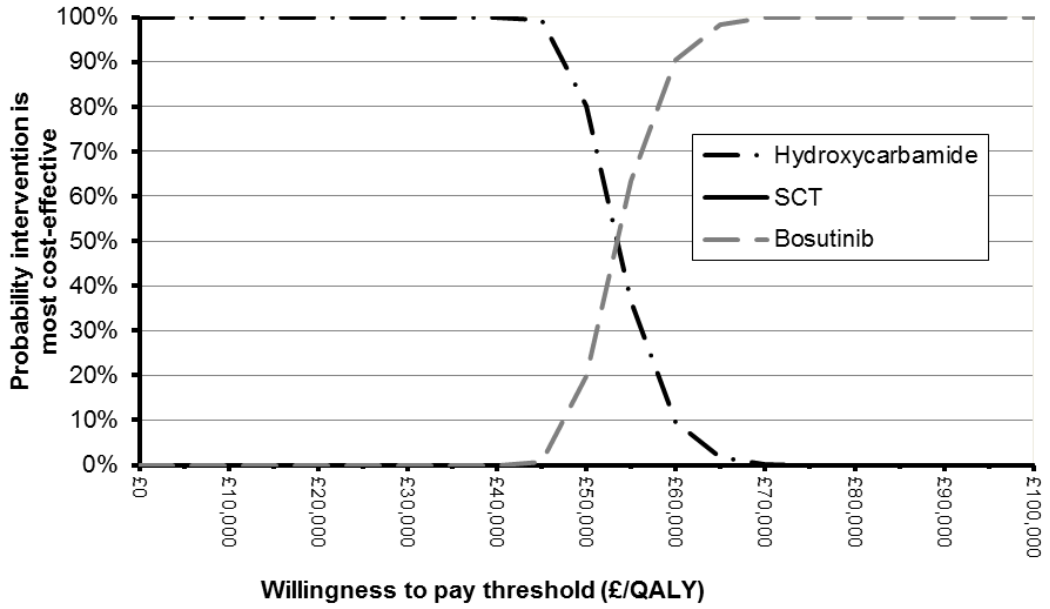


Figure 9 BP Scatter plot – Without PAS

Figure 10 BP cost-effectiveness acceptability curve – without PAS

Figure 11 BP scatter plot – With PAS

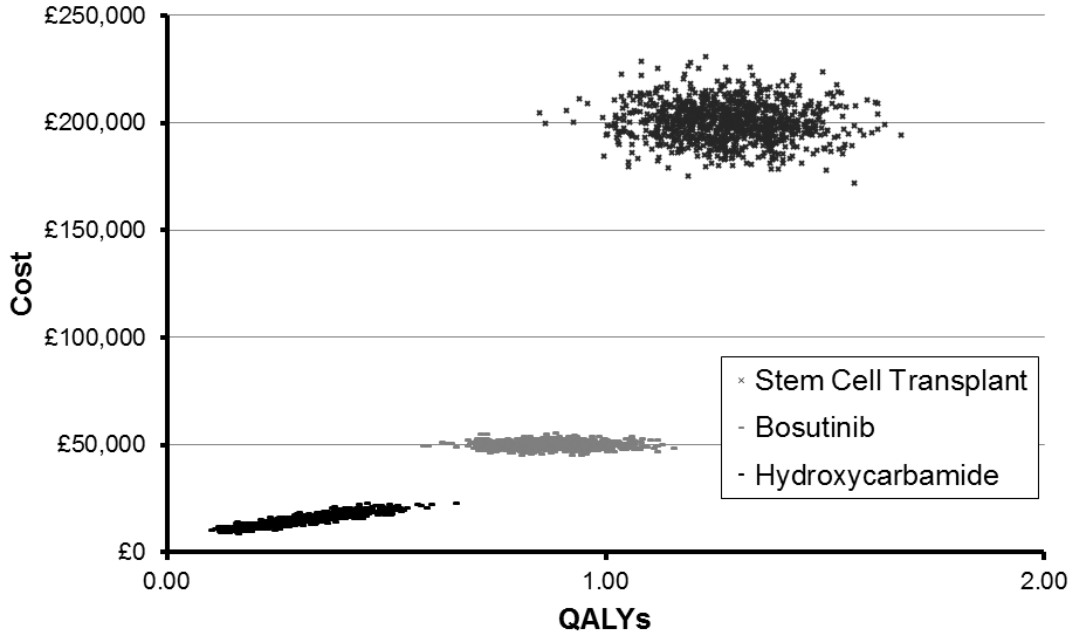
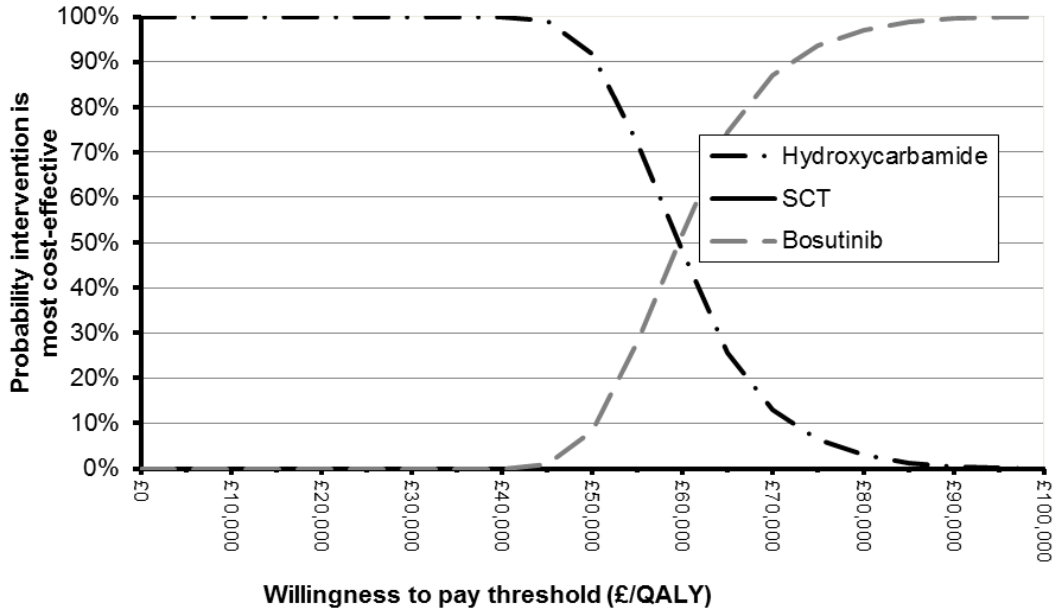


