NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Contains CIC

Pre-meeting briefing
Ponatinib for treating chronic myeloid leukaemia [ID671]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts 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 includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Disease Background

- Chronic myeloid leukaemia (CML) is a rare form of cancer affecting the blood, characterised by an excessive proliferation of myeloid cells at all stage of maturation[1]
- Approximately 95% of people with CML have acquired chromosomal abnormality known as Philadelphia chromosome positive disease (Ph+)[2]
- Office for National Statistics figures for 2014 show 631 people in England were newly diagnosed with CML[3]
- Approximately one third to one half of patients are asymptomatic at diagnosis and identified through routine screening[4]. Over 90% of patients with CML are diagnosed in the early chronic phase[5,6]
- More than 70% of men and nearly 75% of women diagnosed with CML survive for 5 years or more following diagnosis. Prognosis is negatively affected by older age, and how far the disease has progressed at diagnosis[7]

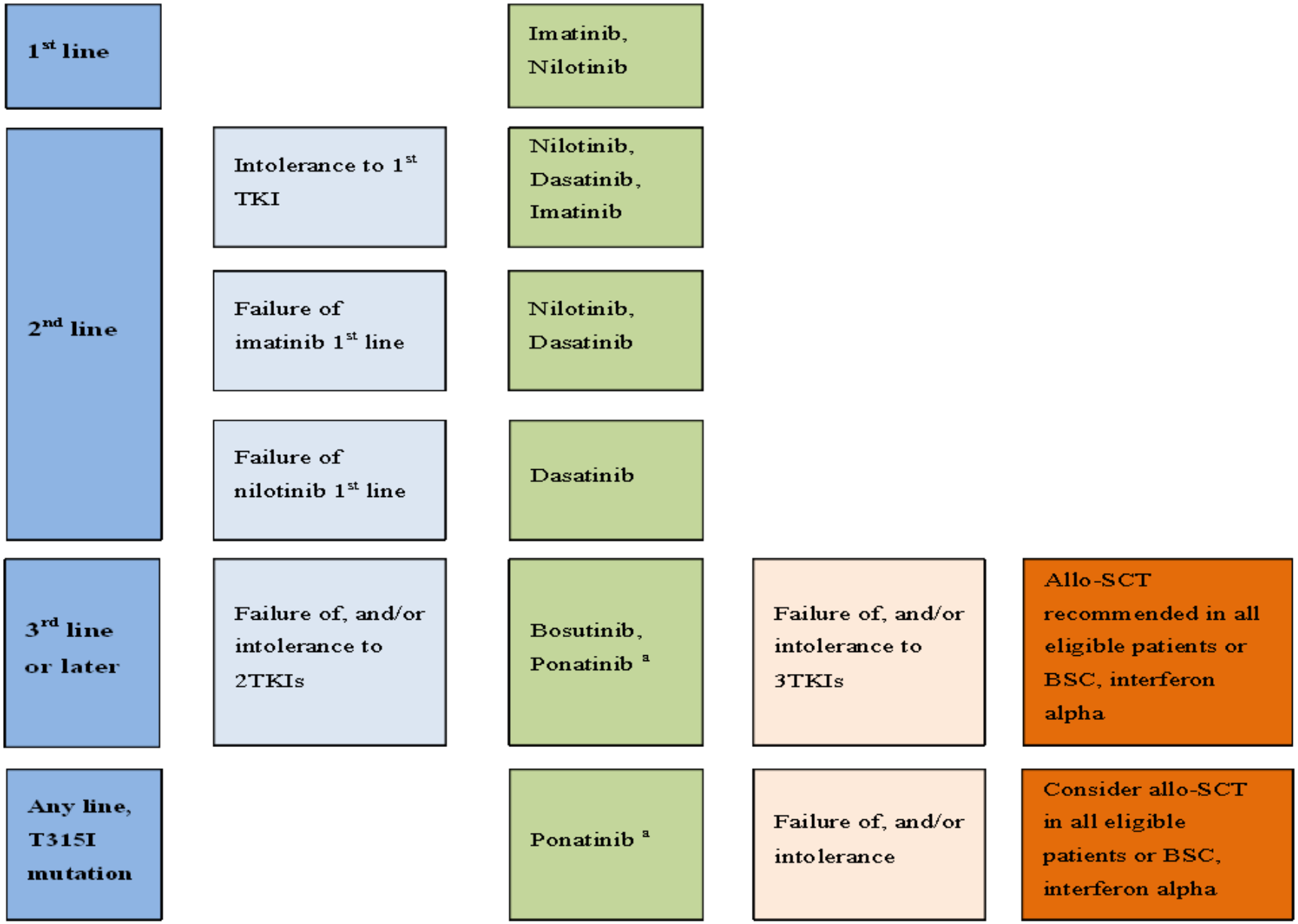
Phases of CML

- CML is typically characterised as having three distinct phases.
  - An initial chronic phase (CP-CML) which lasts for several years
  - An intermediate accelerated phase (AP-CML), which lasts for less than 1.5 years
  - An aggressive blast phase (BP-CML) that is usually fatal within 3 to 6 months
- People with CP-CML can transition to either AP-CML or BP-CML
- The phases are defined mainly by the percentage of blast cells in the blood and bone marrow

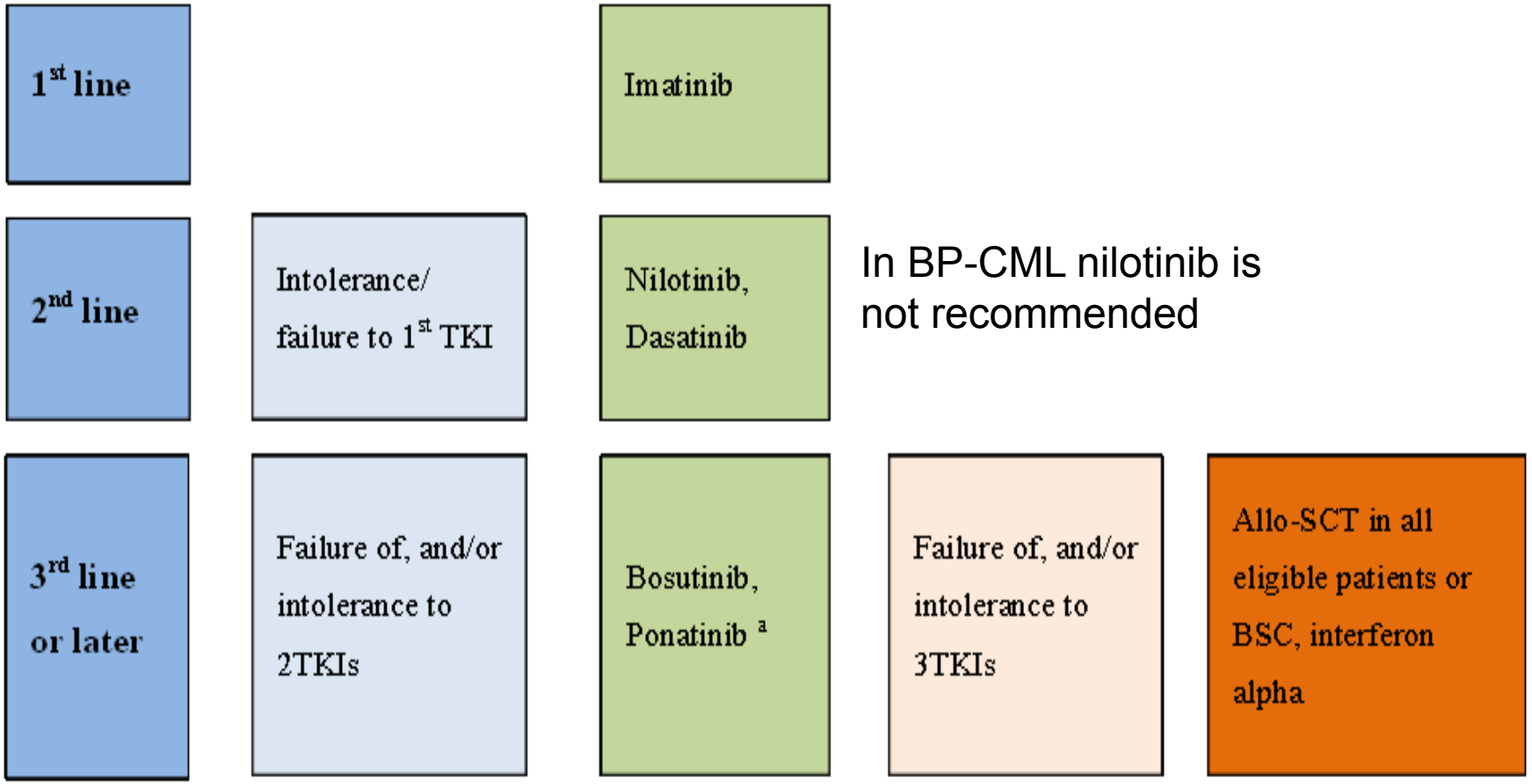
Technology

Details of the technology	Ponatinib (Iclusig, Incyte Corporation)
Marketing authorisation	Adults with CP, AP, or BP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation European marketing authorisation was granted in July 2013
Mechanism of action	Inhibits the kinase activity of native BCR-ABL gene, and all mutant variants, including 'gatekeeper' T315I
Administration	Oral – 15mg, 30mg (Q1, 2017) and 45mg daily dose tablets
Acquisition cost (excl. VAT)	30 tablets: 15mg £2525; 30mg £5050; 45mg £5050. The company has recently submitted a PAS which has been approved by the DH.

Care pathway, patients with chronic phase (CP-)CML



Care pathway,
patients with accelerated (AP-) and blast phase (BP-) CML



Decision problem

	NICE final scope	Any changes made by company
Population	As per marketing authorisation (see notes)[1]	N/A
Intervention	Ponatinib	N/A
Comparator(s)	• Bosutinib • Allo-SCT; with or without chemotherapy • Interferon alfa • BSC (including but not limited to hydroxycarbamide)	Interferon alfa not included. See notes for details.[2]
Outcomes	• Overall survival (OS) • Progression-free survival/ event-free survival • Response rates • Time to response • Duration of response (DoR) • Adverse effects of treatment • Health-related quality of life	Duration of response not used. See notes for details.[3]

Expert Comments (1)

- TKIs are expensive but effective first line treatments for CML, so much so that the majority of patients now die of other causes.
- Generic imatinib becomes available in December 2016, and it is likely that physicians will be encouraged to start all newly diagnosed patients on this.
- The best indicator of outcome in terms of survival is depth of response at various points in the first year, measured by a molecular test known as RQ-PCR
- Optimal response is defined as RQ-PCR results of <10%, <1% and <0.1% at 3, 6 and 12 months respectively after initiating treatment
- For imatinib as a 1st line treatment around 25% of patients fail to achieve these milestones. A further 25% will have changed treatment at 5 years, despite good responses, due to toxicity. For dasatinib and nilotinib the corresponding figures are around 10% and 20% respectively.
- Patients who fail imatinib because of disease resistant are frequently resistant to subsequent drugs. These account for 10 to 15% of CML patients and include those who would benefit from ponatinib

Expert Comments (2)

- Approx 20-25% of patients do not respond satisfactorily to first line treatments (Imatinib/ Nilotinib) due to side effects and toxicity, or they are refractory. One cause of non-response is the acquisition of BCR-ABL mutations.
- Ponatinib provides a more effective treatment (measured by complete cytogenetic response) after failure of 1st line nilotinib than an alternative 2nd generation TKI (nilotinib, dasatinib or bosutinib), reducing the need for subsequent allo-SCT. It is more effective third line treatment following 2nd line treatment with one of the 2nd generation TKIs, than treatment with an alternative 2nd generation TKI. It has superior potency than other TKIs in patients with BCR-ABL mutations, and remains the only oral agent for the treatment of T315I
- Non TKI treatments options for CML (allo-SCT, interferon) have a low response rate of 10-15% and have significant side effects
- Arterial thrombotic events is the most important side effect and is reported in 20% of patients compared to roughly 10% for nilotinib.

Patient/carer perspective (1)
Living with CML

- Profound psychological and emotional impact of a cancer diagnosis
- *"When I was diagnosed, it was like I had been hit by a truck"*
- Often followed a routine blood test
- Scary, feel numb and helpless
- Made worse by being rare
- Symptoms include:
  - fatigue, pain, frequent infections, bruises, fever, joint pain and breathlessness
- Untreated CML will progress and is fatal
- Reassurance needed about uncertainty of future treatments
- An unmet need for some patients

Patient/carer perspective (2)
Current treatments

- Repeated failure is a common experience
- Best supportive care
  - not viewed as a treatment
- Interferon alpha
  - has punishing side effects
- Stem-cell transplant seen as a treatment of last resort
  - for fitter patients
- Common side effects related to TKIs
  - hypertension, abdominal pain, fatigue, dry skin, constipation, rash, headache, fever, joint pain and nausea.
- Severe side effects
  - Tumour lysis syndrome (TLS), liver toxicity and gastrointestinal perforation

Clinical effectiveness

Ponatinib pivotal studies

Study	Location (sites)	Design	Population	Intervention and comparator	Primary outcome measures
PACE	66 centres in 12 countries (including 5 sites in the UK, n=30)	Phase II, single arm open-label, non-comparative study (n=449)	449 Patients (aged ≥ 18 years) with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy	Ponatinib 45mg tablet taken orally once daily (lowered in October 2013)	Major cytogenetic response (MCyR) in patients with CP-CML Major haematologic response (MaHR) in patients with AP-CML, BP-CML and Ph+ ALL

PACE study

- Patients were assigned to 1 of 6 cohorts dependent upon
  - Disease phase (chronic, accelerated or blast)
  - Resistance or intolerance to dasatinib or nilotinib
  - Presence of the T315I mutation
- 5 of the 449 patients were excluded from the effectiveness analysis (but not safety) as they had a history of T315I, unconfirmed at baseline, and had not received nilotinib or dasatinib
- Patients were pre-treated with prior TKIs (imatinib, dasatinib, nilotinib or bosutinib) and conventional therapy
- The following received ponatinib as a 3rd line treatment (after 2 TKIs)
  - CP-CML, 97/270 (36%)[1]; AP-CML, 33/85 (39%); BP-CML, 22/62 (35%)
- The following received ponatinib as a 4th line treatment (after 3 TKIs)
  - CP-CML, 142/270 (53%)[1]; AP-CML, 44/85 (52%); BP-CML, 34/62 (55%)
- Patients received a starting dose of 45mg/day, which was reduced or delayed following AEs. This was lowered in October 2013 at the request of the FDA to 15mg/day in CP-CML who had achieved a major cytogenetic response or better, to 30mg/day in CP-CML who had not, and advanced phase patients

PACE study

- Major cytogenetic response (MCyR), the primary endpoint for CP-CML was measured at any time within the first 12 months after initiation of treatment, and defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR)
- Major haematologic response (MaHR), the primary endpoint for AP-CML and BP-CML, was measured within the first six months after initiation of treatment, and defined as complete haematologic response (CHR) or no evidence of leukaemia (confirmed by blood analyses after ≥28 days)
- Secondary endpoints included: a major molecular response, the time to the response, the duration of the response, PFS, OS, and safety.

Result CP-CML at 12 months

Outcome	All lines (n=267)	3rd line (n=98)	4th line (n=141)
Major cytogenic response (MCyR)	56% (95% CI: 50–62)	67%, 95% CI:=57-76	45%, 95% CI:37-54
Complete cytogenic response	46%	56%, 95% CI:46-66	39%, 95% CI:31-48
Major molecular response	34%	36%, 95% CI: 26-46	33%, 95% CI:26-42
Median time to response	MCyR: 2.8 months (range: 1.6–11.3)	N/R	N/R
Duration of response	1 day to 19.4 months	N/R	N/R
Maintained response	91% (95% CI: 85-95)	N/R	N/R
PFS	12 month: 80%	N/R	N/R
OS	12 month OS: 94%	N/R	N/R

Result CP-CML at 4 years

Outcome	All lines (n=267)	3rd line (n=97)	4th line (n=142)
Major cytogenic response (MCyR)	N/R	71%	49%
Complete cytogenic response	N/R	65%	45%
Major molecular response	N/R	42%	37%
Median time to MCyR	N/R	N/R	N/R
Duration of response[2]	N/R	N/R	N/R
Maintained MCyR[1]	N/R	88%	86%
PFS (median)	56%	68%	52%
OS (median)	77%	79%	80%

Result AP-CML at 12 months

Outcome	All lines (n=83)	3rd line (n=33)	4th line (n=44)
Major haematological response (MaHR) by 6 mo.	55% (95% CI: 44–66)	61%	50%
Major cytogenic response (MCyR)	39%	42%	30%
Complete cytogenic response	24%	30%	16%
MMR	16%	24%	11%
Median time to response	MaHR: 3 weeks (range: 2–25) MCyR: 3.7 months (range: 0.8–9.7)	N/R	N/R
Duration of response	MaHR:1 to 21 months or more (median: 12 months)	N/R	N/R
Maintained response	MaHR at 12 months: 48% MCyR at 12 months: 73%	N/R	N/R
PFS	12 month: 55% (median: 18 mo.)	N/R	N/R
OS	12 month: 84%	N/R	N/R

Result AP-CML at 4 years

Outcome	All lines (n=83)	3rd line (n=33)	4th line (n=46)
Major haematologic response (MaHR) by 6 months	[redacted]		
Major cytogenic response (MCyR)			
Complete cytogenic response			
Major molecular response			
Median time to response	[redacted]	N/R	N/R
Duration of response		N/R	N/R
Maintained response		N/R	N/R
PFS		N/R	N/R
OS		N/R	N/R

Result BP-CML at 12 months and 4 yrs

	At 12 months for BP-CML patients only	At 4 years for BP-CML and Ph+ ALL combined		
Outcome	All lines (n=62)	All lines (n=94)	3rd line (n=38)	4th line (n=48)
MaHR by 6 months	31% (95% CI: 20–44)	[redacted]		
MCyR	23%			
CCyR	18%	N/R		
Median time to response	MaHR: 4.1 weeks (range: 1.7–16.1) MCyR: 1.9 months (range: 0.9–5.5)	N/R	N/R	N/R
Duration of response	MaHR:1 to 20 months or more (median: 5 months)	N/R	N/R	N/R
Maintained response	MaHR at 12 months: 42% MCyR at 12 months: 66%	N/R	N/R	N/R
PFS	12 month: 19% (median: 4 months)	[redacted]	N/R	N/R
OS	12 month OS:29%,median:7 months		N/R	N/R

Results by T315I mutation status

	12 months		4 years	
Outcome	Overall	T315I mutation	Overall	T315I mutation
CP-MCyR	56%	70%	59%	72%
CP-CCyR	46%	66%	54%	70%
CP-PFS	80%	83%	56%	56%
CP-OS	94%	92%	77%	72%
AP-MaHR*	55%	50%	[redacted]	
AP-MCyR	39%	56%		
AP-CCyR	24%	33%		
AP-PFS	55%	N/R	22%	N/R
AP-OS	58%	N/R	51%	N/R
BP-MaHR	31%	29%	[redacted]	
BP-MCyR	23%	29%		
BP-CCyR	18%	21%		
BP-PFS	19%	N/R		
BP-OS	29%	N/R		

Adverse events

At 12 months

- The most common non-haematologic adverse event was a rash, which occurred in patients with CP (40%), AP (29%) and BP (24%)
- The most common haematologic adverse event was thrombocytopenia which occurred in patients with CP (41%), AP (42%) and BP (27%).

Similar figures were reported for the 4 year follow up point

- Adverse events, haematologic, non-haematologic, and arterial occlusive were most common in CP patients and least common in BP patients

Matching-adjusted indirect comparison (MAIC)

- Based on Signorovitch et al (2012)
- In the absence of head-to-head randomised trials, indirect comparisons of treatments across separate trials can be performed
  - These analyses may be biased by cross-trial differences in patient populations, sensitivity to modelling assumptions, and differences in the definitions of outcome measures.
- Aim of MAIC is to lessen confounding, adjusting individual level data from a trial with individual patient level data (e.g. PACE) to match patients on the basis of inclusion/exclusion criteria specified in the ponatinib trial and reweight to match exactly the baseline characteristics reported for the comparator study (Khoury et al.) reported at study level
- It can address several limitations that arise in analyses based only on aggregate data

Indirect treatment comparison

- No direct comparative evidence between ponatinib and the comparator TKIs was identified
- The company therefore conducted a matching adjusted indirect comparison (MAIC) between ponatinib and bosutinib ONLY in CP-CML patients to facilitate an indirect comparison and inform their economic model.
  - No MAIC was done for AP or BP-CML groups due to lack of comprehensive third line setting data.
- MAIC involves using individual patient data to match patient characteristics across separate trails involving different interventions
- MAIC was performed using the baseline characteristics in CP group of patients only.

Best response	Bosutinib Khoury et al. (Phase I/II study) n=118	Ponatinib PACE Cortes et al. (Phase II) n=97[a]	Ponatinib Matching-adjusted n=69[b]
CCyR, n/N (%)	26/108 (24.07%)	63/97 (64.95%)	61.34%
PCyR, n/N (%)	9/108 (8.33%)	6/97 (6.19%)	8.46%
CHR, n/N (%)	44/116 (37.93%)	17/97 (17.53%)	18.19%
No response, n/N (%)	(29.66%)[c]	11/97 (11.34%)	12.01%

CCyR, complete cytogenetic response; CHR, complete haematologic response; PCyR, partial cytogenetic response

[a] Patients in the PACE trial who had received 2 prior TKIs (n=97) were used to inform the MAIC

[b] Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights

[c] For bosutinib, there is no n/N for the 'no response' rate because the value was calculated as 1 minus the other response rates (see clarification response,[28] question A12)

ERG comments

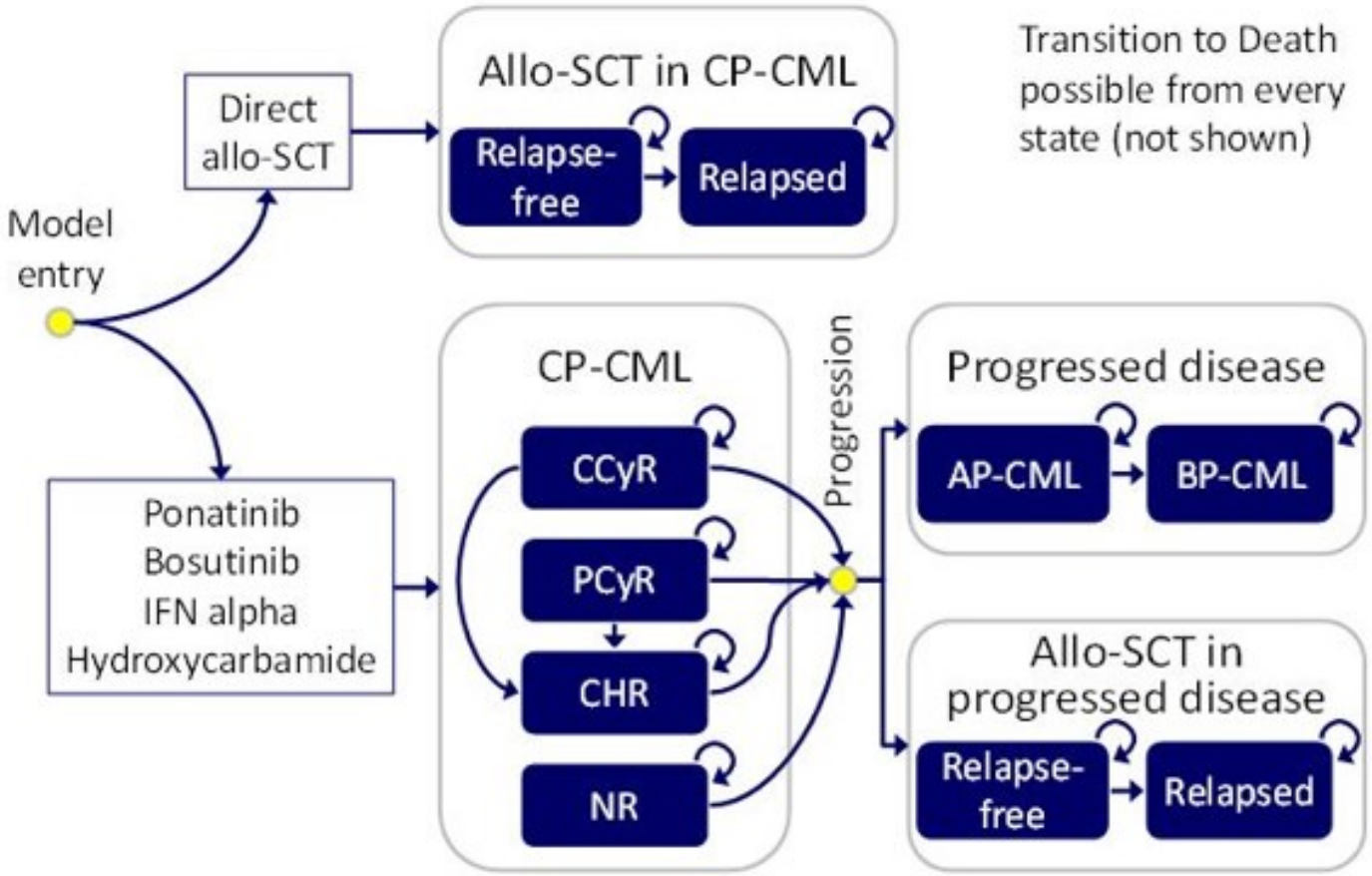
- The ERG is confident that the company identified all relevant studies in its submission
- The ERG considered PACE to be a large well designed non comparative study, and the study population included in the trial to be reflective of the CML population in England
- In the absence of 'within-study' estimates based on randomised comparison (due to ethical considerations), it was necessary to use an alternative approach to make indirect comparison. The MAIC has several limitations:
  - It matches PACE population (said to be reflective of UK practice) onto Khoury et al which is not representative of UK practice
  - Median age of PACE population is 59, but 50 for MAIC
  - The lack of an internal control group increases the potential for bias in the trial results and in the MAIC.
- While the safety and efficacy outcomes for all lines combined met the company's reported power calculation, the majority of those individual lines of therapy were not adequately powered.

Key issues: clinical effectiveness

- What is the committee's view on the evidence base considering it is non comparative and thus has a high potential for bias?
- What is the committee's view on the company's MAIC?
  - The ERG commented that using this methodology the company had to adjust PACE study to fit with bosutinib study, due to absence of individual patient data for bosutinib
- In some of the by line treatment subgroups, the study was insufficiently powered. What is the committee's view on the power of the subgroups?
- The optimal dosing of ponatinib is uncertain. The initial dose (45mg) was lowered during study; therefore it is unclear whether the lower dosing regimen would have been as clinically effective over study period. What is the committee's view on the impact of this uncertainty on the estimate of treatment effect
- Efficacy of treatment in patients with T315I mutation
- The duration of ponatinib treatment uncertain
  - where complete response is achieved, allo-SCT would be considered if eligible, therefore ponatinib treatment would cease;
  - Would patients ineligible for allo-SCT continue treatment indefinitely?

Cost effectiveness evidence

Model structure CP-CML



Model details

- On entering the model patients could receive 1 of 5 interventions:
  - Ponatinib
  - Bosutinib
  - Interferon alfa
  - Hydroxycarbamide (proxy for BSC)
  - Allo-SCT

Non-Allo

- The modelling approach for all non-allo interventions was identical but differed between non-allo and allo-SCT
- Death could occur at any point
- A lifetime horizon was used (up to 100 years)
- The model employed 3 month Markov cycles with a half cycle correction

Model details non-allo-SCT treatments

- Treatment occurred in the first cycle only after which the patients moved into 1 of 4 mutually exclusive and exhaustive states, ranked in descending order of benefit: CCyR; PCyR; CHR; and NR. The model included an option to discontinue ponatinib if non responsive.
- The next possible state besides their existing state for NR and complete haematological response patients was death, disease progression or treatment discontinuation
- Discontinuation of treatment was assumed not to happen for those on interferon alfa or BSC
- Patients in the CCyR or PCyR state could become unresponsive to treatment and regress to complete haematological response

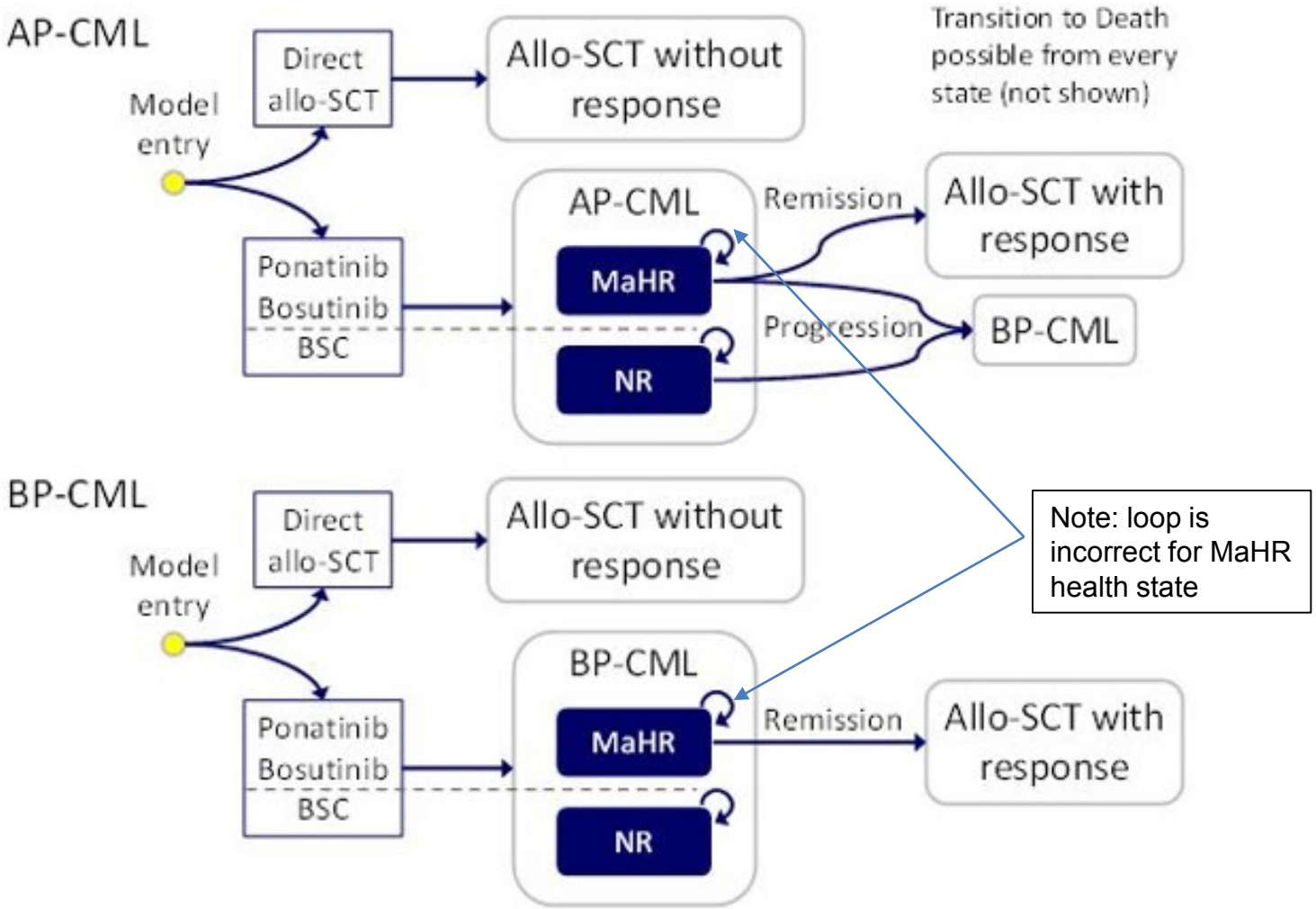
Model details non-allo-SCT treatments

- Following discontinuation of treatment in PCyR, CHR or NR, patients would regress to NR, with possibility of an immediate CHR due to subsequent BSC use. Patients in CCyR were assumed to stay in CCyR
- Following progression patient received allo-SCT if appropriate or entered AP. For AP, next event (beside same) is either death or progression to BP. Once a patient entered the BP state, the only possible event was death.
- For patients receiving allo-SCT, the next event was either death or relapse. Once a patient relapsed the only event possible was death

Model details allo-SCT

- After entering the model, the next event, if moving out of the relapse free state was relapse or death
- Once a patient had relapsed the only next possible state outside of this was death

Model: AP and BP-CML



Model details: AP and BP-CML

- Patients are assumed to have an MaHR or have no response to treatment
- Patients who have an MaHR would have allo-SCT. All patients are assumed suitable for allo-SCT
- For patients starting with AP-CML, the next event after allo-SCT is death. In non-responsive patients, the next event is death or progression to BP, from which the next event is death
- For patients starting with BP-CML, after allo-SCT, the next event is death, for those who are non-responsive the next event is death
- Those who go to allo-SCT on entry can only move to the death state

Clinical data used in models

Variable	Value	Reference
Age (years)	54.5 CP; 54.6 AP; 50.4 BP	MAIC for CP PACE for AP and BP
% male	44.9 CP; 41.8 AP; 60 BP	
Response rates (%) for ponatinib in CP patients	CCyR 61.34; PCyR 8.46; CHR 18.19; NR 12.01	MAIC
Response rates (%) for bosutinib in CP patients	CCyR 24.07; PCyR 8.33; CHR 37.93; NR 29.66	Khoury et al
Response rates (%) for interferon alfa in CP patients	CCyR 0; PCyR 0; CHR 47; NR 53	Dalziel et al
Response rates (%) for BSC in CP patients	CCyR 0; PCyR 0; CHR 41; NR 59	Dalziel et al
Response rates (%) for ponatinib in AP patients	MaHR 55.7; Non-MaHR 44.3	PACE
Response rates (%) for bosutinib in AP patients	MaHR 29.2; Non-MaHR 70.8	Gambacorti-Passerini et al
Response rates (%) for BSC in AP patients	MaHR 0; Non-MaHR 100	Company assumption
Response rates (%) for ponatinib in BP patients	MaHR 31.7; Non-MaHR 68.3	PACE
Response rates (%) for bosutinib in BP patients	MaHR 4.3; Non-MaHR 95.7	Gambacorti-Passerini et al
Response rates (%) for BSC in BP patients	MaHR 0; Non-MaHR 100	Company assumption

Extrapolation of outcomes

- In cases when the company did not have access to patient-level time-to-event data, the company digitised published Kaplan-Meier survivor functions and used the Solver add-in in Excel to generate parametric survivor functions by minimising the sum of squared errors (SSE) between the predicted survival curve and that of the digitised points.
- The company based their choice of parametric model on the AIC and BIC when patient level data were available.
- ERG commented that the method to reconstruct the patient-level data proposed by Guyot et al. could have also been used
- ERG considered that extrapolating survivor functions using sample data alone was inappropriate where there were few events in studies with relatively short duration of follow-up, and should be informed by external clinical data / opinion where possible
- ERG expressed concern that the approach does not give sufficient weight to expert clinical knowledge and the expected shape of the hazard function over time in the target population of patients
- ERG cautioned that using AIC and BIC alone to determine choice of parametric model did not establish whether it is a good model or would result in a clinical plausible estimate of event rates beyond the duration of the study.

OS modelling

	CP-CML model		AP/BP-CML model	
	Function chosen	Function best fit	Function chosen	Function best fit
After allo-SCT in patients with CP and AP-CML	Exponential	Gompertz		
After SCT in AP-CML	Exponential	Gompertz	Exponential	Gompertz
In AP-CML with BSC	Log normal	Log normal	Log normal	Log normal
In BP-CML with BSC	Log logistic	Log logistic	Log logistic	Log logistic
In AP-CML with TKI treatment			[redacted]	
In BP-CML with TKI treatment				
After SCT in BP-CML with remission			Exponential	Log-logistic
After SCT in BP-CML with no remission			Exponential	Gompertz

Assumed adverse event rates (non-vascular)

Adverse event	CP-CML		AP-CML		BP-CML	
	Ponatinib	Bosutinib	Ponatinib	Bosutinib	Ponatinib	Bosutinib
Abdominal pain	[redacted]	0.00%	[redacted]	-	[redacted]	-
Anaemia		6.78%		32.91%		20.31%
Diarrhoea		8.47%		-		-
Hyperglycaemia		0.00%		-		-
Hypophosphatemia		0.00%		-		-
Leukocytopaenia		0.00%		6.33%		18.75%
Lipase increased		0.00%		-		-
Neutropenia		15.25%		17.72%		25%
Pancreatitis		0.00%		-		-
ALT elevation		5.93%		-		-
GGT increased		0.00%		-		-
Thrombocytopenia		26.27%		44.30%		35.94%

Assumed serious adverse event rates

Adverse event	CP-CML		AP-CML		BP-CML	
	Ponatinib	Bosutinib	Ponatinib	Bosutinib	Ponatinib	Bosutinib
Cardiovascular events	[redacted]	-	[redacted]	-	[redacted]	-
Cerebrovascular events		-		-		-
Peripheral vascular event		-		-		-
Venous thromboembolism event		-		-		-

Serious AEs relating to vascular events only occur in patients receiving ponatinib.

Health-related quality of life

- Evidence searches by the company identified 3 studies which provided HRQoL data on the disease[1].
- These involved TTO and/or SG methods, involved the general population and included UK respondents
- The company reported the sources used for utility values in patients with allo-SCT but not how they were selected[2]. One of these had been used in a previous evaluation of CML[3].
- The utility decrements were applied to HRQoL from the UK general population[4]

HRQoL reported by Szabo et al (2010) and utility decrements assumed in model

Health State	**Estimated HRQoL (95% CI)**	**Utility decrement**
CP-CML responding to treatment	0.91 (0.89 – 0.94)	0
CP-CML not responding to treatment	0.73 (0.69 – 0.78)	0.116
AP-CML responding to treatment	0.78 (0.74 – 0.82)	0.064
AP-CML not responding to treatment	0.53 (0.48 – 0.58)	0.316
BP-CML responding to treatment	0.56 (0.52 – 0.60)	0.286
BP-CML not responding to treatment	0.29 (0.24 – 0.33)	0.556
Treatment withdrawal due to SAEs	0.52 (0.46 – 0.58)	0.326

Utility decrements used following allo-SCT in the company model

Period after allo-SCT	Utility decrement	Source.
Up to 3 months post-allo-SCT	0.296	Van Agthoven *et al*.
Between 3 and 6 months post-allo-SCT	0.216	Assumption: midpoint between value up to 3 months and beyond 6 months
6 months and longer post-allo-SCT	0.136	Loveman *et al*.
Post-relapse	0.260	Kantarjian *et al*. and Olaverria *et al*.

Costs – Adverse events

Adverse event	Unit cost (£)	Source
Abdominal pain	752.10	Ref costs 2014/15
Anaemia	1,827.13	NHS ETF 2015/16
Diarrhoea	801.95	Ref costs 2014/15
Hyperglycaemia	1,271.46	Ref costs 2014/15
Hypophosphatemia	721.00	See notes 1
Leukocytopaenia	633.26	See notes 2
Lipase increased	721.00	See notes 1
Neutropenia	633.26	Ref costs 2014/15
Pancreatitis	1,121.98	Ref costs 2014/15

Costs – Adverse events

Adverse event	Unit cost (£)	Source
ALT elevation	1,121.98	Ref costs 2014/15
GGT increased	1,121.98	Ref costs 2014/15
Thrombocytopenia	421.74	Ref costs 2014/15
Serious adverse event		
Cardiovascular events	2,357.00	NHS ETF 2015/16
Cerebrovascular events	2,962.00	NHS ETF 2015/16
Peripheral vascular event	2,872.00	NHS ETF 2015/16
Venous thromboembolism event	552.00	NHS ETF 2015/16

Costs-Treatment cycles*

Intervention	Cost per cycle (£) (ponatinib list price, comparator list prices)
Ponatinib in CP-CML (CCyR)	[redacted]
Ponatinib in CP-CML (PCyR)	
Ponatinib in CP-CML (CHR)	
Ponatinib in CP-CML (NR)	
Dasatinib	7624
Imatinib	5590
Nilotinib	7910
Interferon alfa	6833
Bosutinib	10,714
BSC	38

Other costs

Cost	Value (£)
CP- CML with CCyR	208
CP-CML without CCyR	495
AP- CML	2648
BP-CML	20,319
Average end-of-life care cost	5,765.76
Allo-SCT	60,092
Per-cycle follow-up cost after allo- STC, year 1	12,214
Per-cycle follow-up cost after allo- STC, year 2	3518
Per-cycle follow-up cost after allo- STC, year 3+	420

Company base case CP-CML

(calculated by ERG using ponatinib PAS price and list prices for comparators)

Treatment	LYG	Discounted costs (£)	Discounted QALYs	Deterministic ICER (£/QALY gained)	
				Ponatinib versus comparator	Full Incremental analysis
BSC	4.64	136,666	2.24	15,200	
Bosutinib	8.38	150,811	4.00	18,213	8,072
Interferon alfa	4.72	188,917	2.30	6395	Dominated
Allo-SCT	8.77	209,258	3.93	4042	Dominated
Ponatinib	[redacted]			-	18,213

Probabilistic analyses results
Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values

The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (51%); £30,000 (81%); and £50,000 (91%)

Company base case AP-CML

(calculated by ERG using ponatinib PAS price and list prices for comparators)

Treatment	LYG	Discounted costs (£)	Discounted QALYs	Deterministic ICER (£/(cost per QALY gained)	
				Ponatinib versus comparator	Full Incremental analysis
BSC	1.91	95,263	0.58	14,750	-
Allo SCT	3.20	166,635	1.86	13,279	Extendedly dominated
Ponatinib	[redacted]			-	14,750
Bosutinib	6.77	162,419	2.62	Dominant	Dominant

Probabilistic analyses results
Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values

The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (71%); £30,000 (90%); and £50,000 (99%)

Company base case BP-CML

(calculated by ERG using ponatinib PAS price and list prices for comparators)

Treatment	LYG	Discounted costs (£)	Discounted QALYs	Deterministic ICER ((cost (£) per QALY gained)	
				Ponatinib versus comparator	Full Incremental analysis
Bosutinib	0.85	71,473	0.37	17,601	-
Ponatinib	[redacted]			-	17,601
BSC	1.16	101,961	0.28	Dominant	Dominant
Allo-SCT	1.34	103,748	0.85	Dominant	Dominant

Probabilistic analyses results
Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values

The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (67%); £30,000 (94%); and £50,000 (100%)

ERG comments

- Model structure adopted for the economic evaluation is generally appropriate though similar to other CML topics, there has been a reliance on surrogate endpoints.
- There is inherent uncertainty introduced by the use of a MAIC, and the matching of the PACE study participants to the Khoury et al. (bosutinib) trial participants may have an impact on the relevance of the MAIC population to UK practice.
- The biggest concern of the ERG is that the parametric distributions fitted where individual patient data were not available is inappropriate, and that for all distributions there was insufficient exploration of the impact on the ICER of the selection of alternative curves that were considered plausible
- The model did not take into account any possibility of treatment-related death.
- The ERG believes that the PSA undertaken by the company was not robust because of the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters.

ERG exploratory analyses

- In CP-CML, the ERG varied the choice of parametric curves for OS, PFS, duration of response and relapse-free survival. These changes affected the ICER, as did assuming drug wastage, and reducing costs post-progression in both CP-CML and post allo-SCT for CP-CML patients.
- In AP-CML, the ERG varied the choice of parametric curves among other changes. The largest change in the ICER was caused by the selection of curves.
- In BP-CML, the ERG varied the choice of parametric curves among other changes. The largest changes in the ICER were caused by the selection of curves and the introduction of a 3-month stopping rule for bosutinib

ERG's exploratory deterministic analyses in CP-CML (calculated by ERG using PAS price for ponatinib)

Ref No	Exploratory Analyses	Pon vs Bos	Pon vs BSC	Pon vs allo-SCT
0	N/A (company's base case)	18,213	15,200	4042
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	13,747 – 43,344	12,063 – 22,295	Dominant – 12,091
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	15,319 – 38,710	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	13,747 – 27,616	12,063 – 21,150	Dominant – 12,091
1d	Combining 1b and 1c	15,319 – 25,181	12,063 – 21,150	Dominant – 12,091
2a	Recalculation of the survivor functions (excluding PFS exponentials)	16,297	13,661	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	17,073	14,860	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	18,092	15,424	Dominant
3	Assuming drug wastage	30,754	24,245	16,487

ERG's exploratory deterministic analyses in CP-CML (calculated by ERG using PAS price for ponatinib, comparator list prices)

Ref No	Exploratory Analyses	Pon vs Bos	Pon vs BSC	Pon vs allo-SCT
4	Including a 3 month stopping rule for bosutinib	21,313	15,200	4042
5	No half-cycle correction of intervention costs	17,785	15,709	5472
6	Including treatment-related deaths	18,099	16,810	6143
7a	Costs post-progression in CP-CML or post allo-SCT for CP-CML patients equal to those for BSC.	21,717	18,688	21,712
7b	Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib.	21,584	18,555	21.039
8	Assuming life table data are probabilities not rates	18,226	15,211	4043
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	18,017	15,035	4096
9b	Assuming decrements of HRQoL between CP-CML and other CML states are maintained	17,920	14,954	4125
10	2a, 4,5, 7a, 8 and 9a, using the curves believed most credible by the company	23,059	18,308	27,649
11. ERG base case ICERs	(11a)- 1a, 2a, 4,5, 7a, 8 and 9a (range)	19,986 – 52,121	18,246 – 27,667	18,279 – Dominated
	As 11a, but assuming the same distribution for Duration of response for ponatinib and bosutinib (range)	22,995 – 42,637	N/A	N/A

ERG's exploratory deterministic analyses in AP-CML
(calculated by ERG using PAS price for ponatinib, comparator list prices)

		Cost per QALY gained (£) – Ponatinib vs	
Ref No	Exploratory Analyses	BSC	Allo-SCT
0	N/A (company's base case)	14,750	13,279
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	7479 – 15,861	Dominating – 95,313
2	Recalculation of the survivor functions	10,358	12,217
3	Assuming drug wastage	15,267	14,199
4	No half-cycle correction of intervention costs	16,580	16,465
5	Including treatment-related deaths	14,747	12,671
6	Assuming life table data are probabilities not rates	14,754	13,285
7	2,3, 4, and 6 using the curves believed most credible by the company	12,975	16,412
8 ERG base case ICER	As 7, but choosing alternative distributions in addition to those selected by the company (range)	7475 – 18,005	Dominating – 63,701

ERG's exploratory deterministic analyses in BP-CML
(calculated by ERG using PAS price for ponatinib, comparator list prices)

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,601	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	11,184 – 18,808	8,251 - Dominated
2	Recalculation of the survivor functions	15,812	157,193
3	Assuming drug wastage	18,022	Dominated
4	Incorporating a three-month stopping rule for bosutinib	21,910	Dominated
5	No half-cycle correction of intervention costs	18,396	Dominated
6	Including treatment-related deaths	16,665	Dominated
7	Assuming life table data are probabilities not rates	17,601	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	21,254	102,612
9 ERG base-case ICER	1,2,3, 4,5, and 7 (range)	17,066 – 22,512	4,004 - Dominated

Innovation

- Ponatinib is a significant advance in treatment of CML for patients whose disease is resistant or intolerant to imatinib or 2nd generation tyrosine kinase inhibitors with or without the T315I mutation.
- Few treatment options are available

End of life

CP-CML

- Company's model estimates that patients' life expectancy is more than 4 years regardless of treatment

AP-CML

- Company's model estimates that, on average, those patients receiving bosutinib would live in excess of 6 years; those that receive allo-SCT would live in excess of 3 years, whilst those who receive BSC would live slightly under 2 years
- The model predicts a large extension in health for ponatinib compared with BSC, in excess of 6 years, potentially satisfying criteria for population for whom allo-SCT or bosutinib are not comparators

BP-CML

- the company's model estimates that those patients receiving bosutinib, allo-SCT or BSC would not live greater than two years, although this value increases greatly if it is assumed that OS following allo-SCT is characterised by a Gompertz distribution
- model predicts ponatinib provides >3 months extension of life compared with the comparators and could satisfy the end of life criteria for patients with BP-CML, unless it is assumed that the OS following allo-SCT is lengthier than the company assumed in its base case.

Potential equality issues

- None identified at scoping stage nor in submissions.
- However the company note a number of potential equality benefits from the use of ponatinib namely:
  - It provides an additional treatment option for patients with CML and Ph+ ALL who currently have limited treatment options
  - While allo-SCT is suitable for these patients, there is unequal access to it among ethnic groups due to differences in donor rates
  - Ponatinib is the only TKI active against the T315I mutation

Key issues: cost effectiveness

- The company fitted parametric distributions where individual patient data were not available. Was this appropriate? Or should the company have reconstructed the patient-level data as preferred by the ERG using the Guyot et al. method?
- Did the company fully explore the impact on the ICER of the selection of alternative curves? Is it possible to determine which curves are considered the most plausible.
- The model also ignored any possibility of treatment-related death. What is the committee's view on this?
- What is the committee's view on the company's PSA which the ERG considered was not robust due to the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters?

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Contains AIC, CIC

Pre-meeting briefing
Ponatinib for treating Ph+ acute lymphoblastic leukaemia [ID671]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts 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 includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Disease Background

- Acute lymphoblastic leukaemia (ALL) is a rare form of cancer, characterised by the overproduction and accumulation of immature white blood cells[1]
- ALL accounts for around 20% of all leukaemias in adults and is the most common form of childhood leukaemia
- Approximately 25% of adults with ALL have acquired chromosomal abnormality known as Philadelphia chromosome positive disease (Ph+)[2]
- Cancer research UK figures show that in 2014, 654 people in the UK were newly diagnosed with ALL. The company estimate that 33 people received ponatinib according to its licence indication[3,4]
- Prognosis once diagnosed is poor but improving. Prognosis is usually poorer with Ph+[5]

Treatment phases of Ph+ ALL

- Treatment is usually carried out in 3 stages.
  - Induction: Initial treatments which aim to kill the leukaemia cells in the bone marrow and get the patient into remission
  - Consolidation: Aims to further reduce tumour burden including any leukaemia cells that have penetrated into the central nervous system
  - Maintenance: Involves regular doses of chemotherapy to prevent the leukaemia returning
- During these treatment phases patients are treated with chemotherapy doses including tyrosine kinase inhibitor (TKI) therapy.
- Ponatinib is currently only available to patients with the T315I mutation.

Treatment pathway

- 1st line: Imatinib[1] plus chemotherapy
- 2nd line: Dasatinib[2] plus chemotherapy
- 3rd line: Ponatinib

Following failure of previous line therapy

- On any line of therapy, or treatment, where complete response is achieved, allo-SCT should be considered in all eligible patients
- Patients with the T315I mutation should be routed straight to ponatinib (3rd line)
- Patients who relapse or have refractory disease should receive combination chemotherapy plus an alternative TKI to one previously received.
- In older patients with co-morbidities consider adding corticosteroids to 1st and 2nd line treatment

Technology

Details of the technology	Ponatinib (Iclusig, Incyte Corporation)
Marketing authorisation	Adults with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation European marketing authorisation was granted in July 2013
Mechanism of action	Inhibits the kinase activity of native BCR-ABL gene, and all mutant variants, including 'gatekeeper' T315I
Administration	Oral – 15mg, 30mg (Q1, 2017) and 45mg daily dose tablets
Acquisition cost (excl. VAT)	30 tablets: 15mg £2525 (BNF July 2016); 30mg £5050 (anticipated list price); 45mg £5050 (BNF July 2016). The DH has approved a simple PAS discount of [redacted]

Decision problem

	NICE final scope	Any changes made by company
Population	As per marketing authorisation	N/A
Intervention	Ponatinib	N/A
Comparator(s)	• Established clinical management without ponatinib[1] (including but not limited to best supportive care)	N/A
Outcomes	• Overall survival (OS) • Progression-free survival/ event-free survival • Response rates • Time to response • Duration of response (DoR) • Adverse effects of treatment • Health-related quality of life	See notes

Patient/carer perspective

- Patients are usually diagnosed with ALL following the onset of symptoms, when it has often progressed significantly. 64% of patients are diagnosed following an emergency presentation, the highest of any cancer
- Typically, a Ph+ ALL patient would be treated with induction phase chemotherapy, often including cyclophosphamide, vincristine, adriamycin and dexamethasone (hyper-CVAD) in combination with a TKI (imatinib).
- The chance of relapse is high and disease reoccurrence is considered the most frequent cause of treatment failure
- Although remission can be achieved, allo-SCT is the only curative treatment

Clinical effectiveness

Ponatinib pivotal studies

Study	Location (sites)	Design	Population	Intervention and comparator	Primary outcome measures
PACE	66 centres in 12 countries (including 5 sites in the UK, n=30)	Phase II, single arm open-label, non-comparative study (n=449)	449 Patients (aged ≥ 18 years) with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy	Ponatinib 45mg tablet taken orally once daily (lowered in October 2013)	Major haematologic response (MaHR) in patients with AP-CML, BP-CML and Ph+ ALL

PACE study

- Patients were pre-treated with prior TKIs (imatinib, dasatinib, nilotinib or bosutinib) and conventional therapy
- 14/32 (44%) patients received ponatinib as a 3rd line treatment (after 2 TKIs)
- Ph+ ALL patients were able to maintain 45mg per day for 96% of the entire treatment duration. Average daily dose over the course of the study was 42.3mg (figures at April 2012)

Results

Outcome	Nov 2012, 12 month (n=32)	Feb 2015 (n=32)
Major Haematologic response (MaHR) by 6 mo.	41% (95% CI:24-59)	N/R
Major cytogenetic response (MCyR)	47%	N/R
Complete cytogenetic response	38%	N/R
Median time to response	MaHR: 2.9 weeks (range: 1.6–24); MCyR: 1 month (range: 0.9-3.7)	N/R
Duration of response	MaHR: 2 to 14 months or more (median: 3 months)	N/R
Maintained response	MaHR at 12 months: 8% MCyR at 12 months: 32%	N/R
PFS	12 month: 7% (median 3 months)	N/R
OS	12 month: 40% (median: 8 months)	36 month: 16%

Results by T315I mutation status at 12 months

Outcome	Overall (n=32)	Resistant/ Intolerant (n=10)	T315I mutation (n=22)
Major Haematologic response by 6 months	41%	50%	36%
Major cytogenetic response	47%	60%	41%
Complete cytogenetic response	38%	50%	32%
PFS	12 month: 7%	N/R	N/R
OS	12 month: 40%	N/R	N/R

Adverse events

At 12 months

- The most common non-haematologic adverse event were dry skin (22%), rash (19%), abdominal pain (19%) and constipation (19%)
- The most common haematologic adverse event were anaemia (16%), neutropaenia (12%) and thrombocytopenia (9%)

Similar figures were reported for the 4 year follow up point

- At the 4 year cut off, Ph+ ALL [redacted] patients had a treatment-emergent grade 5 arterial occlusive adverse event
  - Following a review of updated clinical trial data on ponatinib revealing an accumulation of treatment-emergent vascular occlusive events, the EMA issued a set of recommendations regarding the use of ponatinib in November 2013. The EMA recommends that the cardiovascular status of patients be assessed and that cardiovascular risk factors be actively managed prior to, and monitored during, treatment

ERG comments

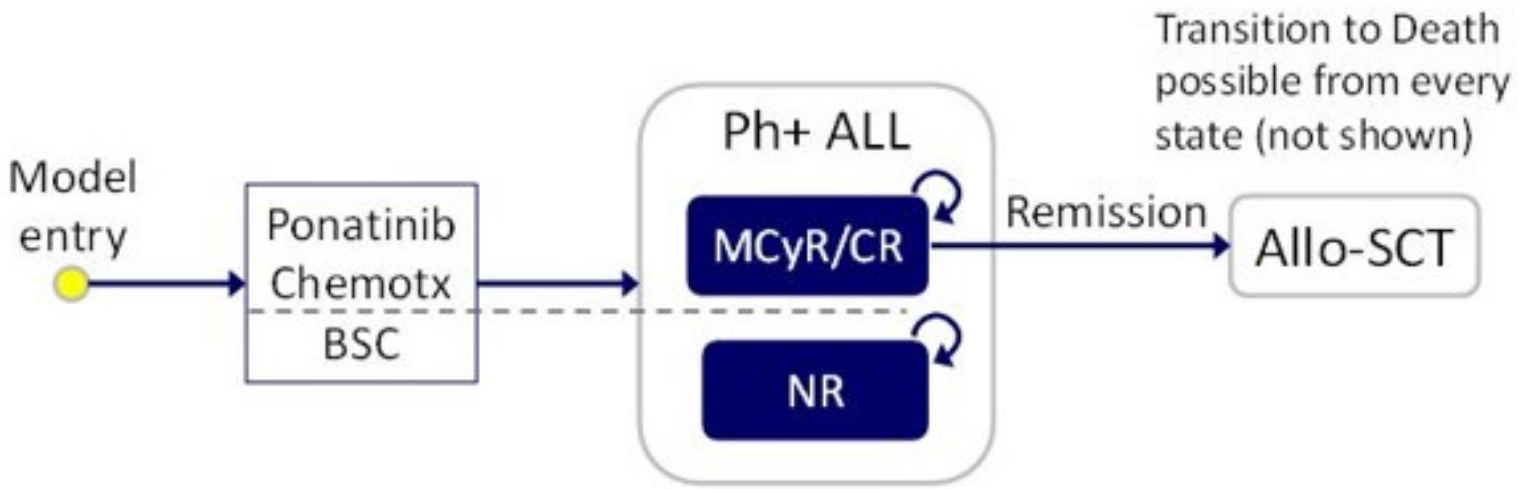
- The ERG is confident that the company identified all relevant studies in its submission
- The ERG considered PACE to be a large well designed non comparative study. It considered that the study population included in the trial was reflective of the Ph+ ALL population in England in terms of age and gender. However the treatment pathway was not since patients received nilotinib which is not used in the NHS
- The ERG noted expert concerns on the primary outcome measure (major haematologic response). The ERG's clinical advisor suggested this to be a weak measure in this patient population who are resistant to tyrosine kinase inhibitors and most likely taking ponatinib as a bridge to allogeneic stem cell transplant.
  - A more appropriate endpoint would have been minimal residual disease levels in the bone marrow (not assessed in PACE study)

Key issues: clinical effectiveness

- There is limited, non comparative evidence base (due to ethical reasons – EMA agreed with the non-comparative design of study)
  - High risk of bias (selection, performance and detection bias) in absence of a comparator
  - Magnitude of treatment effect uncertain in absence of control group
- Small Ph+ ALL subgroup (n=32) lacks statistical power
- Optimal dosing uncertain. Initial dose (45mg) was lowered during study; therefore it is unclear whether the lower dosing regimen would have been as clinically effective over study period
- Duration of treatment uncertain
  - where complete response is achieved, allo-SCT would be considered if eligible
  - Would patients ineligible for allo-SCT continue treatment indefinitely
- Ph+ ALL population in trial similar to population in England, but clinical practice used in PACE trial was not representative of treatment in NHS (people received nilotinib which is not used in routine clinical practice)
- What is the committee's view on the available evidence?

Cost effectiveness evidence

Model structure Ph+ ALL



Model details

- On entering the model patients could receive 1 of 3 interventions:
  - Ponatinib
  - Induction chemotherapy
  - Hydroxycarbamide (proxy for BSC)
- If a patient who received ponatinib or induction chemotherapy had a major cytogenic response or a complete remission (respectively), they were assumed to receive allo-SCT, if eligible
- Patients receiving BSC were assumed to have no response and remain in that state
- Transition to death possible from any state
- A lifetime horizon was used (up to 100 years)
- The model employed 3 month Markov cycles with a half cycle correction

Clinical data used in model

Variable	Value	Reference
Age (years)	53	PACE, CP-CML population
% male	62.5	
Response rates (%) for ponatinib	MyCR 46.88 NR 53.12	PACE
Response rates (%) for induction chemotherapy	CR 37.04; NR 62.96	Tavernier et al
Response rates (%) for BSC	MCyR/CR 0; NR 100	Company assumption
Rates of: Abdominal pain	[redacted]	Ref costs 2014/15
Anaemia		NHS ETF 2014/15
Lipase increased		Assumed to require one day in hospital
Neutropenia		Ref costs 2014/15
Thrombocytopaenia		Ref costs 2014/15
Peripheral vascular event		Ref costs 2014/15
Venous thromboembolism event		Ref costs 2014/15

Extrapolation of outcomes

- In cases when the company did not have access to patient-level time-to-event data, the company digitised published Kaplan-Meier survivor functions and used the Solver add-in in Excel to generate parametric survivor functions by minimising the sum of squared errors (SSE) between the predicted survival curve and that of the digitised points.
- The company based their choice of parametric model on the AIC and BIC when patient level data were available. The ERG cautioned that using AIC and BIC alone to determine choice of parametric model did not establish whether it is a good model or would result in a clinical plausible estimate of event rates beyond the duration of the study.
- ERG commented that the method to reconstruct the patient-level data proposed by Guyot et al. could have been used
- ERG considered that extrapolating survivor functions using sample data alone was inappropriate, particularly in cases where there were few events in studies with relatively short duration of follow-up, and should be informed by external clinical data / opinion where possible
- ERG expressed concern that the approach does not give sufficient weight to expert clinical knowledge and the expected shape of the hazard function over time in the target population of patients

OS modelling

	Function chosen	Function best fit
OS with ponatinib	Exponential	Gompertz – AIC Exponential - BIC
OS after SCT	Log logistic	Log logistic

Health-related quality of life

- PACE study did not collect HRQoL
- The company assumed that utilities for BP-CML reported in Szabo et al. (2010), were applicable for patients with Ph+ ALL

Patient group	Estimated HRQoL (95% CI)	Utility dec. used in model
BP-CML Responding to treatment	0.56 (0.52 – 0.60)	0.286
BP-CMP no response to treatment	0.29 (0.24 – 0.33)	0.556
Treatment withdrawal due to SAEs	0.52 (0.46 – 0.58)	0.326

- The utility decrements applied to allo-SCT are the same as those used for CML

Period after allo-SCT	Utility dec. used in model	Source
Up to 3 months post-allo-SCT	0.296	Van Agthoven et al.
>3 and <6 months post-allo-SCT	0.216	Assumption: midpoint between value up to 3 months and beyond 6 months
≥6 months post-allo-SCT	0.136	Loveman et al.
Post-relapse	0.260	Derived from Kantarjian et al. & Olaverria et al.

Costs

Treatment		Cost (£)	Source
Ponatinib per cycle	Proportion of time receiving each dose [redacted]	[redacted] (list price)	PACE study; ARIAD Pharmaceuticals
Induction chemotherapy per 6 week cycle		17.999.73	BNF
BSC per cycle		4,063.87	Pagano *et al*. 2000
Monitoring and hospital costs per cycle for patients who responded to ponatinib		208.00	
Monitoring and hospital costs per cycle for patients who did not responded to ponatinib		24,070.00	

Company's base case results (ponatinib PAS price)

Deterministic analyses results					
Treatment	Life years gained	Costs (£)	QALYs	ICER (cost per QALY gained) (£)	
				Ponatinib versus comparator	Full Incremental analysis
For whom allo-SCT is suitable					
BSC	0.32	40,875	0.09	26,624	-
Induction chemotherapy	2.96	84,854	1.84	31,123	25,258
Ponatinib	[redacted]			-	31,123
For whom allo-SCT is unsuitable					
BSC	0.32	40,875	0.09		
Ponatinib	[redacted]			33,954	

Probabilistic analyses results
Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values

Company's one-way sensitivity analyses

- For whom allo-SCT is suitable
  - the ICER was very sensitive to the induction chemotherapy response rate with higher response rates generating an ICER for ponatinib as high as [redacted] approximately, per QALY gained

- For whom allo-SCT is unsuitable
  - the ICER was sensitive to the response rate of ponatinib with the value most unfavourable to patients increasing the ICER by up to [redacted] approximately per QALY gained

ERG comments

- ERG considers that the uncertainty in the decision has been considerably underestimated by the company.
- The naïve indirect comparison which resulted in differential OS for those with NR on BSC treatment and those who experience NR on ponatinib treatment.
- Additionally, there was a naïve indirect comparison between ponatinib and induction chemotherapy relating to the proportion of patients that receive MyCR / CR, although the ERG notes that MCyR which was reported in the ponatinib study is harder to achieve than CR, which was reported in the induction chemotherapy study.
- The results of PSA were not considered robust

ERG's deterministic exploratory analyses (ponatinib PAS price)

For whom allo-SCT is suitable		Cost per QALY (£)	
Ref No	Exploratory Analyses	P vs induction chemotherapy	P vs BSC
	Company deterministic base case	31,123	26,624
1	Recalculation of the OS post allo-SCT curve	57,140	53,603
2	Choosing alternative distributions in addition to those selected by company, using the company's fits (range)	23,838 – 52,559	14,203 – 45,218
3	Assuming drug wastage	32,499	26,944
4	No half-cycle correction of intervention costs	43,766	29,568
5	Including treatment related deaths	28,635	25,864
6	Removal of immortality for a small subset of patients	31,989	26,999
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,983
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,959
8	1, 3,4 and 6 using the curves believed most credible by the company	90,325	62,801
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	11,727	31,696
10 ERG	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant – 11,727	7,892 – 31,696

ERG's revised base case analyses (ponatinib PAS price)

For whom allo-SCT is unsuitable		Cost per QALY (£)
Ref No	Exploratory Analyses	Ponatinib vs BSC
0	Company Base Case	33,954
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	25,902 – 36,037
2	Assuming drug wastage	36,835
3	No half-cycle correction of intervention costs	48,073
4	Including treatment related deaths	30,432
5a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant
5b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant
8	2 and 3 using the curves believed most credible by the company	52,317
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	Dominant
10 ERG	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant - Dominant

Innovation

- Ponatinib is a significant advance in treatment of Ph+ALL for patients whose disease is resistant or intolerant to imatinib or 2nd generation tyrosine kinase inhibitors with or without the T315I mutation.
- Few treatment options are available

End of life

- For whom allo-SCT is suitable
  - Company's model estimates that
    - patients receiving induction chemotherapy live more than 6 years
    - patients who receive BSC live less than half a year
  - The model predicts that ponatinib provides an extension of life in excess of 7 years compared with BSC, and is likely to satisfy the end of life criteria where BSC is the only comparator for patients suitable for allo-SCT
- For whom allo-SCT is unsuitable
  - patients receiving BSC live less than half a year
  - Model predicts that ponatinib provides an extension of life of almost 1 year compared with BSC and is likely to satisfy the end of life criteria for patients unsuitable for allo-SCT

Potential equality issues

- None identified at scoping stage nor in submissions.
- However the company note a number of potential equality benefits from the use of ponatinib namely:
  - It provides an additional treatment option for patients with CML and Ph+ ALL who currently have limited treatment options
  - While allo-SCT is suitable for these patients, there is unequal access to it among ethnic groups due to differences in donor rates
  - Ponatinib is the only TKI active against the T315I mutation

Key issues: Cost effectiveness

- What is the committee's view on the treatment effectiveness estimates presented by the company which were considered uncertain by the ERG because the model uses a naive unadjusted indirect comparison
- Major cytogenic response more difficult to achieve than complete remission – unadjusted comparison would be unfavourable to ponatinib. What is the committee's view of the impact of the company's choice of outcome measure.
- The ERG considered the PSA results were not robust. What is the committee's view on those results?
- Setting the same OS for NR independent of treatment reduces the ICER. What is the committee's view on this?

Authors

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ponatinib within its licensed indications for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia.

Background

Chronic myeloid leukaemia (CML) is characterised by the excessive production of white cell precursors by the bone marrow. It progresses through 3 phases: the chronic phase, the accelerated phase and the blast crisis phase. The majority of people are diagnosed in the chronic phase, from which they either go through the accelerated phase, or move directly into blast crisis in which the disease transforms into a fatal acute leukaemia. Acute lymphoblastic leukaemia (ALL) is where there is an excess production of immature lymphocyte-precursor cells called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood.

CML and ALL are rare diseases. In England in 2013, 624 people were diagnosed with CML[i] and 693 with ALL[ii]. The median age at diagnosis for those with CML is between 50 and 60 years, whereas ALL is most common in children, adolescents and young adults, with 65% of cases diagnosed in people aged under 25 years. A second increase in incidence is however observed in people aged over 60 years. A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in 95% of people with CML and 20-30% of adults with ALL.

Current treatment for CML

NICE technology appraisal guidance 251 recommends standard-dose imatinib or nilotinib as options for the treatment of adults with untreated chronic phase Philadelphia-chromosome-positive CML. NICE technology appraisal guidance 70 also recommends imatinib for the treatment of people with untreated Philadelphia-chromosome-positive CML who initially present in the accelerated phase or with blast crisis, and for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.

NICE technology appraisal guidance 241 recommends nilotinib as second-line treatment for people with chronic or accelerated phase Philadelphia-

chromosome-positive CML who are resistant to treatment with standard-dose imatinib or intolerant of imatinib. NICE technology appraisal guidance 241 does not recommend dasatinib or high dose imatinib[1] for the treatment of chronic, accelerated or blast-crisis phase CML. Dasatinib is not recommended for the treatment of people with chronic, accelerated or blast-crisis phase CML whose disease is resistant to treatment with standard-dose imatinib or who are intolerant of imatinib, however it is used in clinical practice in England through the Cancer Drugs Fund (at the time the draft scope was written) only in people with chronic or accelerated phase CML whose disease is refractory to imatinib or who have significant intolerance to imatinib (Grade 3 or 4 adverse events) and significant intolerance to nilotinib (Grade 3 or 4 adverse events). Dasatinib is currently undergoing appraisal by NICE through the Cancer Drugs Fund reconsideration process [ID1006]. High-dose imatinib is 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 299 does not recommend bosutinib for treating Philadelphia-chromosome-positive CML, but it is used in clinical practice in England through the Cancer Drugs Fund (at the time the draft scope was written) only in people with chronic phase CML with significant intolerance to nilotinib (Grade 3 or 4 events) and significant intolerance to dasatinib (Grade 3 or 4 adverse events) if dasatinib is accessed through its current approved CDF indication. Bosutinib is currently undergoing appraisal by NICE through the Cancer Drugs Fund reconsideration process [ID1004].

People who receive treatment with a first- or second-generation tyrosine kinase inhibitor (such as imatinib, nilotinib, dasatinib or bosutinib) may develop drug resistance through a number of mechanisms, one of which is the T315I mutation that interferes with the inhibition of tyrosine kinase.

Other treatment options in clinical practice can include allogeneic stem cell transplantation (if the treatment is suitable and depending on the availability of a suitable donor), interferon alpha or best supportive care (including hydroxycarbamide).

Current treatment for ALL

There is currently no NICE guidance for treating ALL. Treatment is generally divided into 3 phases; induction, consolidation and maintenance. During these treatment phases, newly diagnosed Philadelphia-chromosome-positive ALL is treated with chemotherapy combinations including tyrosine kinase inhibitor therapy such as imatinib or dasatinib. Resistance to tyrosine kinase inhibitors may develop and therapeutic options following resistance to tyrosine kinase inhibitors are limited. Treatment of relapsed disease includes re-induction

[1] The summary of product characteristics (SPC) for imatinib states that the dose may be increased from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg in patients with accelerated phase or blast crisis (see SPC for full details). High dose imatinib refers to doses of 600 mg or 800 mg in the chronic phase disease or 800 mg in the accelerated phase or blast crisis.

therapy followed by an allogeneic stem cell transplant, where a suitably matched related or unrelated donor is found. Dasatinib was available for the treatment of ALL through the Cancer Drugs Fund until November 2015 when it was removed from the Cancer Drugs Fund list.

The technology

Ponatinib (Iclusig, Incyte) is a multi-targeted tyrosine kinase inhibitor, primarily inhibiting the breakpoint cluster region and Abelson (Bcr-Abl) tyrosine kinase found in some receptors on the surface of leukaemia cells where it is involved in stimulating the cells to divide uncontrollably. By blocking Bcr-Abl, ponatinib helps to control the growth and spread of leukaemia cells. Ponatinib is administered orally.

Ponatinib has a marketing authorisation in the UK for treating adult patients with 'chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation' and 'Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation'. The marketing authorisation for ponatinib for CML and Philadelphia-chromosome-positive ALL was based on a single-arm open-label international multicentre trial.[iii]

Ponatinib is used in clinical practice in England through the Cancer Drugs Fund (at the time the draft scope was written) only in people with documented T315I mutation (for both chronic, accelerated or blast phase CML and Philadelphia-chromosome-positive ALL).

Intervention(s)	Ponatinib
Population(s)	• Adults with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia, whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation. • Adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.
Comparators	For people with chronic myeloid leukaemia: • Bosutinib (NICE guidance is in development [ID1004]; funded by the CDF in the interim) • Allogeneic stem cell transplantation (with or without chemotherapy depending on the phase of the disease) • Interferon alpha • Best supportive care (including but not limited to hydroxycarbamide). For people with acute lymphoblastic leukaemia: • Established clinical management without ponatinib (including but not limited to best supportive care).
Outcomes	The outcome measures to be considered include: • overall survival • progression and/or event-free survival • response rates • time to response • duration of response • adverse effects of treatment • health-related quality of life.

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 technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilars should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE pathways	Related Technology Appraisals: Technology Appraisal No. 70, October 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia' (partially updated by NICE technology appraisal guidance 241). Technology Appraisal No. 241, January 2012, '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'. Dasatinib subject to ongoing NICE CDF transition review [ID1006], publication date to be confirmed. Technology Appraisal No. 251, April 2012, Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. Review Proposal Date September 2014. Dasatinib subject to ongoing NICE CDF transition review [ID1014], publication date to be confirmed. Technology Appraisal No. 299, November 2013, 'Bosutinib for the treatment of chronic myeloid leukaemia'. Subject to ongoing NICE CDF transition

	review [ID1004], expected date of publication October 2016. 'Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia' NICE technology appraisals guidance [ID893]. Publication date to be confirmed. 'Blinatumomab for treating Philadelphia-chromosome-positive relapsed or refractory acute lymphoblastic leukaemia' NICE technology appraisals guidance [ID1008]. Publication date to be confirmed. Leukaemia (acute lymphoblastic) – dasatinib (suspended appraisal) NICE Technology Appraisal ID386. Related Guidelines: Cancer Service Guidance (CSGHO), October 2003, 'Improving outcomes in haematological cancers. Guidelines in development: Haematological cancers – improving outcomes (update). Publication expected May 2016. Related NICE Pathways: Blood and bone marrow cancers
Related NHS England Policy	NHS England (2015) National Cancer Drugs Fund List v.6.1: https://www.england.nhs.uk/wp-content/uploads/2016/02/ncdf-list-01-02-16.pdf NHS England (2016) Manual for Prescribed Specialised Services 2016/17 Chapter 29, Blood and marrow transplantation services (all ages). Department of Health (2011) Improving outcomes: a strategy for cancer Department for Health (Modified 2011) Manual for Cancer Services

[i] Cancer Research UK 'Chronic myeloid leukaemia (CML) incidence by sex and UK region'. Accessed May 2016
[ii] Cancer Research UK 'Acute lymphoblastic leukaemia (ALL) incidence by sex and UK region'. Accessed May 2016
[iii] Summary of product characteristcs http://www.medicines.org.uk/emc/medicine/28145. Accessed June 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia ID671

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Incyte Corporation (ponatinib) Patient/carer groups • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • Chronic Myeloid Leukaemia Support Group • Delete Blood Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma Association • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Muslim Council of Britain • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Blood Transfusion Society • British Committee for Standards in Haematology • British Geriatrics Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Blood and Transplant • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Bristol-Myers Squibb (hydroxycarbamide) • Medac UK (hydroxycarbamide) • Nordic Pharma (hydroxycarbamide) • Pfizer (bosutinib) Relevant research groups • Cochrane Haematological Malignancies Group • Elimination of Leukaemia Fund • Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute

Consultees	**Commentators (no right to submit or appeal)**
• British Psychosocial Oncology Society • British Society for Haematology • British Society for Human Genetics • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association • UK Forum on Haemoglobin Disorders • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Ealing CCG • NHS England • NHS South Cheshire CCG • Welsh Government	• National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Company evidence submission

October 2016

File name	Version	Contains confidential information	Date
Ponatinib_ID 671_CiC_Evidence Submission 4 Oct 2016	1.0	Yes. Contains CiC information only (no AiC).	4 October 2016

Contents

List of tables and figures

Abbreviations

Abbreviation	Definition
1G	First generation
2G	Second generation
3G	Third generation
1L	First line
2L	Second line
3L	Third line
4L	Fourth line
5L	Fifth line
ABL	Abelson
AE	Adverse event
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic stem cell transplantation
AP	Accelerated phase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ALT	Alanine aminotransferase
ATC	Anatomical Therapeutic Chemical
AWMSG	All Wales Medicines Strategy Group
BCR-ABL	Breakpoint cluster region-Abelson
BIC	Bayesian Information Criterion
BID	Twice per day
BNF	British National Formulary
BP	Blast phase
BSC	Best supportive care
CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHR	Complete haematologic response
CI	Confidence interval
CMA	Cost-minimisation analysis
CML	Chronic myeloid leukaemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
CR2	Second complete remission
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CUA	Cost-utility analysis
EBMT	European Society for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EHA	European Hematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EOL	End of life
EPAR	European Public Assessment Report
EQ-5D	EuroQoL Five Dimensions health status questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
EUTOS	European Treatment and Outcome Study

Abbreviation	Definition
EFS	Event-free survival
FDA	United States Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in situ hybridization
FLT3	Fms-related tyrosine kinase 3
GVHD	Graft-versus-host disease
HCP	Healthcare practitioner
HMRN	Haematological Malignancy Research Network
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon
IPD	Individual patient data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KIT	KIT proto-oncogene receptor tyrosine kinase
KM	Kaplan–Meier
LY	Life-year
LYG	Life-year gained
MaHR	Major haematologic response
MAIC	Matching-adjusted indirect comparison
MCyR	Major cytogenetic response
mCyR	Minor cytogenetic response
MMR	Major molecular response
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Non-response
OS	Overall survival
OWSA	One-way sensitivity analysis
PACE	Ponatinib Ph+ ALL and CML Evaluation study
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PCyR	Partial cytogenetic response
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
Ph–	Philadelphia chromosome–negative
Ph+	Philadelphia chromosome–positive
PK-PD	Pharmacokinetic-pharmacodynamic
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QD	Once per day
RT-PCR	Reverse transcriptase–polymerase chain reaction
R/I	Resistant or intolerant
RCT	Randomised controlled trial
RDI	Relative dose intensity
RET	Rearranged during transfection proto-oncogene
RFS	Relapse-free survival
RMP	Risk management plan
RS	Relative survival
SAE	Serious adverse event
SE	Standard error

Abbreviation	Definition
SEER	Surveillance, Epidemiology, and End Results
SG	Standard gamble
SHTAC	Southampton Health Technology Assessments Centre
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SRC	Sarcoma
SSE	Sum of squared errors
STA	Single technology appraisal
STC	Simulated treatment comparison
TEAE	Treatment-emergent adverse event
TFS	Transformation-free survival
TKI	Tyrosine kinase inhibitor
TLV	Swedish Dental and Pharmaceutical Benefits Board
ToT	Time-on-treatment
TRAE	Treatment-related adverse event
TTO	Time trade-off
VEGFR	Vascular endothelial growth factor receptor
VOE	Vascular occlusive event
WHO	World Health Organization
WTP	Willingness-to-pay

1 Executive summary

1.1 Disease overview

1.1.1 CML

Chronic myeloid leukaemia (CML) is a rare cancer that accounts for 15% of adult leukaemias.[1] CML is commonly characterised as having three distinct phases: the initial indolent chronic phase (CP-CML), an intermediate accelerated phase (AP-CML) which lasts for less than 1 to 1.5 years, and an aggressive blast phase (BP-CML) that is usually fatal within 3 to 6 months.[2] CML has a median age of onset of 59 years,[3] and in 2014, 631 people in England were diagnosed with the disease.[4] Current treatment options are based on the use of tyrosine kinase inhibitors (TKIs), allogeneic stem cell transplantation (allo-SCT) for suitable patients, and best supportive care (BSC)/palliative care. Despite significant advances in CML therapy following the introduction of first-generation (1G) and second-generation (2G) TKIs, a substantial proportion of patients develop resistance to or intolerance of 1G and 2G TKIs.[5] In England, a small but significant unmet medical need exists for patients who fail the 1G TKI imatinib and a 2G-TKI (dasatinib, nilotinib, or bosutinib) through either known (eg, mutation) or unknown aetiology. For patients in need of third-line (3L) or later-line therapy, only modest clinical evidence supports the efficacy of 2G-TKIs used sequentially, [6] and until recently, no pharmacologic treatment options have existed for patients with the T315I mutation. While bosutinib has recently received a positive recommendation by NICE within its marketing authorisation, it was issued only a conditional marketing approval by the EMA due to the limited data available for patients with an unmet medical need, and it provides only modest response rates among patients in 3L or later.[7, 8] In contrast, the third-generation (3G) TKI ponatinib has full market authorisation without the requirement to provide additional data as the EMA demanded for bosutinib, since its large pivotal trial has already demonstrated high response rates among patients with CML who have failed prior TKI therapy, across all disease phases and all mutation and other clinically relevant patient subgroups.[9] Ponatinib therefore addresses an important unmet need for a patient population that currently has limited treatment options and a very poor prognosis. Additionally, allo-SCT, while the only potentially curative option, remains out of reach for patients with substantial comorbidities, those without donors, or those in certain ethnic minority groups where donor availability is especially scarce,[10] and is less likely to be considered for patients older than 60 years.

1.1.2 Ph+ ALL

ALL is a heterogeneous category of leukaemias with the common feature of proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.[11-13] As with CML, ALL is a rare disease, representing 9% of all leukaemia cases in England.[14, 15] In 2014, 654 people in England were diagnosed with ALL.[14] Ph+ ALL (ALL characterised by the presence of the Philadelphia chromosome) makes up about 25% of adult ALL cases and its incidence increases with age, representing about 40% of ALL cases in patients over 50 years of age.[11-13] Ph+ ALL is a disease associated with very poor prognosis. Even with currently available 1G and 2G TKIs, among patients resistant to and/or intolerant of prior therapy, survival is only 6 to 9 months.[16] Only one 2G TKI is licensed for Ph+ ALL (dasatinib).[17] Likely reflecting the paucity of effective therapies, no NICE guidance is available on the treatment of patients with ALL and the disease is not part of the existing NICE pathway on blood and bone marrow cancers.[18] New therapies are therefore urgently needed for patients with Ph+ ALL. Ponatinib addresses this need with demonstrated ability to achieve unprecedented response rates in this patient population.

1.2 Statement of decision problem

Both CML and Ph+ ALL have poor prognoses and there are inadequate therapeutic options for patients who exhibit resistance or intolerance to 1G- and 2G-TKIs, or who have the T315I mutation.

The goal of the ponatinib single technology appraisal (STA) is to assess the clinical and cost effectiveness of ponatinib within its licensed indications for treating CML and Ph+ ALL. Table 1-1 outlines the decision problem addressed in this submission.

Table 1-1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia, whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation. Adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.	Final scope	
Intervention	Ponatinib	Final scope	
Comparator (s)	For people with CML: • Bosutinib (NICE guidance is in development [ID1004]; funded by the CDF in the interim) • Allogeneic stem cell transplantation (allo-SCT; with or without chemotherapy depending on the phase of the disease) • Interferon alpha • Best supportive care (including but not limited to hydroxycarbamide) For people with Ph+ ALL: • Established clinical management without ponatinib (including but not limited to best supportive care)	For people with CML: • Bosutinib (all phases) • Allo-SCT (all phases) • Interferon alpha (CP-CML) • Hydroxycarbamide as BSC (all phases) For people with Ph+ ALL: • Induction chemotherapy + allo-SCT • BSC	
Outcomes	• Overall survival (OS) • Progression-free survival (PFS)/ event-free survival (EFS) • Response rates • Time to response	Final scope, with exceptions: PFS and DoR are applied only to the CP-CML model	DoR is not considered in the AP/BP-CML model as patients who respond to treatment transition to allo-SCT in the first cycle. Duration of response is not considered in the Ph+ ALL model as patients suited for allo-SCT who respond to treatment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Duration of response (DoR) • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)		transition to allo-SCT in the first cycle. Duration of response is not explicitly modelled for Ph+ ALL patients who are unsuitable for allo-SCT, but is expected to be reflected in the parametric function for OS
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 (QALY) • time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilars should be taken into account.	Final scope	No biosimilars are available for ponatinib.
Subgroups to be considered	None		
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		

1.3 Description of the technology being appraised

Ponatinib is a small-molecule TKI specifically designed through a computational and structure-based approach to target the product of the breakpoint cluster region-Abelson (*BCR-ABL)* oncogene that gives rise to CML and Ph+ ALL.[12, 19, 20] A key breakthrough of ponatinib is its ability to potently inhibit the kinase activity of native BCR-ABL and all mutant variants, including T315I.[21] As a result of this innovation, ponatinib has demonstrated efficacy in all indicated patients whether or not a mutation is present.[9, 22]

In 2015, ponatinib received positive recommendations from the Scottish Medicines Consortium and the All Wales Medicines Strategy Group for its full licensed indication.

Table 1-2. Technology being appraised

UK approved name and brand name	Ponatinib (Iclusig®)
Marketing authorisation/CE mark status	Approved (1 July 2013)
Indications and any restriction(s) as described in the summary of product characteristics	Ponatinib is indicated in adult patients with: • Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation • Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
Method of administration and dosage	45 mg orally once daily (recommended starting dose); 15 mg and 30 mg once daily for dose modifications

1.4 Summary of the clinical effectiveness analysis

The efficacy and safety of ponatinib in patients treated with prior 2G-TKI therapy, including those with the T315I mutation, was demonstrated in two clinical trials: a phase I dose-ranging trial[23] and the pivotal phase II Ponatinib Ph+ ALL and CML Evaluation (PACE) trial.[9] As a result of the highly positive clinical results from these trials, ponatinib has been licensed by the EMA and the FDA (along with several other regulatory bodies around the world) for use in the patient population represented in the trials. The PACE study was a phase 2, single-arm, open-label, international clinical trial conducted at 66 sites. The efficacy and safety of ponatinib was evaluated in 449 patients with CP-CML (n=270), AP-CML (n=85), or BP-CML (n=62), or Ph+ ALL (n=32) who were resistant and/or intolerant (R/I) to dasatinib or nilotinib, or who had the T315I mutation.[9] The majority of the PACE study population represented a group of patients who had not been studied in detail with any other TKI—most patients were in their third or fourth line of therapy.

1.4.1 PACE efficacy

CP-CML—Overall, in the PACE trial, more than half (56%; 95% CI: 50, 62) of patients achieved the primary endpoint, major cytogenetic response (MCyR) by 12 months. Patients responded quickly to ponatinib, with a median time to MCyR of 2.8 months (range 1.6–11.13). A complete cytogenetic response (CCyR) by 12 months was achieved by 46% of patients. At 12 months, the rate of PFS was 80% and OS was 94% (median not yet reached for both).