Figure 12 BP Cost-effectiveness acceptability curve – With PAS



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Table 9 Scenario analysis results – CP (bosutinib vs hydroxycarbamide)

Parameter	Base Case	Sensitivity Analysis	ICER versus hydroxycarbamide	
			Without PAS	With PAS
Base case	N/A	N/A	[redacted]	£20,972
Patient population				
Bosutinib patient population	3rd line CP patient population from Study 200	Post-hoc analysis of 3rd line CP cohort to identify 'unmet need' subpopulation, as requested by the EMA	[redacted]	£20,531
		Full 2rd line CP patient population from Study 200	[redacted]	£18,985
		Combined analysis of patients identified in the post-hoc analysis of 2nd line cohort and 3rd line cohort from Study 200, as requested by the EMA	[redacted]	£19,794
Cohort starting age	54 years (Study 200)	49 years (-10%)	[redacted]	£19,649
		50 years (+10%)	[redacted]	£22,477
Overall survival				
Bosutinib overall survival	MCyR using hazard ratio for survival of 0.37 (Rogers (2012))	MCyR using hazard ratio for survival of 0.156 (lower 95% of pooled estimate, Rogers (2012))	[redacted]	£29,310
		MCyR using hazard ratio for survival of 0.876 (upper 95% of pooled estimate, Rogers (2012))	[redacted]	£16,555
		OS estimated by fitting a parametric curve (exponential) to third-line CP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	£24,273
		Cumulative survival approach (OS = PFS [estimated by fitting a parametric curve to third-line CP cohort in Study 200] + 10 months AP + 6 months BP)	[redacted]	£33,294
Stem Cell Transplant overall survival	Exponential curve fitted to Jabbour (2011)	Weibull curve fitted to Jabbour (2011)	[redacted]	£20,972
		Exponential curve fitted to Oehler (2007)	[redacted]	£20,972
Hydroxycarbamide overall survival	Mean overall survival = 3.5 years (42 months) in **second-line** patients	Mean OS for hydroxycarbamide is adjusted by the ratio of 2nd and 3rd line OS from Study 200 to consider a more 'third-line' OS estimate for hydroxycarbamide. Mean OS for hydroxycarbamide = 2nd line LYs (11.51) divided by 3rd line LYs (10.30) multiplied by 42 = **38 months**	[redacted]	£20,367
		Mean OS = 2 years (lower end of plausible range, Rogers (2012))	[redacted]	£18,630
		Mean OS = 6.5 years (upper end of plausible range, Rogers (2012))	[redacted]	£29,357
Transformation to AP and BP				
Time in blast phase	6 months	13 months (Rogers (2012))	[redacted]	£21,270
		3 months (assumption)	[redacted]	£20,907
Transformation following SCT	Patients cannot transform to AP or BP, but	Patients transform to AP and BP for 10 months and 6 months respectively before death.	[redacted]	£20,972

	remain in CP			
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from Study 200	Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	£21,269
		Time on treatment equal to PFS minus discontinuation due to AEs (Rogers (2012))	[redacted]	£34,677
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial).	[redacted]	£21,082
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011)	Medical management resource use from TA241	[redacted]	£15,619
Cost of CP off treatment health state	Patients receive hydroxycarbamide, costing £12.75 per month	Patients receive further treatment post-discontinuation in CP (e.g. other TKIs or SCT) costing £1040 per month (similar approach to TA241).	[redacted]	£30,513
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP £2,536/month (doubled)	[redacted]	£21,113
		BP £1,268/month(doubled)	[redacted]	£20,789
Cost of death	£6,004 - Dewer & Addicot	£569 – Hoyle (2011)	[redacted]	£21,209
Cost of best supportive care	Best supportive care = hydroxycarbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	£20,177
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	£21,887
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility at screening for CP third-line cohort from Study 200 used for all patients in CP on bosutinib and hydroxycarbamide	[redacted]	£22,043
		Utility at screening for CP third-line cohort from Study 200 used for patients in CP on bosutinib only	[redacted]	£21,374
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011)	[redacted]	£20,972
Interferon on-treatment utility value	Decrement to QoL from interferon treatment	No decrement to QoL from interferon treatment	[redacted]	£20,972
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	£19,409
Model Settings				
Time horizon	50 years	2 years	[redacted]	£105,398
		5 years	[redacted]	£43,625
		10 years	[redacted]	£27,509
		25 years	[redacted]	£21,194

Table 10 Scenario analysis results – AP (bosutinib vs hydroxycarbamide)

Parameter	Base Case	Sensitivity Analysis	ICER vs hydroxycarbamide	
			Without PAS	With PAS
Base case	N/A	N/A	[redacted]	£53,789
Patient population				
Cohort starting age	50 years (Study 200 – AP cohort)	45 years (-10%)	[redacted]	£52,861
		55 years (+10%)		£55,960
Overall survival				
Bosutinib overall survival	OS estimated by fitting exponential curve to AP cohort from Study 200	OS estimated by fitting 2nd best fitting curve (extreme value) to AP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	£50,099
Stem Cell Transplant overall survival	OS estimated by fitting exponential curve to AP cohort from Oehler (2007)	OS estimated by fitting 2nd best fitting curve (Weibull) to Oehler (2007)	[redacted]	£53,789
		OS estimated based on curve (exponential) fitted to 'advanced phase' cohort from Jabbour (2011)	[redacted]	£53,789
Time spent in BP				
Time in blast phase	6 months	13 months (Rogers (2012))	[redacted]	£62,814
		3 months (assumption)		£50,888
Transformation following SCT				
Transformation following SCT	Patients cannot transform to BP, but remain in AP	Patients transform to BP for 6 months before death.	[redacted]	£53,789
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from AP cohort in Study 200	Time on treatment equal to PFS from study 200 (AP to BP)	[redacted]	£78,698
		Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	£54,193
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial).	[redacted]	£53,627
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011)	Medical management resource use from TA241	[redacted]	£34,962
Cost of AP and BP health states	AP £1,268/month BP £1,268/month	AP £2,536/month (doubled)	[redacted]	£74,836
		BP £1,268/month(doubled)		£54,217
Cost of death	£6,004 - Dewer & Addicot	£569 – Hoyle (2011)	[redacted]	£54,050
Cost of best supportive care	Best supportive care = hydroxycarbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	£53,932
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	£54,184
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility for AP and BP cohorts from Study 200 used for all patients in AP and BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT	[redacted]	£48,333

		not included)		
		Utility for AP in Study 200 only used for AP patients on bosutinib in the model (remainder as per base-case)	[redacted]	£49,940
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011)	[redacted]	£54,193
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	£52,519
Model Settings				
Time horizon	50 years	2 years	[redacted]	£86,509
		5 years	[redacted]	£57,777
		10 years	[redacted]	£53,576
		25 years	[redacted]	£54,191

Table 11 Scenario analysis results – BP (bosutinib vs hydroxycarbamide)

Parameter	**Base Case**	**Sensitivity Analysis**	**ICER versus hydroxycarbamide**	
			Without PAS	**With PAS**
Base case	N/A	N/A	[redacted]	£59,191
Patient population				
Cohort starting age	47 years (Study 200 – AP cohort)	42 years (-10%)	[redacted]	£56,105
		52 years (+10%)	[redacted]	£59,995
Overall survival				
Bosutinib overall survival	OS estimated by fitting exponential curve to BP cohort from Study 200	OS estimated by fitting 2nd best fitting curve (Weibull) to BP cohort from Study 200 (15 Feb 2012 snapshot)	[redacted]	£52,248
Stem Cell Transplant overall survival	OS estimated by fitting exponential curve to BP cohort from Oehler (2007)	OS estimated by fitting 2nd best fitting curve (Weibull) to Oehler (2007)	[redacted]	£59,191
		OS estimated based on curve (exponential) fitted to 'advanced phase' cohort from Saussele (2010)	[redacted]	£59,191
Time spent in BP				
Time in blast phase	6 months	13 months (Rogers (2012))	[redacted]	£87,330
		3 months (assumption)	[redacted]	£53,925
Time on treatment				
Bosutinib time on treatment	Lognormal curve fitted to discontinuation data from BP cohort in Study 200	Time on treatment equal to PFS from study 200	[redacted]	£80,486
		Loglogistic curve fitted to discontinuation data from Study 200 (2nd best fitting curve)	[redacted]	£103,491
Dosing				
Bosutinib dose	All patients receive 500mg once daily	Factoring in the proportion of patients in Study 200 who received 300mg/day, 400mg/day, 500mg/day and 600mg/day (assuming patients remained on this dose for the duration of the trial).	[redacted]	£60,368
Costs				
Resource use	Medical management from TA251 (Hoyle, 2011)	Medical management resource use from TA241	[redacted]	£58,604
Cost of AP and BP health states	BP £1,268/month	BP £1,268/month(doubled)	[redacted]	£88,473
Cost of death	£6,004 - Dewer &	£569 – Hoyle (2011)	[redacted]	£59,528

	Addicot			
Cost of best supportive care	Best supportive care = hydroxycarbamide, costing £12.75/month	Additional cost of £100/month in hydroxycarbamide arm only	[redacted]	£60,317
		Additional cost of £100/month in all arms wherever patients receive hydroxycarbamide	[redacted]	£58,121
Cost of SCT	All patients incur cost of FLAG-IDA at £29,212	FLAG-IDA cost removed	[redacted]	£59,191
Utility values				
Source of utility for CP patients on bosutinib or hydroxycarbamide	Utilities derived from IRIS, as reported by TA241 and TA251	Utility from BP cohort in Study 200 used for all patients in BP on bosutinib and hydroxycarbamide (higher than IRIS, smaller sample size) (SCT not included)	[redacted]	£40,130
		Utility from BP cohort in Study 200 only used for BP patients on bosutinib in the model (remainder as per base-case)	[redacted]	£47,605
Source of utility for patients receiving SCT	Utility decrement for SCT as reported in TA241	SCT utility taken from TA251 (Hoyle 2011)	[redacted]	£59,191
Utility values varying with age	Utility values adjusted to account for patient aging	Utility values not adjusted to account for patient aging	[redacted]	£59,159
Model Settings				
Time Horizon	50 years	2 years	[redacted]	£69,870
		5 years		£59,948
		10 years		£59,141
		25 years		£59,191

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Please see section 4.9.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

ADDENDUM to PenTAG report for NICE

Bosutinib for previously treated chronic myeloid leukaemia STA: a single technology appraisal

PenTAG Executive Summary amended for proposed Patient Access Scheme for bosutinib

12th June 2013

In our original report, submitted on 15th May 2013, we assumed the list price for bosutinib of £3,436.67 for 500mg x 28 tablets and £859.17 for 100mg x 28 tablets. NICE recently advised us that Pfizer have applied to the Department of Health (DoH) for a Patient Access Scheme (PAS) for bosutinib. Under this PAS, the price bosutinib would be reduced by approximately [redacted]. The price of bosutinib would then be [redacted] for 500mg x 28 tablets and [redacted] for 100mg x 28 tablets.

In this Addendum, we present the Executive Summary from our original report, revised in the light of the proposed PAS. No other changes have been made to the Executive Summary.

NICE provided Pfizer's PAS template which included base case ICERs, probabilistic sensitivity analyses and scenario analyses. We confirm that the base case results in the PAS template are consistent with the most recent model submitted by Pfizer, which includes the correction of a wiring error identified by PenTAG earlier in the process. As we do not present Pfizer's sensitivity analyses

in this Addendum and conduct several of our own, only the base case results were checked following incorporation of the proposed PAS.

Note that Sections 1.1, 1.2 and 1.3 are unaffected by the proposed PAS. Changes to the Executive Summary begin in Section 1.4, page 8.

Commercial in confidence information is underlined and highlighted turquoise, e.g., [redacted].
Academic in confidence information is underlined and highlighted yellow, e.g., [redacted].

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The patient population described in the Final Scope is: "Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia".

The population considered by Pfizer is a subset of the Scope population: "Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options" (Pfizer submission, p37).

This population is consistent with the revised indication agreed with the European Medicines Agency.

The intervention described in the submission, bosutinib (Bosulif®), 500mg per day taken orally, corresponds to that in the Final Scope.