A 4-year follow-up analysis of ponatinib in patients with CP-CML from the PACE trial showed that responses were durable and the rates of PFS and OS were high, even among patients who had received 2 prior TKIs. Among patients receiving 3L ponatinib, 71% achieved a MCyR and 65% achieved CCyR.[24] Four-year PFS and OS were 68% and 79% respectively (median not reached for both).[24]

AP-CML—The primary endpoint for AP- and BP-CML and Ph+ ALL was major haematologic response (MaHR) by 6 months. Among all patients with AP-CML, MaHR was achieved in 55% (95% CI: 44, 66) and the median time to a MaHR was 3 weeks (range 2 to 25). MCyR was achieved in 39%. The rate of 12-month PFS was 55% (median 18 months). The rate of 12-month OS was 84% (median not reached).[25] Among patients who had received 2 prior TKIs (ie, 3L ponatinib), 61% achieved MaHR.

BP-CML—MaHR by 6 months was achieved in 31% (95% CI: 20, 44) of patients. The median time to response was 4.1 weeks (range 1.7 to 16.1). MCyR was achieved in 23% of patients. The rate of 12-month PFS was 19% (median 4 months). The rate of 12-month OS was 29% (median 7 months).

Ph+ ALL—MaHR by 6 months was achieved in 41% (95% CI: 24, 59) of patients. The median time to response was 2.9 weeks (range 1.6 to 24). Overall, 47% of patients achieved MCyR. The rate of 12-month PFS was 7% (median 3 months). The rate of 12-month OS was 40% (median 8 months).

1.4.2 PACE safety

Clinical evidence in heavily pre-treated patients with CP-, AB-, and BP-CML and Ph+ ALL shows that adverse events associated with ponatinib are manageable and that the rate of treatment discontinuation due to AEs is low (12%).[9, 24]

The most common non-haematologic treatment-related adverse events (TRAEs) were rash (34%), dry skin (32%), and abdominal pain (22%), while the most common haematologic TRAEs were thrombocytopaenia (37%), neutropaenia (19%), and anaemia (13%). While the safety profile of ponatinib is generally similar to that of other TKI agents, important differences were observed in the PACE trial for certain clinically important events, including pancreatitis and cardiovascular events.[9]

The most prominent feature of the safety of ponatinib is vascular occlusion. Among patients with CP-CML the 4-year rates of serious cardiovascular, cerebrovascular, and peripheral vascular events were 11.1%, 9.6%, and 9.3%, respectively.[24] However, clinical evidence shows strong positive correlations between dose intensity and safety.[24] The recommended starting dose of ponatinib is 45 mg, however, dose reductions are recommended to manage adverse events;[22] in the PACE trial, dose reductions to 15 mg were recommended for patients with CP-CML who achieved MCyR or better, to 30 mg/day for CP-CML patients who had not already achieved MCyR, and to 30 mg/day for advanced phase patients.[25] Data from three ponatinib clinical trials, including the PACE study, shows that a 15-mg/day decrease in the average daily dose of ponatinib is associated with a 33% reduction in the risk of serious cardiovascular events.[26] Preliminary data support the maintenance of efficacy among patients with CP-CML who have dose reductions to 15 mg.[25]

1.4.3 PACE study conclusions

The evidence base shows that ponatinib provides an effective treatment for the indicated patients, demonstrating the highest response rates ever observed within this population. Within-group analyses using patients' best response to prior TKI therapy show a marked improvement compared to response rates achieved with a patient's most recent 2G-TKI. Four-year data show that ponatinib provides ongoing benefits with a manageable safety profile.[24]

1.4.4 Strengths and limitations of the evidence base

Ponatinib was specifically designed, studied in trials, and registered for the explicit purpose of meeting the unmet medical need among patients with CML and Ph+ ALL R/I to prior TKI therapy. While it was not possible to design a comparative study against a failed TKI for ethical reasons, the single-arm design of the PACE study was accepted by EMA and the FDA, among several other regulatory bodies. Notably, no other TKIs have been studied in comparative trials involving patients with resistant disease. Only studies of newly diagnosed patients – a population for whom ponatinib is not licensed – involved comparative trial designs. Despite the limitations of being a non-comparative trial, the PACE study is the largest of its kind, having enrolled 449

patients with CP-, AP-, or BP-CML or Ph+ ALL who were R/I to dasatinib or nilotinib, or who had the T315I mutation.[9]

Results of the PACE study show that ponatinib provides the highest response rates ever observed in the population covered by the license. Response rates achieved with ponatinib were associated with a high probability of PFS and OS at 4 years.[24] Furthermore, while response rates to previous therapy are usually a predictor of response to subsequent therapy, within-group analyses of patients in the PACE trial showed that responses achieved with ponatinib exceeded best prior response to the most recent regimen containing a 2G-TKI (dasatinib/nilotinib).

The clinical evidence supporting ponatinib is highly relevant to the decision problem as the subjects in the PACE study represent patients for whom treatment is indicated and who would be treated in clinical practice in England.[22]

An important limitation of the clinical evidence in this submission is the uncertainty around the use of single-arm data for comparators and ponatinib.

- To address the uncertainty that comes from uncontrolled single-arm studies, Incyte has compared the PACE trial results against real-world observational data in patients receiving ponatinib. Among 23 patients in CP (except 1 patient in AP) who had received ≥2 prior TKIs and were treated with ponatinib in the Spanish Compassionate Use Program, the rate of CCyR was 58% (median follow-up 29 months) and 3.5-year PFS was 80%.[27] Adverse events were manageable and no patients on ponatinib had a cardiovascular event.
- To overcome lack of comparative data vs bosutinib and reduce the potential biases of naïve comparisons, we have carried out a matching-adjusted indirect comparison (MAIC) between ponatinib and bosutinib in CP-CML for the first time (described in Section 4.10). MAIC is a well-accepted technique that can help reduce the uncertainty of an indirect comparison where more standard techniques such as mixed treatment comparisons are not possible because of an incomplete network of evidence, as is the case here due to the single-arm design of all relevant clinical trials. Results of the MAIC showed that ponatinib provides considerably higher CCyR rates than bosutinib in the third line (61% vs 24%). The adjusted ponatinib response rates were used to inform the CP-CML economic analysis.

1.5 Summary of the cost-effectiveness analysis

In the absence of head-to-head trial data, three health economic models were developed to assess the cost-effectiveness of ponatinib for the treatment of patients with CML and Ph+ ALL compared to current treatment options in England. The models evaluated the cost-effectiveness of ponatinib in patients initiating treatment while in CP-CML, in advanced CML (accelerated or blast phase), or in Ph+ ALL. All three models were cost-utility analyses (CUAs) with outcome measures of cost per life-years gained (LYG) and cost per quality-adjusted life-years (QALYs) gained (primary outcome for NICE), and a patient lifetime time horizon. The target patient populations were fully aligned with the licenced indication. Table 1-3 summarises the key features of the cost-effectiveness analyses.

Table 1-3. Summary the economic models

Component	Economic model			Justification
	CP-CML	AP-/BP-CML	Ph+ ALL	
Patient population	Adults with CP-CML R/I to imatinib and either dasatinib or nilotinib	Adults with AP-/BP-CML R/I to imatinib and either dasatinib or nilotinib	Adults with Ph+ ALL R/I to imatinib and dasatinib	NICE reference case and ponatinib licenced indication
Age (starting), years	54.50	AP-CML: 54.6 BP-CML: 50.4	53.03	PACE trial
Cohorts	CP-CML	Patients in AP-CML Patients in BP-CML	Patients suitable for allo-SCT Patients unsuitable for allo-SCT	To evaluate outcomes of treatment initiated in any phase of licenced CML indication; Best therapeutic option for patients with Ph+ ALL who achieve complete remission and are suitable for transplantation is allo-SCT[28]
Comparators	Bosutinib Hydroxy-carbamide Interferon alpha Allo-SCT	Bosutinib Hydroxy-carbamide(as BSC) Allo-SCT	Chemotherapy followed by allo-SCT BSC (with or without allo-SCT)	NICE reference case
Perspective	NHS/PSS			NICE reference case
Model structure	Markov			Generally recommended model framework for simulating different health states in economic analyses
Cycle length	3 months (half-cycle correction)			A 3-month cycle parallels the length of model and is short enough to allow fitting of curves; a half-cycle correction was adopted because the cycle length is long
Time horizon	Cohort lifetime (maximum of 400 cycles, up to 100 years)			To capture all important differences in costs or outcomes between the technologies being compared
Discount rates	3.5% (costs and benefits)			NICE reference case
Outcome measures	Cost/QALYs gained Cost/LYG			NICE reference case

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; CP, chronic phase; CUA, cost-utility analysis; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years; R/I, resistant or intolerant.

1.5.1 Cost-effectiveness results

1.5.1.1 CML

Table 1-4 and Table 1-5 present the incremental cost-effectiveness results of the CP-CML and AP-/BP-CML economic analyses. The unprecedented response rates achieved with ponatinib translate into substantial QALY gains and ICERs well below £30,000/QALY, across all CML disease states. The ICERs ranged from [redacted]. Ponatinib incurred lower total cost than bosutinib in AP-CML and both hydroxycarbamide and allo-SCT in BP-CML, and was thus dominant in those comparisons. In the other comparisons, ICERs remained well below the acceptability threshold even for non–end-of-life interventions, ranging from from [redacted].

Areas of uncertainty in the economic analyses include the lack of comparative data in this rare disease, the lack of recent data for the comparators as no recent studies (other than for bosutinib) have been conducted, and the lack of large trials involving this patient group. Another challenge is in extrapolating trial results over long periods of time. Nevertheless, Incyte has tried to explore these challenges in sensitivity analyses, has sought input from experts where available, and has followed prior NICE precedents. To address uncertainty, all models were subjected to sensitivity analyses to determine the parameters that most strongly influenced the results and to investigate the effect of alternative parameters. Clinical validity of the model was also assessed in the CP-CML analysis by comparing the survival estimates generated by the model with those from relevant clinical data. ICERs remained low across several different scenarios. When the efficacy of ponatinib was reduced by 25%, the ICER against bosutinib [redacted]) was still below the threshold for cost-effectiveness.

In summary, low ICERs in the CML economic analyses, coupled with high efficacy for ponatinib, and high unmet clinical need for an effective 3L treatment, demonstrate that ponatinib can be considered a cost-effective intervention for the treatment of CML in England.

1.5.1.2 Ph+ ALL

Table 1-6 summarises the results of the Ph+ ALL analysis. For patients receiving allo-SCT in remission, ponatinib yields an ICER of [redacted]. Among patients not suitable for transplantation, the ICER vs BSC is [redacted]. The cost-effectiveness results for Ph+ ALL should be considered in the context of the high clinical need for these patients with limited treatment options and the potential for ponatinib to be used as a bridge to allo-SCT as clinically appropriate.

Table 1-4. Incremental cost-effectiveness results in CP-CML

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER (£/LYG)	ICER (£/QALYs)
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Interferon alpha	188.917.38	4.02	2.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide	136,666.02	3.95	2.24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	150,810.61	6.09	4.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	209,257.69	6.74	3.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic stem cell transplantation; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years

Table 1-5. Incremental cost-effectiveness results in AP- and BP-CML

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER (£/LYG)	ICER (£/QALYs)
AP-CML								
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Hydroxycarbamide	82,532	1.60	0.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	150,957	5.04	2.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	116,635	2.87	1.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BP-CML								
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Hydroxycarbamide	86,958	1.00	0.28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	63,424	0.77	0.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	103,748	1.27	0.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic stem cell transplantation; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years

Table 1-6. Incremental cost-effectiveness results in Ph+ ALL

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER (£/LYG)	ICER (£/QALYs)
Patients suitable for allo-SCT								
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Induction chemotherapy	69,180.82	2.96	1.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	15,982.70	0.32	0.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients unsuitable for allo-SCT								
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
BSC	15,982.70	0.32	0.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life years

1.5.2 Impact of ponatinib dose reductions

The majority of patients with CP-CML who are maintained on ponatinib are expected to receive the 15-mg dose. The price of the 15-mg tablet is half that of the 30-mg and 45-mg tablets (£2,525 vs £5,050 per pack) and the annual cost of treatment on the 15-mg dose is expected to be lower than that of treatment with bosutinib, for example (£30,742 vs £44,799, based on NHS list prices). Dose reductions, in accordance with Summary of Product Characteristics (SmPC) guidance, will therefore result in a lower overall cost of treatment with ponatinib. In addition, treatment discontinuation is recommended in the SmPC in the event a patient does not achieve a complete haematologic response within 3 months of starting ponatinib, further reducing the overall utilisation and cost of ponatinib in the target population. The economic analyses submitted here accounts for these SmPC requirements on dose and treatment discontinuation.

1.6 Ponatinib as a life-extending treatment at the end of life

Ponatinib meets the criteria to be considered as a life-extending treatment at the end of life, as available data show that the expected survival of patients with advanced CML is 16 months in AP and 5 months in BP.[29] Among patients with ALL who receive BSC, OS is less than 3 months.[30] Results of the de novo economic analyses show that the incremental undiscounted LY gain on ponatinib compared with BSC is [redacted].

1.7 Budget impact

The number of patients with CML or Ph+ ALL eligible to receive ponatinib in England is exceedingly small—we estimate that only 113 people with CML and 33 people with Ph+ ALL per year in England will be potentially eligible for ponatinib according to its licensed indication. Moreover, eligible patients with CML may receive alternative therapies or interventions, such as 2G-TKIs (dasatinib, bosutinib) or allo-SCT. The net budget impact associated with the introduction of ponatinib for CML is projected to be [redacted] over 5 years. This small budget impact for CML would be largely offset by avoiding the use of less effective alternatives. For Ph+ ALL, ponatinib would confer a 1% net savings in each year after its introduction.

Patient access scheme

Incyte acknowledges the inherent uncertainty in pharmacoeconomic analyses of orphan diseases, and the scarcity of data for comparators in the late-line population that is covered by the indication of ponatinib. To help reduce this uncertainty in the modelling and its impact on the ICERs, the company has submitted an application to the Department of Health for a confidential simple patient access scheme (PAS). The application was submitted on the same day that Incyte received the invitation from NICE to participate in an appraisal, and at the time of this submission, we are still awaiting approval of the simple discount PAS from the Department of Health. Once we receive notification from the Department of Health of approval, we will inform NICE. We believe the PAS will further increase the certainty that ponatinib is an acceptable use of NHS resources in the small target population with high unmet medical need. We have thus provided to NICE via its PAS template (as a separate document submitted alongside this evidence submission), information on the impact of the PAS on the economic results.

2 The technology

2.1 Description of the technology

2.1.1 Name and therapeutic class

Brand name: Iclusig®

UK approved name: Ponatinib

Therapeutic class: Ponatinib is a third-generation (3G) antineoplastic protein kinase inhibitor (ATC code L01XE24).

2.1.2 Mechanism of action

Ponatinib is a small-molecule tyrosine kinase inhibitor (TKI), designed through a computational and structure-based approach to target the product of the breakpoint cluster region-Abelson (*BCR-ABL)* oncogene that gives rise to chronic myeloid leukaemia (CML) and Philadelphia-chromosome–positive (Ph+) acute lymphoblastic leukaemia (ALL).[12, 19, 20] Ponatinib was designed with the purpose of potently inhibiting the kinase activity of native (unmutated) BCR-ABL, and all mutant variants, including the "gatekeeper" T315I. Ponatinib presents an extensive network of molecular contacts for optimal fit to the binding cavity of Abelson (ABL) even in the presence of the T315I mutation. The presence of a unique triple bond in the ponatinib structure prevents steric hindrance caused by the bulky isoleucine residue at position 315 in the T315I mutant.[21]

Ponatinib inhibits all clinically relevant mutant BCR-ABL forms in cell cultures, including forms that confer resistance to second-generation (2G) TKIs.[19, 31, 32] Ponatinib also inhibits other kinases involved in clinically relevant signalling pathways, such as members of the VEGFR, PDGFR, and FGFR families of kinases, the SRC family kinases, and kinase KIT, RET, and FLT3.[31]

Furthermore, in vitro mutagenesis accelerated assays with ponatinib showed a reduction in, or total elimination of, resistant clones and an absence of mutations that confer resistance to ponatinib.[31] Consistent with the predictive value these tests have had for other TKIs,[33] it can be assumed that the emergence of resistance in patients treated with ponatinib will be reduced. Thus, ponatinib holds promise for controlling compound mutants involving T315I and other clinically relevant *BCR-ABL* mutants in addition to its general inhibitory action against unmutated *BCR-ABL* kinases.[31]

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Marketing authorisation

On 1 July 2013, the European Commission granted marketing authorisation for ponatinib valid throughout the European Union (EU) for the indications stated below.[34]

On June 2, 2016, Incyte Corporation acquired from ARIAD Pharmaceuticals, Inc the license to ponatinib in Europe and other select countries.

2.2.2 Indications

Ponatinib is indicated in adult patients with:[22]

- Chronic phase (CP), accelerated phase (AP), or blast phase (BP) CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

- Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

In line with the ponatinib indication and the National Institute for Health and Care Excellence (NICE) scope, this submission focuses on the CML and Ph+ ALL patient populations.

2.2.3 Restrictions and contraindications

Ponatinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.[22] No other restrictions or contraindications are stated for ponatinib.

2.2.4 Summary of Product Characteristics

Please see Appendix 1: SmPC.

2.2.5 European public assessment report (EPAR)

Please see Appendix 1: EPAR and Appendix 1: EPAR procedural steps taken and scientific information after authorisation.

2.2.6 Main issues raised by regulatory authorities

The EPAR states that the clinical benefits of ponatinib are considered relevant and outweigh the potential risks of treatment, which to a large extent appear manageable. The Committee for Medicinal Products for Human Use (CHMP) concluded that ponatinib has a positive benefit-risk balance in patients who are intolerant or resistant to dasatinib or nilotinib, and for whom subsequent treatment with imatinib is clinically inappropriate.[35] The magnitude of response rates was considered very clinically relevant, especially for—but not restricted to—CML patients with the T315I mutation. Although it was noted that there were few patients without the T315I mutation who received only one line of therapy with either dasatinib or nilotinib, treatment with imatinib following failure of first line treatment with these agents was considered inappropriate, and thus the use of ponatinib was deemed to be a viable option, as reflected in the wording of the indication.

Another issue noted by the CHMP is that nilotinib is not approved for the treatment of Ph+ ALL, although patients with Ph+ ALL pre-treated with nilotinib were included in the pivotal ponatinib study. This fact was taken into consideration in the wording of the indication.[35]

The EPAR summarised the following important identified risks: pancreatitis, increased amylase and lipase, myelosuppression, thrombocytopaenia, neutropaenia, anaemia, infections, skin reactions, liver function test abnormality, oedema and fluid retention, cardiac failure/left-ventricular dysfunction.[35]

The safety profile of ponatinib is considered similar to that of other TKI agents, but differs in the incidence of several clinically important events. In particular, pancreatitis was identified as one of the major safety concerns associated with ponatinib, occurring in 7.4% of patients participating in two clinical studies (N=230). The incidence of pancreatitis with other TKIs is less than 1%. However, pancreatitis rarely led to ponatinib treatment discontinuation (3 cases among the 230 study subjects).[35]

Unlike the conditional marketing authorisation of bosutinib,[36] the approval of ponatinib was unconditional.[35]

2.2.6.1 Vascular occlusive events (VOEs)

In November 2013, following a review of updated clinical trial data on ponatinib revealing an accumulation of treatment-emergent vascular occlusive events (VOEs) relative to the frequency observed at the time of initial authorisation, the European Medicines Agency (EMA), through its Pharmacovigilance Risk Assessment Committee (PRAC), issued a set of recommendations regarding the use of ponatinib. While confirming the availability of ponatinib for the treatment of leukaemia as per the approved indication, the EMA recommended that the cardiovascular status of patients be assessed and that cardiovascular risk factors be actively managed prior to, and monitored during, treatment.[37]

The EMA initiated an in-depth review of the benefits and risks of ponatinib, and as a result of this process, ARIAD Pharmaceuticals has actively investigated and provided clarification to the PRAC on the following issues:

- Treatment-emergent VOEs and potential underlying mechanisms
- Pharmacokinetic-pharmacodynamic (PK-PD) safety and efficacy analyses
- Optimal proposed starting dose and dose adjustments
- Full benefit–risk assessment for all authorised indications
- Proposals for additional pharmacovigilance and/or risk minimisation measures and future studies

The PRAC concluded its review in October 2014 by issuing an opinion endorsing ARIAD's suggested variations to the Summary of Product Characteristics (SmPC) of ponatinib,[38] the proposed risk management plan (RMP), and additional pharmacovigilance activities. The PRAC concluded that the benefit-risk balance of ponatinib remains favourable in light of the changes to the SmPC and ponatinib should continue to be available to European patients, as per the original approved indication.[37]

2.2.6.2 Restricted medical prescription (SmPC section 4.2)

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia. Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during treatment if clinically indicated.[22]

Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment with ponatinib.[22]

Dose modifications or interruption of dosing should be considered for the management of haematologic and non-haematologic toxicities. In the case of severe adverse reactions, treatment should be withheld.[22]

2.2.6.3 Periodic safety update reports

Incyte will continue to submit periodic safety update reports on ponatinib 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 EMA web-portal.[22]

2.2.6.4 Risk Management Plan (RMP)

Incyte will 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 would be submitted at either the request of the EMA or 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.[22]

2.2.6.5 Additional risk minimisation measures

Incyte will provide a Healthcare Professional Brochure[39] to all physicians who are expected to prescribe ponatinib in countries where ponatinib is marketed. The brochure educates physicians on patient eligibility, safe drug use, and important adverse events (AEs) for which monitoring and dose adjustments are recommended.[22, 39]

2.2.6.6 Obligation to conduct post-authorisation measures

To determine the optimal starting dose of ponatinib and characterise the safety and efficacy of ponatinib following dose reductions after achieving major cytogenetic response (MCyR) in patients with CP-CML, ARIAD/Incyte are conducting a dose-ranging study and will submit the results of this study to the EMA no later than June 2019.[22]

2.2.7 UK launch date

The date of the UK launch was August 2013.

2.2.8 Regulatory approval outside the UK

In addition to its marketing approval in the UK and other members of the EU, ponatinib has been approved for use in several other jurisdictions, including the US, Canada, Australia, Japan and Israel.[40-43]

The approved indication for ponatinib from the US Food and Drug Administration (FDA) is for the treatment of adult patients with:[40]

- T315I-positive CML (CP, AP, or BP) or T315I-positive Ph+ ALL
- CP-, AP-, or BP-CML or Ph+ ALL for whom no other TKI therapy is indicated

The approved indication for ponatinib from Health Canada is for the treatment of adult patients with:[41]

- CP-, AP-, or BP-CML or Ph+ ALL for whom other TKI therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance

Australia's Therapeutic Goods Administration has approved ponatinib or the treatment of adult patients with:[42]

- CP-, AP-, or BP-CML whose disease is resistant to, or who are intolerant of at least two prior TKIs; or where there is a T315I mutation
- Ph+ ALL whose disease is resistant to, or who are intolerant of dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or where there is a T315I mutation

Ponatinib is also approved in Israel for adult patients with:[43]

- CP-, AP-, or BP-CML who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation
- Ph+ ALL who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation

2.2.9 Other UK HTAs

HTAs for ponatinib have been conducted by the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). As a result of these completed HTAs, ponatinib is reimbursed for the EMA-approved indication in Scotland (as of 13 April 2015)[44] and Wales (as of 9 January 2015)[45]. Ponatinib is not subject to any other ongoing HTAs in the UK.

2.3 Administration and costs of the technology

2.3.1 Administration and costs

Ponatinib is available as 15 and 45-mg film-coated tablets for oral administration. A 30-mg film-coated tablet is approved by the EMA and has a price approved by the Department of Health. The 30-mg tablet will be on the market in the UK in early 2017 and no later than the conclusion of this STA. The licensed dose is 45 mg QD, with an option for reduced dosing (30 mg or 15 mg QD) at the physician's discretion. Treatment with ponatinib should continue as long as the patient does not show evidence of disease progression or unacceptable toxicity. If a complete haematologic response (CHR) has not occurred by 3 months, consideration should be given to discontinuing ponatinib.[22] Table 2-1 presents the associated costs for ponatinib.

Table 2-1. Costs of the technology being appraised

<table>
<tr><th></th><th>Cost</th><th>Source</th></tr>
<tr><td>Pharmaceutical formulation</td><td>Film-coated tablets
Each film-coated tablet contains either 15, 30, or 45 mg of ponatinib (as hydrochloride).</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Acquisition cost (excluding VAT)</td><td>15mg, 30 tablets: GBP 2525
30mg, 30 tablets (licensed, not yet available; Q1 2017 launch): GBP 5050
45mg, 30 tablets: GBP 5050</td><td>Incyte; BNF</td></tr>
<tr><td>Method of administration</td><td>Oral</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Doses</td><td>15 mg, 30 mg and 45 mg
The recommended starting dose is 45 mg of ponatinib. Dose reductions should be considered to manage toxicity.</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Dosing frequency</td><td>Once daily, with or without food</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Average length of a course of treatment</td><td>Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Average cost of a course of treatment†</td><td>Average monthly cost weighted by doses as administered in the PACE study (CP-CML cohort, all lines of therapy)
<table>
<tr><th>Dose</th><th>Proportion of days on dose</th><th>Cost per pack (£)</th><th>Tablet count</th><th>Cost per day (£)</th><th>Weighted cost (£)</th><th>Weighted average cost per month* (£)</th></tr>
<tr><td>0 mg</td><td>[redacted]</td><td>—</td><td>—</td><td>—</td><td>[redacted]</td><td>—</td></tr>
<tr><td>15 mg</td><td></td><td>2,525</td><td>30</td><td>84.17</td><td></td><td>—</td></tr>
<tr><td>30 mg</td><td></td><td>5,050</td><td>30</td><td>168.33</td><td></td><td>—</td></tr>
<tr><td>45 mg</td><td></td><td>5,050</td><td>30</td><td>168.33</td><td></td><td>—</td></tr>
<tr><td>Total</td><td></td><td>—</td><td>—</td><td>—</td><td></td><td>[redacted]</td></tr>
</table>
*Drug costs were adjusted for dose and % days on dose/relative dose intensity. Values reported in this table are rounded to two decimal places, but calculations were made using numbers carrying more decimals; calculations using rounded numbers may not yield the exact total cost per month due to rounding.</td><td>PACE trial, individual patient-level data on file</td></tr>
<tr><td>Anticipated average interval between courses of treatments</td><td>No interval between treatment courses occurs. Once-daily treatment continues uninterrupted as long as there is no evidence of disease progression or unacceptable toxicity.</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Anticipated number of repeat courses of treatments</td><td>Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Dose adjustments*</td><td>30 mg or 15 mg once daily; dose reductions should be considered to manage toxicity; and if necessary, temporary treatment discontinuation to manage AEs</td><td>Ponatinib SmPC[22]</td></tr>
<tr><td>Anticipated care setting</td><td>Outpatient</td><td></td></tr>
</table>

BNF, British National Formulary; AEs, adverse events.

*Dose modifications or interruption of dosing should be considered for the management of haematologic and non-haematologic toxicities. In the case of severe adverse reactions, treatment should be withheld. For further information on recommended dose adjustments to manage treatment-related toxicities, please refer to the ponatinib SmPC.[22]

†Average monthly cost considering the full CP-CML cohort (ie, all lines of therapy).

2.3.2 Patient access scheme (PAS)

Incyte Biosciences UK Ltd has proposed to the Department of Health a PAS for ponatinib. The PAS will provide a simple discount to the list price of ponatinib, with the discount applied at the point of purchase. The PAS template was submitted to the Department of Health on the same day Incyte received an invitation from NICE to participate in this appraisal, and was then duly forwarded by the Department of Health to PASLU for review on 28 August 2016. As the PAS has not yet been approved by the NHS, it is not included in the present technology appraisal submission but is detailed in the accompanying NICE PAS template, submitted separately but alongside this document.

2.4 Changes in service provision and management

2.4.1 Additional service requirements

2.4.1.1 Companion diagnostics

No additional diagnostic tests are needed to identify patients eligible for ponatinib. Ponatinib is active against unmutated and mutated *BCR-ABL*, including, but not limited to the T315I mutation. In the PACE study (Cortes et al. 2013), response rates were high among patients with CP-CML who did not have detectable *BCR-ABL* mutations, as well as among patients with mutations other than T315I.[9] Since responses were observed regardless of the presence or absence of, or the type of mutation, analyses of mutation status are not necessary in every case, and a patient can be successfully treated with ponatinib without undergoing prior mutation testing, if it is not available.[9] Accordingly, the European Commission and other regulatory bodies have approved ponatinib without the need for a required companion diagnostic test.[40-42]

Nevertheless, testing for mutations is routine management for patients with CML and ALL, in part because available TKIs are often ineffective against certain mutations, such as T315I.[11, 46, 47] Moreover, the test for the T315I mutation is part of the array of mutational testing which is routinely done in CML patients who become resistant to a TKI, as recommended by European LeukemiaNet (ELN) guidelines.[46, 47] The test is routinely available in England.

According to a survey of clinical experts in the UK, mutation testing is routine practice among patients with CML.[48] Two-thirds of healthcare practitioner (HCP) respondents stated that mutation testing would be performed upon disease progression, failure of first-line (1L) treatment, relapse, loss of response, or some other problem. For patients with CP-CML who are not responding to treatment, results of the survey show that mutation testing is usually performed upon disease progression.[48]

Although T315I mutation testing is essential for all other TKIs in order to exclude the adoption of an ineffective therapy, this is not needed for ponatinib, since it is active against the T315I mutation and all other mutations, as well as native BCR-ABL.[19, 31, 32] Because response to treatment with ponatinib is high regardless of mutation status and testing for mutations is already routine practice for patients with CML and ALL, Incyte does not expect a need for additional T315I mutation testing with ponatinib beyond current clinical practice; ie, the availability of ponatinib should not by itself lead to any more demand for mutation analyses.

2.4.1.2 Administration requirements

Ponatinib is a film-coated tablet that is administered orally once daily, with or without food, and thus has no particular administration requirements.[22]

2.4.2 Resource use

Patients will receive ponatinib as outpatients. Treatment will be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia. Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during treatment if clinically indicated. Patients should be monitored for response according to standard clinical guidelines.[22]

Table 2-2 lists the resource use and costs associated with ponatinib treatment.

Table 2-2. Resource use and costs associated with ponatinib

<table>
<tr><th>Resource use</th><th></th><th>Source</th></tr>
<tr><td>Setting of care</td><td>Outpatient</td><td></td></tr>
<tr><td>Staff costs</td><td>Haematologist: £150.38/visit
Cardiologist*: £150.38/visit</td><td>NHS Reference Costs 2014–2015†; assumption</td></tr>
<tr><td>Administration costs</td><td>None are expected</td><td></td></tr>
<tr><td>Monitoring and tests</td><td>Resources used for monitoring patients treated with ponatinib are the same as for other TKIs. According to the 2013 ELN recommendations for managing CML, patient response to treatment can be assessed using either molecular and/or cytogenetic testing.[47] The resource use and costs to manage patients with CP-CML who respond to treatment are outlined below. These costs are not specific to ponatinib and instead reflect the resource use and cost for any TKI used to manage CML.
Per-cycle* resource use and unit costs in CP-CML with response
<table>
<tr><th>Resource</th><th>Resource use</th><th>Cost (£)</th></tr>
<tr><td>Nurse-led outpatient visit</td><td>0.29</td><td>66.42</td></tr>
<tr><td>Haematologist-led outpatient visit</td><td>0.93</td><td>150.38</td></tr>
<tr><td>Full blood count</td><td>1.13</td><td>3.01</td></tr>
<tr><td>Cytogenetic analysis</td><td>0.58</td><td>6.99</td></tr>
<tr><td>Bone marrow aspiration (with biopsy)</td><td>0.03</td><td>517.50</td></tr>
<tr><td>FISH</td><td>0.22</td><td>6.99</td></tr>
<tr><td>PCR</td><td>0.79</td><td>25.00</td></tr>
<tr><td>Flow Cytometry</td><td>0.09</td><td>6.99</td></tr>
<tr><td>Cytochemistry analysis</td><td>0</td><td>6.99</td></tr>
<tr><td>Blood film exam</td><td>0.50</td><td>3.01</td></tr>
<tr><td>Blood chemistry</td><td>1.13</td><td>1.19</td></tr>
<tr><td>Blood transfusion</td><td>0.01</td><td>121.85</td></tr>
</table>
*3-month period.</td><td>UK HCP Survey;[48] NHS Reference Costs 2014–2015; Szczepura et al. 2006 HTA[49]; NHS Blood and Transplant Price List 2014/15</td></tr>
</table>

CP, chronic phase; CML, chronic myeloid leukaemia; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction.

*Assumed 0.5 cardiologist visit every 3 months. Assumed the same visit cost as for haematologist; this estimate is deemed conservative as according to the UK HCP survey, 9 of 12 experts suggested cardiologist visits will occur less frequently than once every 6 months.[48]

†WF01A service code 303 (Non-Admitted Face to Face Attendance, Follow-up; Clinical Haematology).

2.4.3 Required infrastructure

TKI therapy is standard treatment for patients with CML and Ph+ ALL,[18, 28] and thus no additional NHS infrastructure will be required to incorporate ponatinib into the clinical pathway of care.

2.4.4 Patient monitoring

Requirements for patient monitoring associated with TKIs indicated for treatment of CML or Ph+ ALL are listed in Table 2-3. With regards to complete blood counts and liver function tests, patient monitoring with ponatinib is similar to that recommended for other TKIs. Ponatinib, however, is associated with an increased risk of pancreatitis. Specifically, per SmPC guidance, serum lipase should be monitored every 2 weeks for the first 2 months and then periodically thereafter.[22] Therefore, blood analyses will include an amylase test to diagnose and monitor acute pancreatitis.

Per SmPC guidance, before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed. Throughout treatment with ponatinib, cardiovascular status should continue to be monitored, and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised.[22] Furthermore, patients receiving ponatinib should be monitored for evidence of thromboembolism and vascular occlusion and if decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed.[22] To account for additional cardiovascular monitoring associated with ponatinib, one cardiology visit every 6 months (0.5 per cycle) is incorporated into the economic model.[48]

Overall, compared with current clinical practice, it is expected that ponatinib will require more careful patient monitoring for pancreatitis, cardiovascular status, and vascular occlusion.

Table 2-3. Patient monitoring for TKIs according to SmPCs

	Imatinib (Glivec®)[50]	Nilotinib (Tasigna®)[51]	Dasatinib (Sprycel®)[17]	Bosutinib (Bosulif®)[7]	Ponatinib (Iclusig®)[22]
Complete blood count	Regularly	Every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated	Advanced CML or Ph+ ALL • Weekly for first 2 months, then monthly thereafter, or as clinically indicated CP-CML • Every 2 weeks for 12 weeks, then every 3 months thereafter or as clinically indicated	Weekly for the first month and then monthly thereafter, or as clinically indicated	Every 2 weeks for the first 3 months and then monthly or as clinically indicated
Liver function	Transaminases, bilirubin, alkaline phosphatase should be monitored regularly	Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated	—	Prior to treatment initiation and monthly for the first 3 months of treatment, and as clinically indicated	Monitored periodically, as clinically indicated
Serum lipase	—	Monthly or as clinically indicated	—	—	Every 2 weeks for the first 2 months and then periodically thereafter
Vascular occlusion	—	—	—	—	Monitoring for evidence of thromboembolism and vascular occlusion should be performed and if decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed

	Imatinib (Glivec®)[50]	Nilotinib (Tasigna®)[51]	Dasatinib (Sprycel®)[17]	Bosutinib (Bosulif®)[7]	Ponatinib (Iclusig®)[22]
Cardiac risk	Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully	Cardiovascular status should be evaluated and cardiovascular risk factors monitored and actively managed according to standard guidelines	Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately	Monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating therapy and as clinically indicated	Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment Monitor patients for signs or symptoms consistent with heart failure Blood pressure should be monitored and managed at each clinic visit
Electrolytes	—	Hypokalaemia or hypomagnesaemia must be corrected prior to nilotinib administration and should be monitored periodically during therapy	—	Hypokalaemia or hypomagnesaemia must be corrected prior to administration and should be monitored periodically during therapy	—
Blood lipids	—	Assess at month 3 and 6 after initiating therapy and at least yearly during chronic therapy	—	—	—
Blood glucose	—	Monitor during treatment, as clinically indicated	—	—	—
Renal function	Should be evaluated prior to the start of imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction	—	—	Assess prior to treatment initiation and closely monitor during therapy, with particular attention in those patients who have pre-existing renal compromise or in those patients exhibiting risk factors for renal dysfunction	—

ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; CP, chronic phase; ECG, electrocardiogram; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor; —, not detailed in the SmPC.

2.4.5 Concomitant therapies

No concomitant medications are specified in the SmPC.[22] In the phase 1 study (Cortes et al. 2012)[23] and the phase 2 PACE study (Cortes et al. 2013),[9] AEs were managed with dose reduction or treatment interruption.

2.5 Innovation

2.5.1 Breakthrough in TKI therapy

Ponatinib represents a significant advance in the treatment of CML and Ph+ ALL, where patients who are resistant or intolerant (R/I) to imatinib or 2G-TKIs, including those with and without the T315I mutation, have few treatment options to improve their chance of survival. Resistance and intolerance remain important challenges to address. Approximately 30%–40% of patients with CP-CML treated with imatinib develop resistance or intolerance to the drug.[5] Pharmacologic treatment options for patients who have received both imatinib and a 2G-TKI are currently limited, reinforcing the high unmet medical need among resistant or intolerant patients in the third line.

A key breakthrough of ponatinib is its molecular design. Five critical regions in the overall structure of ponatinib were optimised to specifically overcome resistance to 1G- and 2G-TKIs.[52] For example, the triple bond ethynyl linker allows ponatinib to span the bulky side chain present in *BCR-ABL* mutant isoforms.

As a result of this innovation, ponatinib has demonstrated efficacy in all indicated patients, including those R/I to prior TKIs and patients with resistance-conferring *BCR-ABL* isoforms such as the T315I mutation for which no other TKI is effective.[9] Ponatinib has demonstrated high and durable responses in patients with CP-CML regardless of *BCR*-ABL mutation status. Among PACE trial CP-CML patients with 0, 1, or ≥2 *BCR-ABL1* mutations at baseline based on next-generation sequencing, the rate of MCyR by 12 months ranged from 50%–61%.[53] The major molecular response (MMR) rate at any time was 29%–45%. These responses were sustained for at least 2 years in 87% (MCyR) and 65% (MMR) of patients; for patients with compound mutations, responses were sustained in 90% and 92%, respectively. Mutation status at baseline had no effect on overall survival (OS) at 2 years, which was estimated to be 86%. In addition to the positive and durable responses achieved with ponatinib regardless of baseline mutation status, no mutation, single or compound, has been shown to confer primary or secondary resistance to ponatinib in CP-CML patients.[53]

Response rates to previous therapy are usually a predictor of response to subsequent therapy, responses achieved with ponatinib exceeded responses achieved with the last prior TKI, generally nilotinib or dasatinib, by two- to ten-fold. For example, patients with CP-CML in the PACE trial had a best response to their most recent regimen containing dasatinib or nilotinib of only 26% for MCyR and 3% for MMR; by 12 months of treatment with ponatinib, a response of MCyR was seen in 56% of patients and of MMR in 34%.[9] These improved response rates achieved with ponatinib were associated with a high probability of progression-free survival (PFS) and OS at 4 years.[24]

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

3.1.1 Chronic myeloid leukaemia (CML)

CML, a rare disease accounting for only 15% of adult leukaemias,[1] is a neoplastic disease characterised by an excessive proliferation of myeloid cells at all stages of maturation.[54] It is distinguished by the presence of an aberrant chromosome translocation between chromosomes 9 and 22, which produces the Philadelphia (Ph) chromosome.[55] This exchange of genetic material occurs in the haematopoietic stem cell and generates an oncogene called *BCR-ABL*, which is located on the Ph chromosome. Following this exchange, the Ph chromosome encodes an oncoprotein that is a constitutively active form of ABL tyrosine kinase, which promotes cell proliferation, and alters cell adhesion and apoptosis.[54, 56, 57]

In the absence of treatment, prognosis of patients with CML is poor; the expected survival is 3–5 years from diagnosis. CML is commonly characterised as having three distinct phases: the initial indolent chronic phase (CP-CML), an intermediate accelerated phase (AP-CML) which lasts for less than 1 to 1.5 years, and an aggressive blast phase (BP-CML) that is usually fatal within 3 to 6 months.[2] The disease may present at any age; however, the median age of onset in the UK is 59 years.[3]

Approximately one-third to one-half of patients with CML are asymptomatic at diagnosis and are identified through routine screening. When symptoms are present, they are often nonspecific, such as fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain.[2, 58]

More than 90% of CML patients are diagnosed in the early, chronic phase of the disease.[59] Abnormal results in routine full blood count, such as low erythrocyte count (anaemia) or elevated leukocyte counts (leukocytosis), neutrophils (neutrophilia), and platelets (thrombocytosis), may suggest CML.[2, 58] Circulating immature cells and bone marrow hypercellularity (ie, excess of cells) are indicative of myeloproliferative disorders such as CML.[2, 58]

A CML diagnosis is confirmed by the existence of the Ph+ chromosome in peripheral blood and/or bone marrow cells. The methods used for detecting the *BCR-ABL1* fusion gene are conventional cytogenetics (karyotyping), fluorescence in situ hybridization (FISH), and reverse transcriptase–polymerase chain reaction (RT-PCR).[1, 47]

The different phases of CML are defined mainly by the percentage of blast cells in peripheral blood and in bone marrow, but can also be defined by other laboratory and clinical parameters, as detailed in Table 3-1.[1] The stage of the disease at diagnosis is an important prognostic factor and may predict the pattern of disease progression.[60]

Table 3-1. Definitions of accelerated and blast phases of CML

CML phase	Definition according to the WHO Criteria[1]
AP	• Blasts 10%–19% of white blood cells in peripheral and/or nucleated bone marrow cells • Peripheral blood basophils ≥20% • Persistent thrombocytopaenia (<100 x 10^9/L) unrelated to therapy, or persistent thrombocytosis (>1000 x 10^9/L) unresponsive to therapy • Increasing spleen size and increasing white blood cell count unresponsive to therapy • Cytogenetic evidence of clonal evolution
BP	• Blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells • Extramedullary blast proliferation • Large foci or clusters of blasts in the bone marrow biopsy

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; WHO, World Health Organization.

As previously mentioned, the majority of the patients are diagnosed in the chronic phase of the disease.[59] If treated only with cytoreduction, patients progress to more advanced stages within 3 to 5 years from diagnosis. Progression to advanced stages is associated with a decreased response to treatment and a poorer prognosis.