The comparators in the Final Scope are as follows:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML)
- Hydroxycarbamide
- Interferon alpha
- Best supportive care

However, we disagree with Pfizer's assumptions for treatment sequences, as explained in Section 1.5.2, p10).

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence of bosutinib (Bosulif®) in treatment of adult patients with Ph+ CML was reviewed. The entire clinical evidence for bosutinib comes from a single arm, phase I/II multi-centre trial, Study 200. Because no RCT evidence was identified, separate clinical effectiveness evidence was submitted for the Scope defined comparators. Thirteen non-randomised comparator studies were included.

1.2.1 Bosutinib

Study 200 (Phase II) examined the efficacy and safety of bosutinib 500mg daily in 546 Ph+ CML patients with previous imatinib failure. Patients in all three phases of Ph+ CML were recruited; second line CP (N=288), third line CP (N=118), AP (N=76) and BP (N=64). In addition, based on

EMA recommendation, a subgroup of patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (population of unmet clinical need) was identified and analysed post hoc. Baseline characteristics across all phases of the disease and lines of treatment are summarised in Table 1.

Table 1. Study 200 baseline patient characteristics

Population	**Age (years) [Median (range)]**	**Male [N (%)]**	**CML duration (years) [Median (range)]**	**IM duration (years) [Median (range)]**	**ECOG performance status N (%)**		
					0	*1*	*2*
CP2L (n=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.11–22.06)	NR	41 (54%)	33 (43%)	2 (3%)
BP (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.35–14.46)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need (N=52)[b]	58 (19-81)	31 (605)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, ECOG = Eastern Cooperative Oncology Group performance status, IM = imatinib, N = number of participants, NR = not reported

a Information taken from Cortes (2012)[1]

b Information taken from EPAR

In the complete population of Study 200, bosutinib was associated with good cytogenetic and haematological response rates and overall survival (Table 2). However, the OS data from Study 200 for CP patients is very immature. Cytogenetic and haematological responses were also observed among participants with mutations that would confer the use of nilotinib or dasatinib inappropriate (Table 3). Apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical need population. For example, MCyR was 60%, 42.9%, 60% and 18.2 % for second and third line CP and AP and BP unmet clinical need population respectively. However these response rates are based on very small sample sizes (N=3–21) and are therefore uncertain.

Table 2. Study 200 cytogenetic and haematological response rates for full Study 200 population

	Evaluable population			
	MCyR March 2011	*CCyR March 2011*	*CHR March 2011*	*K-M estimates of OS at 2 years*
CP2L	53.4%	41.4%	84.7%	90.6%[a]
CP3L	38.9%	30.6%	73.3%	84.0%[a]
AP	34.8%	24.6%	34.8%	65.6%[b]
BP	29.6%	20.4%	15%	35.4%[c]

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase

a 24 month minimum follow-up, median OS had not yet been reached

b 12 month minimum follow-up, median OS had not yet been reached

c 18 month minimum follow-up, median OS for BP patients was 11.1 months

Table 3. Study 200 response rates by baseline mutation

Mutation	**CP2L CHR [n/N %]**	**CP2L MCyR [n/N %]**	**CP3L CHR [n/N %]**	**CP3L MCyR [n/N %]**	**AP & BP CHR [n/N %]**	**AP & BP MCyR [n/N %]**
Y253	2/2 100%	2/2 100%	5/6 83%	4/6 67%	1/7 14.3%	2/7 28.6%
E255	0/2 0%	2/3 67%	NA	NA	0/4 0%	1/3 33.3%
F317	4/4 100%	3/4 75%	4/8 50%	1/7 14%	0/9 0%	0/6 0%
F359	8/9 89%	4/9 44%	0/2 0%	1/2 50%	0/2 0%	1/2 50%

Notes: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, n = numbers of participants with response, N = number of participants with mutation, NA = not applicable

Bosutinib was found to have an acceptable safety profile across all phases of the disease and lines of treatment. Low rates of transformation to the next phase of CML were observed on bosutinib treatment for both chronic and advanced phase populations (Table 4). Adverse events were mainly restricted to gastrointestinal toxicities (Table 4) and in the majority of cases these toxicities were mild in severity. The most common haematological events across all phases of the disease and lines of treatments in both the chronic and advanced phases of the disease were thrombocytopaenia, neutropaenia and anaemia. Severe cases of anaemia seemed to be more pronounced at the more advanced stages of the disease (Table 4). The profile of AE associated with bosutinib appears to be more similar to those associated with nilotinib than with dasatinib. In comparison, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections,

haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[2] In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI.

Table 4. Study 200 safety

	CP2L	CP3L	AP	BP
Rates of disease transformation to the next phase of CML	3.8%	4%	6.4%	NA
Treatment discontinuation	58% (36 months minimum follow-up)	76% (24 months minimum follow-up)	NR	NR
Treatment discontinuation due to AE	23%	22%	23.7%	9.4%
Diarrhoea	85.3%	82.4%	85.5%	65.6%
Nausea	45.5%	48.7%	44.7%	50%
Vomiting	36.7%	39.5%	44.7%	39.1%
Rash	36%	26.9%	32.9%	31.3%
Thrombocytopenia Grade 3/4	24%	25.4%	32.9%	26.6%
Neutropenia Grade 3/4	18%	14.4%	14.5%	20.3%
Anaemia Grade 3/4	13%	5.1%	30.3%	18.8%

Abbreviations: AP = accelerated phase, BP = blast phase, CP2L = second line chronic phase, CP3L = third line chronic phase, NA = not applicable, NR = not reported

EQ-5D data were collected in Study 200. The mean EQ-5D utilities, averaged mostly over the first two years of treatment, were [redacted] in the CP 2nd-line, 3rd-line, AP and BP populations respectively.

1.2.2 Comparator treatments

No studies reporting on interferon alpha in a refractory setting were identified. One study reported on both SCT and HU,[3] one study reported on HU only,[4] and 11 studies reported on SCT only.[5-15] However only 7 studies[3, 4, 6, 7, 10, 12, 13] were considered in Pfizer's submission as five SCT studies did not stratify results by disease phase.