The risk of progression can be estimated by several disease features at diagnosis, allowing CML patients to be stratified according to their risk of disease progression. Various scoring systems for risk stratification have been developed. The most widely used is the Sokal Scoring System,[61] developed when chemotherapy was the standard treatment for CML. Another scoring system is the Hasford score, validated in patients treated with interferon alpha.[62] Most recently, the European Treatment and Outcome Study (EUTOS) score was developed to predict response to TKI treatment.[63]

3.1.2 Acute lymphoblastic leukaemia (ALL)

ALL is a heterogeneous category of leukaemias with the common feature of proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. Overall, ALL represents about 20% of all leukaemias in adults, and is the most common form of childhood leukaemia.[11-13] Ph+ ALL (ALL characterised by the presence of the Ph+ chromosome) makes up about 25% of adult ALL cases but is relatively rare among children, accounting for just 3% of paediatric ALL cases. The incidence of Ph+ ALL increases with age, representing about 40% of ALL cases in patients over 50 years of age.[11-13]

In contrast to CML, patients with ALL experience more typical symptoms, including fatigue, fever, sweating, weight loss, dyspnoea, infection, and bleeding. Less than 10% of patients develop symptomatic central nervous system (CNS) infiltration.[11, 20]

ALL diagnosis requires a physical examination, complete blood count with differential and platelets, a blood chemistry profile, a disseminated intravascular coagulation panel, a tumour lysis syndrome panel, bone marrow aspiration, and biopsy haematopathologic characterisation.[11] Morphological identification of lymphoblasts by microscopy and immunophenotypic determination of lineage commitment and developmental stage by flow cytometry are essential for correct diagnosis of ALL.[64] In general, the diagnosis of ALL requires ≥20% bone marrow lymphoblasts upon analysis of bone marrow aspirate and biopsy.[11] Chromosomal analysis still plays an important role in the initial cytogenetic work-up of Ph+ ALL.[64] The same diagnostic procedures are used to identify the *BCR-ABL1* fusion (Ph+ chromosome) as described for CML in Section 3.1.1.[11]

Patient age, as well as immunophenotypic and cytogenetic features, provide prognostic information that can be used for treatment selection. Specifically, age greater than 35 years at diagnosis, initial leukocyte count of greater than 30 x 10^9/L, and the presence of cytogenetic abnormalities are associated with poorer prognosis.[11] The most frequent cytogenetic abnormality is the presence of the Ph+ chromosome, occurring in 25% of adult patients with ALL.[12] Patients with the Ph+ chromosome typically have a worse prognosis than those without the abnormality.[65]

3.2 Effects of CML and Ph+ ALL on patients, carers and society

3.2.1 CML

Since the introduction of the first generation (1G) TKI, imatinib, patient survival has dramatically improved, with ≥5-year OS ranging between 83%–97%.[47] Although fewer patients die from the disease now compared to prior to the advent of TKI therapy, most patients must continue therapy indefinitely. The chronic nature of the disease places a tremendous burden on patients, their families, and society. Receiving a suitable TKI and adhering to treatment is crucial for successful long-term outcomes.[66, 67] Most patients will remain in CP for years, and although many patients have few symptoms during this time, approximately a third experience moderate-to-severe symptoms (fatigue, drowsiness, sleep problems, muscle soreness/cramping, and failing memory)

that impact their ability to function and reduce their health-related quality of life (HRQoL).[68] Fatigue has been reported as the most common symptom among patients receiving long-term TKI therapy.[69] In terms of HRQoL, younger adult patients are particularly vulnerable to physical and emotional burden that interferes with their capacity to work and carry out regular daily activities.[69]

Although patients who achieve a durable response to TKIs may achieve a life-span comparable to that of the general population,[70] TKI failure is a significant concern for patients with CML.[71] Patients with primary or secondary resistance to one TKI have an increased risk of progression, and this risk increases further in patients who are resistant to two or three TKIs.[72] TKI failure also increases the economic burden of the disease.[73, 74] TKI failure within 1 year of starting therapy leads to higher total healthcare costs compared with a treatment course without TKI failure, with inpatient care largely driving the higher medical costs associated with failure.[73] Moreover, the economic burden of TKI failure increases with each line of therapy.[74] Therefore, resistance and intolerance to therapy is expected to pose a significant burden on healthcare costs and patient HRQoL and mortality.[75]

3.2.2 Ph+ ALL

Scarce data exist on the disease burden and HRQoL of patients with Ph+ ALL, and thus, compared to CML, much less is known about the impact of Ph+ ALL on patients and society. Ph+ ALL is a disease associated with very poor prognosis and in which allogeneic haematopoietic stem cell transplantation (allo-SCT) offers the only chance for a cure.[12, 76] Even with treatment, many adult patients with ALL die prematurely and lose decades from their lives.[77] Furthermore, compared to Philadelphia chromosome–negative (Ph–) ALL, patients with Ph+ ALL generally have a shorter remission duration and poorer survival.[12]

The aim of using a TKI as induction treatment is to quickly achieve full remission in adult patients with Ph+ ALL. For patients who experience a complete response after induction therapy, allo-SCT offers the best chance of survival and is well established as the mainstay of treatment in Ph+ ALL.[11, 78] The development of TKI therapy has moderately improved survival in patients with Ph+ ALL. However, patients may still experience rapid disease progression, and there remains a significant unmet need, particularly in TKI R/I patients for whom OS is only 6 to 9 months.[16]

3.3 Clinical pathways of care

3.3.1 CML

3.3.1.1 TKIs approved in the UK for CML

Due to the key role of tyrosine kinase activity in CML, current treatment is based on the use of rationally designed TKIs. TKIs approved for use in the UK include:

- Imatinib (Glivec®, Novartis Pharmaceuticals)
- Dasatinib (Sprycel®, Bristol-Myers Squibb)
- Nilotinib (Tasigna®, Novartis Pharmaceuticals)
- Bosutinib (Bosulif®, Pfizer)
- Ponatinib (Iclusig®, Incyte Corporation)

Imatinib (Glivec®) was the first TKI to demonstrate significant clinical benefit compared to non–TKI-based therapy,[79] and rapidly became the gold standard of care for 1L therapy in newly diagnosed CML patients.[80] Patients on imatinib thus represent a large proportion of the treated CML patient population; however, approximately 30%–40% of patients in CP-CML develop resistance or intolerance to imatinib and require additional therapy.[5] Subsequent to imatinib, three 2G-TKIs were developed for CML: dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®).[5] Dasatinib and nilotinib have demonstrated clinical benefit compared to imatinib when

used in newly diagnosed patients, and both of these 2G-TKIs and bosutinib have shown benefit in patients who have developed intolerance or resistance to imatinib.[5, 81, 82] Bosutinib has also been studied prospectively in patients who have failed imatinib and therapy with a 2G-TKI, dasatinib or nilotinib.[8] Bosutinib is the most recent 2G-TKI approved for the treatment of adult patients with Ph+ CP-, AP-, and BP-CML previously treated with one or more TKIs, and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options.[7]

Prior to market authorisation of the 3G-TKI ponatinib (July 2013), pharmacologic treatment options approved for treatment of CML patients in Europe who had received both imatinib and a 2G-TKI were limited, focusing on the use of an alternative 2G-TKI or investigational therapies.[47, 83, 84] Options were notably lacking for patients with the T315I mutation, which is the most frequent mutation seen in the BCR-ABL kinase domain.[85, 86] Historically, the T315I mutation has been a predictor of poor efficacy of 1G- and 2G-TKI–based therapies in CML patients.[87] Table 3-2 provides information on the indication, formulation, and dosage and administration for TKIs approved and available in the UK for treatment of CML.

Table 3-2. Approved TKIs for the treatment of CML available in England

	Imatinib (Glivec®)[50]	Dasatinib (Sprycel®)*[17]	Nilotinib (Tasigna®)[51]	Bosutinib (Bosulif®)[7]	Ponatinib (Iclusig®)[22]
CML indication	Adult and paediatric patients with: • Newly diagnosed Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment • Adult and paediatric patients with Ph+ CML in CP after failure of IFN alpha therapy, or in AP or BP	Adult patients with: • Newly diagnosed Ph+ CML in CP • CP-, AP-, and BP-CML R/I to prior therapy including imatinib mesilate • Lymphoid blast CML with resistance or intolerance to prior therapy	Adult patients with: • Newly diagnosed Ph+ CP-CML • Ph+ CP- and AP-CML R/I to prior therapy including imatinib Efficacy data in patients with CML in blast crisis are not available.	Adult patients with: • Ph+ CP-, AP-, or BP-CML previously treated with one or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options	Adult patients with: • CP-, AP-, or BP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
Formulation	Hard capsules in strengths of 50 mg and 100 mg Film-coated tablets in strengths of 100 mg and 400 mg	Film-coated tablets in strengths of 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg	Hard capsules in strengths of 150 mg and 200 mg	Film-coated tablets in strengths of 100 mg and 500 mg	Film-coated tablets in strengths of 15 mg, 30 mg, and 45 mg
Administration	Oral	Oral	Oral	Oral	Oral
Starting dose	Adult patients with CP-CML: 400 mg/day Adult patients with AP- or BP-CML: 600 mg/day Paediatric patients: 340 mg/m^2/day (not exceeding 800 mg)	Adult patients with CP-CML: 100 mg QD Adult patients with AP- or BP-CML: 140 mg QD	Adult patients with newly diagnosed Ph+ CP-CML: 300 mg BID Adult patients with Ph+ CP- or AP-CML who are R/I to prior therapy: 400 mg BID	500 mg QD	45 mg QD
Dose adjustments	CP-CML: Increase to 600 or 800 mg/day AP/BP-CML: Increase to a maximum of 800 mg/day (given as 400 mg BID) Doses may be reduced or interrupted to manage AEs	CP-CML: Increase to 140 mg QD AP/BP-CML: Increase to 180 mg QD Doses may be reduced or interrupted to manage AEs	Dose escalations are not permitted. Doses may be reduced or interrupted to manage AEs	Dose escalation to 600 mg QD (doses >600 mg/day should not be given) Doses may be reduced or interrupted to manage AEs	Dose escalations are not permitted. Doses may be reduced or interrupted to manage AEs

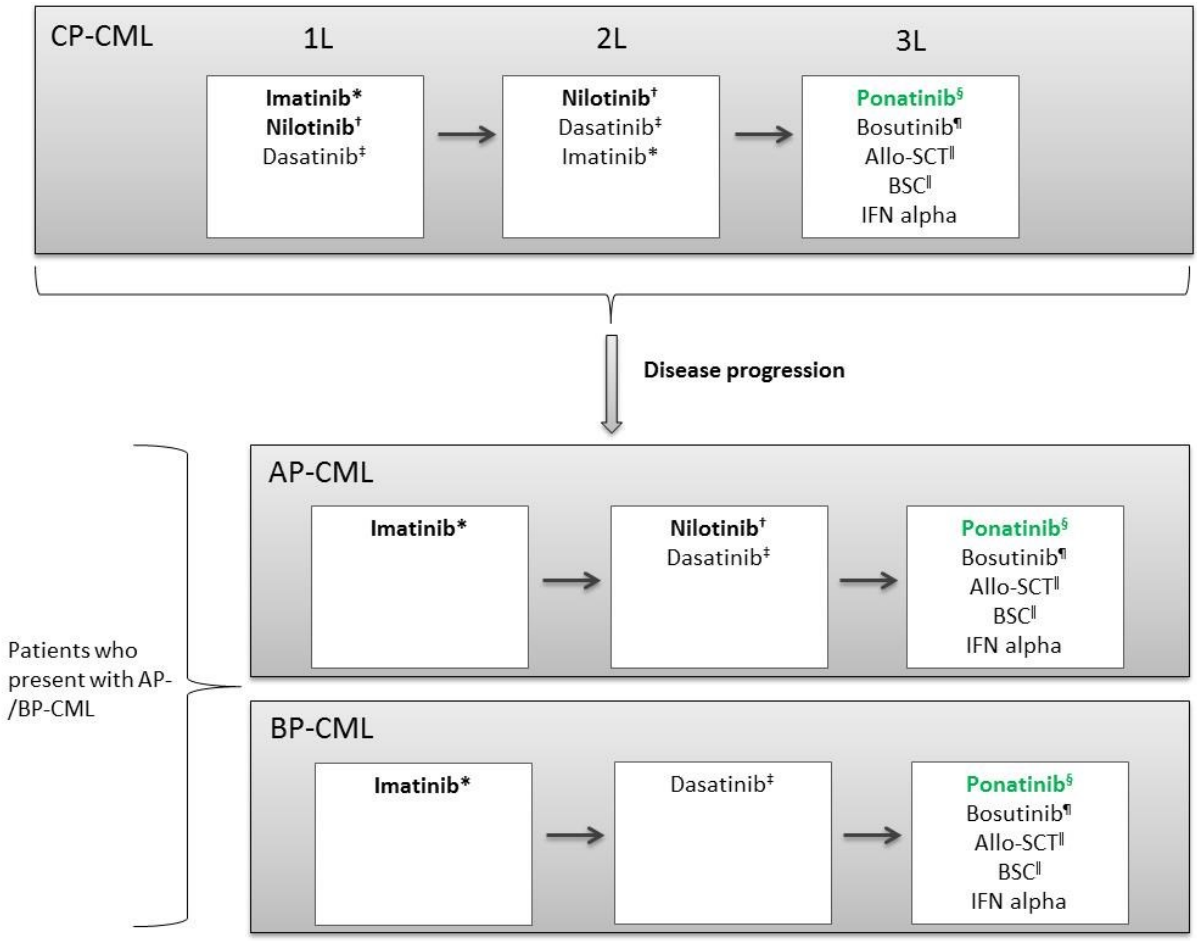
ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BID, twice daily; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; IFN, interferon; Ph+, Philadelphia chromosome–positive; QD, once daily; R/I, resistant/intolerant; TKI, tyrosine kinase inhibitor.

*Dasatinib is available through the CDF for the treatment of CP- and AP-CML in patients who are refractory to imatinib, or who have significant intolerance to imatinib or nilotinib.[88] Dasatinib was previously available for the treatment of BP-CML through the CDF but it was delisted in March 2015.[89]

3.3.1.2 Ponatinib for the treatment of CML

Figure 3-1 presents where ponatinib would fit in the clinical pathway of care for CML in England. Ponatinib would be used in third line after treatment failure with imatinib and either nilotinib or dasatinib (if used through the Cancer Drugs Fund [CDF]).

Figure 3-1. Clinical pathway of care for patients with CML



1L, first line; 2L, second line; 3L, third line; allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; IFN, interferon.

*NICE recommends standard-dose imatinib (400 mg) for 1L treatment for adults with Ph+ CP-CML.[90] In clinical practice, imatinib is used 2L in patients who are intolerant to another prior TKI therapy (eg, nilotinib), but not in the case of prior TKI-resistance.[47] NICE recommends imatinib for CML that initially presents in AP or BP, and for CML that presents in CP and then progresses to AP/BP, if imatinib has not been used previously.[91]

†Nilotinib is recommended by NICE in 1L and 2L therapy for adult patients with Ph+ CP-CML if cost is discounted through PAS.[90, 92] NICE recommends nilotinib for AP-CML in adults whose CML is resistant to treatment with standard-dose imatinib or who have imatinib intolerance and if nilotinib is made available through PAS.[92]

‡Dasatinib is indicated for the treatment of adult patients with newly diagnosed Ph+ CML in the chronic phase; CP-, AP-, or BP-CML with resistance or intolerance to prior therapy including imatinib mesilate; and lymphoid blast CML with resistance or intolerance to prior therapy.[17] Dasatinib is available through the CDF for the treatment of CP- or AP-CML in patients who are refractory to imatinib, or who have significant intolerance to imatinib or nilotinib.[88] Dasatinib was previously available for the treatment of BP-CML through the CDF but it was delisted in March 2015.[89]

§Ponatinib is approved for adult patients with CP-, AP-, or BP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.[22]

¶Bosutinib is conditionally licensed for the treatment of adult patients with Ph+ CP-, AP-, and BP-CML previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.[7] NICE recommends bosutinib as an option, within its conditional marketing authorisation, for Ph+ CP-, AP-, and BP-CML in adults when they have previously had one or more TKI; and imatinib, nilotinib, and dasatinib are not appropriate; and the company provides bosutinib with the discount agreed in the PAS (as revised in 2016).[93]

‖Allo-SCT and BSC are used in clinical practice but are not part of the NICE clinical pathway of care.[47]

CP-CML: NICE recommends standard-dose imatinib (400 mg) for 1L treatment for adults with Ph+ CP-CML.[90] In clinical practice, imatinib is also used second-line in patients who are intolerant to another prior TKI therapy (eg, nilotinib), but not in the case of prior TKI-resistance.[47] Nilotinib is recommended by NICE in 1L and 2L therapy for adult patients with Ph+ CP-CML, if cost is discounted through PAS.[90, 92] At the time of writing this submission, NICE does not recommend dasatinib for first- or second-line treatment of CML.[90] NICE recommends bosutinib as an option, within its marketing authorisation with a PAS discount as revised in 2016.[93]

Assuming that NICE approves dasatinib for use according to its indication,[17] ponatinib would be recommended as 3L therapy in patients who fail prior therapy with imatinib and who are R/I to dasatinib or nilotinib.

AP/BP-CML: NICE recommends imatinib for CML that initially presents in AP or BP, and for CML that presents in CP and then progresses to AP/BP, if imatinib has not been used previously.[91] NICE recommends nilotinib for AP-CML in adults whose CML is resistant to treatment with standard-dose imatinib or who have imatinib intolerance and if nilotinib is made available through PAS.[92] NICE recommends bosutinib as an option for patients with AP- or BP-CML, within its marketing authorisation, if made available with a PAS discount, as revised in 2016.[93] Assuming that NICE approves dasatinib for use according to its indication for advanced CML,[17] ponatinib would therefore be used in the third line in AP-CML patients who are resistant to 2L nilotinib or dasatinib, and used in the third line in BP-CML patients who fail treatment with imatinib and dasatinib.

Other treatment options for people with TKI-R/I CML include interferon alpha (in rare cases), hydroxycarbamide (hydroxyurea), and allo-SCT.[92] Although allo-SCT and best supportive care (BSC) are not part of the NICE clinical pathway of care, they have been incorporated into Figure 3-1 because of their use in clinical practice for patients with advanced CML and no other recommended treatment options.

Based on this anticipated place in therapy, the TKI comparators included in the economic evaluation of ponatinib for the treatment of CML are bosutinib, hydroxycarbamide (as a proxy for BSC), interferon alpha, and direct allo-SCT (ie, proceeding to allo-SCT without first having received ponatinib or bosutinib in an attempt to achieve remission prior to transplant).

3.3.1.3 Unmet medical need concerning treatment of CML

There is currently a significant unmet need for patients who fail imatinib and a 2G-TKI. Even though sequential use of 2G-TKIs is common in clinical practice and is recommended in clinical practice guidelines,[47] there is only a modest evidence base supporting the efficacy of sequential use of 2G-TKIs in patients who are R/I to prior therapy.[8, 23, 94, 95] In addition, dasatinib and nilotinib have only been studied in registrational trials in patients failing imatinib and these studies were non-comparative.[17, 51] Thus, the sequential use of 2G-TKIs is not an approved indication for these drugs.[17, 51] The use of ponatinib in third line or later is supported by strong clinical evidence and is in accordance with the approved indication.[9, 22-24] Existing data on sequential use of currently available 2G-TKIs show that the response rates for these treatments are low and of shorter duration compared to those achieved with ponatinib.[6, 9, 94-101]

For patients who have failed treatment on dasatinib or nilotinib, no other TKIs—other than ponatinib—have received full EMA approval based on registration-quality trials demonstrating treatment efficacy and safety. Only limited data are available to support bosutinib in patients with an “unmet medical need”, defined in the bosutinib EPAR as patients for whom either dasatinib or nilotinib may not be considered suitable treatment after failure of the other 2G-TKI due to a pre-existing medical condition, TKI intolerance, or mutation which would be expected to confer resistance to that therapy, as well as patients who have received prior imatinib only but for whom dasatinib or nilotinib may not be considered a suitable treatment for the above referenced reasons.[36] In the bosutinib study upon which the conditional approval is based, only 21 patients with CP-CML met these criteria for unmet medical need.[102] This underlies the decision of the EMA to grant only conditional marketing authorisation to bosutinib, requiring its manufacturer to fill this evidence gap by conducting a single-arm, open-label, multi-centre efficacy and safety study of bosutinib in patients with Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.[36]

Furthermore, the CML indications for ponatinib and bosutinib are not directly comparable with respect to TKI resistance and intolerance. Bosutinib has a broader, less precise indication than ponatinib; that is, the wording of the bosutinib indication does not specifically require resistance or intolerance, and allows clinicians to prescribe it in earlier lines of therapy if they consider other TKIs are not clinically appropriate, despite the paucity of evidence for bosutinib in those settings.[7] Additionally, ponatinib is recommended for patients with the T315I mutation, which cannot be treated with any other TKI, including bosutinib.[7, 22] Finally, compared with ponatinib, bosutinib has been shown to provide only modest benefit to heavily pre-treated patients with CML; the proportion of patients who achieve a CCyR as their best response was only 24.1% with bosutinib (Khoury et al. 2012)[8] compared to 65% with ponatinib (Hochhaus et al. 2015).[24]

3.3.1.3.1 Further unmet need considerations

Other treatment options for patients who have received and failed 2G-TKI therapy include interferon alpha and allo-SCT. Interferon alpha, however, is recommended only in the rare circumstances in which a TKI cannot be used.[47] Hydroxycarbamide does not affect the natural history of CML and is considered only as palliative treatment.[54] Allo-SCT is expensive relative to TKI therapy in high-income European countries such as England,[103] has largely been reserved for younger patients, is associated with equity issues, and has a poor short-term prognosis;[104-106] as a result, it is not a viable option for many CML patients.

Despite significant advances in CML therapy following the introduction of TKIs (imatinib, dasatinib, and nilotinib), a substantial proportion of patients discontinue therapy over time due to resistance (attributable in about half the cases to emergence of *BCR-ABL* kinase domain mutations) and intolerance. Approximately 30%–40% of patients with CP-CML treated with imatinib develop resistance or intolerance to the drug.[5] Ponatinib was specifically designed to inhibit all variants of BCR-ABL, including those that confer resistance to 1G- and 2G-TKIs. The most evident clinical application for ponatinib is, therefore, treatment of patients who have experienced failure of a 2G-TKI. As a more potent, inhibitory TKI, ponatinib offers treatment advantages for patients lacking defined resistance mutations, but who still develop resistance by other mechanisms. Ponatinib also represents an important new treatment option for patients with advanced CML as it may serve as a "bridge" to allo-SCT by inducing remission in patients prior to the procedure. With the approval of the first 3G-TKI, ponatinib,[22] there is finally an effective treatment option for patients with CP-, AP-, or BP-CML where imatinib and either dasatinib or nilotinib have failed, including where there is prior TKI resistance or intolerance or CML that is T315I mutation-positive.

One strategy in the management of TKI resistance and intolerance is using alternative TKIs in sequential lines of treatment. Between 3% and 15% of patients receiving 1L nilotinib or dasatinib are R/I to treatment,[71, 107, 108] and more than 50% of patients receiving second-line (2L) nilotinib or dasatinib fail to respond to treatment.[109-111] Although 50%–60% of patients treated with 2L 2G-TKIs achieve a MCyR response (40%–50% complete cytogenetic response [CCyR]), up to 70% of these patients discontinue treatment within 4 to 5 years, suggesting a significant failure rate over time.[47] The high percentage of patients treated with 2L TKIs, and the associated discontinuation rate, underscores the importance of TKI resistance and intolerance in patients with CML.[94, 112, 113] The onset and development of resistance has been linked to several factors, including poor treatment compliance, changes in gastrointestinal absorption and metabolism of the drug, alterations in apoptosis and DNA repair mechanisms, and the presence of *BCR-ABL* mutations.[21, 114, 115] The best characterised mechanism of resistance to TKI treatment is the occurrence of point mutations in the kinase domain of *BCR-ABL*.[116, 117] About 40% of patients who develop imatinib resistance have (baseline or acquired) mutations in *BCR-ABL*,[118] although the proportion of patients with mutations varies depending on the stage of the disease and the screening method used to detect mutations.[119] Over 100 point mutations coding for single amino acid substitutions in the *BCR-ABL* kinase domain have been identified among patients with CML resistant to imatinib. Over 60% of the mutations have been detected in seven amino acids, with T315I being the most frequent.[85, 114] The T315I mutation is present in 16%, 23%, and 63% of patients in CP-, AP-, and BP-CML, respectively. The development of mutations is associated with a poorer prognosis and a higher risk of progression to AP-CML and BP-CML.[21, 120, 121] Patients with a mutation that confers resistance to imatinib are more likely to develop serial

mutations, which increases the risk of becoming resistant to 2G-TKI therapy.[46] Between 20%–35% of patients treated with 2G-TKIs develop new mutations in *BCR-ABL*.[111, 122-124] Moreover, in patients where two or more TKIs have failed, the risk of developing leukaemic clones with one or more mutations (ie, serial mutations) is high. This is the main cause of progression to AP- and BP-CML, where the OS is poor and success of "rescue" therapy, including allo-SCT, is very low.[124-128]

Clinical data have confirmed that achievement of CCyR is predictive of increased survival[129, 130] and long-term modelling studies have shown that patients who achieve this endpoint could be expected to have a near-normal life expectancy.[131] In fact, recent data have demonstrated that patients with newly diagnosed CP-CML who achieve at least a CCyR within a year of treatment initiation experience an OS similar to that of the general population.[132] However, when used after failure of both imatinib and a 2G-TKI, the treatment efficacy of all of the remaining treatment options available today, expressed in terms of CCyR, is modest.[8, 23, 94, 95] Thus, in order to improve long-term survival, it is vital that patients have access to effective treatment options with proven efficacy in both third- (3L) and fourth-line (4L) settings.

Therefore, pharmacologic treatment options for patients who have received both imatinib and a 2G-TKI are currently limited, with modest evidence-based efficacy supporting the sequential use of 2G-TKIs. As a 3G-TKI, ponatinib offers the best chance of the available treatment options to achieve a response in a patient population with limited treatment options.

3.3.2 Ph+ ALL

3.3.2.1 TKIs approved in the UK for Ph+ ALL

Prior to EU marketing authorisation of ponatinib (July 2013),[22] the only TKIs indicated for use in Ph+ ALL were imatinib (Glivec®) and dasatinib (Sprycel®).[17, 50] No formal recommendations on imatinib have been issued by NICE. Dasatinib was previously available for the treatment of ALL through the CDF but it was delisted in November 2015.[89] Table 3-3 provides information on the EMA-approved TKIs for the treatment of Ph+ ALL.

Table 3-3. Approved TKIs for the treatment of Ph+ ALL

	Imatinib (Glivec®)[50]	Dasatinib (Sprycel®)[17]	Ponatinib (Iclusig®)[22]
Ph+ ALL indication	Adult and paediatric patients with: • Newly diagnosed Ph+ ALL integrated with chemotherapy Adult patients with: • Relapsed or refractory Ph+ ALL as monotherapy	Adult patients with: Ph+ ALL with resistance or intolerance to prior therapy	Adult patients with: Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
Formulation	Hard capsules in strengths of 50 mg and 100 mg Film-coated tablets in strengths of 100 mg and 400 mg	Film-coated tablets in strengths of 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg	Film-coated tablets in strengths of 15 mg and 45 mg
Administration	Oral	Oral	Oral
Starting dosage	600 mg/day	140 mg QD	45 mg QD
Dose adjustments	Dose escalations are not permitted. Doses may be reduced or interrupted to manage AEs.	Dose increase to 180 mg QD is allowed in patients who do not achieve haematologic/cytogenetic response at the recommended starting dose Doses may be reduced or interrupted to manage AEs	Dose escalations are not permitted. Doses may be reduced or interrupted to manage AEs.

ALL, acute lymphoblastic leukaemia; Ph+, Philadelphia chromosome–positive; QD, once daily; TKI, tyrosine kinase inhibitor.

Patients with imatinib-resistant Ph+ ALL have limited treatment options. Treatment options are further restricted for patients with imatinib-resistant Ph+ ALL who subsequently fail therapy with a 2G-TKI. As such, these patients are extremely difficult to treat and have significant unmet medical need. According to a study of 421 adult patients with relapsed ALL conducted by Tavernier et al. (2007),[133] most adult patients with relapsed disease could not be successfully treated with currently available therapies. They concluded that allo-SCT was the best therapeutic option for these patients.

In patients for whom allo-SCT is not suitable, the only other option is BSC. Clinical evidence derived from a single-centre retrospective study by Pagano et al. (2000)[30] supports the use of a palliative regimen consisting of a 6-week course of vincristine and prednisone as BSC for relapsing ALL patients.

3.3.2.2 Unmet medical need concerning treatment of Ph+ ALL

As mentioned previously, the presence of the Ph+ chromosome is associated with poor prognosis in patients with ALL. However, multiple clinical trials with BCR-ABL–specific TKIs have demonstrated significantly superior initial responses, including higher complete response rates without additional toxicity compared to controls (ie, patients who received chemotherapy alone).[134] In addition, studies suggest that better long-term outcomes are possible. There is, however, little or no evidence to date that allo-SCT, the mainstay of treatment for this disease, is (or will ever be) a dispensable part of therapy.[65]

Improved outcomes following allo-SCT have been observed in patients who received pre-transplant imatinib regimens. As a result, induction with imatinib followed by allo-SCT is considered to be the gold standard for first-line therapy, and the only treatment with curative potential in adult Ph+ ALL patients.[134]

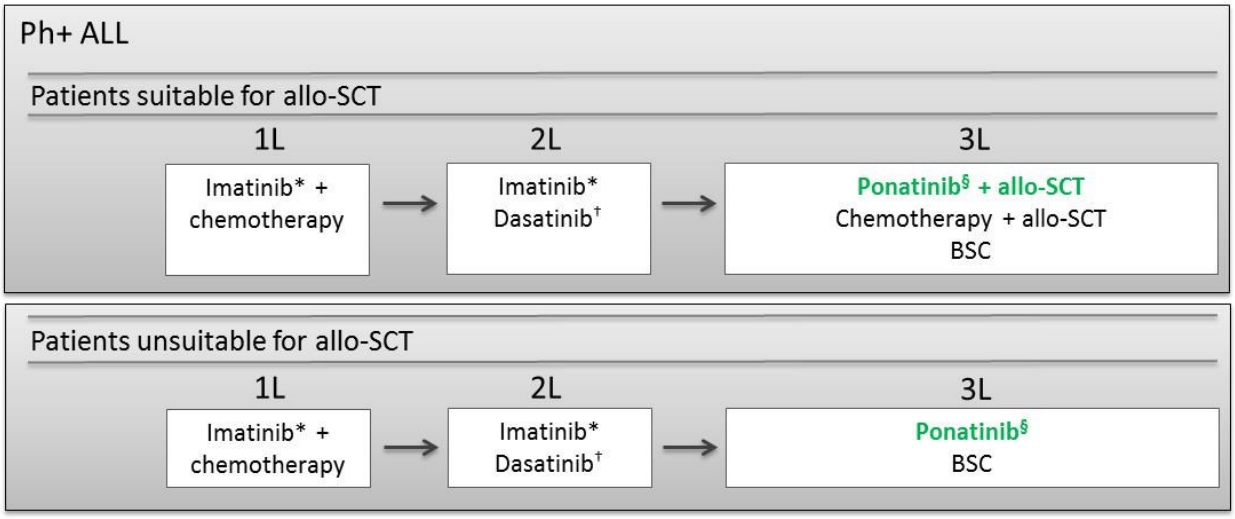
Up to 30% of patients with refractory or relapsed Ph+ ALL are refractory to imatinib. Even in patients who initially respond, resistance to imatinib develops rapidly (median time to relapse is 2.2 months).[135] The use of 2G-TKIs in patients with Ph+ ALL who are R/I to imatinib offers some additional survival benefit, although the gain is minimal. When Ph+ ALL patients who are R/I to imatinib are treated with dasatinib, the median length of PFS is 3.1 to 4.0 months.[16]

Treatment options for patients with imatinib-resistant Ph+ ALL who subsequently fail therapy with a 2G-TKI are limited, and minimal data exist on the treatment of patients who have experienced failure of 2G-TKIs. As such, this patient population is extremely difficult to treat.

3.3.2.3 Ponatinib for the treatment of Ph+ ALL

Ponatinib is indicated in adult patients with Ph+ ALL for whom other TKI therapy is not appropriate, including Ph+ ALL that is T315I mutation-positive or where there is prior TKI resistance or intolerance. Figure 3-2 presents a clinical pathway of care for Ph+ ALL with 3L ponatinib after treatment failure with prior TKI therapy (eg, imatinib or dasatinib). Prior to the approval of ponatinib, the only options these patients had after failure of TKI therapy were allo-SCT or palliative BSC. With the approval of ponatinib, a 3G-TKI, there is another treatment option for this difficult-to-treat patient population. Based on the improved outcomes associated with pre-transplant imatinib regimens,[134] it is anticipated that ponatinib will be used as a bridge to allo-SCT in patients who are R/I to prior TKI therapy.

Figure 3-2. Clinical pathway of care for patients with Ph+ ALL



BSC, best supportive care.

*Imatinib is indicated for treatment of adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy or relapsed or refractory Ph+ ALL as monotherapy.[50] No formal recommendation of imatinib for treatment of Ph+ ALL has been issued by NICE.

†Dasatinib is indicated for treatment of adult patients with Ph+ ALL with resistance or intolerance to prior therapy.[17] Dasatinib was previously available for the treatment of ALL through the CDF but it was delisted in November 2015.[89]

§Ponatinib is indicated for adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.[22]

With this anticipated place in therapy, the main comparators included in the economic evaluation of ponatinib for the treatment of Ph+ ALL are reinduction chemotherapy followed by allo-SCT in patients suitable for transplantation or BSC in the form of vincristine and prednisone for patient when allo-SCT is not an option.

3.4 Life expectancy and epidemiology

3.4.1 Survival

3.4.1.1 CML

Mortality used to be higher in CML; based on England-specific data from the National Cancer Intelligence Network, the 5-year relative survival (RS) rate of patients aged 15–64 years has increased from 59% for patients diagnosed in the 2000–2003 time period, to 87% for patients diagnosed in 2008–2010.[136] Similarly, for patients aged 65 and older, 5-year RS rose from 22% patients diagnosed in 2000–2003 to 44% for those diagnosed in 2008–2010.[136]

Recent data from patients participating in six prospective clinical trials published by Sasaki et al.[132] indicate that since TKIs came into use, the OS rate in patients with newly diagnosed CP-CML is only slightly lower than that of the general population. Furthermore, with effective treatment (ie, if patients achieve at least a CCyR within a year of starting therapy with a TKI), the OS rate is similar to that of the general population.[132] In line with these findings, real-world data from the UK population-based Haematological Malignancy Research Network (HMRN) for the period 2004–2015 show the 5-year OS (95% CI) of patients with CML is 77.7% (72.3, 82.2) and the 5-year RS is 89.8% (84.0, 93.6).[3] Among patients presenting with AP-CML, survival has increased substantially since the advent of TKI therapy, with an estimated 8-year OS rate >75%.[137] Among patients with BP-CML treated with TKI therapy, however, median OS is 7–11 months, only a modest improvement compared to the pre-TKI era.[138]

Recently, Pulte et al. 2016 conducted a survival analysis of patients with haematologic cancers (including ALL and CML) identified from the Surveillance, Epidemiology, and End Results (SEER) database.[139] The report shows that, although 5-year RS in CML has dramatically

improved since 1997, between the periods of 2005–2008 and 2009–2012, the excess mortality rate has not decreased for patients aged ≥65 years and remains in the range of 50% or higher.[139] Furthermore, despite improvements in survival for patients with CML in general, survival in older patients remains low in comparison to younger patients (ie, those aged 50–59 years).[139]

Data on survival outcomes in patients with CML who received more than one prior TKI show that OS decreases with each subsequent line of therapy.[140] Akosile et al. demonstrated that among patients with CP-CML in second or later-line therapy, the 5-year OS for patients who received 3L TKI therapy was 53% (median OS in 3L therapy was not estimable); for patients who received 4L or later therapy, 5-year OS was 38% (median OS, 34 months).[140]

Patients with CML may be candidates for allo-SCT depending on the availability of a suitable donor and the eligibility of the patient. Based on data from the British Society of Blood and Marrow Transplantation,[141] the UK HMRN,[3] and national population statistics,[142, 143] approximately 1 in 12 CML patients in England receives allo-SCT. One study of patients receiving allo-SCT after TKI therapy (Jabbour et al. 2011), showed that the estimated 2-year OS for patients with CP-CML after transplantation was 72%.[144]

3.4.1.2 Ph+ ALL

Over the past two decades, survival in adult ALL has improved only marginally and remains poor, particularly for patients aged ≥50 years.[136, 139] According to England-specific data from the National Cancer Intelligence Network, over the 2000–2010 time period, survival in adult patients with ALL improved only slightly (by 8%) among adults <65 years and remained unchanged in patients ≥65 years.[136] The 5-year RS rate of patients aged 25–64 years was only 37% (2008–2010), while for patients 65 years and older, the 5-year RS was only 12.7% during the same time period.[136] Pulte et al. 2016 (SEER database) have published similar results for survival in ALL, reporting a 5-year excess mortality rate of 70% for patients with ALL aged 50–59 years, which increases to 90% for patients aged ≥75 years.[139] These data reflect the urgent need for therapeutic advances in adult patients with ALL.

In line with these data, the estimated UK-specific average number of years of life lost in adult (≥20 years) ALL is 28.[77] This substantial loss of life is much greater than the years of life lost from many other cancers, including those of the lung and breast.[77, 145] There are limited data available on the life expectancy of the indicated Ph+ ALL patient population, but it is known that prognosis is poor for patients who relapse, even with treatment. Patients who fail imatinib and are treated with dasatinib have a median OS of only 6–9 months,[16] while patients who receive salvage chemotherapy after first relapse and proceed to allo-SCT have a median OS of only 3–10 months.[133] Reflecting these poor outcomes, salvage chemotherapy followed by allo-SCT is rarely used in clinical practice.[28]

3.4.2 Incidence and prevalence

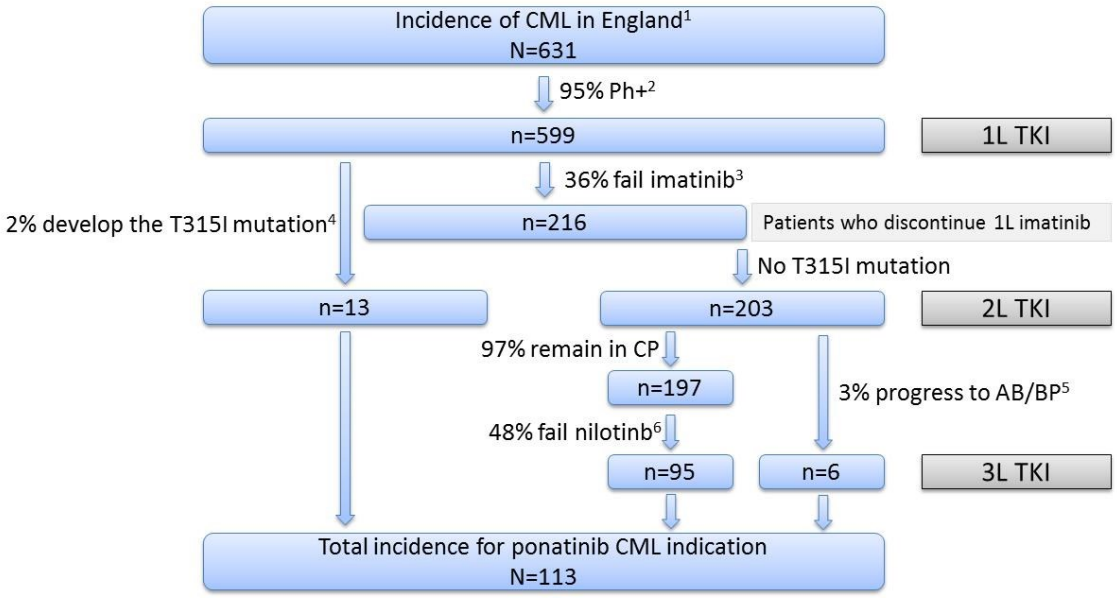
3.4.2.1 CML

CML is a rare disease accounting for 8% of leukaemia cases and 0.2% of all new cancer diagnoses in the UK.[15, 146] In 2014, 631 people in England were diagnosed with CML.[4] The European age-standardised incidence of CML in England is 1.3 per 100,000 persons (2013).[146] To date, there is no specific information on the prevalence of CML in England; however, according to Roman et al. 2016, the 10-year prevalence of CML in the UK is 8.5 per 100,000 people.[3]

In England, the number of patients with CML eligible to receive ponatinib according to its licensed indication is estimated to be 113. Figure 3-3 illustrates the derivation of this estimate. The overall annual incidence of newly diagnosed CML, assuming a stable incidence of CML since 2014, is 631.[4] Of these, 95% will be Ph+ (n=599).[147] Assuming all newly diagnosed patients are treated with 1L imatinib, treatment will fail in 36% (n=216) of people,[148] including 2% of patients (n=13) who will develop the T315I mutation;[149] the remaining patients who fail 1L imatinib (n=203) will discontinue for other reasons. Patients without the T315I mutation are assumed to be treated with 2L nilotinib; of these 3% (n=6) will progress to AP/BP[113] and, of the remaining 197 patients, 48% (n=95) will fail treatment.[111] These patients will be eligible for

ponatinib in third line. We therefore estimate that 113 people in England, including patients with the T315 mutation, will be eligible for ponatinib according to its licensed indication. See Section 4.13.2.3 for additional details on this estimation. Note that the number of patients are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers, due to rounding error.

Figure 3-3. Estimated number of patients with CML eligible to receive ponatinib in England



1L, first line; 2L, second line; 3L, third line; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

References: 1) Office of National Statistics 2014;[4] 2) Goldman 2009;[147] 3) Kalmanti et al. 2014;[148] 4) Hughes et al. 2015;[149] 5) Giles et al. 2013;[113] 6) Kantarjian et al. 2011.[111]

Note: The number of patients presented in this figure are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this figure, due to rounding error.

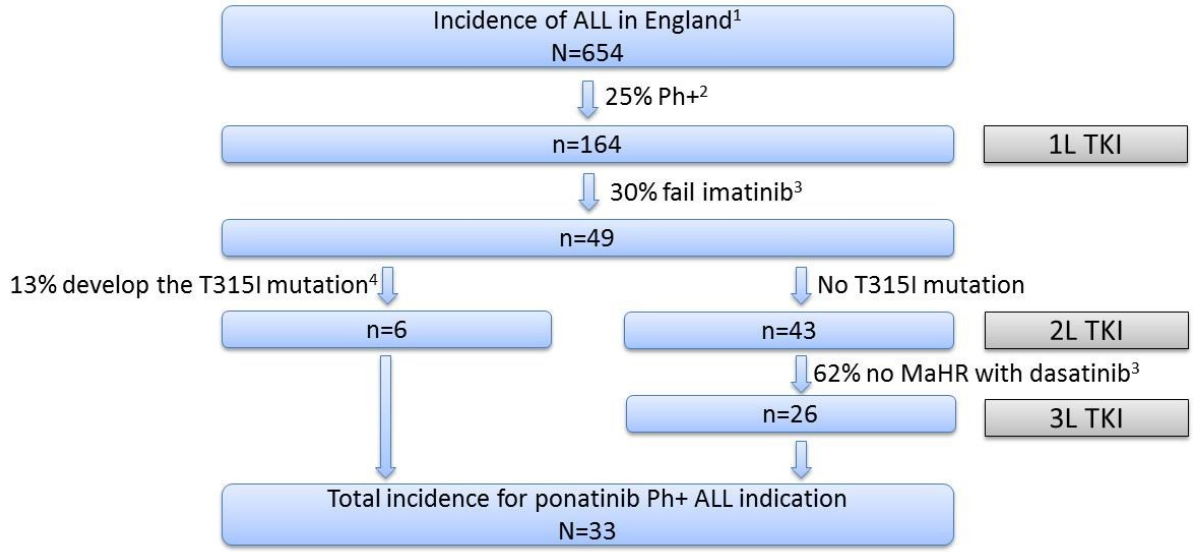
3.4.2.2 Ph+ ALL

As with CML, ALL is a rare disease representing 9% of all leukaemia cases in England.[14, 15] In 2014, 654 people in England were diagnosed with ALL. The European age-standardised incidence rate for ALL is approximately 1.2 per 100,000 people (2013).[14] However, most cases of ALL occur in children; ALL in adults represents only 20%–30% of all ALL cases.[11-13] Ph+ ALL is even rarer; it accounts for approximately 25% of ALL cases[150] and occurs mostly in adults.[151, 152] There is no specific information on the prevalence of Ph+ ALL in England, although the prevalence of ALL in the EU is reported to be 10 per 100,000 people.[153] However, as is the case for ALL incidence, the vast majority of prevalent cases are paediatric in nature. Although prognosis in children tends to be very good, survival in adult Ph+ ALL is poor. Therefore, we can assume that the incidence and prevalence of adult Ph+ ALL broadly coincide.