In summary, the clinical effectiveness evidence for the comparator treatments is very poor. Hydroxycarbamide was considered to be a proxy for best supportive care. Participants in the comparator studies appear to be younger, and most of the comparator studies are small and the outcomes reported vary. Pfizer describe the HU comparator studies as "not strictly eligible" (p89 Pfizer Submission) for inclusion and only three included SCT studies[7, 10, 13] are considered to be a good quality evidence according to the Chambers (2009)[16] criteria (Pfizer submission, p216). This

further highlights the difficulty inherent to such naïve comparisons and impedes any comparisons of Study 200 with comparator studies.

The CP cost-effectiveness model used data from Kantarjian (2007)[3] for the clinical effectiveness of HU and Jabbour (2011)[10] for the clinical effectiveness of SCT. Of particular importance for the model are:

- OS after SCT in CP of 72% at year 2 in Jabbour (2011)[10]
- OS for HU in CP of 77% at year 2 and 70% at year 3 in Kantarjian (2007)[3]

No safety data were reported for HU, and the grade 3–4 graft versus host disease reported in SCT studies varied across the lines of treatment as well as the studies from 6.25% to 40%.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

First, the main weakness of the clinical effectiveness evidence is the fact that no RCT evidence was identified. The only clinical evidence for bosutinib comes from Study 200, a phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML. Similarly, the evidence for comparator treatments comes from 13 non-randomised comparator studies.

Second, the bosutinib licence is intended for treatment of adult patients with CP, AP and BP Ph+ CML patients previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. However only 52 of the 546 patients in Study 200 fulfilled the criteria for this unmet need population.

Third, Pfizer do not state the nature of treatments given after bosutinib failure. This means that the relevance of the OS data from Study 200 is uncertain, because many patients may have proceeded to take a different TKI on bosutinib failure. Also, the OS data in CP is very immature, which means that it is difficult to estimate mean OS, a key driver of the cost-effectiveness of bosutinib.

Fourth, we cannot stress enough, that the naïve comparison of the single arm Study 200 with non-randomised comparator studies is predisposed to bias. The evidence for the two comparator treatments, HU and SCT, is taken from small studies with populations that mostly did not meet the unmet need criteria.

Fifth, Pfizer present no evidence for the clinical effectiveness of IFN, which is one of the comparator treatments in the CP economic model.

1.4 Summary of cost-effectiveness evidence submitted by the manufacturer

Pfizer conducted a systematic review for cost-effectiveness evidence relating to the decision problem. This did not identify any relevant studies for bosutinib.

Pfizer therefore developed a *de novo* economic model to answer the decision problem. The model developed was an "area-under-the-curve" cohort model where patients could be on or off the principal treatment in the treatment arm and patients could undergo transformation to later disease phases (accelerated and blast crisis phase). Patients could start in either the chronic phase, accelerated phase or blast crisis phase and these are denoted the CP, AP and BP models.

Pfizer consider the following four treatment sequences in the CP model:

- Bosutinib followed by hydroxycarbamide, denoted (Bosutinib, HU),
- Hydroxycarbamide, denoted HU,
- Stem cell transplant, denoted SCT,
- Interferon followed by hydroxycarbamide, denoted (IFN, HU).

For the AP and BP models, they consider the same treatment sequences but without (IFN, HU).

Overall survival was estimated for (Bosutinib, HU) in the CP model using a MCyR surrogate method, which has been used previously by PenTAG in TA241. They did not however use this method to estimate overall survival for comparator treatments, instead extrapolating from trials and using clinical expert opinion. Overall survival for (Bosutinib, HU) in the AP and BP models was estimated by extrapolating from Study 200.

Time on bosutinib treatment was estimated by extrapolating from Study 200. Time on interferon treatment was extrapolated from clinical expert opinion. Patients did not discontinue hydroxycarbamide treatment and patients who received a stem cell transplant were assumed to receive no further drug treatment.

Resource uses and costs were generally based on previous assessments by PenTAG, TA241 and TA251.

Pfizer base their estimates of utilities on those that we, PenTAG, used in TA251 and TA241. Their only departure from our previous assumptions is their estimate of the utility after stem cell transplant in CP, where they assume 0.71, versus our TA251 estimate of 0.80. Importantly, for the estimated utility under bosutinib treatment, they prefer the utilities that we have used previously for utilities for TKIs to those from their Study 200.

1.4.1 CP model results

Pfizer's analysis showed that (Bosutinib, HU) was more effective and more costly than HU (ICER £21,000 per QALY), and more effective and less costly than SCT, i.e., (Bosutinib, HU) dominates. Pfizer found that (IFN, HU) was less effective and more costly than HU (HU dominates). The ICER of (Bosutinib, HU) versus (IFN, HU) was £19,000 per QALY.

Table 5. Pfizer CP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	(IFN, HU)	SCT
Life years	12.75	3.52	3.62	6.60
QALYs	7.26	2.43	2.42	3.70
Costs	£130,752	£29,473	£38,268	£171,539

QALYs and costs discounted at 3.5% per annum

1.4.2 AP model results

Pfizer's AP base case results showed that similar to the CP model (Bosutinib, HU) was more effective and more costly than HU (ICER £54,000 per QALY), and that (Bosutinib, HU) dominates SCT.

Table 6. Pfizer AP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	4.48	1.37	3.02
QALYs	2.76	0.90	1.96
Costs	£126,237	£26,078	£178,093

QALYs and costs discounted at 3.5% per annum

1.4.3 BP model results

Pfizer's BP base case results showed that (Bosutinib, HU) was more effective and more costly than HU (ICER £59,000 per QALY). The results also showed that (Bosutinib, HU) was less effective and less costly than SCT (ICER £380,000 per QALY).

Table 7. Pfizer BP model life years, QALYs and costs

Intervention	(Bosutinib, HU)	HU	SCT
Life years	1.77	0.54	2.64
QALYs	0.88	0.28	1.28
Costs	£49,936	£14,170	£200,526

QALYs and costs discounted at 3.5% per annum

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

In this section, we highlight our key areas of disagreement with Pfizer's analysis. As a result of our critique of their model, we have developed PenTAG base case ICERs (Section 1.7, p16) for each of the CP, AP and BP models. In order to develop our base case, we have adjusted the following items in Pfizer's CP model:

- The method of estimation of OS for all comparators using our "cumulative survival method",
- Mean overall survival on HU,
- Mean overall survival after SCT,
- Resource use in CP CML.

We have changed just the first item in Pfizer's AP and BP models.

1.5.1 Model wiring errors

We discovered an important wiring error in the version of the model that Pfizer originally sent us on 14th March 2013. Pfizer sent as a corrected version of their model on 19th April 2013. Their base case ICER for bosutinib versus HU in CP then decreased from [redacted] per QALY. When the proposed PAS is incorporated, their original model gives a base case ICER for bosutinib versus HU in CP of £25,000 per QALY, which falls to £21,000 per QALY after correction of the wiring error.

In order to check the wiring of Pfizer's cost-effectiveness model, we built a model that is completely independent of their model. We feel confident that there are no major wiring errors in Pfizer's corrected model because the results from our independent model are very similar to those of Pfizer's model.

1.5.2 Comparator treatment sequences

Pfizer model the four treatment sequences in CP in Section 1.4, p8. In addition, we believe it is important to model the sequence (Bosutinib, SCT) for patients eligible for SCT. In summary, we assume the following comparator treatment sequences for CP:

- (Bosutinib, HU),
- (Bosutinib, SCT) (only for those eligible for SCT),
- HU,
- SCT (only for those eligible for SCT),
- (IFN, HU).

For the AP and BP models, we assume the same comparators, but without (IFN, HU).

We believe that the most important comparison in all model phases is (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT. Furthermore, we understand that a minority of patients (<30%) will be eligible for SCT and hence (Bosutinib, HU) versus HU is the most important treatment comparison in all disease phases.

1.5.3 Method of overall survival (OS) estimation

As stated in Section 1.4, p8, in the CP model, Pfizer use very different methods to estimate OS across treatments in the CP model. We believe that this lack of consistency, the lack of randomised evidence, and problems specific to the estimation of OS for bosutinib using the MCyR surrogate relationship leads to the following important prediction that lacks face validity. The mean time on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) (shown in Figure 1 below). We believe, and clinical expert advice confirms, that this is unreasonable. Furthermore, this assumption dramatically biases the cost-effectiveness in favour of (Bosutinib, HU) versus HU because the price of HU is negligible.

Figure 1.

[redacted]

Although OS for all treatments is consistently estimated by extrapolating trial data in the AP and BP model, we believe there are still serious problems with Pfizer's method of estimating OS for all treatments in AP and BP. This similarly leads to the implausible prediction that, in both the AP and BP models, the mean time on 4th-line HU in the (Bosutinib, HU) arm is substantially greater than the mean time on 3rd-line HU in the HU arm.

Instead, we suggest that a far more parsimonious method is required to estimate OS across comparators. Indeed, we suggest such a method, which we describe as the Cumulative Survival method. We believe that it is far preferable for estimating OS for all comparator treatments for all model phases. We believe that it should be regarded as the default method, and that we should depart from this method only if there is high quality evidence to suggest that bosutinib treatment affects survival even after it has ceased.

The key assumption of the Cumulative Survival method is that in the (Bosutinib, HU) and (IFN, HU) arms, the life expectancy of those patients who survive to start 4th-line HU treatment equals the life expectancy of those patients who start 3rd-line HU treatment in the HU arm. In Figure 1, the heights of the HU sections then become approximately equal. Similarly, in the (Bosutinib, SCT) arm, the life expectancy of those patients who start 4th-line SCT treatment equals the life expectancy of those patients who start 3rd-line SCT treatment in the SCT arm.

The revised cost-effectiveness results are then:

- In the CP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases substantially, from £21,000 to £48,000 per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is £42,000 per QALY.
- In the AP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from £54,000 to £65,000 per QALY. In their base case, Pfizer predict that (Bosutinib, HU) dominates SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is £60,000 per QALY.
- In the BP model, Pfizer's base ICER for (Bosutinib, HU) versus HU then increases from £59,000 to £89,000 per QALY. In their base case, Pfizer estimate an ICER of £380,000 for (Bosutinib, HU) versus SCT, with (Bosutinib, HU) cheaper and less effective than SCT. However, under the Cumulative Survival method, we believe that, for patients eligible for SCT, it is more appropriate to compare (Bosutinib, SCT) versus SCT, for which the ICER is £85,000 per QALY, i.e., (Bosutinib, SCT) gives poor value versus SCT.

Of all the changes we make to Pfizer's model, this has the largest impact on the estimated cost-effectiveness of bosutinib.

1.5.4 OS for HU in CP

Relevant data for OS on HU for patients in CP is sparse. Pfizer estimated OS for HU in CP CML for their base case using data from the study by Kantarjian and colleagues (2007).[3] We used this study for this purpose in TA251. Pfizer claim that the agreed estimate of mean OS for HU in CP was 3.5 years in TA251, and they therefore use this value in their base case. However, we disagree. Instead, we calculated a mean OS of 7.0 years in TA251.[17(p164)] Furthermore, the 3.5 years estimated by Pfizer is clearly incompatible with the Kaplan-Meier OS curve from this study.

The quality of the evidence from Kantarjian and colleagues (2007)[3] to inform OS for HU in CP is clearly poor, given the small patient sample and the fact that most patients in this study did not even take HU. Nonetheless, we agree with Pfizer that this study appears to be the best available for this purpose.

Pfizer's base case ICER for (Bosutinib, HU) versus HU then increases from £21,000 to £32,000 per QALY, and the cost-effectiveness of (Bosutinib, HU) versus SCT is unchanged.

1.5.5 OS after SCT in CP

Relevant data for OS after SCT for patients in CP is also sparse. Pfizer's base case estimate of OS after SCT for patients in CP was based on data from the study Jabbour and colleagues (2011).[10] Whilst we agree that this study is relevant, the sample size is extremely small, with only 16 CP patients contributing to the estimates of OS. Instead, we use data from the study by Oehler and colleagues (2007),[12] in our base case, as it is relevant, has a much larger sample of 72 patients and reports OS that is more consistent with the OS from two other relevant studies. Our estimated OS of 11.6 years is far greater than Pfizer's estimate of 6.6 years.

Pfizer's base ICER for (Bosutinib, HU) versus HU then remains unchanged, and (Bosutinib, HU) still dominates SCT, but the cost-effectiveness of (Bosutinib, HU) deteriorates versus SCT.