In England, we estimate that 33 patients with Ph+ ALL will be eligible to receive ponatinib according to its licensed indication. Figure 3-4 illustrates the derivation of this estimate. Assuming a stable incidence of ALL since 2014, the annual number of new ALL diagnoses would be 654.[4] Among patients with ALL, 25% (n=164) will have the Ph+ chromosome.[150] Assuming all patients with Ph+ ALL are treated with 1L imatinib, 30% (n=49) will fail 1L treatment;[16] of these, 13% (n=6) will develop the T315I mutation[154] and the remaining 87% (n=43) will not. Among patients without the T315I mutation and treated with 2L dasatinib (assuming it is recommended by NICE), 62% (n=26) will fail to achieve major haematologic response (MaHR) with treatment and will be eligible for ponatinib in the third line.[16] Therefore, we estimate that 33 people in England, including patients with the T315 mutation, will be eligible for ponatinib according to its licensed indication. See Section 4.13.2.3 for additional details on this estimation. Note that the

number of patients are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers, due to rounding error.

Figure 3-4. Ph+ ALL: Estimated number of patients with Ph+ ALL eligible to receive ponatinib in England



1L, first line; 2L, second line; 3L, third line; ALL, acute lymphoblastic leukaemia; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

References: 1) Office of National Statistics 2014;[4] 2) Fielding et al. 2007;[150] 3) Lilly et al. 2010;[16] 4) Pfeifer et al. 2012.[154]

Note: The number of patients presented in this figure are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this figure, due to rounding error.

3.5 NICE guidance and pathways

The NICE haematological cancers service guidance provides recommendations on haematological cancer care, including diagnosis and disease management, to achieve best outcomes for adult patients:

- Guidance on Cancer. Services Improving Outcomes in Haematological Cancers, published May 2016.[155]

3.5.1 CML

CML is part of the existing NICE pathway on blood and bone marrow cancers.[18] Relevant NICE guidance is based on technology appraisal guidance (TA401, TA251, TA241, and TA70)[90-92] and the guidance on cancer services identified above.[155]

- TA401: Bosutinib for previously treated chronic myeloid leukaemia, published 24 August 2016[93]
- TA251: Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia, published 25 April 2012.[90]
- TA241: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of TA70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, published 13 January 2012.[92]
- TA70: Guidance on the use of imatinib for chronic myeloid leukaemia, published 22 October 2003.[91]

TA251 and TA241 have partially replaced TA70.

3.5.2 First-line therapy for patients with CML

Standard-dose imatinib (400 mg/day) is recommended as an option for the 1L treatment of adults with Ph+ CP-CML.[90] Imatinib is also recommended for CML that initially presents in the AP or BP, and for CML that presents in the CP and then progresses to the AP/BP, if imatinib has not been used previously.[91]

Nilotinib is recommended as an option for the 1L treatment of adults with Ph+ CP-CML if nilotinib is made available through the PAS.[90]

Dasatinib has marketing authorisation throughout the EU for treatment of adult patients with newly diagnosed Ph+ CP-CML.[17] At the time of writing this submission, however, NICE does not recommend dasatinib for the 1L treatment of Ph+ CP-CML.[90]

3.5.3 Second-line therapy for patients with CML

Nilotinib is recommended for the treatment of Ph+ CP- and AP-CML in adults whose CML is resistant to treatment with standard-dose imatinib or who have imatinib intolerance and if nilotinib is made available through PAS.[92]

Bosutinib has marketing authorisation for treating patients with Ph+ CML who were previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.[7] NICE recommends bosutinib as an option, within its marketing authorisation, for Ph+ CP-, AP-, and BP-CML in adults when they have previously had one or more TKI; and imatinib, nilotinib, and dasatinib are not appropriate; and the company provides bosutinib with the discount agreed in the PAS.[93]

At the time of writing this submission, dasatinib is not recommended as a 2L treatment for adults with CP-, AP-, or BP-CML who have imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.[92] High-dose imatinib (600 mg or 800 mg in CP-CML or 800 mg in AP/BP-CML) is not recommended for the treatment of Ph+ CP-, AP-, or BP-CML that is resistant to standard-dose imatinib.[92]

3.5.4 Ph+ ALL

No NICE guidance is available on the treatment of patients with ALL and the disease is not part of the existing NICE pathway on blood and bone marrow cancers.[18]

3.6 Other clinical guidelines

3.6.1 European LeukemiaNet (ELN) recommendations for CML

In Europe, one of the most important and relevant guidelines for the treatment of CML is the ELN recommendations. The latest ELN treatment recommendations for CML were published in 2013 (reviewed in 2015)[72] with the ELN recommending 1L treatment with imatinib (400 mg QD), nilotinib (300 mg BID), or dasatinib (100 mg QD) for patients with CP-CML.[47] Recognising that it is difficult to recommend one 1L TKI over another, the ELN suggests that disease characteristics (high risk, chromosomal abnormalities in Ph+ cells) and patient comorbidities may offer insight on the most appropriate TKI therapy because these factors play a role in predicting expected efficacy and safety outcomes of a chosen therapy in a given circumstance.[47]

The ELN recommends that imatinib, nilotinib, and dasatinib can also be used in second or subsequent lines for the treatment of CP-CML, at the standard or at a higher dose (eg, 400 mg BID for imatinib, 400 mg BID for nilotinib, and 70 mg BID or 140 mg QD for dasatinib). However, for patients who received imatinib in the first-line, the ELN recommends that the drug be changed as opposed to increasing the imatinib dose.[47] The ELN recommendations state that the therapeutic choice in second and subsequent lines of treatment also depends on mutational status, on the safety profile of each TKI, and adverse reactions to previous TKI therapies.[47]

A review of the 2013 ELN recommendations state that a change in TKI therapy is mandatory in the case of treatment failure (resistance) or in the event that a patient has side effects

(intolerance) that would interfere with dosing, diminish HRQoL, or be potentially life-threatening.[72] Specifically, the review of the ELN recommendations state that, in the case of intolerance, 2L therapy can include any other available TKI, including imatinib after using a 1L 2G-TKI. In the case of 1L treatment failure, the review of the ELN recommendations state that imatinib no longer fits in the treatment scheme and 2L therapy follows one of three sequences:[72]

- Imatinib failure → any other available and approved TKI (dasatinib, nilotinib, bosutinib, ponatinib)
- Nilotinib failure → dasatinib, bosutinib, ponatinib
- Dasatinib failure → nilotinib, bosutinib, ponatinib

The ELN treatment recommendations for advanced CML (ie, AP- and BP-CML) are based on results of single-arm, retrospective, and prospective studies, and on panel members' experience. For newly diagnosed TKI-naïve AP/BP-CML patients, treatment should be started with imatinib (400 mg BID) or dasatinib (70 mg BID or 140 mg QD). Allo-SCT is recommended for all patients with BP-CML and for AP-CML nonresponders (ie, patients who have failed to achieve an optimal response). Chemotherapy may be required prior to allo-SCT to control the disease and induce a minimum level of remission. For patients who progress from CP to AB/BP and who have received one or more prior TKIs, the ELN recommends any TKI not previously used, or ponatinib in patients with the T315I mutation, followed by allo-SCT.[47] Although no firm evidence shows better outcomes for CML patients treated first with a 2G-TKI versus imatinib, patients with AP/BP-CML are thought to benefit more from therapy with 2G-TKIs.[72]

3.6.2 European Society for Medical Oncology (ESMO) for ALL

The ESMO clinical practice guidelines recommend combination chemotherapy and TKI (eg, imatinib 400–800 mg/day) for 1L treatment of patients with newly diagnosed Ph+ ALL.[28] For patients with relapsed ALL, there is no standard treatment protocol. The ESMO guidelines state that patients with Ph+ ALL who fail treatment with imatinib should be offered new-generation TKIs (eg, nilotinib, dasatinib, ponatinib). For patients who achieve complete remission and are suitable candidates for transplantation, allo-SCT is considered to be the best therapeutic option.[28]

3.6.3 National Comprehensive Cancer Network (NCCN) guidelines

3.6.3.1 CML

The NCCN guidelines are also an important source of information for guidance on CML disease management. According to the NCCN, imatinib, nilotinib, and dasatinib are recommended 1L therapy options for CP-CML. Factors that may influence choice of 1L therapy include risk score, age, ability to tolerate therapy, and the presence of comorbidities. First-line treatment recommendations for AP-CML include investigational therapies, imatinib, and 2G-TKIs. Allo-SCT is also a treatment option; however, its use depends upon response to prior TKI therapy. The guidelines recommend that omacetaxine be considered for patients who are R/I to two or more TKIs. Recommendations for 1L treatment of BP-CML include investigational therapies and, if feasible, allo-SCT preceded by induction chemotherapy plus a TKI or a TKI alone. Due to the complicated nature of the disease, it is strongly recommended that patients with advanced CML are managed in specialised centres.[1]

As a result of demonstrated efficacy with TKI therapy, allo-SCT is not recommended as 1L therapy for newly diagnosed CP-CML. The procedure is, however, recommended for patients who present with BP-CML at diagnosis, patients with the T315I mutation and other *BCR-ABL1* mutations that are resistant to all TKIs, and for patients intolerant to all TKIs. The NCCN recommends that all patients who fail to meet response milestones while on 1L TKI therapy be evaluated for allo-SCT suitability. In cases of disease progression to AP- or BP-CML while receiving TKI therapy, the NCCN recommends the use of an alternate TKI as a "bridge" to allo-SCT.[1]

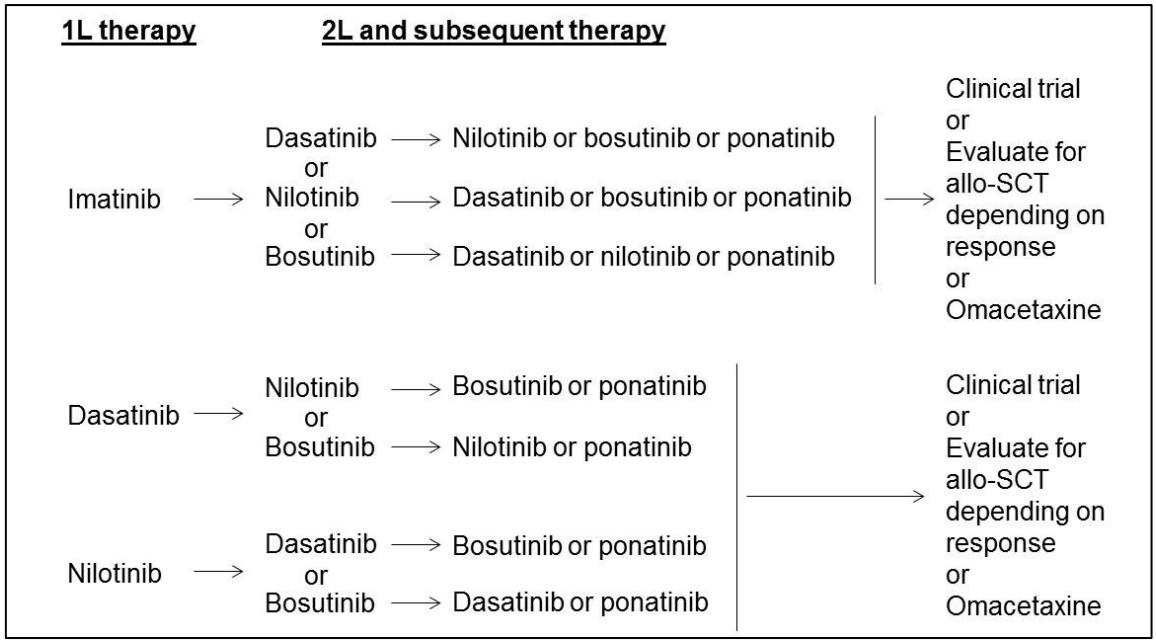
In addition to consideration in the first-line, the NCCN guidelines recommend nilotinib, dasatinib, and bosutinib as treatment options in the second and subsequent lines.[1] Although common in

clinical practice, sequential use of dasatinib and nilotinib is not supported by the clinical efficacy data reported in the approved labels. As noted earlier, neither nilotinib nor dasatinib received regulatory approval based on, or supported by, studies with sequential use of 2G-TKIs.[17, 51] This is different from ponatinib, the efficacy of which in sequential use was demonstrated in the clinical trials conducted prior to its approval.[9, 23]

Figure 3-5 details the recommended treatment algorithm for patients with CML who exhibit cytogenetic or haematologic resistance while receiving TKI therapy. In cases of disease progression, selection of subsequent TKI is based on previous therapy and/or the results of mutational testing.[1] Supportive care recommendations include the use of hydroxycarbamide for symptomatic thrombocytosis and leucocytosis.[1]

The NCCN Evidence Blocks™, a visual representation of important information related to specific recommendations, provide a useful means to compare potentially appropriate interventions.[156] Compared to bosutinib, dasatinib, and nilotinib, ponatinib is rated highest for "efficacy" and "consistency of data" in the 3L setting.[157]

Figure 3-5. NCCN guideline recommendations for patients with CML who exhibit cytogenetic or haematologic resistance to TKIs



Adapted from the NCCN Guidelines for CML, version 1 (2016).[1]

Allo-SCT, allogeneic stem cell transplantation.

3.6.3.2 Ph+ ALL

The first-line treatment approach for adult patients with Ph+ ALL is different from the approach used to treat paediatric ALL, with treatment modifications suggested for older patients and those with substantial comorbidities. In contrast, relapsed/refractory disease is managed in a consistent manner, regardless of age. According to the 2016 NCCN guidelines for treatment of Ph+ ALL in adults:[11]

- Treatment in a clinical trial is recommended whenever possible.
- For adult patients younger than 65 years of age or with no substantial comorbidities, induction therapy with chemotherapy plus a TKI is recommended. Allo-SCT should be considered if a complete response is achieved. After allo-SCT, treatment with a TKI should be considered. If allo-SCT is not possible, maintenance therapy plus a TKI should be instituted.

- For patients 65 years of age and older or with substantial comorbidities, a TKI plus either corticosteroids or chemotherapy is recommended as induction therapy. If a complete response is achieved, consolidation therapy should consist of either the TKI alone or in combination with either corticosteroids or chemotherapy, followed by maintenance therapy plus a TKI.
- In the event of relapsed/refractory disease, *ABL* mutational testing should be considered. As with CML, there is the potential for imatinib-resistant *BCR-ABL* mutations to arise, including the T315I mutation. Treatment options for relapsed/refractory disease include: investigational therapy, a different TKI with or without corticosteroids or chemotherapy, or allo-SCT.

The NCCN guidelines note that ponatinib has shown activity in patients with TKI-resistant Ph+ leukaemia, including those with Ph+ ALL and the T315I mutation.[11]

3.7 Issues relating to current clinical practice

CML

Per NICE recommendations, imatinib and nilotinib should be used first-line for patients with Ph+ CP-CML and nilotinib or imatinib are used second-line depending on which agent was previously used (eg, nilotinib for patients R/I to standard-dose imatinib and imatinib for patients currently receiving interferon alpha). Imatinib is also recommended for patients who initially present with Ph+ AP/BP-CML.[18] Although dasatinib is not recommended by NICE at the time of writing this submission it is available through the CDF,[88] and is thus accessible to CP- and AP-CML patients in England (dasatinib was previously available for the treatment of BP-CML through the CDF but it was delisted in March 2015).[89] Bosutinib has been recently recommended by NICE within its marketing authorisation, with conditions as noted above.[93] Prior to its recommendation, bosutinib was only available to patients in England through the CDF.[88, 89] The extent to which dasatinib and bosutinib are used in clinical practice is uncertain, although, as described below, a recent HCP survey has provided insight into current treatment use in England by line of therapy.[48] Regardless, no evidence-based recommendations exist for patients who have failed ≥2 TKIs—a patient population with recurrence caused by low compliance, side effects, or true TKI resistance.[72]

A survey of clinical experts was conducted in 2016 to gain a better understanding of current clinical practice for the treatment of CML in England (see Appendix 14: Cost and healthcare resource identification, measurement, and valuation).[48] Results of the survey showed that imatinib is used first line in 63% of patients with CP-CML; 1L nilotinib is used in over a third of newly diagnosed patients. In patients who are R/I to 1L imatinib, nilotinib is the 2L treatment of choice in 72% (failure due to resistance) and 68% (failure due to intolerance) of patients. Dasatinib is used in 20%–25% of patients who required 2L treatment.[48] In patients with CP-CML who fail 2L treatment due to resistance or intolerance, dasatinib is used third line in most cases (60%). Of note, there is a lack of clinical evidence to support dasatinib for sequential use in R/I patients treated with a prior 2G-TKI, and sequential use is not an approved indication for the drug.[17] According to the survey results, bosutinib is used in about 20%–25% of patients with CP-CML who fail a 2L TKI. At 3L failure, patients are most often treated with TKIs, allo-SCT, or hydroxycarbamide: a substantial proportion of patients (55%) receive bosutinib, approximately a fifth receive a transplantation, and 10% receive hydroxycarbamide.[48]

For CP-CML, there may be some uncertainty in the need for and timing of allo-SCT. Traditionally, allo-SCT has offered the best chance for long-term survival, yet since the introduction of TKIs, survival for patients with CML has improved substantially even in the absence of transplantation. The timing of allo-SCT is now typically third or fourth line after failure with prior TKIs, but this situation is becoming more complex with the use of 2G-TKIs in the 1L setting. That is, there is uncertainty as to whether physicians should consider allo-SCT in second line if patients are R/I to 1L nilotinib or dasatinib.[47] According to the 2013 ELN treatment recommendations, allo-SCT could be considered 2L after failure of 1L nilotinib or dasatinib. According to the results of the UK

HCP survey, however, allo-SCT is used after 3L treatment failure, and then in only 22% of patients.[48]

Ph+ ALL

NICE has made no formal recommendations for the treatment of adult patients with ALL and as such the disease is not part of the leukaemia clinical pathway of care.[18] EMA-approved TKIs available for patients with Ph+ ALL include imatinib and dasatinib. Imatinib has market authorisation for first-line treatment of Ph+ ALL in combination with chemotherapy and for treatment of relapsed or refractory Ph+ ALL as monotherapy[50], but it has not been appraised by NICE. Dasatinib was available through the CDF until November 2015 for treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy, including imatinib.[89] The extent to which these TKIs are used in current clinical practice for treatment of adult Ph+ ALL is unknown. According to European guidelines, combination chemotherapy plus imatinib is standard practice for newly diagnosed Ph+ ALL and patients who fail treatment with imatinib should be offered a new-generation TKI (eg, dasatinib).[28] These TKIs, however, are not available for patients with Ph+ ALL in England. Relapsed Ph+ ALL continues to present a major clinical challenge in particular, due to the limited availability of treatments.

3.8 Equality

No equality issues relate to ponatinib for treatment of adult patients with CML and Ph+ ALL. It is a therapy for patients who have very limited treatment options; ponatinib can address the unmet need for patients who develop resistance or intolerance to current TKI therapy. Ponatinib would provide an additional treatment option in the clinical pathway of care for patients with CML and would offer a new treatment option for Ph+ ALL. Although allo-SCT is an option for both patients with CML and Ph+ ALL, this intervention depends on donor availability, which is unequal across ethnic/minority groups.[10] In addition, it is the only TKI active against the T315I mutation. In the PACE study (Cortes et al. 2013), response rates were high among patients with CP-CML who did not have detectable *BCR-ABL* mutations, as well as among patients with mutations other than T315I.[9] Therefore, regardless of mutation status, all indicated patients with CML may benefit from ponatinib.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Systematic literature review (SLR) overview

Two comprehensive SLRs were conducted to identify randomised controlled trials (RCTs) and observational studies reporting the safety and efficacy of current treatments for adult patients being treated for CML (CP, AP, or BP) and Ph+ ALL in the second line or later. The SLRs were conducted in accordance with the requirements of NICE[158, 159] and the Centre for Reviews and Dissemination (CRD) guidance.[160]

4.1.2 Search strategies

As the goal of the clinical SLRs was to be as broad as possible, PICOS criteria (participants, interventions, comparators, outcomes, and study design) were designed to capture studies evaluating all lines of therapy for CML and Ph+ ALL beyond first line.

Searches for literature published between January 2000 and January/February 2016 were conducted in EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Health Technology Assessment (HTA) database, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). Abstracts from the following conferences were also searched from 2013 to February 2016:

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

Review articles were manually searched for relevant publications.

Bibliographic databases were originally searched using predefined search strategies adapted from those described in the Single Technology Appraisal (STA) for bosutinib.[161] A revision to the EMBASE and MEDLINE search strategies was subsequently made to improve the sensitivity of the clinical trial search filter to non-randomised prospective studies. The conference abstract search strategy was also revised to improve sensitivity. Updated searches were conducted in July 2016. Of note, the updated CML clinical search did not include dasatinib and nilotinib as comparators, as these were not included in the decision problem issued by NICE. See Appendix 2: Search strategies for relevant clinical studies for the original, revised, and updated search strategies used in the CML and Ph+ ALL SLRs.

4.1.3 Study selection

In a pilot screening phase, two researchers applied the inclusion/exclusion criteria to a sample of abstracts to ensure that the criteria were understood and that interpretation was consistent. Following this pilot phase, relevant studies were identified in two stages. Two researchers independently examined all titles and abstracts to determine potential relevancy. Full-text screening was conducted for articles that were not definitively categorised via title/abstract. Discrepancies were addressed through discussion.

Criteria describing the relevant population, interventions, comparators, outcomes, trial design, and language restrictions used to determine the relevance of each record are detailed in Table 4-1. Study selection criteria related to target population were developed based on the approved SmPC indication for ponatinib. Relevant interventions were identified via the approved SmPC indications and current guidelines.[1, 47, 72] The remaining criteria (comparators, outcomes, trial design, and language restrictions) were intentionally kept broad to permit a comprehensive view of the literature. When designing our SLR for CML (prior to receipt of the pre-invitation draft scope in June 2016), we did not include interferon alpha as a comparator because it is rarely used to treat CML in the UK.[18, 47, 82] In the bosutinib appraisal, it was also the conclusion of the committee that interferon alpha is not used in clinical practice.[93] Given the lack of clinical data on

the use of interferon alpha for treatment of relapsed patients (post-TKI—in particular those treated with ≥2 prior TKIs—and post-other treatments) we excluded interferon alpha as a comparator in the updated SLR.

Table 4-1. Eligibility criteria used in the clinical search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with CML or Ph+ ALL R/I to prior treatments • Patients must have received at least one prior treatment for their disease	• Animal studies, in vitro studies, and studies in healthy populations
Interventions	• CML: Ponatinib, dasatinib*, nilotinib*, bosutinib, hydroxycarbamide, stem cell transplantation, and BSC • Ph+ ALL: Ponatinib, stem cell transplantation, and BSC	• Imatinib, as it is primarily used in the first line and does not represent a direct comparator for ponatinib
Comparators	• All potential comparators (eg, placebo, BSC, active intervention), as well as studies with no comparator (ie, single-arm trials)	—
Outcomes	• Response rates, OS, PFS, RFS, time on treatment, maintenance of response, TFS, AEs, intervention doses, RDI	• Mixed-population studies (ie, those including 1L and later patients) that do not present results in 2L or later patients separately from those in 1L patients
Trial design	• RCTs (including crossover studies), non-randomised single-arm trials, and observational studies (retrospective and prospective) • Reviews, SLRs, and meta-analyses to identify relevant articles for manual reference searching	• Letters, comments, editorials, case reports, and pharmacokinetic studies, models (economic or mathematical), surveys, adherence studies, prognostic studies, epidemiological studies, studies of treatment prescribing patterns, and dose-escalation studies • Studies with fewer than 10 patients overall (across all treatment arms) and abstracts without sufficient information
Language restrictions	• No limitation by language in searches	• Studies in languages other than English excluded during screening

1L, first line; 2L, second line; AE, adverse event; BSC, best supportive care; CML, chronic myeloid leukaemia; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RDI, relative dose intensity; RFS, relapse-free survival; R/I, resistant or intolerant; SLR, systematic literature review; TFS, transformation-free survival.

*Original and revised searches only; in line with the decision problem, the updated CML SLR conducted in July 2016 did not include trials with dasatinib and/or nilotinib.

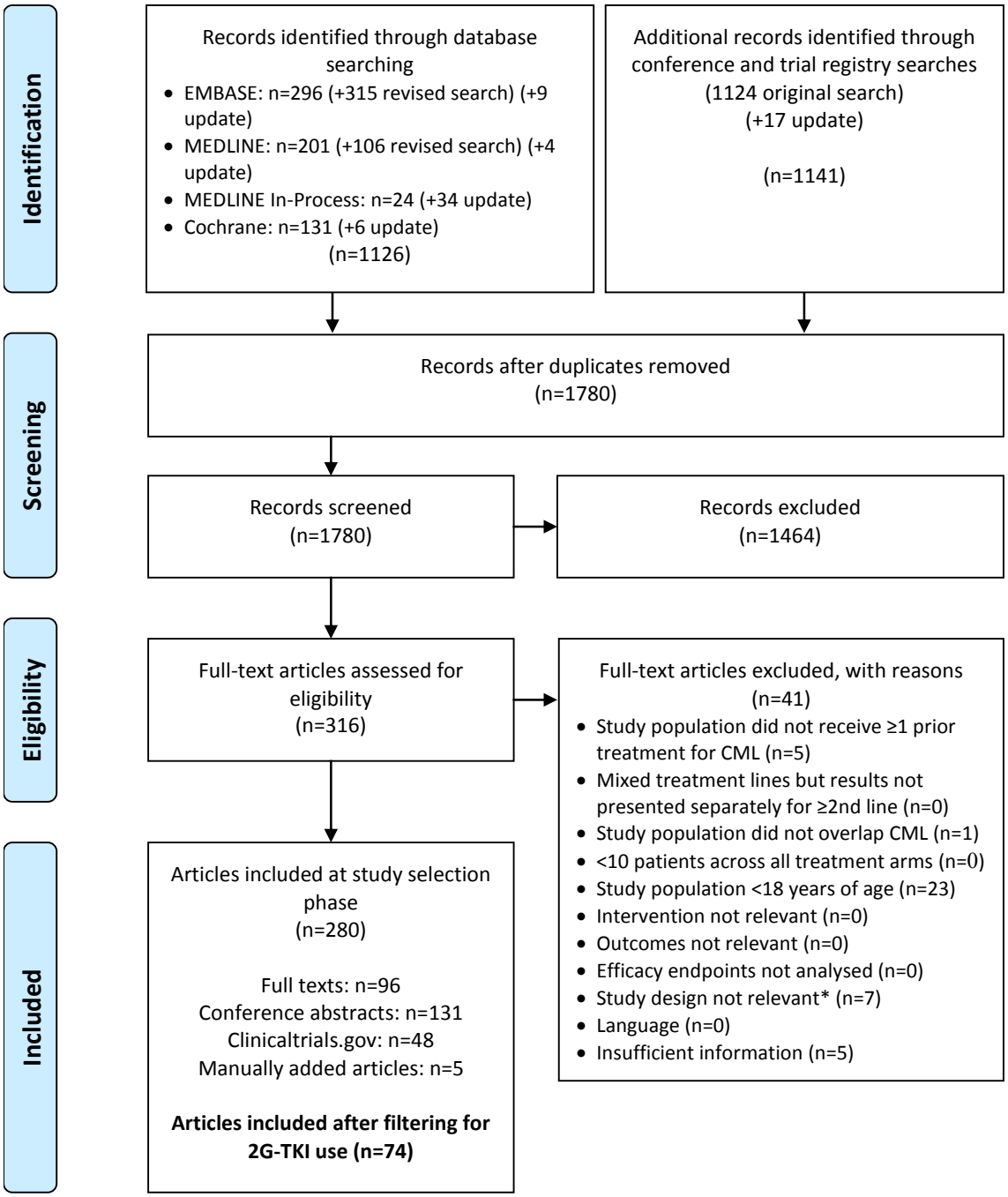
4.1.4 Flow diagram for clinical evidence

The PRISMA flow diagrams for clinical evidence in CML (Figure 4-1) and Ph+ ALL (Figure 4-2) show the SLR process including the total number of records identified in the searches and the reasons for study exclusion.

The goal of the clinical SLRs was to be as broad as possible. However, for the purposes of modelling the use of ponatinib according to its approved SmPC indication in adult patients with CP-, AP-, or BP-CML who are resistant to dasatinib or nilotinib or who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate,[22] the SLR results were filtered to include only the studies conducted in patients who had received a

2G-TKI prior to the investigational treatment. After filtering, a total of 74 publications provided results pertaining to the post–2G-TKI CML patient population (Figure 4-1).

Figure 4-1. PRISMA flow diagram for clinical evidence in CML



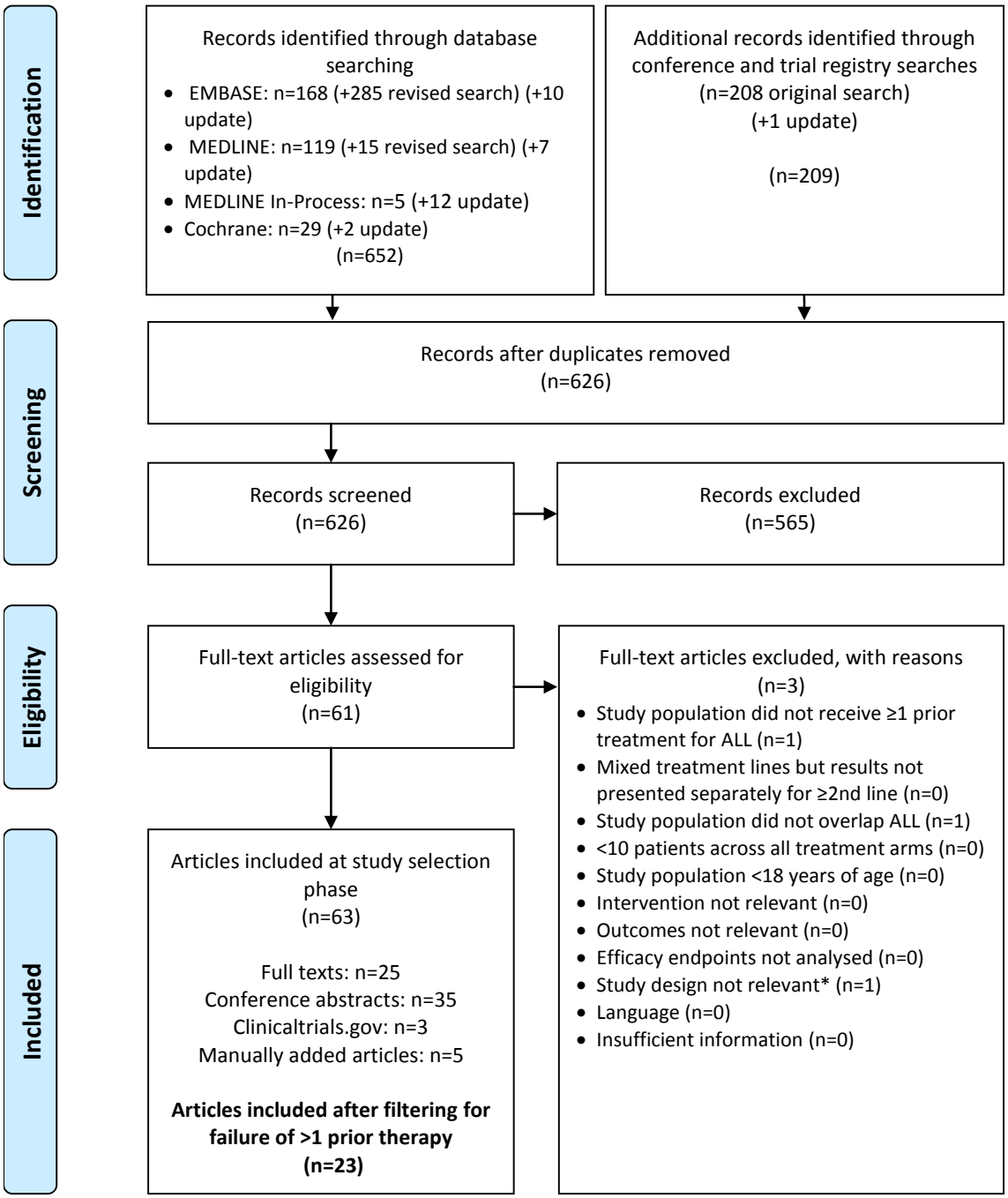
2G-TKI, second- generation TKI.

*Reviews, meta-analyses, SLRs, HRQoL studies, epidemiological studies. In other words, not a randomised controlled trial, single-arm trial, or observational study (either retrospective or prospective).

Similar to the CML SLR, the search of the literature for Ph+ ALL was broad to capture as many relevant studies as possible. Despite the broadness of the search, no studies were identified in patients reflecting the population for which ponatinib is indicated and the NICE scope. Due to the nature of the broad search, however, studies in which patients received allo-SCT while in first complete remission (CR1) were included at the study selection phase. Studies meeting the inclusion criteria were thus further filtered to select those in patients who had failed any prior

therapy to best reflect the patient population for which ponatinib is indicated, considering the absence of literature published after 2G-TKI failure in patients with ALL. After filtering, a total of 23 publications provided results pertaining to patients with Ph+ ALL who had failed at least one prior therapy (Figure 4-2).

Figure 4-2. PRISMA flow diagram for clinical evidence in Ph+ ALL



*Reviews, meta-analyses, SLRs, HRQoL studies, epidemiological studies. In other words, not a randomised controlled trial, single-arm trial, or observational study (either retrospective or prospective).

The complete lists of included studies (before filtering) for the CML and Ph+ ALL SLRs are presented in Appendix 16: Complete list of included studies identified in the SLR.

4.1.5 Primary studies and associated publications

CML Clinical SLR: Of the 74 publications pertaining to the post–2G-TKI CML patient population, 33 were considered primary studies and 41 were associated publications (eg, abstracts including long-term follow-up data, patient subgroup analyses, etc).

Ph+ ALL Clinical SLR: Overall, 23 publications were in patients with Ph+ ALL who had failed at least one prior therapy; of these, 17 were considered primary studies and 6 were associated publications.

4.1.6 Excluded studies

Excluded studies for the CML and ALL SLRs are listed in Appendix 17: Complete list of studies excluded in the SLR.

4.2 List of relevant randomised controlled trials

No RCTs comparing ponatinib with other relevant therapies for the treatment of CML in the post–2G-TKI setting or for the treatment of Ph+ ALL in patients R/I to prior therapy were identified in the SLR.

4.3 Summary of methodology of the relevant randomised controlled trials

Not applicable; see Section 4.2.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Not applicable; see Section 4.2.

4.5 Participant flow in the relevant randomised controlled trials

Not applicable; see Section 4.2.

4.6 Quality assessment of the relevant randomised controlled trials

Not applicable; see Section 4.2.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Not applicable; see Section 4.2.

4.8 Subgroup analysis

Not applicable. No subgroup analyses were carried out as no RCTs comparing ponatinib with other relevant therapies for the treatment of CML in the post–2G-TKI setting or of Ph+ ALL in patients R/I to prior therapy were identified in the SLR.

4.9 Meta-analysis

Not applicable; see Section 4.2. No RCTs comparing ponatinib with other relevant therapies for the treatment of CML in the post–2G-TKI setting or of Ph+ ALL in patients R/I to prior therapy were identified in the SLR. The traditional approach to mixed treatment comparison or network meta-analysis is not feasible given that all relevant studies identified in the SLR are single-arm. In this case, however, a MAIC can be an appropriate technique to use, as described by Signorovitch et al. 2010 and 2012.[162, 163] Therefore in the absence of head-to-head trials, non-RCT (single-arm) studies identified in the CML SLR, described in Section 4.11, were used to carry out a MAIC for the de novo CP-CML economic analysis. The objective of the MAIC was to adjust the main effectiveness outcomes of ponatinib (as included in the cost-effectiveness model) with the baseline characteristics of relevant comparator studies according to the NICE scope (specifically, bosutinib). Details of the non-RCT trials included in the MAIC and the methods of this comparison are covered in Section 4.10.

4.10 Indirect and mixed treatment comparisons

Search strategy

4.10.1 Details of search strategy

The MAIC was informed by the clinical SLR. Details of the search strategies are provided in Section 4.1.2.

Study selection

4.10.2 Details of treatments compared

As noted above, the MAIC was informed by the clinical SLR. The study selection process is detailed in Section 4.1.3.

4.10.3 Trial selection process criteria

The criteria used in the trial selection process are detailed in Section 4.1.3.

4.10.4 Summary of trials

Table 4-2. Summary of the trials used to carry out the MAIC analysis for ponatinib in CML

Study	Bosutinib	Ponatinib
Khoury et al. 2011 (Phase 1/2 trial)[8]	Yes	—
Cortes et al. 2013 (PACE)[9]	—	Yes

4.10.5 Rationale for exclusion

Other therapies for the treatment of CML in the post–2G-TKI setting include the 2G-TKIs dasatinib and nilotinib. In accordance with the NICE scope, in which the only TKI comparator is bosutinib, neither dasatinib nor nilotinib is included in the MAIC.[164]

In addition to TKI therapy, treatment options in clinical practice for adults with CML include BSC (including hydroxycarbamide) and allo-SCT (depending on the availability of a suitable donor and the eligibility of the patient).[47] No studies for BSC were identified in the SLR. Allo-SCT studies were identified in the setting of post–2G-TKI, but were not included in the MAIC. The rationale for this was that although allo-SCT is considered a relevant comparator in the sense that these interventions provide complete context for health economic evaluation, the MAIC was done for response categories (CCyR, partial cytogenetic response [PCyR], [CHR, non-responder [NR]), which are not directly applicable in the context of transplantation. The simulation in the economic model for the SCT arm is such that an indirect comparison was not appropriate.

Methods and outcomes of included studies

4.10.6 Rationale for chosen outcome measure

The main effectiveness outcome measures for the MAIC are best response rate (cytogenetic and haematologic) and duration of response. Outcome measures of CML treatment efficacy as such OS, event-free survival (EFS), and transformation-free survival (TFS) require long follow-up times, and this may delay the approval and availability of new treatments for patients with CML.[165] CP-CML has a relatively long disease course, and with high response rates achieved with available treatments, survival-based outcome measures are not practical. To address the shortcoming of using long-term outcomes, shorter-term measures of treatment efficacy, such as response rates, are widely recognised as surrogate endpoints of survival.[8, 9, 165, 166]

Cytogenetic response as a surrogate outcome for OS has been used in prior NICE technology appraisals (TA241 and TA251)[90, 92] and HTAs by Rogers et al. 2012,[82] Pavey et al. 2012,[167] and

Loveman et al. 2012.[168] Supporting cytogenetic response as a surrogate for OS in these evaluations is a recent systematic review and meta-analysis of studies evaluating 1L treatment with imatinib, dasatinib, or nilotinib that showed an association between CCyR and MMR and long-term OS.[169]

Surrogate endpoints can provide early indications of treatment success, and can also identify patients who would benefit from switching therapies.[165] In line with this, the 2013 ELN recommendations for the management of CML recommend monitoring for CHR and CCyR/PCyR response to evaluate treatment efficacy, regardless of which TKI is used.[47]

4.10.7 Trial populations

The trial population in PACE (Cortes et al. 2013)[9] included adults with CP-, AP-, or BP-CML or Ph+ ALL who were R/I to dasatinib or nilotinib or who had developed the T315I mutation after any TKI therapy. For ponatinib, individual patient data (IPD) from patients in the PACE trial who had received 2 prior TKIs (n=97) were used to inform the MAIC.[170]

The bosutinib phase 1/2 trial was a two-part study: Part 1 was a dose-escalation study in patients with CP-CML (and one patient with AP-CML) who had developed resistance to prior treatment with imatinib (ie, 2L bosutinib).[8] Part 2 of the study evaluated the efficacy and safety of bosutinib across different lines of therapy, including ≥3L bosutinib in patients previously treated with imatinib and dasatinib and/or nilotinib. Khoury et al. 2012 report the results for adults with Ph+ CP-CML who had received prior treatment with imatinib followed by dasatinib and/or nilotinib (ie, results for the 3L cohort).[8] The total population (N=118) in the phase 1/2 bosutinib trial included patients with CP-CML who had prior treatment with imatinib followed by dasatinib or nilotinib (n=114) and patients for whom prior imatinib therapy failed, and who were either intolerant to nilotinib (n=1) or R/I to prior nilotinib and dasatinib therapy (n=3; 4L).[8]

The MAIC was performed using baseline characteristics and effectiveness data for the CP-CML patient subgroups in each trial. The CP-CML trial populations are the same as those specified in the NICE scope,[164] namely, adults whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

No MAIC was performed to adjust for baseline characteristics in AP/BP-CML when evaluating effectiveness outcomes in this subset of patients with advanced disease due to a lack of comprehensive data in the 3L setting. Instead, to inform the AP/BP-CML economic model, response rates were taken from the AP/BP-CML cohort of the PACE study; duration of response is irrelevant in the AP/BP-CML model as patients who respond to treatment transition to allo-SCT in the first cycle. No MAIC was performed to adjust for baseline characteristics in Ph+ ALL due to a lack of applicable data for comparators.

4.10.8 Differences in patient populations

The summary of baseline characteristics of the trial populations used in the MAIC are outlined in Section 4.10.15.

4.10.9 Additional study details

Please see Appendix 6: Methods, results, outcomes, and quality assessment of the relevant trials in the indirect or mixed treatment comparison, for tables of the methods, results and outcomes, and participants' baseline characteristics.

Risk of bias

4.10.10 Quality assessment

Please see Appendix 8: Quality assessment of the relevant non-randomised and non-controlled evidence.

4.10.11 Bias and adjustments

Baseline characteristics considered to have prognostic value may be sources of bias in individual trials. For example, age,[171] sex,[172], and race[173] have been reported to affect outcomes in CML. To address potential sources of bias between studies, adjustments to match baseline characteristics were carried out as described in Section 4.10.12. Please refer to the next section for complete details on the baseline values for bosutinib and PACE trials, and the adjusted values for the 3L PACE population.

Methods of analysis and presentation of results

4.10.12 Methodology

A MAIC was conducted to adjust for differences in baseline characteristics between the PACE study (primary publication by Cortes et al. 2013)[9] and the phase 1/2 bosutinib study (Khoury et al. 2012)[8]. The methodology is described in detail in Signorovitch et al. 2012.[162] Briefly, a MAIC involves using IPD from one or more trials of one intervention to match baseline patient characteristics with those from trials with another intervention. Using this approach, individual patients treated with ponatinib in the PACE study were assigned weights such that: (1) the weighted mean baseline characteristics in PACE exactly matched those reported for patients treated with bosutinib and, (2) each patient's weight was equal to his or her estimated odds of being treated with bosutinib versus ponatinib. Weights meeting these conditions were obtained from a logistic regression model for the propensity of being treated with bosutinib vs ponatinib, with individual patient values for all matched-on baseline characteristics included as predictors.

The weights obtained with this process were then used to produce matching-adjusted estimates of the main effectiveness outcomes of ponatinib as included in the cost-effectiveness model; ie, best response rates and duration of response.

An alternative approach to MAIC is simulated treatment comparison (STC).[174] Although STC is conceptually very similar to MAIC, STC may be less well suited for outcomes that typically require non-linear models, such as time-to-event (eg, PFS, OS) or binary outcomes (eg, response rates).

4.10.12.1 Trial source data

The IPD for ponatinib used to inform the MAIC were those obtained from CP-CML patients in the PACE trial who had received 2 prior TKIs (n=97).[170] The MAIC employed the most recent IPD from PACE, based on a data cut-off of 3 August 2015.