1.5.6 Medical management costs in CP

Pfizer's assumptions for medical management, monitoring and testing are based on those that we originally used in TA251,[17] which in turn were taken from a 2009 Oxford Outcomes survey. However, Pfizer seem unaware that after the first NICE committee meeting for TA251, our assumptions were challenged by Novartis, the manufacturer of nilotinib. In response, we amended some of our assumptions for resource use in CP CML in TA251, and these were accepted by the NICE committee.

These changes plus changes to resource use assumptions for patients after SCT are reflected in our base case assumptions. When we amend Pfizer's model, their ICER for (Bosutinib, HU) versus HU decreases from £21,000 to £16,000 per QALY and (Bosutinib, HU) continues to dominate SCT.

1.5.7 Line of treatment

Pfizer base their economic evaluation on data on 3rd-line use of bosutinib in Study 200. Furthermore, they believe that bosutinib is unlikely to be used 2nd-line. However, we believe that bosutinib will be used mostly either as 2nd- or 3rd-line. Whilst we believe that it is more likely to be used 2nd-line, we cannot be certain of this. Therefore, our base case analysis also assumes 3rd-line use of bosutinib, and we consider use of bosutinib in 2nd-line in an important scenario analysis.

Pfizer estimate the mean time on 3rd-line bosutinib in CP from Study 200 as [redacted]. Based on the Kaplan-Meier data from Study 200 we requested from Pfizer, we estimate the mean time on 2nd-line bosutinib as being far longer, at [redacted].

Changing Pfizer's model for this estimate and for the 2nd-line MCyR from Study 200, Pfizer's base case ICER for (Bosutinib, HU) versus HU for CP increases substantially, from £21,000 to £42,000 per QALY and (Bosutinib, HU) changes from dominating SCT to being more costly and more effective than SCT (ICER £21,000 per QALY).

1.5.8 Utilities

In short, we accept Pfizer's utilities. However, we believe that there are strong arguments that we should instead use the utilities from Study 200 for bosutinib treatment, and our estimate of 0.80 after SCT in CP in preference to their estimate of 0.71.

In the first case, Pfizer's ICER for (Bosutinib, HU) versus HU in CP increases marginally, from £21,000 to £22,000 per QALY.

In the second case, based on Pfizer's analysis, (Bosutinib, HU) still dominates SCT in CP, but to a lesser extent.

1.5.9 End of Life criteria

Pfizer claim that bosutinib meets NICE's End of Life criteria for use in AP and BP. They do not claim this for CP CML. By contrast, we believe bosutinib does not meet the criteria in any phase of CML. We believe that bosutinib does not qualify in AP and BP due to lack of robustness of the estimates of extension to life.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- Pfizer's analysis was clearly described in their report.
- We found only one important wiring error in Pfizer's model.
- The structure of Pfizer's model is mostly consistent with the natural history of CML.
- With the exception of the Cumulative Survival method, Pfizer clearly studied TA241 and TA251 in detail and adapted their model accordingly.
- The time on bosutinib treatment from Study 200 is mature.
- Extrapolations for time on bosutinib treatment appear reasonable.
- The modelled unit costs seem appropriate.
- The modelled utilities are plausible.

1.6.2 Weaknesses

- The clinical effectiveness evidence is taken from a single non-randomised trial (Study 200).
- Only a small subset of the patient population in Study 200 reflects the population indicated for bosutinib.
- Although some effectiveness results are presented for the patients indicated for bosutinib, some key effectiveness results, such as time on bosutinib treatment, are not.
- OS for patients on bosutinib in CP is very immature.
- In Pfizer's model, all patients were assumed to receive hydroxycarbamide following bosutinib failure. Instead, we believe that some patients would receive SCT after bosutinib.
- Pfizer's important prediction that the mean time in the CP model on 4th-line HU in the (Bosutinib, HU) arm is far greater than the mean time on 3rd-line HU in the HU arm ([redacted] versus 2.6 years respectively) lacks face validity.
- We believe that Pfizer's estimate of mean OS on HU in CP is logically flawed, as described in Section 1.5.4, p13.
- We believe that Pfizer's estimate of mean OS after SCT in CP is biased, as described in Section 1.5.5, p13.

1.6.3 Areas of uncertainty

There is substantial uncertainty in almost all the key parameters of Pfizer's model. Much of this has already been discussed above, but some of the key parameters which are uncertain include:

- The line of treatment that clinicians would use bosutinib if it were recommended by NICE,
- Mean OS on bosutinib in all phases, specifically for patients unsuited to TKIs,

- Mean time on bosutinib treatment in all phases, specifically for patients unsuited to TKIs,
- Mean OS on HU in all phases of CML,
- Mean OS after SCT in all phases of CML,
- Utilities for patients after SCT.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Summaries of the derivation of our base case ICERs and sensitivity analyses are given in the following tables below:

- Table 8 and Table 9 (CP)
- Table 10 (AP)
- Table 11 (BP)

The key treatment comparisons are highlighted in bold: (Bosutinib, SCT) versus SCT for those eligible for SCT and (Bosutinib, HU) versus HU for those not eligible for SCT.

Our base case ICERs for these key comparisons are as follows:

- CP model
    - (Bosutinib, HU) versus HU £49,000 per QALY
    - (Bosutinib, SCT) versus SCT £43,000 per QALY
- AP model
    - (Bosutinib, HU) versus HU £65,000 per QALY
    - (Bosutinib, SCT) versus SCT £60,000 per QALY
- BP model
    - (Bosutinib, HU) versus HU £89,000 per QALY
    - (Bosutinib, SCT) versus SCT £85,000 per QALY

Table 8. Derivation of PenTAG base case CP CML ICERs (£ per QALY)

	Intervention	**(Bosutinib, HU) versus**			**(Bosutinib, SCT) versus**		
	Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
	Pfizer base case	**21,000**	Dominant	19,000		n/a	
1[b]	Cumulative survival method	**48,000**	Dominant	53,000	73,000	**42,000**	80,000
2	Medical management costs revised	**16,000**	Dominant	14,000		n/a	
3[c]	Mean OS of HU increased from 3.5 to 7.0 years	**32,000**	n/c	n/c		n/a	
4	Mean OS of SCT increased from 6.6 to 11.6 years	**n/c**	Dominant	n/c		n/a	
1+2[b]		**43,000**	Dominant	48,0000	65,000	**38,000**	71,000
1+3[b]		**54,000**	Dominant	61,000	246,000	**42,000**	409,000
1+4[b]		**48,000**	52,000[a]	53,000	49,000	**47,000**	51,000
2+3+4		**27,000**	Dominant	14,000		n/a	
1+2+3+4[b]	**PenTAG base case**	**49,000**	Dominant	56,000	73,000	**43,000**	81,000

n/c – Not changed from Pfizer base case

Shading indicates cost-effectiveness of bosutinib: white – INHB of bosutinib +ve at WTP £20,000 and £30,000 per QALY; dark grey – INHB of bosutinib −ve at WTP £20,000 and £30,000 per QALY; light grey – INHB of bosutinib +ve at WTP £20,000 per QALY and −ve at WTP £30,000 per QALY or vice versa

a (Bosutinib, HU) is less costly and less effective than SCT

b Interferon is more costly and more effective than hydroxycarbamide

c Interferon is less costly and less effective than hydroxycarbamide

Table 9. Important scenario analyses applied to PenTAG base case for CP model

Intervention	(Bosutinib, HU) versus			(Bosutinib, SCT) versus		
Comparator	***HU***	*SCT*	*IFN*	*HU*	***SCT***	*IFN*
PenTAG base case	**49,000**	Dominant	56,000	73,000	**43,000**	81,000
2nd-line CML cohort from Study 200	**53,000**	25,000	55,000	62,000	**45,000**	65,000
Mean OS for HU decreased from 7.0 to 3.5 years (−50%)	**43,000**	39,000[a]	48,000	42,000	**n/c**	43,000
Mean OS for HU increased from 7.0 to 10.5 years (+50%)	**56,000**	Dominant	66,000	217,000	**n/c**	332,000
Mean OS for SCT decreased from 11.6 to 5.8 years (−50%)	**n/c**	Dominant	n/c	386,000	**38,000**	1.4m
Mean OS for SCT increased from 11.6 to 17.4 years (+50%)	**n/c**	40,000[a]	n/c	46,000	**51,000**	48,000
On bosutinib treatment until transformation to AP	**135,000**	287,000	168,000	n/c	**n/c**	n/c
Bosutinib and HU utility set to Study 200 utility	**52,000**	Dominant	61,000	75,000	**46,000**	82,000
SCT utility set to TA251 utility	**n/c**	121,000[a]	n/c	59,000	**46,000**	63,000

n/c – Not changed from PenTAG base case
Shading as in Table 8
a (Bosutinib, HU) is less costly and less effective than SCT

Table 10. Derivation of PenTAG base case AP CML

	Intervention	(Bosutinib, HU) versus		(Bosutinib, SCT) versus	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	**54,000**	Dominant	n/a	
1	Cumulative survival method	**65,000**	Dominant	97,000	**60,000**
1	**PenTAG base case**	**65,000**	Dominant	97,000	**60,000**

Shading as in Table 8

Table 11. Derivation of PenTAG base case BP CML

	Intervention	(Bosutinib, HU) versus		(Bosutinib, SCT) versus	
	Comparator	*HU*	*SCT*	*HU*	*SCT*
	Pfizer base case	**59,000**	380,000[a]	n/a	
1	Cumulative survival method	**89,000**	229,000[a]	163,000	**85,000**
1	**PenTAG base case**	**89,000**	229,000[a]	163,000	**85,000**

Shading as in Table 8
a Bosutinib is less costly and less effective than SCT

REFERENCES

1. Cortes J, Kantarjian H, Kim DW, et al. Bosutinib as Therapy for Chronic Phase Chronic Myeloid Leukemia Following Resistance or Intolerance to Imatinib: 36-month Minimum Follow-up Update. 54th Annual Meeting of the American Society of Hematology, 2012.
2. Rogers G, Hoyle M, Thompson Coon J, et al. Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: a systematic review and economic evaluation. Health Technol Assess 2012;16:1-410.
3. Kantarjian H, O'Brien S, Talpaz M, et al. Outcome of patients with Philadelphia chromosome-positive chronic myelogenous leukemia post-imatinib mesylate failure. Cancer 2007;109:1556-60.
4. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. Haematologica 2011;96:1779-82.
5. Benedicte D, Emmanuel B, Nicole R, et al. Impact of prior second-generation tyrosine kinase inhibitors on the outcome of hematopoietic stem cell transplantation for chronic myeloid leukemia In 52nd Annual Meeting of the American Society of Hematology, 2010.
6. Bornhauser M, Kroger N, Schwerdtfeger R, et al. Allogeneic haematopoietic cell transplantation for chronic myelogenous leukaemia in the era of imatinib: a retrospective multicentre study. Eur J Haematol 2006;76:9-17.
7. Holroyd A, Philips E, Szydlo R, et al. Response to tyrosine kinase inhibitor therapy in patients undergoing allogeneic hematopoietic stem cell transplantation for advanced phase chronic myeloid leukemia, In 52nd Annual Meeting of the American Society of Hematology, 2010, 2010.
8. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. Cancer 2007;110:340-4.
9. Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after Bcr-Abl kinase mutation-related imatinib failure. Blood 2006;108:1421-3.
10. Jabbour E, Cortes J, Santos FP, et al. Results of allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia patients who failed tyrosine kinase inhibitors after developing BCR-ABL1 kinase domain mutations. Blood 2011;117:3641-7.
11. Markiewicz M, Dzierzak-Mietla M, Wisniewska-Piaty K, et al. The favorable results of allo-HSCT in TKI-resistant CML, In 53rd Annual Meeting of the American Society of Hematology, In 53rd Annual Meeting of the American Society of Hematology, 2011, 2011.

12. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. Blood 2007;109:1782-9.
13. Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1880-5.
14. Schleuning M, Scholten M, van Bienzen A, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia after prior treatment with nilotinib or dasatinib, In 52nd Annual Meeting of the American Society of Hematology, 2010.
15. Weisser M, Schleuning M, Haferlach C, et al. Allogeneic stem-cell transplantation provides excellent results in advanced stage chronic myeloid leukemia with major cytogenetic response to pre-transplant imatinib therapy. Leuk Lymphoma 2007;48:295-301.
16. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol 2009;62:1253-1260 e4.
17. Hoyle M, Pavey T, Ciani O, et al. Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. National Institute for Health and Clinical Excellence (NICE): Peninsula Technology Assessment Group (PenTAG), University of Exeter 2011.