Response rates for bosutinib were sourced from the phase 1/2, open-label, two-part study by Khoury et al. 2012.[8] The second part of this study evaluated the efficacy and safety of bosutinib (500 mg/day) across multiple CP-CML patient subpopulations. The response rates applied in the model were those for the total population (N = 118), comprising patients who had failed imatinib as well as either dasatinib or nilotinib (n = 114), and patients who had failed imatinib, dasatinib, and nilotinib (n = 4). Baseline characteristics available for the indirect comparison of bosutinib vs ponatinib were T315I mutation status, sex, median age, race, duration of CML, and Eastern Cooperative Oncology Group (ECOG) performance status.

Reported medians were interpreted, for matching purposes, as a binary characteristic. For instance the median age of 53.0 years was transformed into a binary variable age >53.0 years, with a frequency of 50%. Ideally, matching should be based on clinically relevant risk factors that impact on the relative treatment effects. However, there is no well-established procedure regarding how the risk factors to be matched should be identified; therefore, all available variables were used in the analysis.

4.10.13 Programming language

Please see Appendix 7: Programming language used in the MAIC analysis.

4.10.14 Examples of how to present the results of the analysis

Not applicable.

4.10.15 Results

Table 4-3 presents baseline characteristics of the ponatinib cohort, before and after the matching with bosutinib. The effective sample size (computed as the square of the summed weights divided by the sum of the squared weights) in the PACE trial decreased from 97 to 69 as a consequence of the matching process. Table 4-4 shows the best response rates before and after matching with bosutinib characteristics.

After matching, the best response rate with ponatinib for CCyR is reduced by 3.61% (64.95% unmatched vs 61.34% after matching), while PCyR is increased by 2.27% (6.19% unmatched vs 8.46% after matching) (Table 4-4). After matching, MCyR (PCyR + CCyR) is marginally reduced, from 71.13% in the base-case to 69.80%.

Table 4-3. Baseline patient characteristics for bosutinib and ponatinib cohorts included in the MAIC and the matching-adjusted ponatinib cohort

Baseline parameter	Bosutinib Khoury et al. 2011 (Phase 1/2 trial)[8]	Ponatinib Cortes et al. 2013 (IPD PACE)[170]	Ponatinib Matching-adjusted
Number of patients, n	118	97	69*
Median age, % >56.0 years	50.0	53.6	50.0
Sex, % male	44.9	51.5	44.9
T315I mutation at study entry, %	5.9	30.9	5.9
Race, % white	72.0	79.4	72.0
Median duration of CML, % >6.7 years	50.0	42.3	50.0
ECOG PS, % with 1	26.5	29.9	26.5

CML, chronic myeloid leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IPD, individual patient data.

*Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.

Table 4-4. Best response rates before and after the matching with bosutinib characteristics

Best response	Bosutinib Khoury et al. 2011 (Phase 1/2 trial)[8]	Ponatinib Cortes et al. 2013 (IPD PACE)[170]	Ponatinib Matching-adjusted
Number of patients, n	118	97	69*
CCyR	24.07%	64.95%	61.34%
PCyR	8.33%	6.19%	8.46%
CHR	37.93%	17.53%	18.19%
No response	29.66%	11.34%	12.01%

CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IPD, individual patient data; PCyR, partial cytogenetic response.

*Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.

Figure 4-3 shows the Kaplan-Meier (KM) survival estimates of the matching-adjusted duration of response for ponatinib. After matching, duration of CCyR and PCyR estimates were slightly lower than duration of response in the unmatched base-case.

Figure 4-3. Kaplan-Meier survival estimates of the duration of response for ponatinib before and after the matching with bosutinib characteristics

4.10.16 Statistical assessment of heterogeneity

Not applicable. The MAIC addresses issues of heterogeneity between trials by incorporating IPD that reduces observed cross-trial differences.[162]

4.10.17 Justification of random or fixed effects model

Not applicable.

4.10.18 Sensitivity analyses

Not applicable. There was no uncertainty about the relevance of the two studies included in the MAIC.

4.10.19 Discussion of results

To inform the health economic analysis, we have performed a MAIC to adjust the main effectiveness outcomes of ponatinib—best response rates and duration of response—with the baseline characteristics of bosutinib. Using IPD from the PACE trial, a reliable comparison between ponatinib and bosutinib was possible, limiting biases possibly influencing outcomes across these trials. Notably, we adjusted for all usable baseline characteristics available in the Khoury et al. 2012 publication, including T315I mutation status, sex, median age, race, duration of CML, and ECOG performance status. Some of these baseline characteristics are considered to have prognostic value (ie, age,[171] sex,[172] and race[173]), while the predictive importance of other characteristics is undefined in the literature. Incorporating all available baseline characteristics helps to minimise the risk of bias between groups.

After adjusting for differences in patient baseline characteristics between the phase 1/2 bosutinib trial (Khoury et al. 2012) and the PACE trial (Cortes et al. 2012), the best response rate with ponatinib for CCyR was reduced by 3.61% and PCyR increased by 2.27%. Overall, MCyR with ponatinib was marginally reduced, from 71.13% in the base-case to 69.80% after matching. After matching, duration of CCyR and PCyR estimates were slightly lower than response rates in the unmatched base-case. Therefore, the adoption of the MAIC analysis (rather than a naïve comparison) is conservative with respect to the cost-effectiveness of ponatinib.

Cross-trial differences in baseline characteristics between bosutinib and ponatinib have been addressed in our MAIC to provide an unbiased indirect comparison of main effectiveness outcomes between ponatinib and bosutinib. Matching-adjusted ponatinib response rates for CCyR, PCyR, CHR, and no response, as well as matching-adjusted duration of response with ponatinib, are used to inform the cost-effectiveness model for CP-CML.

Although the MAIC incorporated all the baseline variables reported in the bosutinib study as covariates in the propensity score regression, there remains a potential bias due to unobserved confounders. The resulting uncertainty in the primary efficacy index in the model is addressed in a specific scenario analysis, which tests the effects of an arbitrary large range (±25%) of cytogenetic response rates on ICER results.

4.11 Non-randomised and non-controlled evidence

4.11.1 List of relevant non-randomised and non-controlled evidence

In the CML clinical SLR, 33 primary studies remained after filtering the study selection results by prior 2G-TKI use (seven single-arm non-RCTs, 23 observational studies, and three publications considered "Other", all of which were indirect comparisons of ponatinib and a comparator or comparators). All of the non-RCTs were single-arm, open-label trials, except for one which did not report blinding (Giles et al. 2010[95]). Of the 23 observational studies, 17 were retrospective in design and six were prospective. Ten primary studies were focused on ponatinib, three on bosutinib, one on dasatinib, three on nilotinib, one on dasatinib and nilotinib (head-to-head), and five on allo-SCT. Ten studies evaluated multiple TKIs without reporting results separately. Of the 41 publications associated with the 33 primary CML studies, six were considered potentially relevant for further analysis based on the NICE scope. No studies evaluating the efficacy/effectiveness of BSC in CML were identified.

In the Ph+ ALL clinical SLR, 17 primary studies remained after filtering of the study selection results by patients who had failed at least one prior therapy (two single-arm non-RCTs, 14 observational studies, and one indirect comparison of ponatinib and allo-SCT). All of the non-RCTs were single-arm, open-label trials. Of the 14 observational studies, 11 were retrospective in design and three were prospective. Four primary studies were focused on ponatinib, ten on allo-SCT, and three on outcomes after relapse. Of the five publications associated with the 17 primary Ph+ ALL studies, one was considered potentially relevant for further analysis (Cortes et al. 2015)[175] as it reports long-term follow-up data for Ph+ ALL patients in the PACE trial. No studies evaluating the treatments for patients with Ph+ ALL who had failed dasatinib were identified. No studies evaluating the efficacy of BSC in Ph+ ALL were identified.

Table 4-5 (CML) and Table 4-6 (Ph+ ALL) provide details of all non-randomised/non-controlled evidence identified in the SLR as well as the study inclusion/exclusion status for the purposes of populating the cost-effectiveness models included in this submission.

Table 4-5. List of non-randomised and non-controlled evidence identified as potentially relevant in the CML clinical SLR

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
NCT00660920	**Cortes et al. 2012**[23] **Talpaz et al. 2015**[176]	To determine the maximum tolerated dose or recommended dose of oral ponatinib administered once daily	CP-, AP-, BP-CML CP-CML	Ponatinib	None	Included: Pivotal phase 1 trial for ponatinib Included: Minimum 4-year follow-up of pivotal phase 1 trial for ponatinib
PACE/ NCT01207440	**Cortes et al. 2013**[9] **Hochhaus et al. 2015**[24]	To determine the efficacy of ponatinib in patients with CML or Ph+ ALL who are R/I to either dasatinib or nilotinib, or who have the T315I mutation	CP-, AP-, BP-CML and Ph+ ALL CP-CML	Ponatinib	None	Included: Pivotal phase 2 trial for ponatinib Included: 4-year follow-up of pivotal phase 2 trial for ponatinib
NCT01667133	**Kyo et al. 2014**[177]	To evaluate the safety and efficacy of ponatinib in Japanese patients with CML after failure of dasatinib or nilotinib or with Ph+ ALL after failure of prior TKIs due to resistance or intolerance	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	None	Excluded: Interim analysis of ongoing phase 1/2 study, published in abstract form; results not reported by line of therapy; incomplete reporting of response categories
NCT01592136	**Jeyakumar et al. 2013**[178]	To evaluate the efficacy and safety of ponatinib in patients with CML R/I to imatinib, dasatinib, and nilotinib (CP, AP) or R/I to imatinib and dasatinib (BP, Ph+ ALL)	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	None	Excluded: Observational study published in abstract form; separate response-rate results for BP-CML and Ph+ ALL not reported; less complete reporting of response categories compared with clinical trial data for ponatinib available from PACE
—	**Milojkovic et al. 2014**[179]	To examine efficacy of ponatinib in patients failing multiple TKIs	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	None	Excluded: Observational study published in abstract form; results reported only for CP-CML; results not stratified by line of therapy; less complete reporting of response categories compared with clinical trial data for ponatinib available from PACE

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
Pearl Observation Study	**Nicolini et al. 2015**[180]	To evaluate safety and efficacy of ponatinib in patients with CML (any phase) R/I to prior TKIs, in university and non-university hospitals, benefiting from the national ponatinib compassionate use program	CP-, AP-, BP-CML	Ponatinib	None	Excluded: Observational study published in abstract form; results not stratified by disease phase or line of therapy; less complete reporting of response categories compared with clinical trial data for ponatinib available from PACE
—	**Abulafia et al. 2015**[181]	To characterise patients with CML who received ponatinib and to assess the effectiveness and safety profile of ponatinib outside of clinical trials	CP-, AP-, BP-CML	Ponatinib	None	Excluded: Observational study published in abstract form; results not stratified by line of therapy; less complete reporting of response categories compared with clinical trial data for ponatinib available from PACE
PACE and bosutinib phase 1/2/ NCT01207440 and NCT00261846	**Levy et al. 2014**[182]	To examine efficacy outcomes previously validated as predictors of long-term survival, as well as treatment duration and reason for study drug discontinuation, as surrogates for overall benefit–risk in CP-CML patients treated with 3L ponatinib vs bosutinib	CP-CML	Ponatinib	Bosutinib	Excluded: Indirect analysis using ponatinib data from the PACE study
—	**Lipton et al. 2015**[6]	To compare the efficacy of ponatinib and 2G-TKIs (bosutinib, dasatinib, and nilotinib) in patients with CP-CML R/I to ≥1 prior 2G-TKI	CP-CML	Ponatinib	Dasatinib, nilotinib, bosutinib	Excluded: Indirect analysis of ponatinib versus other TKIs using published data
PACE and EBMT/ NCT01207440	**Nicolini et al. 2015**[183]	To compare OS among CML and Ph+ ALL patients with the BCR-ABL1 T315I mutation treated with ponatinib (in PACE) versus allo-SCT (in the EBMT registry)	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	Allo-SCT	Excluded: Indirect analysis of ponatinib versus allo-SCT; focused on patients with the T315I mutation

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
NCT00261846	**Khoury et al. 2012**[8]	To assess the efficacy and safety of bosutinib after treatment with multiple TKIs (imatinib and dasatinib and/or nilotinib) in patients with Ph+ CP-CML	CP-CML	Bosutinib	None	Included: Pivotal phase 1/2 trial for bosutinib providing results in the CP-CML population
	Kantarjian et al. 2014[184]	To characterise toxicities associated with bosutinib and describe toxicity management in Ph+ leukaemia patients (2L CP, 3L-4L CP [CP3L], and ADV leukaemia [AP/BP, ALL])	CP-CML (data for advanced CML was combined with ALL data and not extracted)			Included: Reports Grade 3/4 TEAEs occurring in ≥10% of patients treated with bosutinib
	Gambacorti-Passerini et al. 2015[185]	To present the durability of response and long-term (≥4 years) safety of bosutinib in the fully enrolled advanced leukaemia cohort of the phase 1/2 study	AP-, BP-CML			Included: Reports results for patients with AP- and BP-CML in the pivotal phase 1/2 trial for bosutinib
	Gambacorti-Passerini et al. 2014[186]	To evaluate the long-term efficacy and safety of bosutinib as 3L therapy in CP-CML patients after prior TKI failure (follow-up to Khoury et al. 2012)	CP-CML			Included: 48-month follow-up of patients with CP-CML in the pivotal phase 1/2 trial for bosutinib
NCT00811070	**Nakaseko et al. 2015**[187]	To evaluate the safety and pharmacokinetics (part 1) and efficacy and safety (part 2) of bosutinib in Japanese Ph+ CP-CML or AP-/BP-CML patients R/I to previous imatinib (2L) or imatinib plus dasatinib/nilotinib (3L)	CP-, AP-, BP-CML	Bosutinib	None	Excluded: phase 1/2 study with small sample size of patients in 3L (N=11); results not reported by disease phase for 3L subgroup

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
Spanish Compassionate Use program	**Garcia-Gutierrez et al. 2015**[188] **Garcia-Gutierrez et al. 2015**[189]	To present safety and efficacy data for CP-CML patients treated with bosutinib in 4L	CP-CML	Bosutinib	None	Excluded: Observational study including only patients with CP-CML treated with bosutinib in 4L; clinical trial data for bosutinib in 3L available from pivotal phase 1/2 trial Excluded: Abstract of the full publication described above
—	**Quintas-Cardama et al. 2007**[98]	To report results of treating patients with dasatinib after sequential failure with both imatinib and nilotinib	CP-, AP-, BP-CML	Dasatinib	None	Excluded: Dasatinib not a comparator per NICE scope
—	**Giles et al. 2010**[95]	To study the efficacy of nilotinib in patients with CML following failure of imatinib and dasatinib	CP- and AP-CML	Nilotinib	None	Excluded: Nilotinib not a comparator per NICE scope
ENACT/ NCT00302016	**Nicolini et al. 2009**[100]	To evaluate the safety and efficacy of nilotinib in patients with CP-, AP-, or BP-CML who were either resistant to or intolerant of both imatinib and dasatinib	CP-, AP-, BP-CML	Nilotinib	None	Excluded: Nilotinib not a comparator per NICE scope
ENACT and CAMN107AIL01/ NCT00302016 and NCT00264160	**Koren-Michowitz et al. 2010**[190]	To report data from a combined cohort of 2 expanded access clinical trials of therapy with nilotinib in imatinib R/I CML patients in all clinical disease phases, ENACT (Expanding Nilotinib Access in Clinical Trials) and CAMN107AIL01	CP-, AP-, BP-CML	Nilotinib	None	Excluded: Nilotinib not a comparator per NICE scope
—	**Garg et al. 2009**[94]	To report response rates and long-term results of using a 2G-TKI after failure of imatinib and another 2G-TKI (3L)	CP-, AP-, BP-CML	Nilotinib	Dasatinib	Excluded: Nilotinib and dasatinib not comparators per NICE scope

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
—	**Ibrahim et al. 2010[96]**	To present experience managing patients in CP with a 3rd TKI who have failed both imatinib and 2L dasatinib or nilotinib	CP-CML	Nilotinib/dasatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope
—	**Russo Rossi et al. 2013[191]**	To assess the long-term outcome of a large series of CML patients who received dasatinib or nilotinib as 3L TKI therapy	CP-, AP-, BP-CML	Nilotinib/dasatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope
—	**Ribeiro et al. 2015[101]**	To evaluate outcomes in patients with CML treated with a 3rd TKI after imatinib and nilotinib/dasatinib failure	CP-, AP-, BP-CML	Nilotinib/dasatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope
—	**Salihoglu et al. 2015[192]**	To report single-centre experience with CML patients who received 2G-TKIs as a 3L treatment option	CP-CML	Nilotinib/dasatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope
—	**Busque et al. 2015[193]**	To evaluate in an unbiased, population-based registry the patterns of utilisation of CML treatments in the 2L and 3L settings in order to assess the discordance between real-life data and those expected from clinical trials	CML (phase NR)	Nilotinib/dasatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope
—	**Cortes et al. 2011[97]**	To determine the clinical value of achieving different levels of cytogenetic response for patients treated with a second or subsequent TKI, as determined by the impact on survival and survival free from transformation to AP and BP	CP-CML	Nilotinib/dasatinib/ bosutinib/bafetinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope; observational study
—	**Lomaia et al. 2015[194]**	To report outcomes in patients with CP-CML treated with 3L therapy	CP-CML	Nilotinib/dasatinib/ bosutinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope; observational study

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
—	**Lee et al. 2014**[195]	To evaluate the response rates and outcomes of 3L TKI therapy in the treatment of patients with CP-CML	CP-CML	Nilotinib/dasatinib/ bosutinib/radotinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope; observational study
—	**Goldberg et al. 2015**[196]	To determine patient characteristics and emergent AEs that might underlie real-world treatment choices	CML (phase NR)	Nilotinib/dasatinib/ bosutinib/ponatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope; observational study
—	**Akosile et al. 2015**[140]	To analyse the long-term outcome of patients receiving multiple TKIs	CP-CML	Nilotinib/dasatinib/ bosutinib/ponatinib	None	Excluded: Nilotinib and dasatinib not comparators per NICE scope; observational study
—	**Jabbour et al. 2011**[144]	To compare outcomes of allo-SCT in patients with and without a *BCR-ABL1* mutation who are resistant to TKI therapy	CP-, AP-, BP-CML	Allo-SCT	None	Included: Observational study of allo-SCT for the treatment of CML R/I to prior TKI therapy at one centre in the US
—	**Jabbour et al. 2007**[197]	To analyse the short-term transplant-related toxicity among patients who received nilotinib or dasatinib before allo-SCT	CP-, AP-, BP-CML	Allo-SCT	None	Excluded: Transplant-related toxicity not a component of economic model
—	**Nair et al. 2015**[198]	To examine the clinical characteristics, SCT outcomes, and long-term follow-up of patients diagnosed with CP-CML who fail initial TKI treatment and to identify predictors of post-SCT survival, relapse, and nonrelapse mortality	CP-, AP-, BP-CML	Allo-SCT	None	Excluded: More comprehensive data are available (OS data not provided by phase, results not clearly presented for patients with prior imatinib and one additional TKI)
—	**Piekarska et al. 2015**[199]	To analyse outcomes of patients with CML undergoing SCT after exposure to ≥2 TKIs (including dasatinib and/or nilotinib)	CP-, AP-, BP-CML	Allo-SCT	None	Excluded: Patient population does not match that considered in economic model as it is not specified if patients proceeded to allo-SCT due to TKI failure (publication suggests that the TKI was discontinued to proceed with planned allo-SCT)

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
—	**Breccia et al. 2010**[200]	To report the outcome of 12 CML patients resistant to imatinib, who underwent allo-SCT following 2L treatment with dasatinib and/or nilotinib	CP-, AP-, BP-CML	Allo-SCT	None	Excluded: Patient population does not match that considered in economic model as TKI was discontinued to proceed with planned allo-SCT (ie, not due to TKI failure); small sample size (N=12)

2G, second generation; 2L, second line; 3L, third line; 4L, fourth line; ADV, advanced; ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; EBMT, European Society for Blood and Marrow Transplantation; NR, not reported; OS, overall survival; Ph+, Philadelphia chromosome–positive; R/I, resistant or intolerant; SCT, stem cell transplantation; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

Table 4-6. List of non-randomised and non-controlled evidence identified as potentially relevant in the Ph+ ALL clinical SLR

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
PACE/ NCT01207440	**Cortes et al. 2013**[9] **Cortes et al. 2015**[175]	To determine the efficacy of ponatinib in patients with CML or Ph+ ALL who are R/I to either dasatinib or nilotinib, or who have the T315I mutation	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	None	Included: Pivotal phase 2 trial for ponatinib (PACE) Included: 3-year follow-up of pivotal phase 2 trial for ponatinib (PACE)
PACE and EBMT/ NCT01207440	**Nicolini et al. 2015**[183]	To compare OS among CML and Ph+ ALL patients with the BCR-ABL1 T315I mutation treated with ponatinib (in PACE) versus allo-SCT (in the EBMT registry)	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	Allo-SCT	Excluded: Indirect analysis of ponatinib versus allo-SCT; focused on patients with the T315I mutation
NCT01667133	**Kyo et al. 2014**[177]	To evaluate the safety and efficacy of ponatinib in Japanese patients with CML after failure of dasatinib or nilotinib or with Ph+ ALL after failure of prior TKIs due to resistance or intolerance	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	None	Excluded: Interim analysis of ongoing phase 1/2 study, published only in abstract form; few (n=12) patients with Ph+ ALL; results not reported by line of therapy
NCT01592136	**Jeyakumar et al. 2013**[148]	To evaluate the efficacy and safety of ponatinib in patients with CML R/I to imatinib, dasatinib, and nilotinib (CP, AP), or patients with BP-CML or Ph+ ALL R/I to imatinib and dasatinib	CP-, AP-, BP-CML and Ph+ ALL	Ponatinib	None	Excluded: Observational study published in abstract form; separate response-rate results for BP-CML and Ph+ ALL not reported; less complete reporting of response categories compared with clinical trial data for ponatinib available from PACE

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
—	**Cornelissen et al. 2001**[201]	To report the results from 127 transplantations performed between 1988–1999 with grafts identified and procured by the National Marrow Donor Program for adult patients with poor-risk ALL	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified); 2-year OS in CR2/3 was 17%
—	**Doney et al. 2011**[202]	To perform a retrospective analysis of consecutive adult patients with ALL who underwent allo-SCT with full-intensity conditioning between 1998–2006	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified; OS data in CR2 not reported)
—	**Doney et al. 2003**[203]	To further define factors associated with acceptable NRM and long-term DFS	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified; OS data in CR2 not reported)
—	**Gorin et al. 2014**[204]	To compare the outcome after T cell-replete haploidentical transplant and autologous transplant	Acute leukaemia	Allo-SCT	Auto-SCT	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified; OS data in CR2 not reported)
—	**Pascual et al. 2016**[205]	To analyse the non-TBI conditioning regimens for allo-SCT in adult patients with ALL	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (reinduction regimens remission rates not specified); 16-month OS in CR2 was 32%
—	**Santoro et al. 2016**[206]	To analyse results of unmanipulated haploidentical-SCT for adults with ALL and to identify prognostic factors	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified); 2-year OS in >CR1 was 32%
—	**Stein et al. 2009**[207]	To evaluate reduced-intensity conditioning followed by peripheral blood SCT for adult patients with high-risk ALL	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified); KM curve for OS in >CR1 shows 2-year OS of ~55%

Study ID	Publication	Objective	Population	Intervention	Comparator	Included/excluded?
—	**Terwey et al. 2008**[208]	To evaluate the benefits and risks of reinduction chemotherapy before allo-SCT in relapsed or refractory ALL	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (% of Ph+ ALL patients who achieve CR with reinduction therapy not detailed); 2-year OS was 33% in relapsed/refractory patients and 25% in patients in CR2
—	**Tekgunduz et al. 2016**[209]	To analyse the results of ALL patients who were treated with allo-SCT in routine practice in Turkey	ALL	Allo-SCT	None	Excluded: More comprehensive data are available (% of Ph+ ALL patients who achieve CR with reinduction therapy not detailed); 2-year OS of 40 patients in ≥CR2 was ~20%)
—	**Uysal et al. 2016**[210]	To report the outcomes of patients with ALL who were treated with allo-HSCT at a single centre in Turkey	ALL	Allo-SCT	None	Excluded: Results not reported separately for patients who received allo-SCT in CR1 vs ≥CR2
—	**Fielding et al. 2007**[150]	To examine the outcome of 609 adults with recurring ALL, all of whom were previously treated on the MRC UKALL12/ECOG2993 study	ALL	Choice of therapy†	None	Excluded: More comprehensive data are available (no data were collected on regimens used to achieve a CR2; rate of CR2 not measured; survival in CR2 not reported)
—	**Kantarjian et al. 2010**[211]	To define the precise outcome of adults with ALL who achieve CR in second or subsequent CR	ALL	Choice of therapy‡	None	Excluded: More comprehensive data are available (reinduction regimens and remission rates not specified); KM curve for OS in ≥CR2 shows 2-year OS of 38%)
NCT0000270	**Tavernier et al. 2007**[133]	To assess the efficacy of reinduction therapy according to risk groups defined in front-line therapy; to evaluate post-remission strategies after achievement of a CR2 and to evaluate the utility of allo-SCT in the setting of 2L therapy	ALL*	Choice of therapy§	None	Included: Provides comprehensive data on the reinduction regimens used to induce CR2 and the % of patients with Ph+ ALL who achieve CR; 2-year OS in CR2 was 38%

2L, second line; ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; auto-SCT, autologous stem cell transplantation; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; CR, complete remission; CR2, second complete remission; CR3, third complete remission; DFS, disease-free survival; EBMT, European Society for Blood and Marrow Transplantation; OS, overall survival; Ph+, Philadelphia chromosome–positive; MRC, Medical Research Council; NRM, nonrelapse mortality; SCT, stem cell transplantation; TBI, total body irradiation.

*Excluding mature B-cell ALL.

†Choice of therapy after relapse was left to the discretion of physician and patient.

‡Salvage treatment regimen depended on study period, prior induction therapy response, and timing of relapse.

[§]Salvage treatment was investigator's choice according to initial induction and consolidation regimen, duration of first remission, disease features at relapse, and availability of a suitable allogeneic donor.

4.11.2 Justification for study exclusion

Table 4-5 provides justification for exclusion of studies identified in the CML clinical SLR. The NICE scope specifies bosutinib, allo-SCT, interferon alpha, and BSC as appropriate comparators for ponatinib. Thus, all studies of other TKIs (dasatinib, nilotinib, bafetinib, radotinib) have been excluded.

Both ponatinib and bosutinib have been evaluated in phase 1/2 clinical trials in Japan. However, the ponatinib study, by Kyo et al. 2014,[177] has been published only in abstract form with interim analyses, and its results were reported in insufficient detail to populate the cost-effectiveness models (namely, missing stratification by line of therapy and incomplete reporting of response categories). In the bosutinib study, by Nakaseko et al. 2015,[187] patients in the line of treatment relevant to this submission (ie, 3L) were included as an "exploratory cohort", and results for this small subgroup (n=11) were not reported by disease phase, making it impossible to determine whether the reported results apply to CP-, AP-, and/or BP-CML. Consequently, both of these studies have been excluded from further discussion.

For ponatinib and bosutinib, data from observational studies were not used in the models as for all relevant model parameters the clinical trial data available for these two comparators were more comprehensive. For example, Jeyakumar et al. 2013 presented 9-month results from an expanded access programme for ponatinib at two institutions, but this observational study was published only in abstract form and response rates for BP-CML and Ph+ ALL were only reported pooled, not separately.[178]

No clinical trials were identified for allo-SCT; therefore, the most suitable observational study, Jabbour et al. 2011,[144] was selected for inclusion in the model. Jabbour et al. is a relatively recent observational study in 47 patients with prior TKI use. It provided KM OS curves by phase of disease, which were required for economic modelling of ponatinib. Nair et al. did not present KM OS curves by disease phase and the results were not clearly stratified by prior TKI use (eg, results were described for patients with prior imatinib alone, prior imatinib plus another TKI, and prior imatinib plus chemotherapy ± another TKI).[198] Both Piekarska et al.[199] and Breccia et al.[200] evaluated a patient population that had not necessarily undergone allo-SCT as a result of TKI failure (ie, TKI was discontinued to proceed with transplantation), which does not match the population modelled in the ponatinib pharmacoeconomic analysis.

Studies reporting results of indirect analyses of previously published data were also excluded, since data from the primary publications could be used instead of these second-hand reports. One indirect analysis (Nicolini et al. 2015[183]) reported previously unpublished data from the European Blood and Marrow Transplantation (EBMT) database. As these data were specific to patients with the T315I mutation, this study was excluded.

Table 4-6 provides justification for exclusion of studies identified in the Ph+ ALL clinical SLR. As for CML, the PACE study (Cortes et al. 2013)[9] provides the most comprehensive data of ponatinib for the Ph+ ALL patient population. The NICE scope specifies established clinical management without ponatinib (including but not limited to BSC) as the appropriate comparator for ponatinib. Several observational studies evaluating allo-SCT in patients with ALL who relapsed following induction chemotherapy were identified in the SLR. Although post–allo-SCT survival data for the Ph+ patient population after relapse were not identified in the SLR, studies have shown that Ph+ ALL is not a risk factor for lower survival post–allo-SCT (Cornelissen et al. 2001)[201] and Ph+ disease status does not influence OS in patients undergoing allo-SCT (Tekgunduz et al. 2016).[209]

Tavernier et al. 2007,[133] a prospective observational study of 421 relapsed patients who were enrolled in the LALA-94 trial, provides the most comprehensive data for reinduction chemotherapy followed by allo-SCT in patients with ALL after first relapse. This study reports both outcomes of reinduction therapy by salvage regimen (data available for Ph+ ALL) and OS in second complete remission (CR2) following allo-SCT. These data are used to model the outcomes of comparator induction chemotherapy followed by allo-SCT in remission. As reported

in Tavernier et al. 2007, the 2-year OS for the 61 patients who received allo-SCT while in CR2 was 38% (median 10.4 months).[133]

Evidence from the other studies identified in the Ph+ ALL clinical SLR shows that 2-year survival post–allo-SCT in CR2 or beyond ranges from 17%–55%.[201, 206-209, 211] In the retrospective observational study by Kantarjian et al. 2010,[211] 2-year OS was 38% for adults with acute ALL in ≥CR2; ie, the same survival rate reported by Tavernier et al. 2007. In general, data from the published literature are in line with the survival outcomes reported by Tavernier et al. 2007.[133]

In addition, none of the other studies identified in the SLR report the rate of remission with salvage treatment by risk groups (ie, Ph+ ALL), unlike Tavernier et al. 2007, which reports the remission rates with reinduction therapy, by salvage regimen, for patients with Ph+ ALL. Thus, as Tavernier et al. 2007 provides the most comprehensive data that are in line with other published studies, it was selected for inclusion in this submission.[133]

4.11.3 Summary of methodology of relevant non-randomised and non-controlled evidence

Five of the studies identified in the CML and Ph+ ALL SLRs have been included in this submission, along with six associated publications (including long-term follow-up and/or subgroup analyses). The clinical evidence includes: two primary studies evaluating ponatinib, one primary study evaluating bosutinib, a single retrospective observational study focused on allo-SCT in relapsed CML, and one prospective observational study evaluating treatment outcomes in patients with ALL who relapse after 1L therapy.

Table 4-7 provides a comparative summary of the methodology of the included publications.

Table 4-7. Comparative summary of methodology of included studies

Study ID	Publication	Population	Intervention	Comparator	Study type	Study design
NCT00660920	**Cortes et al. 2012**[23] **Talpaz et al. 2015**[176]	CP-, AP-, BP-CML CP-CML	Ponatinib	None	Non-RCT	Phase 1, single-arm, multicentre, open-label
PACE/ NCT01207440	**Cortes et al. 2013**[9] **Cortes et al. 2015**[175] **Hochhaus et al. 2015**[24]	CP-, AP-, BP-CML and Ph+ ALL CP-CML	Ponatinib	None	Non-RCT	Phase 2, single-arm, multicentre, open-label
Bosutinib phase 1/ 2 trial/ NCT00261846	**Khoury et al. 2012**[8] **Kantarjian et al. 2014**[184] **Gambacorti-Passerini et al. 2015**[185] **Gambacorti-Passerini et al. 2014**[186]	CP-CML CP-CML AP-, BP-CML CP-CML	Bosutinib	None	Non-RCT	Phase 1/2, single-arm, multicentre, open-label
—	**Jabbour et al. 2011**[144]	CP-, AP-, BP-CML	Allo-SCT	None	Observational	Retrospective
—	**Tavernier et al. 2007**[133]	ALL	Investigator's choice*	None	Observational	Prospective

ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; Ph+, Philadelphia chromosome–positive; RCT, randomised controlled trial..

*Salvage treatment was investigator's choice according to initial induction and consolidation regimen, duration of first remission, disease features at relapse, and availability of a suitable allogeneic donor.

As noted in Table 4-7, three of the relevant studies are non-randomised, single-arm trials and two are retrospective observational analyses. The results of the comprehensive SLRs indicate that these types of studies are common in this disease area, which is likely related to the rarity of CML and ALL[1] and the difficulty in identifying and enrolling eligible patients. In fact, no RCTs were identified in the CML or Ph+ ALL SLRs.

4.11.3.1 PACE trial

The PACE study was an international, phase 2, single-arm, open-label, clinical trial conducted at 66 sites. The efficacy and safety of ponatinib was evaluated in 449 patients with CP-, AP-, or BP-CML or Ph+ ALL who were R/I to dasatinib or nilotinib, or who had the T315I mutation.[9] This study has been published by Cortes et al. 2013. An overview of the PACE trial design and methodology is presented in this section.

The patient population evaluated in the PACE study was heavily pre-treated with prior TKIs and conventional therapy, relatively advanced in their diagnosis, and resistant to or intolerant of prior TKIs. Study inclusion criteria specifically required patients to be resistant to or intolerant of dasatinib or nilotinib, or to have developed the T315I mutation after any TKI therapy. Intolerance to prior TKIs was defined as the persistence of toxicity despite treatment modification to the maximum extent specified by the manufacturer. Patients with CP-CML were considered resistant to a prior TKI if they met one of the following criteria:[9]

- No cytogenetic response or failure to achieve CHR 3 months after therapy initiation
- Less than minor cytogenetic response (mCyR) 6 months after therapy initiation
- Less than PCyR 12 months after therapy initiation
- Development of new *BCR-ABL* mutation(s) without CCyR at any point during therapy
- Development of new clonal evolution without CCyR at any point during therapy
- Loss of cytogenetic response at any point during therapy
- Progression of disease at any point during therapy

Additional resistance criteria for advanced disease (AP-CML, BP-CML, and Ph+ ALL) are noted in the Cortes et al. publication.[9]

Key inclusion criteria were:[9]

- Previous treatment with and subsequent resistance to or intolerance of dasatinib or nilotinib, or development of the T3151 mutation after any TKI therapy, including imatinib
- Age ≥18 years
- ECOG performance status ≤2
- Normal pancreatic function and adequate renal and hepatic function
- Normal QT by the Fridericia method (QTcF) interval (≤450 ms in males and ≤470 ms in females)

Key exclusion criteria included:[9]

- TKI treatment within 7 days prior to receiving the first dose of ponatinib
- Receipt of certain therapies within a specific time frame prior to receiving ponatinib (time frame and prior therapy were specific for each phase of CML)
- Lack of recovery from AEs from prior treatments
- Concomitant medications known to be associated with Torsades de Pointes
- Prior treatment with ponatinib
- Stem cell transplant <60 days prior to receiving first dose of ponatinib

- Evidence of ongoing graft-versus-host disease (GVHD) or GVHD requiring immunosuppressive therapy
- Concurrent treatment with immunosuppressive agents, other than short-course corticosteroids
- History of pancreatitis or alcohol abuse
- Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL)

Patients were also excluded if they were in CCyR (CP-CML) or MaHR (AP-CML, BP-CML, or Ph+ ALL) at baseline (14 patients with AP-CML had MaHR at baseline and were considered nonresponders for the purposes of the analysis).[9]

Patients received ponatinib at a starting dose of 45 mg orally once daily.[9] Dose reductions were recommended following AEs. In addition, in October 2013, following a request by the FDA, study investigators were instructed to decrease the dose from 45 to 15 mg/day in all CP-CML patients who had achieved a MCyR or better, to 30 mg/day in CP-CML patients who had not already achieved MCyR, and to 30 mg/day for advanced phase patients.[25] Prospective dose reductions in all CP-CML patients in the absence of AEs were introduced in the trial to reduce the risk of VOEs.[22]

Table 4-8 provides the primary and secondary endpoints in the PACE trial.[9]

Table 4-8. Description and definition of primary and key secondary endpoints in the PACE study (Cortes et al. 2013)[9]

	Disease state at study entry	Response criteria	Definition*
Primary endpoint	CP-CML	MCyR at any time within the first 12 months	MCyR defined as CCyR or PCyR
	AP-CML	MaHR within the first 6 months	MaHR defined as CHR or NEL
	BP-CML		MaHR consisting of CHR or NEL
	Ph+ ALL		
Secondary endpoints	CP-CML	Haematologic response: CHR	
		Cytogenetic responses: Confirmed MCyR	Confirmed MCyR defined as two assessments of CCyR or PCyR at least 28 days apart For CP patients with PCyR at study start, confirmed MCyR is defined as two assessments of CCyR at least 28 days apart
		Molecular response: MMR	
	AP-CML	Cytogenetic responses: • CCyR • PCyR • Confirmed MCyR	Confirmed MCyR defined as two assessments of CCyR or PCyR at least 28 days apart
	BP-CML		
	Ph+ ALL		

ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; NEL, no evidence of leukaemia; PCyR, partial cytogenetic response; Ph+ = Philadelphia chromosome–positive.

*Complete definitions of response criteria can be found in Appendix C of the Cortes et al. (2013) publication.[9]

4.11.3.2 Comparator data

The bosutinib phase 1/2 study was an international, single-arm, open-label, clinical trial conducted at 58 centres and was a two-part study: Part 1 was a dose-escalation study in patients with CP-CML (and one patient with AP-CML) who had developed resistance to prior treatment with imatinib (ie, 2L bosutinib), while Part 2 of the study evaluated the efficacy and safety of bosutinib across different lines of therapy, including ≥3L bosutinib in patients previously treated with imatinib and dasatinib and/or nilotinib.[8] Khoury et al. 2012 report the results for adults with

Ph+ CP-CML who had received prior treatment with imatinib followed by dasatinib and/or nilotinib (ie, results for the 3L cohort).[8] While the bosutinib trial (NCT00261846) included 570 patients with Ph+ leukaemias, including those in 2L,[212] the bosutinib publication identified in the SLR and included here was a subanalysis of the patient population with CP-CML who were treated with bosutinib in the 3L or 4L setting.[8, 186] The total population (N=118) evaluated in the Khoury et al. 2012 subanalysis included patients with CP-CML who had prior treatment with imatinib followed by dasatinib or nilotinib (n=114) and patients for whom prior imatinib therapy failed, and who were either intolerant to nilotinib (n=1) or R/I to prior nilotinib and dasatinib therapy (n=3; 4L).[8] The publication by Kantarjian et al. 2014[184] reported long-term safety results for all CP-CML patients treated in the pivotal bosutinib study, include patients who received 3L bosutinib. Efficacy and safety of bosutinib in patients with advanced CML (AP/BP) was also investigated in the bosutinib trial, with the results of this analysis reported by Gambacorti-Passerini et al. 2015.[185]

Key inclusion criteria in the Khoury et al. 2012 study were: Adults (≥ 18 years) with Ph+ CP-CML, prior treatment with imatinib followed by dasatinib and/or nilotinib; ECOG PS 0-1; adequate bone marrow, hepatic, and renal function; no antiproliferative or antileukemia treatment within 7 days of bosutinib initiation (except hydroxyurea or anagrelide); no allo-SCT within 3 months.[8] Key exclusion criteria were: Ph– and *BCR-ABL*−negative CML; overt leptomeningeal leukaemia (free of CNS involvement for <2 months); extramedullary disease only; GVHD (for part 1, no prior GVHD allowed; for part 2, no treated or untreated GVHD within 60 days of study initiation); documented history of T315I *BCR-ABL* mutation; pregnant or breastfeeding; prior history of imatinib intolerance or exposure to Src, Abl, or Src/Abl kinase inhibitors (part 1 only).[8]

Patients received bosutinib at a starting dose of 500 mg orally once daily. Dose escalations were permitted up to 600 mg per day if CHR or CCyR were not achieved by weeks 8 and 12 respectively. Dose reductions to 300 mg/day were allowed in 100-mg increments for AEs.[8] The primary outcomes were MCyR by 24 weeks (CP-CML, Khoury et al. 2012)[8] and confirmed overall haematologic response (OHR) maintained or achieved by week 48 (AP-/BP-CML, Gambacorti-Passerini et al. 2015).[185]

4.11.3.3 Strengths and limitations of the study designs

Patient recruitment is a known challenge in rare disease clinical trials. Although head-to-head RCTs are the gold standard for evaluating comparative effectiveness, they are not always feasible, especially in the context of rare diseases.[213, 214] In the absence of RCT evidence in the post–2G-TKI CML setting, the potential biases of the existing evidence must be examined and accounted for in indirect analyses.

Single-group studies, whether clinical trials or observational studies, are associated with an array of potential biases, the most important of which is a lack of a comparator group. Since CML is a disease with a particularly poor prognosis in the absence of treatment, with expected survival being approximately 3–5 years from diagnosis,[2] spontaneous disease regression would be unexpected. Therefore, responses obtained with current treatment in single-arm trials can be informative. However, there is a risk for biases arising from variable patient population characteristics across studies, inconsistency in reporting of endpoint results, and heterogeneity of study design and endpoint definitions.[6, 215] Observational studies can also suffer from biases related to differing opinions about treatment among healthcare providers.[216]

To provide appropriate comparative data across current treatments for CML in the post–2G-TKI setting, while addressing the potential biases noted above and the limitations of naïve comparisons, a matching-adjusted indirect comparison has been conducted between ponatinib and bosutinib. See Section 4.10 for further details on this analysis.

4.11.4 Statistical analysis of the non-randomised and non-controlled evidence

4.11.4.1 PACE analysis

The efficacy population included all patients who were assigned to a cohort (N=444). Patients with missing baseline bone marrow blast results or cytogenetic assessments were excluded from

per protocol analyses.[25] The safety population included all patients who received one or more doses of ponatinib (N=449).[9]

The power calculations were as follows:[9]

- Cohort A (R/I CP-CML): 100 patients were expected to provide at least 85% power to distinguish between a null response rate of 20% and an alternative response rate of 35%.
- Cohort B (T315I CP-CML): 60 patients were needed to provide approximately 98% power to distinguish between a null response rate of 10% and an alternative response rate of 35%.
- Cohorts C to F (R/I and T315I AP-CML, and BP-CML/Ph+ ALL): 40 patients in each cohort (160 patients total) provided an approximately 89% power to distinguish between the null response rate of 10% and an alternative response rate of 30%.
- An anticipated higher relative proportion of R/I patients to T315I patients required over-enrolment of the R/I cohorts (Cohorts A, C, and E) to ensure full T315I patient enrolment. Initially, 350 patients were planned; protocol amendment 2 adjusted the study plan to enrol approximately 450 patients to ensure reaching the planned sample sizes of the T315I cohorts.

4.11.5 Participant flow in the studies

4.11.5.1 PACE trial

Patients were grouped into 6 cohorts as follows:[9]

- CP-CML R/I to dasatinib or nilotinib with the T315I mutation
- CP-CML R/I to dasatinib or nilotinib without the T315I mutation
- AP-CML R/I to dasatinib or nilotinib with the T315I mutation
- AP-CML R/I to dasatinib or nilotinib without the T315I mutation
- BP-CML or Ph+ ALL R/I to dasatinib or nilotinib with the T315I mutation
- BP-CML or Ph+ ALL R/I to dasatinib or nilotinib without the T315I mutation

Table 4-9 summarises the distribution of patients in each of the six cohorts.

Table 4-9. Distribution of patients in the six cohorts in PACE (Cortes et al. 2013)[9]

	CP-CML n (%)	AP-CML n (%)	BP-CML n (%)	Ph+ ALL n (%)	Total
Total (n)*	270	85	62	32	449
Resistant/intolerant to dasatinib or nilotinib	256 (95)	80 (94)	61 (98)	30 (94)	427 (95)
Resistant	214 (84)	74 (93)	59 (97)	27 (90)	374 (88)
Intolerant only	40 (16)	6 (8)	2 (3)	2 (7)	50 (12)
Not specified	2 (1)	0 (0)	0 (0)	1 (3)	3 (1)
T315I mutation	64 (24)	18 (2)	24 (39)	22 (69)	128 (29)

ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; Ph+, Philadelphia chromosome–positive.

*Includes 5 additional patients (3 with CP-CML and 2 with AP-CML who were not assigned to any cohort having failed imatinib alone and not having the T315I mutation, but treated).

Table 4-10 presents the characteristics of participants in the studies included in the submission, across treatment groups.

The PACE study evaluated 449 patients in total, 417 of whom had CML (270 in CP, 85 in AP, 62 in BP), and 32 of whom had Ph+ ALL. This study evaluated a large population of patients with CP-CML treated in the ≥3L setting, with 251 patients treated with 3L, 4L, or fifth-line (5L) ponatinib.[9]

4.11.5.2 Comparator data

The bosutinib phase 1/2 trial (NCT00261846) included 570 patients with Ph+ leukaemias;[212] the Khoury et al. 2012 publication included in the submission was a subanalysis of 118 patients with CP-CML who had received 2 prior TKIs (3 patients [2.5%] had received imatinib, dasatinib, and nilotinib and were treated in with 4L bosutinib). Gambacorti-Passerini et al. 2015 report the results of the subanalysis of 167 patients with advanced CML, including 58 patients with AP-CML (n=30) or BP-CML (n=28) in ≥3L.[185]

Jabbour et al. 2011 evaluated the use of allo-SCT in the post–2G-TKI setting in 47 patients with CP-, AP-, and BP-CML.[144] Therefore, all phases of CML have been evaluated across interventions. Tavernier et al. 2007 included 421 patients with ALL across five risk categories, including 81 patients with Ph+ ALL.[133]

The median age of patients across ponatinib and bosutinib studies was generally 50 years or older (though patients with BP-CML in the bosutinib trial by Gambacorti-Passerini et al. 2015 were slightly younger, with a median age of 47 years). With a median age of 44 years, patients were slightly younger in the Jabbour et al. allo-SCT study.[144] In Tavernier et al., the overall median age of patients at relapse was 34 years, with Ph+ ALL patients relapsing having a median age of 46 years.[133]

Table 4-10. Characteristics of participants in the studies across treatment groups

Study ID	Publication	Intervention	N	Age, median (range), y	Male, n (%)	Disease phase, n	No. of prior TKIs, n (%)	Duration of prior treatment with TKIs, median (range)	Prior TKIs, n (%)
NCT00660920	**Cortes et al. 2012**[23] **Talpaz et al. 2015**[176]	Ponatinib (single-arm)	81 (total); 60 (CML)	CP-CML: 55 (27–85) AP-CML: 61 (42–77) BP-CML: 51 (26–73)	CP-CML: 21 (49) AP-CML: 6 (67) BP-CML: 5 (62)	CP-CML: 43 AP-CML: 9 BP-CML: 8	CP-CML: • ≥2: 42 (98) • ≥3: 27 (63) AP-CML: • ≥2: 9 (100) • ≥3: 8 (89) BP-CML: • ≥2: 8 (100) • ≥3: 6 (75)	NR	CP-CML: • Dasatinib: 37 (86) • Nilotinib: 24 (56) • Imatinib + dasatinib or nilotinib: 19 (44) • Imatinib + dasatinib + nilotinib: 21 (49) AP-CML: • Dasatinib: 9 (100) • Nilotinib: 7 (78) • Imatinib + dasatinib or nilotinib: 2 (22) • Imatinib + dasatinib + nilotinib: 7 (78) BP-CML: • Dasatinib: 8 (100) • Nilotinib: 5 (62) • Imatinib + dasatinib or nilotinib: 3 (38) • Imatinib + dasatinib + nilotinib: 5 (62)
PACE/ NCT01207440	**Cortes et al. 2013**[9] **Cortes et al. 2015**[175]	Ponatinib (single-arm)	449 (total); 417 (CML); 32 (Ph+ ALL)	CP-CML: 60 (18–94) AP-CML: 60 (23–82) BP-CML: 53 (18–74) Ph+ ALL: 62 (20–80)	NR	CP-CML: 270 AP-CML: 85 BP-CML: 62 Ph+ ALL: 32	CP-CML: • 1: 19 (7) • 2: 98* (36) • 3: 141 (52) • 4: 12 (4) AP-CML: • 1: 5 (6) • 2: 33 (39) • 3: 44 (52) • 4: 3 (4) BP-CML: • 1: 3 (5)	CP-CML: 5.4 y (0.4–13.3) AP-CML: 5.1 y (0.3–12.1) BP-CML: 2.0 y (0.1–11.6) Ph+ ALL: 1.2 (0.1–8.2)	CP-CML: • Imatinib: 261 (97) • Dasatinib: 217 (80) • Nilotinib: 184 (68) • Bosutinib: 24 (9) AP-CML: • Imatinib: 84 (99) • Dasatinib: 70 (82) • Nilotinib: 56 (66) • Bosutinib: 5 (6) BP-CML: • Imatinib: 58 (94)

Study ID	Publication	Intervention	N	Age, median (range), y	Male, n (%)	Disease phase, n	No. of prior TKIs, n (%)	Duration of prior treatment with TKIs, median (range)	Prior TKIs, n (%)
							• 2: 22 (35) • 3: 34 (55) • 4: 3 (5) Ph+ ALL: • 1: 6 (19) • 2: 14 (44) • 3: 12 (38) • 4: 0		• Dasatinib: 58 (94) • Nilotinib: 41 (66) • Bosutinib: 4 (6) Ph+ ALL: • Imatinib: 27 (84) • Dasatinib: 30 (94) • Nilotinib: 13 (41) • Bosutinib: 0
	Hochhaus et al. 2015[24]	Ponatinib (single-arm)	270	2 prior TKIs: 57 (22–87) 3 prior TKIs: 63 (21–87) 4 prior TKIs: 67 (58–94)	NR	CP-CML: 270	2 prior TKIs: 97 (36) 3 prior TKIs: 142 (53) 4 prior TKIs: 12 (4)	NR	2 prior TKIs: • Imatinib: 94 (NR) • Dasatinib: 64 (NR) • Nilotinib: 35 (NR) • Bosutinib: 1 (NR) 3 prior TKIs: • Imatinib: 142 (NR) • Dasatinib: 137 (NR) • Nilotinib: 137 (NR) • Bosutinib: 10 (NR) 4 prior TKIs: • Imatinib: 12 (NR) • Dasatinib: 12 (NR) • Nilotinib: 12 (NR) • Bosutinib: 12 (NR)
NCT00261846	**Khoury et al. 2012[8]**	Bosutinib (single-arm)	118	56 (20–79)	53 (45)	CP-CML: 118	0: 0 1: 0 2: 115 (97) 3: 3 (3)	Imatinib: 2.7 y (0.02–6.6) Dasatinib: 17.7 mo (1.1–47.9) Nilotinib: 9.2 mo (0.8–38.9)	• Imatinib + dasatinib: 87 (74) • Imatinib + nilotinib: 28 (24) • Imatinib + dasatinib + nilotinib: 3 (3)
	Kantarjian et al. 2014[184]	Bosutinib (single-arm)	118	56 (20–79)	53 (45)	CP-CML: 118	0: 0 1: 0 2: 115 (97)	NR	• Imatinib + dasatinib: 88 (75) • Imatinib + nilotinib: 27 (23)

Study ID	Publication	Intervention	N	Age, median (range), y	Male, n (%)	Disease phase, n	No. of prior TKIs, n (%)	Duration of prior treatment with TKIs, median (range)	Prior TKIs, n (%)
							3: 3 (3)		• Imatinib + dasatinib + nilotinib: 3 (3)
	Gambacorti-Passerini et al. 2015[185]	Bosutinib (single-arm)	167[†]	AP-CML: 51 (18–83) BP-CML: 47 (19–82)	AP-CML: 44 (56) BP-CML: 42 (66)	AP-CML: 79 BP-CML: 64	AP-CML: • 0: 0 • 1: 49 (62) • ≥2: 30 (38) BP-CML: • 0: 0 • 1: 36 (56) • ≥2: 28 (44)	AP-CML: • Imatinib: 35.6 mo (0.6–108.3) • Dasatinib: 6.9 mo (0.1–30.4) • Nilotinib: 4.3 (0.8–34.0) BP-CML: • Imatinib: 21.2 mo (0.9–62.6) • Dasatinib: 7.0 mo (1.4–34.6) • Nilotinib: 1.0 mo (0.1–19.3)	AP-CML: • Imatinib: 79 (100) • Dasatinib: 25 (32) • Nilotinib: 15 (19) BP-CML: • Imatinib: 64 (100) • Dasatinib: 22 (34) • Nilotinib: 11 (17)
	Gambacorti-Passerini et al. 2014[186]	Bosutinib (single-arm)	119	56 (20–79)	53 (45)	CP-CML: 119	0: 0 1: 0 2: 115 (97) 3: 4 (3)	NR	• Imatinib + dasatinib: 88 (74) • Imatinib + nilotinib: 27 (23) • Imatinib + dasatinib + nilotinib: 4 (3)
—	**Jabbour et al. 2011[144]**	Allo-SCT (single-arm)	47	44 (19–64)	27 (57)	First CP: 16 AP: 12 BP: 9 Second CP: 10	0: 0 ≥1: 47 (100) 2: 29 (62) 3: 5 (11)[‡]	Imatinib: 15 mo (1–57) Second TKI: NR	Prior 1L TKI, n (%): • Imatinib: 47 (100) Prior 2L TKI(s), n (%): • Dasatinib: 13 (28) • Nilotinib: 13 (28) • Bosutinib: 3 (6) Prior 3L TKI(s), n (%): • Dasatinib: 3 (6) • Nilotinib: 1 (2) • Bafetinib (INNO406): 1 (2)

Study ID	Publication	Intervention	N	Age, median (range), y	Male, n (%)	Disease phase, n	No. of prior TKIs, n (%)	Duration of prior treatment with TKIs, median (range)	Prior TKIs, n (%)
—	**Tavernier et al. 2007[133]**	Investigator's choice[§]	421	Overall: 34 (15–62) Ph+ ALL: 46 (18–56)	Overall: 280 (67) Ph+ ALL: 47 (58)	Group 1 (standard-risk): 179 Group 2 (high-risk): 118 Group 3 (Ph+ ALL): 81 Group 4 (CNS+): 14 Group 5 (Excluded): 30	None	NA	NA

1L, first line; 2L, second line; 3L, third line; allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CNS+, central nervous system-positive; CP, chronic phase; mo, month; NA, not applicable; NR, not reported; TKI, tyrosine kinase inhibitor; y, year.

*One patient was misclassified in this study; the model considers the actual cohort of 97 patients.

[†]Data from 24 patients with ALL were reported in the publication but are not included here.

[‡]Table 1 reports an n (%) of 4 (8.5) but the text on page 3642 of the publication reports an n of 5 (11).

[§]Salvage treatment was investigator's choice according to initial induction and consolidation regimen, duration of first remission, disease features at relapse, and availability of a suitable allogeneic donor.

4.11.6 Quality assessment of the relevant non-randomised and non-controlled evidence

Each study identified for inclusion in Section 4.11.1 was subjected to quality assessment.

4.11.7 Methods for quality assessment of the relevant non-randomised and non-controlled evidence

Quality assessment of all relevant studies identified in the SLR was conducted independently by two researchers, with disagreements resolved by a third researcher.

Assessment of RCT evidence was to be aligned with NICE guidance[159]; however, no RCTs were identified in the literature search. The Chambers et al. 2009 checklist was used to determine the quality of non-RCT studies (Table 4-11).[217]

Table 4-11. Criteria used for quality assessment of non-RCT studies

	Chambers criteria 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?

Quality rating: Good, if the answer is ''yes'' to criteria 1–8; satisfactory, if the answer is ''yes'' to criteria 2, 4–7; poor, if the answer is not ''yes'' to one or more of the criteria listed for ''satisfactory.''

Using the Chambers criteria, non-RCT study quality could be scored as good, satisfactory, or poor. The quality assessment of non-RCTs is intended to give reviewers an indication of the calibre of research data available in this field. Synthesis of this information for further data analysis is not planned.

4.11.8 Summary of results of quality assessment of the relevant non-randomised and non-controlled evidence

Overall, based on the Chambers scoring method, four and one of the primary studies were categorised as good and poor quality, respectively (Table 4-12). The primary ponatinib (Cortes et al. [2012, 2013][9, 23]), bosutinib (Khoury et al.[8]), and Tavernier et al. studies were the only studies that received a good score, with a small caveat—although consecutive recruitment was a mandatory criterion for a good or satisfactory score, all four studies failed to report this detail. The quality score has not been downgraded based on this failure to report but the lack of clarity has been noted by the addition of an asterisk to this score (ie, "good*").

No studies received a satisfactory score. The poor score for Jabbour et al.[144] was primarily due to its apparently retrospective design; prospective recruitment was a mandatory criterion for a good or satisfactory score.

The associated publications were also assessed for quality. The two conference abstracts/presentations reporting follow-up data for ponatinib (Talpaz et al. [2015][176], Cortes et al. [2015],[175] and Hochhaus et al. [2015][24]) received a poor score due to lack of data reported on loss to follow-up or due to an unknown percentage of patients included at baseline who were follow up. This score is misleading as these were conference abstracts/presentations describing long-term follow-up data from a study with a good quality score for its primary publication. The Gambacorti-Passerini et al. 2014 conference abstract, Gambacorti-Passerini et al. 2015 publication, and Kantarjian et al. 2014 publication received a good* score.

Table 4-12. Summary of quality assessment scores for all relevant non-RCT studies identified in the CML and Ph+ ALL SLRs

Publication	Quality score per Chambers criteria
Primary studies	
Cortes et al. 2012[23] (NCT00660920)	Good*
Cortes et al. 2013[9] (PACE/NCT01207440)	Good*
Khoury et al. 2012[8] (NCT00261846)	Good*
Tavernier et al. 2007[133]	Good*
Jabbour et al. 2011[144]	Poor
Associated publications	
Talpaz et al. 2015[176] (NCT00660920)	Poor
Cortes et al. 2015[175] (PACE/NCT01207440)	Poor
Hochhaus et al. 2015[24] (PACE/NCT01207440)	Poor
Kantarjian et al. 2014[184] (NCT00261846)	Good*
Gambacorti-Passerini et al. 2015[185] (NCT00261846)	Good*
Gambacorti-Passerini et al. 2014[186] (NCT00261846)	Good*

*Studies did not report whether patients were recruited consecutively. As this was a mandatory criterion to avoid a score of "poor", this lack of clarity has been noted but the study scores have not been downgraded.

4.11.9 Complete quality assessment

The CRD guidance does not recommend relying solely on quality scores when assessing study quality.[160] Therefore, the responses to each question in the Chambers criteria for all relevant studies are included in Appendix 8: Quality assessment of the relevant non-randomised and non-controlled evidence.

4.11.10 Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

All relevant studies identified in the clinical SLR reported efficacy results in the CML population. See Section 4.11.12 for further details.

4.11.11 Graphical presentation of effectiveness data

Not applicable.

4.11.12 Outcomes from relevant non-randomised and non-controlled studies identified in the clinical SLR

Table 4-13 presents the outcomes from relevant studies identified in the CML and Ph+ ALL SLRs and included in this submission.

4.11.12.1 PACE trial efficacy (12-month follow-up)

Patients with CP-CML: Of the total PACE study CP-CML patient population at baseline, only 26% had previously achieved MCyR or better with their prior TKI (either dasatinib or nilotinib), and only 3% had achieved MMR. With ponatinib, 56% achieved MCyR any time within the first 12 months (primary endpoint) (95% CI 50%–60%), of which 46% reached CCyR and 34% reached MMR.[9] Patients responded quickly to ponatinib, with a median time to MCyR of 2.8 months (range 1.6–11.13). The duration of response ranged from 1 day to 19.4 months (median not reached) and the estimated rate of sustained response of at least 12 months was 91% (95%

CI 85%–95%). A CCyR by 12 months was achieved by 46% of patients. At 12 months, the rate of PFS was 80% and OS was 94% (median not yet reached for both). Three patients in CP-CML progressed to AP-CML or BP-CML; two additional patients with previous history of AP-CML returned to accelerated phase.[9]

Patients with AP-CML: Overall, 39% reached MCyR (24% with CCyR), 55% (95% CI 44%–66%) reached MaHR by 6 months, and 16% achieved MMR. The median time to MaHR was 3 weeks (range 2–25 weeks), and the duration of response ranged from 1 to 21 months or more (median: 12 months), with 48% of patients estimated to remain in MaHR at 12 months. The median time to MCyR was 3.7 months (range 0.8–9.7 months), with 73% of the patients estimated to maintain this response at 12 months. For patients in AP-CML, PFS and OS were estimated to be 55% (median 18 months) and 84% at 12 months, respectively.[9]

Patients with BP-CML: Among patients in BP, 31% (95% CI 20%–44%) had a MaHR by 6 months. The duration of response ranged from 1 to 20 months or more (median 5 months), and the estimated rate of a sustained response of at least 12 months was 42%. The median time to MaHR for responders was 4.1 weeks (range 1.7–16.1 weeks). Furthermore, MCyR was reached in 23% of patients, and 18% had a CCyR. The median time to MCyR for responders was 1.9 months (range 0.9–5.5 months), with an estimated 66% of responding patients maintaining this response for at least 12 months. In BP-CML, the rate of PFS at 12 months was estimated to be 19% (median 4 months).

Patients with Ph+ ALL: Among patients with Ph+ ALL, 41% had a MaHR by 6 months. The median time to response was 2.9 weeks (range 1.6–24 weeks), and the duration of response was 2 to 14 months or more (median 3 months). Approximately 8% of patients had a sustained response of at least 12 months. Furthermore, 47% patients with Ph+ ALL had a MCyR after a median follow up of 6 months (range, 0.1–19), and 38% had a CCyR. The median time to a MCyR was 1 month (range 0.9–3.7 months), with approximately 32% of responders having a sustained response of at least 12 months. The rate of PFS in patients with Ph+ ALL was 7% at 12 months (median 3 months). The rate of OS at 12 months was 40% (median 8 months). [9]

Ponatinib was effective regardless of *BCR-ABL* mutational status.[9] For example, among patients with CP-CML treated with two previous TKIs, overall MCyR for the entire cohort was 67%, with response rates of 63% in R/I patients and 77% in T315I mutation-positive patients.[9]

4.11.12.2 Median follow-up and treatment discontinuation

Median (range) follow-up among patients in the PACE trial as reported by Cortes et al. 2013 was 15 (0.1–25) months for CP, 16 (3.6–25) months for AP, 6 (0.1–21) months for BP, and 6 (0.1–19) months for Ph+ ALL.[9] Overall, 12% of patients discontinued treatment due to AEs. Treatment was discontinued due to lack of efficacy in 4% of patients and due to progressive disease in 19% of patients.[9]

4.11.12.3 Long-term results from the PACE trial (4-years)

The phase 2 PACE trial has a long duration of follow-up with a median of 48.2 months (range, 0.1–58.5).[24] A 4-year follow-up analysis of ponatinib in patients with CP-CML from the PACE trial showed that responses were durable and the rates of PFS and OS were high, even among patients who had received 2 prior TKIs. Among patients receiving 3L ponatinib, 71% achieved a MCyR and 65% achieved CCyR.[24] At 4 years, PFS and OS rates for ≥3L ponatinib in patients with CP-CML were 56% and 77%, respectively. PFS and OS rates were similar for 3L and 4L therapy (3L PFS: 68%; 4L PFS: 52%; 3L OS: 79%; 4L OS: 80%) but both outcomes, PFS and OS, were reduced to 11% with 5L therapy.[24]

As reported by Cortes et al. 2015, among patients with Ph+ ALL in the PACE trial, the 36-month OS was 16% (median not reported).[175] For advanced CML, only short-term data have been published (Cortes et al. 2013).[9] Long-term follow-up data for the whole cohort (all lines of therapy), however, are reported in the ponatinib clinical study report (CSR) (PACE data cut-off, 3 August 2015)[25] and will be included in the updated SmPC. Long-term unpublished MaHR rates from the PACE trial were [redacted] among all patients with AP-CML and [redacted] among all patients with BP-CML (median follow-up of 32 months for AP-CML and 6 months for BP-CML).[25] Among patients with AP-CML (any line), estimated 4-year PFS and OS were [redacted]%,

respectively.[25] Long-term survival results for BP-CML are presented only for the BP-CML/Ph+ ALL combined cohort (ie, not separately for BP-CML and Ph+ ALL), with 2-year PFS and OS of [redacted]%, respectively.[25]

4.11.12.4 Comparator outcomes

CML

The longest duration of follow-up for efficacy outcomes with bosutinib was 31.1 months (range, 0.3–89.1) for patients with CP-CML, 28.4 months (range, 0.3–88.6) for AP-CML, and 10.4 months (range, 0.4–79.9) for BP-CML (Kantarjian et al.[184] reported results with bosutinib over a follow-up duration of ≥36 months [unless patients discontinued earlier] but response rates were only provided in the context of dose reduction and no additional efficacy results were reported).[185, 186] CCyR was achieved in 24%–26% of patients with CP-CML treated with ≥3L bosutinib, and the 2-year PFS and OS rates were 73% and 84%, respectively.[8, 186] Patients with AP- and BP-CML without CHR at baseline who were treated with ≥3L bosutinib had an overall haematologic response rate of 29% and 4%, respectively, at 48 weeks. Four-year OS rates were 45% and 17% for AP- and BP-CML, respectively. Median OS for patients with advanced CML treated with ≥3L bosutinib was 33.4 months (95% CI, 14.6, not reached) for AP-CML and 8.9 months (95% CI, 4.1–17.4) for BP-CML.[185]Cytogenetic and molecular response rates with allo-SCT were reported by Jabbour et al. (2011).[144] Although most patients in this study had received a prior 2G-TKI before undergoing allo-SCT, 38% had received only imatinib prior to the transplantation procedure. With a median follow-up of 22 months, CCyR was the best response in 23% of patients across all CML phases (CP, AP, and BP) and complete molecular response (CMR) was the best response in 66% of patients. The estimated 2-year OS for patients with CP-CML was 72%. PFS was not reported.

Ph+ ALL

As reported by Tavernier et al. 2007, the response rate to reinduction chemotherapy among patients with Ph+ ALL was 37%. After a median follow-up of 4.3 years, patients who received allo-SCT after achieving complete remission had a 2-year OS of 38% (median 10.4 months). OS was much lower for patients who received allo-SCT after failure of reinduction chemotherapy or at the time of relapse; 2-year OS rates were 12% and 8%, respectively.[133]

Table 4-13 presents the outcomes from relevant studies identified in the CML and Ph+ ALL SLRs and included in this submission.

Table 4-13. Results of relevant non-randomised and non-controlled evidence

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
NCT00660920	**Cortes et al. 2012[23]**	Ponatinib (single-arm)	CP-, AP-, BP-CML	Median (range), wk • CP-CML: 73 (7–140) • AP-/BP-CML and Ph+ ALL: 13 (2–121)	Best response achieved on ponatinib, n/N (%) *CP-CML, 3L setting* • CHR: 7/7 (100) • MCyR: 16/18 (89) • CCyR: 14/18 (78) • MMR: 13/19 (68) *CP-CML, 4L setting* • CHR: 8/9 (89) • MCyR: 11/20 (55) • CCyR: 10/20 (50) • MMR: 5/21 (24) *AP- and BP-CML and Ph+ ALL, ≥3L setting for AP-/BP-CML* • MaHR: 8/20 (40) • MCyR: 5/19 (26) • CCyR: 3/19 (16) • MMR: 2/22 (9) Duration of response, median (range), wks *CP-CML, all patients* • MCyR: not reached (8–117+) • MMR: not reached (12–105+) *Advanced disease (AP-/BP-CML, Ph+ ALL), all patients*	NR	NR

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
	Talpaz et al. 2015[176]		CP-CML	Median (range), mo: 49.9 (1.7–69.9)	• MaHR: 16 (0.1–64) *CP-CML, all lines (n=43), %** • MCyR: 72 • CCyR: 65 • MMR: 56 Duration of response • Median not reached (MCyR, CCyR, MMR)	NR	NR
PACE/ NCT01207440	**Cortes et al. 2013[9]**	Ponatinib (single-arm)	CP-, AP-, BP-CML and Ph+ ALL	Median (range), mo • CP-CML: 15 (0.1–25) • AP-CML: 16 (3.6–25) • BP-CML: 6 (0.1–21) • Ph+ ALL: 6 (0.1–19)	Response on ponatinib, n/N (%; 95% CI) *CP-CML, 3L* • MCyR: NR/98 (67; 57, 76) • CCyR: NR/98 (56; 46, 66) • MMR: NR/98 (36; 26, 46) *CP-CML, 4L* • MCyR: NR/141 (45; 37, 54) • CCyR: NR/141 (39; 31, 48) • MMR: NR/141 (33; 26, 42) *AP-CML, 3L* • MaHR: NR/33 (61) • MCyR: NR/33 (42) • CCyR: NR/33 (30) • MMR: NR/33 (24)	Results not reported by line *CP-CML* 12-mo OS: 94% Median (95% CI), mo: NR (NR) *AP-CML* 12-mo OS: 84% Median (95% CI), mo: NR (NR) *BP-CML* 12-mo OS: 29% Median (95% CI), mo: 7 (NR) *Ph+ ALL* 12-mo OS: 40%	Results not reported by line *CP-CML* 12-mo PFS: 80% Median (95% CI), mo: NR (NR) *AP-CML* 12-mo PFS: 55% Median (95% CI), mo: 18 (NR) *BP-CML* 12-mo PFS: 19% Median (95% CI), mo: 4 (NR) *Ph+ ALL* 12-mo PFS: 7%

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
					AP-CML, 4L • MaHR: NR/44 (50) • MCyR: NR/44 (30) • CCyR: NR/44 (16) • MMR: NR/44 (11) *BP-CML, all lines (by 6 months)* • MaHR: NR/62 (31; 20, 44) • MCyR: NR/62 (23; NR) • CCyR: NR/62 (18; NR) *Ph+ ALL, all lines (by 6 months)* • MaHR: NR/32 (41; 24, 59) • MCyR: NR/32 (47; NR) • CCyR: NR/32 (38; NR) Duration of response *CP-CML* • MCyR: 1 day–19.4 mo • Median (95% CI), mo: Not reached (NE, NE) *AP-CML* • MaHR: 1–21+ mo • Median (95% CI), mo: 12 (NR) *BP-CML* • MaHR: 1–20+ mo	Median (95% CI), mo: 8 (NR)	Median (95% CI), mo: 3 (NR)

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
					• Median (95% CI), mo: 5 (NR) *Ph+ ALL* • MaHR: 2–14+ mo • Median (95% CI), mo: 3 (NR)		
	Cortes et al. 2015[175]		CP-, AP-, BP-CML and Ph+ ALL	Median (range), mo • Overall: 35.3 (0.1–52.5)	Response on ponatinib, n/N (%) *See Cortes et al. 2013* As of 2 February 2015, no patients with Ph+ ALL remained on treatment	Results not reported by line *Ph+ ALL* 36-mo OS, %: 16%	NR
	Hochhaus et al. 2015[24]		CP-CML	Median (range), mo • Overall: 48.2 (0.1–58.5) • 2 prior TKIs: 48.2 (0.4–58.2) • 3 prior TKIs: 48.5 (0.2–58.5) • 4 prior TKIs: 28.2 (0.1–49.9)	Response on ponatinib, n/N (%) *CP-CML, 2 prior TKIs (3L)* • MCyR: NR/97 (71) • CCyR: NR/97 (65) • MMR: NR/97 (42) *CP-CML, 3 prior TKIs (4L)* • MCyR: NR/142 (49) • CCyR: NR/142 (45) • MMR: NR/142 (37) *CP-CML, 4 prior TKIs (5L)* • MCyR: NR/12 (58) • CCyR: NR/12 (33) • MMR: NR/12 (8)	*All CP-CML (n=267)* 48-mo OS, %: 77 Median (95% CI): Not reached (NE, NE) *2 prior TKIs* 48-mo OS, %: 79 Median (95% CI): Not reached (NE, NE) *3 prior TKIs* 48-mo OS, %: 80 Median (95% CI): Not reached (NE, NE) *4 prior TKIs* 48-mo OS, %: 11 Median (95% CI), mo: 38.9 (NR)	*All CP-CML (n=267)* 48-mo PFS, %: 56 Median (95% CI): Not reached (NE, NE) *2 prior TKIs:* 48-mo PFS, %: 68 Median (95% CI): Not reached (NE, NE) *3 prior TKIs* 48-mo PFS, %: 52 Median (95% CI): Not reached (NE, NE) *4 prior TKIs (47-month PFS)* 47-mo PFS, %: 11 Median (95% CI), mo: 11.1 (NR)

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
					Duration of response: NR		
NCT00261846	**Khoury et al. 2012[8]**	Bosutinib (single-arm)	CP-CML	Median (range), mo: 28.5 (0.3–56.2)	Best cumulative response achieved with bosutinib, n/N (%) <u>*CP-CML, ≥3L*</u> • CHR: 44/68 (65) • CCyR†: 26/108 (24) • PCyR: 9/108 (8) • MCyR: 35/108 (32) • MMR: 16/105 (15) Duration of response, median • MCyR: Not reached • CCyR: Not reached	<u>*CP-CML, ≥3L*</u> 1 y: 91% 2 y: 83% Median (95% CI): Not reached (NR)	<u>*CP-CML, ≥3L*</u> 1 y: 77% 2 y: 73% Median (95% CI): Not reached (NE, NE)
	Kantarjian et al. 2014[184]		CP-CML	≥36 mo, unless discontinued earlier	NA (only responses post–dose reduction provided)	NR	NR
	Gambacorti-Passerini et al. 2015[185]		AP-, BP-CML	Median (range), mo: • AP-CML: 28.4 (0.3–88.6) • BP-CML: 10.4 (0.4–79.9)	Responses achieved with bosutinib, n/N (%; 95% CI) <u>*AP-CML, ≥3L*</u> • OHR (48 wks): 7/24 (29; NR) • MCyR (cumulative by 4 y): 4/23 (17; NR) <u>*BP-CML, ≥3L*</u> • OHR (48 wks): 1/23 (4; NR) • MCyR (cumulative by 4 y): 3/22 (14; NR)	OS, % (95% CI) <u>*AP-CML, ≥3L*</u> • 1 y: 73 (53, 85) • 4 y: 45 (25, 63) Median (95% CI), mo: 33.4 (14.6, not reached) <u>*BP-CML, ≥3L*</u> • 1 y: 39 (22, 57) • 4 y: 17 (6, 33) Median, mo (95% CI): 8.9 (4.1, 17.4)	NR

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
					Duration of response, median (95% CI), wks *AP-CML, ≥ -* • OHR: Not reached (102.0, not reached) • MCyR: 24.0 (13.4, not reached) *BP-CML, ≥ -* • OHR: 48.0 (24.0, not reached) • MCyR: 34.3 (4.0, not reached)		
	Gambacorti-Passerini et al. 2014[186]		CP-CML	Duration (range), mo: 31.1 (0.3–89.1)	Responses achieved with bosutinib, n/N (%; 95% CI) *CP-CML (evaluable patients), ≥3L* • MCyR: 37/112 (33; NR) • CCyR: 29/112 (26; NR) Duration of response: NR	*≥3L* 2-year OS, %: 84 Median OS: NR	NR
—	**Jabbour et al. 2011[144]**	Allo-SCT (single-arm)	CP-, AP-, BP-CML	Median (range), mo: 22 (5–53)	Best response, n (%) *All patients‡* • CCyR: 11/47 (23) • CMR: 31/47 (66) • MMR: 1/47 (2) Duration of response: NR Time to relapse, median (range), mo: 6 (0–44)	% (95% CI) *All patients‡* Estimated 2-y OS: 63 (49, 78) *CP-CML* Estimated 2-y OS: 72 (49, 96) *AP-CML* Estimated 2-y OS: 59 (41, 77)	NR

Study ID	Publication	Intervention	Disease and phase	Duration of follow-up	Response	OS	PFS/EFS
—	**Tavernier et al. 2007[133]**	Investigator's choice[§]	ALL	Median (range), y: 4.3 (NR)	Response to reinduction chemotherapy, n/N (%) Ph+ ALL: 30/81 (37)	Medians: NR OS, % (95% CI) *All patients who received allo-SCT* 2-y OS: NR 5-y OS: 25% Median: 6.7 mo *Allo-SCT after CR achievement (n=61)* 2-y OS: 38% 5-y OS: 33% Median: 10.4 mo *Allo-SCT after failure of reinduction chemo (n=24)* 2-y OS: 12% 5-y OS: 12% Median: 2.6 mo *Allo-SCT at time of relapse (n=14)* 2-y OS: 8% 5-y OS: 8% Median: 4.1 mo	NR

2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CMR, complete molecular response; CP, chronic phase; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; mo, month; NE, not estimable; NR, not reported; OS, overall survival; PCyR, partial cytogenetic response; PFS, progression-free survival; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukaemia; TKI, tyrosine kinase inhibitor; wk, week; y, year.

*Results not reported by line (60% of patients had received ≥3 prior TKIs) or for advanced CML.

[†]Evaluable patients had a baseline disease assessment. Patients with CCyR at baseline were considered nonresponders for assessment of cytogenetic response.

[‡]Includes results from patients who received allo-SCT post- imatinib (ie, 2L allo-SCT); these patients represented <50% of the total population.

[§]Salvage treatment was investigator's choice according to initial induction and consolidation regimen, duration of first remission, disease features at relapse, and availability of a suitable allogeneic donor.

4.12 Adverse reactions

4.12.1 Adverse reactions associated with ponatinib

Adverse reactions associated with ponatinib are described in Sections 4.12.2–4.12.4.

4.12.2 Adverse reactions reported in studies identified in the clinical SLR

4.12.2.1 PACE trial safety

Ponatinib has a generally well tolerated and manageable safety profile. In the PACE trial, the median treatment duration for the ponatinib safety population was 12.8 months (range: 1 day to over 24.8 months). Fifty-five percent of the study population had a dose reduction during this time, and 67% of the patients had at least one dose interruption. The most common non-haematologic AEs reported in the PACE study were skin reactions (34% of patients had rash and 32% developed dry skin) and abdominal pain (22%), which were primarily Grade 1 or 2 in severity. The most common non-haematologic treatment-related AEs (TRAEs) in the PACE study are summarised in Table 4-14.[9]

Table 4-14. Non-haematologic AEs with a frequency ≥10% and Grade 3 or Grade 4 events with an incidence of >1% in the total study population in the PACE study (Cortes et al. 2013)[9]

	CP-CML		Total number of patients (N=449)	
Non-haematologic treatment-related AEs	**Any grade n (%)**	**Grade 3/4 n (%)**	**Any grade n (%)**	**Grade 3/4 n (%)**
Rash*	107 (40)	10 (4)	153 (34)	16 (4)
Dry skin	104 (39)	5 (2)	142 (32)	7 (2)
Abdominal pain	74 (27)	20 (7)	101 (22)	27 (6)
Headache	63 (23)	5 (2)	84 (19)	6 (1)
Lipase increased	57 (21)	27 (10)	80 (18)	47 (10)
Fatigue	51 (19)	4 (1)	78 (17)	7 (2)
Constipation	53 (20)	3 (1)	73 (16)	5 (1)
Myalgia	46 (17)	3 (1)	71 (16)	3 (1)
Arthralgia	45 (17)	6 (2)	70 (16)	7 (2)
Nausea	38 (14)	1 (0)	60 (13)	1 (0)
ALT increased	31 (11)	9 (3)	47 (10)	14 (3)
Pancreatitis	19 (7)	17 (6)	29 (6)	24 (5)
Hypertension	25 (9)	6 (2)	33 (7)	11 (2)
AST increased	24 (9)	5 (2)	37 (8)	10 (2)
Blood amylase increased	16 (6)	4 (1)	26 (6)	9 (2)
Gamma-glutamyl transferase increased	11 (4)	4 (1)	20 (4)	7 (2)
Dyspnoea	13 (5)	4 (1)	23 (5)	5 (1)
Cardiac failure	3 (1)	2 (1)	6 (1)	5 (1)

*Includes erythematous and papular rash.
AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CML, chronic myeloid leukaemia; CP, chronic phase.

The most common haematologic TRAEs in the PACE study were thrombocytopaenia (37%), neutropaenia (19%), and anaemia (13%) (Table 4-15).[9]

Table 4-15. Haematologic TRAEs with a frequency ≥10% and Grade 3 or Grade 4 events with an incidence of >1% in the total study population in the PACE study (Cortes et al. 2013)[9]

	CP-CML		Total number of patients (N=449)	
Haematologic TRAEs	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade ¾ n (%)
Thrombocytopaenia	111 (41)	86 (32)	167 (37)	132 (29)
Neutropaenia	44 (16)	38 (14)	84 (19)	75 (17)
Anaemia	27 (10)	15 (6)	60 (13)	40 (9)
White blood cell count decreased	11 (4)	7 (3)	19 (4)	13 (3)
Pancytopaenia	2 (<1)	2 (<1)	8 (2)	7 (2)
Febrile neutropaenia	1 (<1)	1 (<1)	7 (2)	7 (2)

AE, adverse event; CML, chronic myeloid leukaemia; CP, chronic phase; TRAE, treatment-related adverse event.

Non-haematologic serious AEs (SAEs) occurring in >1% of patients were pancreatitis (5%), abdominal pain (2%), increased lipase (2%), diarrhoea (1%), pyrexia (1%), and myocardial infarction (1%). Haematologic SAEs occurring in >1% of patients were thrombocytopaenia (2%), anaemia (1%), neutropaenia (1%), febrile neutropaenia (1%), and pancytopaenia (1%). Eighteen patients discontinued due to death. Five deaths were assessed by the investigators as being possibly or probably related to treatment with ponatinib: one patient with CP-CML had pneumonia and one patient with CP-CML had an acute myocardial infarction; one patient with AP-CML had fungal pneumonia; one patient with BP-CML had a gastric haemorrhage; and one patient with Ph+ ALL had cardiac arrest. Other reported reasons for death were: sepsis or septic shock (n=4); cardiac arrest (n=2); congestive cardiac failure (n=2); cardiopulmonary failure (n=1); dehydration (n=1); the hyperviscosity syndrome (n=1); neoplasm progression (n=1); and small intestinal obstruction (n=1).[9]

Arterial thrombotic events were observed in the PACE trial. Cardiovascular, cerebrovascular, and peripheral vascular events considered, at least, possibly related to treatment by the investigator, were observed in 2.2%, 0.7%, and 1.6% of patients, respectively. Regardless of treatment causality of these AEs, 7.1% of patients had cardiovascular events, 3.6% had cerebrovascular events, and 4.9% had peripheral vascular events (Table 4-16). Two patients discontinued ponatinib following occurrence of one event. Of the remaining patients, 36% experienced one or more additional events. Cardiovascular, cerebrovascular, and peripheral vascular treatment-related SAEs (TRSAEs) were observed in 2.0%, 0.4%, and 0.4% of patients, respectively. Regardless of treatment relationship, 5.1% had cardiovascular SAEs, 2.4% had cerebrovascular SAEs, and 2.0% had peripheral vascular SAEs. While 55% of these patients had a previous history of ischaemic disease at the point of study enrolment, 95% had one or more risk factors (hypertension, diabetes, hypercholesterolaemia, obesity) and/or history of ischaemic disease, non-ischaemic cardiac disease, or venous thromboembolism.[9] Long-term data show that the cumulative incidence of arterial occlusive events increased over time.[24] At 4-years follow-up, among all patients with CP-CML, serious cardiovascular, cerebrovascular, and peripheral vascular events occurred in 11.1%, 9.6%, and 9.3% of patients, respectively. However, the exposure-adjusted incidence of newly occurring arterial occlusive events (and dose intensity) decreased with longer duration of ponatinib treatment.[24]

Table 4-16. Arterial thrombotic events observed in the PACE trial (Cortes et al. 2013)[9]

AE	% TRAE	% TRAE and non-TRAE	% TRSAE	% TRSAE and non-TRSAE
Cardiovascular	2.2	7.1	2.0	5.1
Cerebrovascular	0.7	3.6	0.4	2.4
Peripheral vascular	1.6	4.9	0.4	2.0

TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

4.12.2.2 Grade ≥3 AEs and comparator data

Table 4-17 and Table 4-18 summarise the most common Grade 3 or higher adverse reactions reported in relevant studies identified in the clinical CML and ALL SLRs.

The most common ≥Grade 3 AEs (treatment-emergent [TEAEs] and TRAEs) across all phases of CML in the pivotal ponatinib trials were thrombocytopaenia (20%–35%), neutropaenia (10%–26%), anaemia (2%–21%), and increased lipase (7%–13%).[9, 23, 24]

In the 4-year follow-up data from the PACE trial, Hochhaus et al. (2015)[24] provided the incidence of ≥Grade 3 AEs in patients with CP-CML by number of prior TKIs. The rates of ≥Grade 3 AEs in patients receiving 3L, 4L, and 5L ponatinib were 86%, 89%, and 100%, respectively (data not shown). In the 3L, the most common Grade 3/4 non-haematologic TEAEs and haematologic toxicities in patients with CP-CML treated with ponatinib were thrombocytopaenia (35%), abdominal pain (14%), hypertension (12%), and increased lipase (10%).

According to long-term follow-up data (≥36 months) published by Kantarjian et al.,[184] the most common Grade 3/4 non-haematologic TEAE in patients with CP-CML treated with ≥3L bosutinib was diarrhoea (9%), and the most common Grade 3/4 haematologic toxicities were thrombocytopaenia (26%), neutropaenia (15%), and anaemia (7%). Similar to CP-CML, the most common Grade 3/4 non-haematologic TEAE reported in the Gambacorti-Passerini et al. publication[185] for patients with AP- and BP-CML treated with bosutinib was diarrhoea (4% and 5%, respectively), while the most common Grade 3/4 haematologic toxicities in patients were thrombocytopaenia (AP: 44%; BP: 36%), neutropaenia (AP: 18%; BP: 25%), and anaemia (AP: 33%; BP: 20%).

The only ≥Grade 3 AE reported in the Jabbour et al. publication was the rate of Grade 3/4 graft-versus-host disease (GVHD). Across all phases of CML, 17% of patients experienced Grade 3/4 GVHD (median follow-up: 22 months).[144]

As reported by Cortes et al. 2013, among patients with Ph+ ALL in the PACE trial, the most common non-haematologic ≥Grade 3 TRAEs were increased lipase (6%), abdominal pain (6%), rash (3%), constipation (3%), increased ALT (3%), hypertension (3%), and increased AST (3%).[9] The most common haematologic TRAEs were neutropaenia (12%), anaemia (12%), thrombocytopaenia (6%), febrile neutropaenia (6%), and decreased white-cell count (3%). Cortes et al. 2015 did not report 3-year follow-up safety results for patients with Ph+ ALL.[175] Tavernier et al. 2007 did not report adverse reactions associated with salvage therapy in relapsed ALL.[133]

Table 4-17. Adverse reactions associated with treatments for CML from relevant studies identified in the SLR

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
NCT00660920	**Cortes et al. 2012[23]**	TRAEs (N=81), line of therapy NR* Non-haematologic events, n (%) • Increased lipase: 6 (7) • Pancreatitis: 4 (5) • Increased amylase: 2 (2) • Prolonged QT interval: 2 (2) Haematologic events, n (%) • Thrombocytopaenia: 16 (20) • Neutropaenia: 8 (10) • Anaemia: 2 (2)	NR	NR	NR
	Talpaz et al. 2015[176]	—	NR	—	—

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
PACE/ NCT01207440	**Cortes et al. 2013[9]**	NR	TRAEs (N=270), line of therapy NR†	TRAEs (n=85), line of therapy NR †	TRAEs (n=62), line of therapy NR †
			Non-haematologic, n (%) • Increased lipase: 27 (10) • Abdominal pain: 20 (7) • Pancreatitis: 17 (6) • Rash: 10 (4) • Increased ALT: 9 (3) • Dry skin: 5 (2) • Headache: 5 (2) • Arthralgia: 6 (2) • Hypertension: 6 (2) • Increased AST: 5 (2) Haematologic, n (%) • Thrombocytopaenia: 86 (32) • Neutropaenia: 38 (14) • Anaemia: 15 (6) • Decreased white-cell count: 7 (3)	Non-haematologic, n (%) • Increased lipase: 11 (13) • Pancreatitis: 5 (6) • Abdominal pain: 4 (5) • Rash: 3 (4) • Hypertension: 3 (4) • Increased AST: 3 (4) • Increased blood amylase: 3 (4) • Increased ALT: 2 (2) • Increased γ-glutamyltransferase: 2 (2) Haematologic, n (%) • Thrombocytopaenia: 28 (33) • Neutropaenia: 22 (26) • Anaemia: 8 (9) • Decreased white-cell count: 5 (6) • Pancytopaenia: 2 (2) • Febrile neutropaenia: 2 (2)	Non-haematologic, n (%) • Increased lipase: 7 (11) • Rash: 2 (3) • Fatigue: 2 (3) • Increased ALT: 2 (3) • Pancreatitis: 2 (3) • Increased blood amylase: 2 (3) • Cardiac failure: 2 (3) • Dry skin: 1 (2) • Abdominal pain: 1 (2) • Headache: 1 (2) • Hypertension: 1 (2) • Increased AST: 1 (2) • Increased γ-glutamyltransferase: 1 (2) • Dyspnoea: 1 (2) Haematologic, n (%) • Thrombocytopaenia: 16 (26) • Anaemia: 13 (21) • Neutropaenia: 11 (18) • Pancytopaenia: 3 (5) • Febrile neutropaenia: 2 (3)

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
	Hochhaus et al. 2015[24]	—	Grade 3/4 TEAEs in ≥20% (any grade) of patients (n=97), 3L Non-haematologic and haematologic, n (%) • Thrombocytopaenia: 34 (35) • Abdominal pain: 14 (14) • Hypertension: 12 (12) • Increased lipase: 10 (10) • Rash: 4 (4) • Arthralgia: 4 (4) • Headache: 3 (3) • Fatigue: 3 (3) • Pain in extremity: 3 (3) • Myalgia: 2 (2) • Dry skin: 1 (1) • Constipation: 1 (1) • Nausea: 1 (1) • Pyrexia: 1 (1) • Back pain: 1 (1) Grade 3/4 TEAEs in ≥20% (any grade) of patients (N=270), 2L–5L Non-haematologic and haematologic, n (%) • Thrombocytopaenia: 95 (35) • Hypertension¶: 34 (13) • Increased lipase: 33 (12) • Abdominal pain: 27 (10) • Rash: 10 (4) • Headache: 9 (3) • Dry skin: 9 (3) • Constipation: 7 (3) • Arthralgia: 8 (3) • Pain in extremity: 9 (3) • Fatigue: 6 (2)	—	—

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
NCT00261846	**Khoury et al. 2012[8]**	—	Grade 3/4 TRAEs (N=118), ≥3L[§] Non-haematologic, n (%) • Diarrhoea: 10 (8) • Rash: 5 (4) Grade 3/4 laboratory abnormalities on therapy (N=118), n (%) • Anaemia: 10 (8) • Thrombocytopaenia: 30 (25) • Elevated ALT: 8 (7) • Neutropaenia: 23 (19) • Elevated AST: 4 (3) • Hypocalcaemia: 6 (5) • Hypophosphataemia: 3 (2) • Hypermagnesaemia: 14 (12) • Elevated lipase: 8 (7)	—	—

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
	Kantarjian et al. 2014[184]	—	Grade 3/4 TEAEs occurring in ≥10% (any grade) of patients (N=118), ≥3L[§] Non-haematologic, n (%) • Diarrhoea: 10 (9) • Pleural effusion: 4 (3) • Headache: 4 (3) • Back pain: 3 (3) • Rash: 3 (3) • Fatigue: 2 (2) • Abdominal pain: 1 (1) • Arthralgia: 1 (1) • Decreased appetite: 1 (1) • Dyspnoea: 1 (1) • Nausea: 1 (1) • Vomiting: 1 (1) Grade 3/4 laboratory abnormalities on therapy (N=118), n (%) • Thrombocytopaenia[‖]: 31 (26) • Neutropaenia[‖]: 18 (15) • Anaemia[‖]: 8 (7) • Elevated ALT: 7 (6) • Elevated AST: 3 (3)	—	—

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
	Gambacorti-Passerini et al. 2015[185]	—	—	Grade 3/4 TEAEs occurring in ≥10% (any grade) of patients (n=79), 2L and ⩾3L Non-haematologic, n (%) • Diarrhoea: 3 (4) • Nausea: 2 (3) • Vomiting: 3 (4) • Rash: 3 (4) • Abdominal pain: 3 (4) • Fatigue: 4 (5) • Headache: 2 (3) • Dyspnoea: 7 (9) • Pneumonia: 9 (11) • Elevated ALT: 6 (8) • Elevated AST: 4 (5) • Pleural effusion: 4 (5) • Chest pain: 2 (3) Haematologic, n (%) • Thrombocytopaenia: 35 (44) • Anaemia: 26 (33) • Neutropaenia: 14 (18) • Leukopaenia: 5 (6) • Leukocytosis: 3 (4)	Grade 3/4 TEAEs occurring in ≥10% (any grade) of patients (n=64), 2L and ⩾3L Non-haematologic, n (%) • Diarrhoea: 3 (5) • Nausea: 1 (2) • Vomiting: 2 (3) • Pyrexia: 2 (3) • Rash: 2 (3) • Abdominal pain: 2 (3) • Fatigue: 3 (5) • Headache: 4 (6) • Dyspnoea: 2 (3) • Constipation: 1 (2) • Pneumonia: 5 (8) • Elevated ALT: 1 (2) • Abdominal pain upper: 2 (3) • Back pain: 1 (2) • Pleural effusion: 2 (3) • Peripheral oedema: 1 (2) • Bone pain: 2 (3) Haematologic, n (%) • Thrombocytopaenia: 23 (36) • Anaemia: 13 (20) • Neutropaenia: 16 (25) • Leukopaenia: 12 (19) • Leukocytosis: 2 (3) • Febrile neutropaenia: 2 (3)

Study ID	Publication	Most common ≥Grade 3 AEs			
		All patients	CP-CML	AP-CML	BP-CML
	Gambacorti-Passerini et al. 2014[186]	—	Grade 3/4 TEAEs occurring in ≥20% (any grade) of patients (N=119), 3L or 4L Non-haematologic, n (%) • Diarrhoea: NR (9) Grade 3/4 haematologic toxicities (N=119), n (%) • Thrombocytopaenia: NR (26) • Neutropaenia: NR (16) • Anaemia: NR (7)	—	—
—	**Jabbour et al. 2011[144]**	Grade 3/4 GVHD, n/N (%): 8/47 (17)	—	—	—

3L, third line; 4L, fourth line; 5L, fifth line; AE, adverse event; allo-SCT, allogeneic stem cell transplantation; ALT, alanine aminotransferase; AP, accelerated phase; AST, aspartate aminotransferase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; GVHD, graft-versus-host disease; NR, not reported; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

*≥98% of CML patients had received ≥2 prior TKIs; AE results include 5 patients with Ph+ ALL and 16 patients with AML or other diagnoses.

†92% of patients with CP-CML and 95% of patients with AP-/BP-CML had received ≥2 prior TKIs.

‡Population evaluated for safety NR. Total population included 39 and 21 CP- and AP-CML patients, respectively. Population evaluated for efficacy consisted of 37 and 17 patients with CP- and AP-CML, respectively.

¶241/270 (89%) patients had elevated blood pressure at baseline (148/270 [55%] had ≥140 mm Hg systolic or ≥90 mm Hg diastolic); 187/270 (69%) patients experienced any increase from baseline in blood pressure on study.

§CP ≥3L patient population includes patients for whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy (n=1) or resistant or intolerant to prior nilotinib and dasatinib therapy (n=3; 4L). Because of low n, data were not shown separately.

‖Individual haematologic TEAEs were clustered with the related terms from investigations.

Table 4-18. Adverse reactions associated with treatments for Ph+ ALL from relevant studies identified in the SLR

Study ID	Publication	Most common ≥Grade 3 AEs ALL, n (%)
PACE/ NCT01207440	Cortes et al. 2013[9]	TRAEs (N=32) in Ph+ ALL, line of therapy NR* Non-haematologic • Increased lipase: 2 (6) • Abdominal pain: 2 (6) • Rash: 1 (3) • Constipation: 1 (3) • Increased ALT: 1 (3) • Hypertension: 1 (3) • Increased AST: 1 (3) Haematologic • Thrombocytopaenia: 2 (6) • Neutropaenia: 4 (12) • Anaemia: 4 (12) • Decreased white-cell count: 1 (3) • Febrile neutropaenia: 2 (6)
—	Cortes et al. 2015[175]	NR†
—	Tavernier et al. 2007[133]	NR†

*82% of patients with Ph+ ALL had received ≥2 prior TKIs.

†Cortes et al. 2015 and Tavernier et al. 2007 do not report TEAEs/TRAEs in patients with ALL

4.12.3 Additional adverse reactions

The most recent AE data for ponatinib are reported in the CSR (data cut-off, 3 August 2015). Table 4-19 lists the most common Grade ≥3 AEs in patients with CML and Ph+ ALL.

Table 4-19. TRAEs/TEAEs associated with ponatinib (PACE data cut-off, 3 August 2015)

AE	Most common Grade ≥3 AEs CP-CML (N=97)*	AP-CML (N=85)	BP-CML (N=62)	Ph+ ALL (N=32)
TRAEs/TEAEs reported in >5% of patients, n (%)				
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukocytopaenia	[redacted]	[redacted]	[redacted]	[redacted]
Increased lipase				
Neutropaenia				
Febrile neutropaenia	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]
Elevated ALT				
Gamma-glutamyltransferase increased				
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	[redacted]
VOEs (number of events per 100 patient-years)				
CV event	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular event				
Peripheral arterial occlusive event	[redacted]	[redacted]	[redacted]	[redacted]
Serious venous thrombotic event	[redacted]	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; ALT, alanine aminotransferase; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; CSR, clinical study report; CV, cardiovascular; Ph+, Philadelphia chromosome–positive; VOEs, vascular occlusive events.

*Patients treated with two prior TKIs.

Sources: PACE study CSR[25], CP-CML, 14.3.1.3.1.2.6 (p2280–2291); AP-CML, Table 14.3.1.8.1.9 (p3296–3312); BP-CML, Table 14.3.1.8.2.10.1 (p3552); Ph+ ALL, Table 14.3.1.8.2.10.2 (p3569); VOEs, Section 14.3.5 Other Safety Measurements, Table 2.2 (p6124–6126).

4.12.4 Brief overview of ponatinib safety in relation to the decision problem

Haematologic and non-haematologic AEs

Overall, clinical evidence in heavily pre-treated patients with CP-, AB-, and BP-CML and Ph+ ALL shows that TEAEs associated with ponatinib are manageable and that the rate of treatment discontinuation due to AEs is low.[9, 24] Many of the AEs observed in patients treated with ponatinib (such as anaemia, neutropaenia, and thrombocytopaenia) are characteristics features of the disease, and the absence of head-to-head comparative data hinders drawing conclusions about how treatment contributes to the occurrence of these AEs.[35] When indirectly compared with bosutinib, however, the incidences of these AEs reported with ponatinib were similar.[8, 9, 23, 24, 184, 186] The cost-effectiveness models for CP-CML and AP/BP-CML incorporates Grade 3/4 TEAEs/TRAEs for bosutinib and ponatinib, as described in Section 5.

While the safety profile of ponatinib is generally similar to that of other TKI agents, important differences were observed in the PACE trial for certain clinically important events, including pancreatitis and cardiovascular events.

Pancreatitis

In the PACE trial (Cortes et al. 2013), the most common serious adverse event (SAE) was pancreatitis, occurring in 7.4% of patients treated with ponatinib.[9] Pancreatitis occurred within the first 2 months of treatment in 86% of patients and was reversible, with most cases resolving within 1 week of treatment interruption. Of note, pancreatitis is uncommon with other TKIs.[35] The ponatinib SmPC provides detailed recommendations on dose modifications for patients who develop pancreatitis.[22]

Vascular AEs

During the 4-year PACE follow-up, serious cardiovascular, cerebrovascular, and peripheral vascular events occurred in 11.1%, 9.6%, and 9.3% of patients with CP-CML, respectively.[24] Per SmPC guidance, patients treated with ponatinib should have a baseline cardiovascular assessment and monitor cardiovascular status throughout treatment.[22] We therefore note that the safety profile of ponatinib will be associated with an additional cost of a cardiology visit, scheduled once every six months according to the UK HCP survey.[48] These additional costs will be fully incorporated into the evaluation of cost-effectiveness.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Clinical benefits and harms of ponatinib

CP-CML

Substantial cytogenetic responses are achieved with ponatinib in heavily pre-treated patients with CP-CML,[9] with high rates maintained over time (up to 4-years follow-up).[24] In patients with CP-CML receiving ponatinib in the 3L, 4-year PFS, defined as death, development of AP or BP, loss of CHR in absence of cytogenetic response, loss of MCyR, or increasing white blood cell count without CHR, was 68% and OS was 79% (median not reached for both).[9, 24] These results are notable in patients who have failed 2 prior TKIs.[140] With regards to disease transformation, of the total CP-CML patient population including those receiving 4L and 5L ponatinib, only 3% (9/267) of patients transformed from CP to AP-/BP-CML.

A MAIC in CP-CML showed that ponatinib provides superior efficacy and durability of response vs bosutinib (see Section 4.10.15). Compared to bosutinib, with a best response of 24.1% (CCyR), the matching-adjusted response rate with ponatinib was 61.3%. In the PACE study, the proportion of patients who achieved CCyR on ponatinib and maintain their response at 4 years is [redacted]% (unpublished data, CSR);[25] after matching, the proportion of patients on ponatinib maintaining CCyR at 4 years is 89%. With bosutinib, the probability of maintaining a CCyR at 4 years is 54%, as reported by Gambacorti-Passerini et al. 2014.[186] The bosutinib maintenance of response data, however, are biased in that they include patients with newly achieved response as well as patients who had already achieved response at baseline and maintained response

during the study.[186] Conversely, maintenance of response data with ponatinib reported in the PACE trial represent only the percentage of patients who had failed prior therapy and achieved a response on ponatinib treatment. Of note, patients with CP-CML treated with bosutinib in the phase 1/2 study were followed for only 2 years after treatment discontinuation,[186] limiting long-term follow-up comparisons between trials.[25]

Ponatinib should be used after failure of one 2G-TKI, since adequate evidence are lacking to support the benefit of sequential use of 2G-TKIs (including bosutinib) as an effective strategy for patients with CML in whom prior 2G-TKI therapy has failed. This position in therapy for ponatinib is reflected in the SmPC, based on robust data from the PACE trial. Bosutinib was granted a "conditional approval" by the EMA in 2013 because only a minority of patients in the phase 1/2 bosutinib trial (eg, n=21, 3L CP-CML) met the criteria for the "unmet medical need" subpopulation;[102] additional efficacy data are needed to confirm the benefit of bosutinib in the intended indication.[36] In comparison, the study population of the PACE trial aligns fully with the ponatinib indication, for use after failure of one 2G-TKI.

AP/BP-CML

MaHR rates achieved with 3L ponatinib in AP-CML (median follow-up of 16 months) and all lines of ponatinib in BP-CML (median follow-up of 6 months) in the PACE trial were 61% and 31%, respectively.[9] In comparison, Gambacorti-Passerini et al. 2015 only report achieved and maintained MaHR rates with ≥3L bosutinib for AP- and BP-CML (38% and 8%, respectively).[185] These data cannot be directly compared with the achieved MaHR response rates from the PACE trial. Considering this limitation, it may be more appropriate to compare achieved MaHR with ponatinib to achieved OHR with bosutinib. The definitions of MaHR and OHR largely overlap, though the more stringent criteria required for MaHR make it more difficult to achieve (MaHR is defined as CHR + no evidence of leukaemia [NEL] whereas OHR is defined as CHR + NEL + minor haematologic response + return to CP [if applicable]).[9, 185] Within 48 weeks of starting ≥3L bosutinib, achieved OHR rates were 29% (AP-CML) and 4% (BP-CML).[185] The MaHR rates achieved with ponatinib in AP- and BP-CML are notable in light of the low OHR rates achieved with bosutinib in the 3L setting.

Among patients in AP-CML treated with ponatinib, 1-year OS rate was 84% (median not reached), 1-year PFS was 55% (median 18 months), and the proportion of patients maintaining a MaHR 12 months or longer was 48%. OS was much lower for patients with BP-CML, with only 29% of patients surviving for 1 year (median 7 months); 1-year PFS was 19% (median 4 months), and the proportion of patients maintaining a MaHR 12 months or longer was 42%.[9] The 1-year OS with ≥3L bosutinib was 73% (median 33.4 months) in AP-CML and 39% (median 8.9 months) in BP-CML. PFS results were not reported. The 1-year probability of maintaining OHR response with ≥3L bosutinib was 80% (median not reached) in AP-CML and 38% (median 48 weeks) in BP-CML; however, these results cannot be directly compared with data from the PACE trial because maintenance of response with bosutinib reflects both achieved responses and responses maintained from baseline.[185]

Allo-SCT

Only limited data on allo-SCT after failure of two TKIs, and no studies for BSC (hydroxycarbamide) in the post–2G-TKI setting, were identified in the CML SLR. As such, comparing outcomes with ponatinib against these treatments is difficult. Nevertheless, Jabbour et al. 2011 provide data for allo-SCT in the post–2G-TKI setting.[144] OS was lower among patients with CP-CML who underwent transplantation than the observed survival with ponatinib in the PACE trial (72% [2-year OS] vs 79% [4-year OS], respectively).[9, 144]

Ph+ ALL

Few data are available to compare ponatinib with established clinical practice for the indicated patient population, as specified in the SmPC and NICE scope. Data from the single-arm PACE study (Cortes et al. 2013) show that ponatinib demonstrates remarkable response rates in patients with Ph+ ALL who were previously treated with one or more TKIs: MaHR was 41% and MCyR was 47%, with 12-month PFS and OS of 7% and 40%, respectively.[9] Current treatment guidelines recommend allo-SCT for suitable patients with Ph+ ALL.[28] Among patients with ALL

who relapse and receive allo-SCT after achieving a CR2 with reinduction chemotherapy, 2-year OS post–allo-SCT is 38%.[133] The situation is less favourable for patients who receive allo-SCT after reinduction failure or at the time of relapse, with 2-year OS of 12% and 8%, respectively.[133] For patients who are R/I to prior TKI therapy and suitable candidates for allo-SCT, ponatinib represents a "bridge" to allo-SCT by improving the rate of achieving complete remission prior to transplantation.

Safety

While the safety profile of ponatinib is generally similar to that of other TKIs, important differences were observed in the PACE trial for a few clinically important events, including pancreatitis and cardiovascular events.[9]

Benefit-risk balance

Treatment options are limited for patients who have failed, or are intolerant to 2L TKI therapies such as dasatinib and nilotinib. When used after failure of both imatinib and a 2G-TKI, the efficacy of all of the remaining treatments available today, expressed in terms of CCyR, is modest.[8, 23, 94, 95] Thus, in order to improve long-term survival, it is vital that patients have access to effective treatment options with proven efficacy in patients treated with ≥2 prior TKIs. Ponatinib offers significant clinical benefit to patients in any phase of CML treated with ≥2 prior TKIs, with manageable TRAEs/TEAEs. Pancreatitis and cardiovascular AEs require patients receiving ponatinib be monitored periodically to minimise the risk of potentially serious outcomes.[22]

Overall, available clinical evidence supports a positive benefit-risk ratio for ponatinib. As stated in the EPAR, "the clinical benefits are considered relevant and outweigh the potential risks, which to large extent appear manageable."[35] Subsequent to the EPAR, updated clinical trial data revealed an accumulation of VOEs related to treatment; however, after a thorough investigation of ponatinib safety and changes to the SmPC, the PRAC concluded that the benefit-risk balance of ponatinib remained favourable.[37]

4.13.2 Strengths and limitations of the clinical evidence base for ponatinib

4.13.2.1 Internal and external validity of clinical evidence base

Study design features

The clinical evidence base in this submission has several strengths including the size of the enrolled patient population and the duration of study follow-up. The patient populations of both the PACE and phase 1/2 bosutinib trials were among the largest of any trial investigating TKIs in patients who failed two or more prior TKIs. Compared to bosutinib, however, stronger clinical evidence supports ponatinib. With 449 patients enrolled, PACE is the largest trial of heavily pre-treated patients with CML. In addition, the PACE study CML and ALL patient populations are the same populations for which ponatinib is licensed.[22] This is not the case for bosutinib, which received a conditional approval based on a subgroup of patients with unmet need (52 patients overall and 21 patients with CP-CML; including 2L patients).[102] As such, much stronger clinical evidence is available supporting the use of ponatinib in its indicated population than for bosutinib. Furthermore, PACE has provided opportunities to evaluate long-term OS and PFS with 4-year data available.[24] Patients in the phase 1/2 bosutinib trial were followed over the long term, but not beyond 2 years after bosutinib discontinuation.[8]

In the PACE clinical study,[9] ponatinib exhibited clinically meaningful responses in all disease stages in this heavily pre-treated patient population. The response rates achieved in each of the six study cohorts met or exceeded the pre-specified statistical criteria for success. In both CP-CML cohorts, and in the AP-CML R/I cohort (ie, the 3 largest cohorts), the 95% CI on the observed response rate also exceeded the pre-specified response rate. In addition, per-protocol and sensitivity analyses on the original planned sample size yielded similar results to the treated population used for primary analysis of the primary endpoints, confirming the robustness of the results of the primary analysis.[25]

Addressing the lack of controlled trial

The evidence base in this submission includes only non-randomised and observational studies. PACE (Cortes et al. 2013)[9] and the phase 1/2 bosutinib trial (Khoury et al. 2012)[8] are non-randomised, single-arm trials. The allo-SCT study (Jabbour et al. 2011)[144] was an observational, retrospective study and the relapsed ALL study (Tavernier et al. 2007)[133] was an observational prospective study.

Head-to-head RCTs are considered the gold standard for evaluating comparative effectiveness, but are not always feasible in the context of rare diseases like CML and Ph+ ALL.[213, 214] For ethnical reasons, a randomised study of ponatinib was not possible and the EMA and FDA agreed with the non-comparative design of the study. Furthermore, all other TKIs evaluated in patients with resistance had a non-comparative design for their pivotal trials.[8, 95, 98, 100]

Although a main limitation of the clinical evidence is that it comes from uncontrolled studies, and is thus lacking direct comparator data, patients in the PACE study may function as controls of themselves because a baseline record is available of a patient's best response to their most recent regimen containing dasatinib or nilotinib. This baseline response can be compared with response rates achieved with ponatinib. For example, as reported by Hochhaus et al. 2015, a best response of CCyR was achieved with the most recent 2G-TKI in only 20% of patients with CP-CML who had received two prior TKIs. With 3L ponatinib, CCyR in these same patients was 65%.[24] Responses achieved with ponatinib exceeded responses achieved with the last prior TKI.

Nevertheless, to address the lack of comparative trial data providing a direct head-to-head comparison of ponatinib with bosutinib, we have carried out an indirect comparison designed to adjust for differences in baseline characteristics between PACE and the phase 1/2 bosutinib trial to control for differences in patient populations that could influence outcomes between these studies (see Section 4.10: Indirect and mixed treatment comparisons; Sections 4.10.2–4.10.15). Briefly, a matching-adjusted indirect comparison (MAIC) in CP-CML further indicated that ponatinib provides superior efficacy and durability of response vs bosutinib. In the MAIC, the PACE trial (Cortes et al. 2013)[9] patient population was matched to the phase 1/2 bosutinib trial (Khoury et al. 2012)[8] by adjusting for baseline characteristics—T315I mutation status, sex, age, race, duration of CML, and ECOG performance status. Compared to bosutinib, with a best CCyR response of 24.1%, the matching-adjusted CCyR rate with ponatinib was 61.3%. In the PACE study, the proportion of patients maintaining CCyR at 4 years with ponatinib is [redacted]% (unpublished data, CSR)[25] and after matching patient population baseline characteristics to those in the phase 1/2 bosutinib trial rate of CCyR maintenance at 4 years is 89%. With bosutinib, the probability of maintaining a CCyR (either maintained from baseline or newly achieved during bosutinib treatment) at 4 years is 54%, as reported by Gambacorti-Passerini et al. 2014.[186] Of note, unlike for bosutinib, maintenance of response with ponatinib reflects only patients without a response at baseline and who achieved response after treatment; therefore the bosutinib data present a source of bias for higher maintenance of response.

Validation of PACE results against observational data

In the real-world setting, ponatinib demonstrates response rates and a safety profile that parallel the results of the PACE study.[27] Garcia-Gutierrez et al. 2016 published data from the Spanish Compassionate Use Program on ponatinib treatment among 23 patients in first or second CP (except 1 patient in AP).[27] Patients in this program were heavily pre-treated at baseline, with 37% having received two prior TKIs and 62% having received ≥3 prior TKIs. The median age of diagnosis was 56 years. Overall, 58% of patients achieved a CCyR after a median follow-up of 29 months (range 3–53) and PFS by 3.5 years was 80%. The rates of treatment discontinuation were 25% due to AEs and 25% due to lack of efficacy, while 37% of patients proceeded to allo-SCT and 13% of patients died. As in the PACE study, no differences in response rates were observed between patients with or without mutations in the Spanish Compassionate Use Program. Regarding the safety of treatment, ponatinib use in the real-world appears to be associated with manageable AEs.[27] The most common non-haematologic AEs were liver toxicity (20%), lipase increase (10%), and hypertension (15%) and no patients on ponatinib had a

cardiovascular event.[27] These findings from the Spanish Compassionate Use Program indicate that the favourable benefit-risk profile observed for ponatinib in the PACE study is consistent with real-world clinical experience with this drug.

Generalisability to clinical practice in England

The clinical evidence supporting ponatinib is highly relevant to the decision problem as the subjects in the PACE study represent patients for whom treatment is indicated,[22] parallel the population described in the NICE scope,[164] and represent the population who will be treated in clinical practice in England. The median age of patients enrolled in the PACE trial was the same as the median age of disease onset for CML in the UK, 59 years.[3] Of note, generalising study findings to patients with certain comorbidities should be done with caution because patients were excluded from the trial if they had a condition or illness that, in the opinion of the investigator or the medical monitor, would have compromised patient safety or interfered with evaluation of the safety of the drug.[9] Nevertheless, the PACE study imposed few exclusion criteria, and in particular, there were no criteria in place to exclude patients based on prior cardiovascular morbidity or patients at risk of having a cardiovascular event.[9]

The outcomes assessed in the PACE trial are equally relevant to clinical practice. First, according to the 2013 ELN recommendations for managing CML, patient response to treatment can be assessed using either molecular or cytogenetic testing. Whenever possible, both cytogenetic and molecular tests are recommended until CCyR and MMR are achieved.[47] Per PACE study protocol, response assessments were performed periodically: for CP-CML, once every 3 months; for AP/BP-CML, after cycles 1 and 2 (28 days each) and every 2 months thereafter. Tests for molecular response and mutations were assessed by a central laboratory.[9] Second, to address the shortcoming of using long-term outcomes, shorter-term measures of treatment efficacy, such as response rates, are recognised as surrogate endpoints of survival in CML (see Section 4.10.6).[8, 9, 82, 165] Importantly, the PACE trial has provided 4-year follow-up data on ponatinib in patients with CP-CML and demonstrated high rates of PFS and OS, even among patients who had received 2 prior TKIs (4-year PFS and OS were 68% and 79% respectively [median not yet reached for both]).[24]

Ponatinib vs sequential use of 2G-TKIs

Despite the inclusion of nilotinib and dasatinib as options for second and subsequent lines in the ELN recommendations, it should be noted that regulatory approval of nilotinib and dasatinib was not based on, or supported by, studies with sequential use of 2G-TKIs.[17, 51] Thus, the sequential use of 2G-TKIs is not an approved indication in the SmPC for these drugs, nor has this type of usage been evaluated for safety or efficacy in registration trials or by any HTA agencies in any country. This differs from ponatinib—its efficacy after failure of a 2G-TKI was demonstrated in the clinical trials conducted prior to its approval[9, 23] and its cost-effectiveness has been recognised by several HTA agencies, including the SMC,[218] AWMSG,[219] and the Swedish Dental and Pharmaceutical Benefits Board (TLV).[220]

Existing data on sequential use of currently available 2G-TKIs show that the response rates for these treatments are low and of shorter duration compared to those achieved with ponatinib.[9, 94-96] Lipton et al. 2015 performed a systematic literature review of nilotinib, dasatinib, bosutinib, and ponatinib clinical studies.[6] An indirect analysis of the retrieved study results showed that the probability of response with sequential 2G-TKI use is lower than that expected with ponatinib.[6] When looking specifically at studies in patients with CP-CML treated with ponatinib (Cortes et al. 2013)[9] or bosutinib (Khoury et al. 2012)[8]—the only other treatment with an indication for sequential use post–2G-TKI treatment[7]—the results suggest superior efficacy of ponatinib. As these data do not come from head-to-head studies they must be interpreted with caution. Nonetheless, these indirect comparisons are likely more biased against ponatinib than in favour of it. The pivotal ponatinib trial (Cortes et al. 2013) included a larger proportion of patients with resistance (88% overall) to prior TKIs than intolerance.[9] In contrast, studies of other TKIs (Khoury et al. 2012 and Ibrahim et al. 2010) have tended to include more intolerant patients.[8, 96] Previous studies with nilotinib (Kantarjian et al. 2011) and dasatinib (Ibrahim et al. 2010) clearly demonstrated that, in patients challenged with a new TKI, treatment resistance was associated

with much lower response rates than treatment intolerance.[96, 111] Furthermore, compared to the pivotal bosutinib trial, the pivotal ponatinib trial had more patients treated with multiple TKIs.[7, 22]

4.13.2.2 Life expectancy

According to real-world data from the UK population-based HMRN 2004–2015, the 5-year OS of patients with CML is 77.7%; the 5-year RS is 89.8%.[3] The vast majority of these patients would be in their first line of therapy (over a 10-year follow-up only 36% of patients on 1L imatinib discontinue treatment).[148] Survival is somewhat lower for patients with AP-CML, although the estimated 8-year OS rate remains above 75%.[137] Among patients with BP-CML treated with TKI therapy, however, median OS is still only 7–11 months.[138] A report published by Pulte et al. 2016 using data obtained from the SEER database shows that, among patients with CML aged <60 years, 5-year RS is 80% (in 2009–2012).[139] In addition, Pulte et al. show that with increasing age, survival decreases sharply. For example, among patients with CML aged 65–69 years, 5-year RS is 56.7%; RS continues to decrease with each increasing age category.[139] Data presented by Pulte et al. 2016 indicate that excess mortality in CML remains an important challenge to be addressed.

For patients with resistant disease, survival decreases with each subsequent line of therapy.[140] Among patients with CP-CML who received 3L or 4L TKI therapy, 5-year OS rates of 53% and 38%, respectively, have been reported.[140] In the PACE study population of heavily pre-treated patients, long-term survival rates with ponatinib are notable: 4-year OS for CP-CML is 80% in 3L and 79% in 4L (Hochhaus et al. 2015).[24]

4.13.2.3 Estimate of the number of people with the particular therapeutic indication for which the technology is being appraised

Table 4-20 and Table 4-21 present the estimated annual number of people with CML and ALL who would be eligible for ponatinib treatment in England.

Table 4-20. Estimated number of patients with CML eligible for ponatinib

Population	Estimated incidence	Assumption	Reference
CML in England	631	The annual incidence of CML has been stable since 2014 (631 people in England were diagnosed with CML in 2014)	Office of National Statistics Cancer Statistics Registrations, England 2014
People with Ph+ CML and treated with a 1L TKI (imatinib)	599	95% of those diagnosed with CML are Ph+; all diagnosed patients are treated with a 1L TKI (imatinib)	Goldman, 2009;[147] assumption
People who develop the T315I mutation during 1L treatment and are therefore eligible for 2L ponatinib	13	2% of 1L patients treated with imatinib or dasatinib develop the T315I mutation	Hughes et al. 2015[149]
People for whom 1L imatinib treatment is unsuccessful and are treated with a 2L TKI	203	36% of 1L patients discontinue imatinib; all are treated with a 2L TKI (except patients with the T315I mutation)	Kalmanti et al. 2015[148]; assumption
Patients for whom 2L TKI treatment is unsuccessful and are eligible for 3L ponatinib in CP	95	48% of 2L patients discontinue nilotinib due to lack of efficacy (progression) or intolerance (AEs) and eligible for a 3L TKI (patients progressing to AP/BP are not double counted)	Kantarjian et al. 2011[111]

Patients for whom 2L TKI treatment is unsuccessful and progress to AP or BP and are eligible for 3L ponatinib in AP/BP	6	3% of patients treated with nilotinib in 2L progress to AP/BP	Giles et al. 2013[113]
Total incident population eligible to receive ponatinib under its licensed CML indication	113	Annual number of patients eligible for ponatinib	

1L, first line; 2L, second line; 3L, third line; AEs, adverse events; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

Note: The number of patients presented in this figure are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this figure, due to rounding error.

Table 4-21. Estimated number of patients with Ph+ ALL eligible for ponatinib

Population	Estimated incidence	Assumption	Reference
ALL in England	654	The annual incidence of ALL has been stable since 2014 (654 people in England were diagnosed with ALL in 2014)	Office of National Statistics Cancer Statistics Registrations, England 2014
People with Ph+ ALL and treated with a 1L TKI (imatinib)	164	25% of those diagnosed with Ph+ ALL; all diagnosed patients are treated with a 1L TKI (imatinib)	Fielding et al. 2007;[150] assumption
People who fail imatinib because of T315I mutation therefore eligible for 2L ponatinib	6	13% of 1L patients treated with imatinib develop T315I mutation	Pfeifer et al. 2012[154]
People for whom 1L imatinib treatment is unsuccessful and are treated with 2L dasatinib	43	30% of patients treated in 1L are refractory to imatinib and relapse occurs after a median of 2.2 months (patients with T315I mutation are not double counted)	Lilly et al. 2010[16]
Patients for whom 2L dasatinib treatment is unsuccessful (failure to achieve MaHR) and are eligible for 3L ponatinib	26	62% of patients treated with dasatinib in 2L fail to achieve MaHR	Lilly et al. 2010[16]
Total incident population eligible to receive ponatinib under its licensed Ph+ ALL Ph+ indication	33	Annual number of patients eligible for ponatinib	

1L, first line; 2L, second line; 3L, third line; ALL, acute lymphoblastic leukaemia; MaHR, major haematologic response; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

Note: The number of patients presented in this figure are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this figure, due to rounding error.

4.13.2.4 Consideration as a 'life-extending treatment at the end of life'

Table 4-22 presents the data available to assess the suitability of ponatinib as a life-extending treatment at the end of life. Ponatinib would meet the end-of-life criteria for eligible patients with AP- or BP-CML and patients with Ph+ ALL.

Table 4-22. End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**AP/BP-CML** Among patients with AP-CML or BP-CML, median OS on BSC (ie, therapy other than TKI and allo-SCT) has been shown to be 16 months in AP and 5 months in BP (Kantarjian et al. 2007).[29] We estimated OS of the AP-/BP-CML populations with BSC to be 1.91 years (23 months) in AP and 1.16 years (14 months) in BP. These estimates are conservative. See economic analysis results Section 5.4.6.6; Table 5-55. Survival and QALY results). BSC source: Kantarjian et a. 2007[29] **Ph+ ALL** Among patients with ALL who receive BSC, OS has been shown to be only 2.6 months (Pagano et al. 2000).[30] We estimated OS on BSC to be 0.33 years (4 months) in Ph+ ALL. See economic analysis results Section 5.5.6.6.1; Table 5-76. Survival and QALY results). BSC source: Pagano et al. 2000[30]
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	**AP/BP-CML** Results of the AP-/BP-CML de novo economic analysis show that the incremental undiscounted LY gain on ponatinib compared with BSC is [redacted] (see Section 5.4.6.6.1; Table 5-55. Survival and QALY results). **Ph+ ALL** Results of the Ph+ ALL de novo economic analysis show that the incremental undiscounted LY gain on ponatinib compared with BSC is [redacted] (see Section 5.5.6.6.1; Table 5-76. Survival and QALY results).
The treatment is licensed or otherwise indicated for small patient populations	6 people with AP/BP and 33 people with Ph+ ALL in England will be eligible for ponatinib according to its licensed indication. Sources: Estimates were derived using the 2014 incidence for newly diagnosed CML and ALL in England and data from the published literature. See Table 4-20 and Table 4-21 for the breakdowns of how the estimates were calculated.

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; CP, chronic phase; LY, life-year; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive; OS, overall survival.

4.14 Ongoing studies

4.14.1 PACE and OPTIC trials

Follow-up evaluations of patients enrolled in the PACE trial are ongoing.[221] The most recent data available at the time of writing this submission are the 4-year follow-up; these data were presented by Andreas Hochhaus at the ASH Annual General Meeting in 2015 and are described in detail in this submission.[24] No additional data from the PACE trial are likely to become available within the next 12 months.

OPTIC is a multicentre, randomised, open-label, phase 2 trial initiated in 2015 to evaluate the efficacy and safety of a range of three ponatinib starting doses.[222] Adult patients with CP-CML

resistant to at least two prior TKIs are eligible to participate in the trial. Patients are randomised to one of three treatment cohorts. Patients in Cohort A receive ponatinib 45 mg QD, while patients in Cohorts B and C receive ponatinib 30 mg QD and 15 mg QD, respectively. The primary outcome measure is MCyR by 12 months, defined as 0%–35% of Ph+ cells in the bone marrow. Secondary outcome measures will evaluate treatment safety, including the rates of VOEs, AEs, and SAEs over a 24-month timeframe. The estimated patient enrolment is 450 and the estimated study completion date is December 2018.[222] No data from the OPTIC trial will become available within the next year.

4.15 Ponatinib dose reduction in patients with CP-CML

The starting dose of ponatinib in the PACE study (45 mg) is the recommended starting dose per the SmPC.[22] Dose modifications or interruption of dosing are appropriate strategies to manage haematologic and non-haematologic toxicities. In the trial, dose reductions to manage AEs occurred in 55% of the patients.[9] In the phase 2 trial, dose reductions were recommended following AEs. In addition, in October 2013, following a request by the FDA, study investigators were instructed to decrease the dose from 45 to 15 mg/day in all CP-CML patients who had achieved a MCyR or better, to 30 mg/day in CP-CML patients who had not already achieved MCyR, and to 30 mg/day for advanced phase patients.[25] Prospective dose reductions in all CP-CML patients in the absence of AEs were introduced in the trial to reduce the risk of VOEs.[22]

Preliminary efficacy data from the PACE trial are available on the maintenance of response in all CP-CML patients who underwent dose reduction for any reason. Table 4-23 shows these data for patients who achieved MCyR and MMR on 45 mg; similar data are available for patients who achieved MCyR and MMR on 30 mg. The majority of patients who underwent dose reduction in the PACE trial maintained response (MCyR and MMR) for the duration of currently available follow-up. Most patients who ultimately reduced daily dose to 15 mg initially had their dose reduced to 30 mg for a period of time. A proportion of patients did not undergo any dose reduction, based on an individual benefit-risk assessment.[22]

Table 4-23. Maintenance of response in CP-CML patients who achieved MCyR or MMR on 45 mg dose (data extraction 7 April 2014)[22]

	Achieved MCyR on 45 mg/day (N=87)		Achieved MMR on 45 mg/day (N=63)	
Duration of dose reduction	**Number of patients**	**Maintained MCyR**	**Number of patients**	**Maintained MMR**
No dose reduction	23	18 (78%)	18	11 (61%)
Dose reduction to 30 mg only	25	24 (96%)	13	11 (85%)
≥ 90 day	21	20 (95%)	11	10 (91%)
≥ 180 day	11	10 (89%)	5	4 (80%)
≥ 360 day	5	4 (80%)	2	1 (50%)
Any dose reduction to 15 mg	39	39 (100%)	32	30 (94%)
≥ 90 day	32	32 (100%)	27	26 (96%)
≥ 180 day	10	10 (100%)	6	6 (100%)
≥ 360 day	6	6 (100%)	3	3 (100%)

MCyR, major cytogenetic response; MMR, major molecular response

A study published by Mauro et al. 2015 using real-world data among US patients initially on the 45-mg ponatinib dose showed that 42% of patients had dose reductions within 6 months of starting therapy;[223] doses were reduced to 30 mg or 15 mg in 29% and 13% of patients, respectively.[223] Dorer et al. 2016 published a post-hoc multivariate analysis of the impact of dose intensity on AEs using data from three ponatinib clinical trials. Results of this analysis showed that a 15-mg/day decrease in the average daily dose of ponatinib was associated with a 33% reduction in the risk of serious cardiovascular events.[26] The efficacy and safety of three ponatinib starting doses (15-mg, 30-mg, and 45-mg) will be evaluated in the OPTIC trial.[222] Data at 4-year follow-up from the PACE trial confirm that CCyR is maintained in over [redacted]% of the patients (unpublished data, CSR).[25]

5 Cost effectiveness

5.1 Published cost-effectiveness studies in CML and Ph+ ALL

5.1.1 Identification of studies

Economic SLRs were carried out separately for CML and Ph+ ALL. As with the clinical CML search strategy, the economic portion of the SLR was designed to identify relevant evidence published from January 2000–January 2016. The economic Ph+ ALL SLR was designed to identify relevant evidence published from January 2000–February 2016. Updated searches were carried out in July 2016. Searches were also conducted in accordance with the requirements of NICE[158, 159] and the CRD guidance.[160] In order to capture all relevant data, the economic SLRs were developed to broadly encompass the treatment landscape for CML and Ph+ ALL.

Bibliographic databases were searched with the predefined search strategies outlined in Appendix 11: Search strategy for cost-effectiveness studies. The search strategies were adapted from those described in a prior STA for bosutinib, which were previously adapted from a systematic review published by PenTAG.[161] The searches were designed to be broad to ensure adequate sensitivity.

Searches were conducted in EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and Cochrane CENTRAL and HTA using Ovid®; the NHS Economic Evaluation Database (EED) using the University of York CRD database; and EconLit using ProQuest.

In addition to bibliographic databases, a targeted search of the NICE website was conducted and abstracts from the following conferences were searched from 2013–present: International Society for Pharmacoeconomics and Outcomes Research (ISPOR), ASCO, ASH, and EHA. Review articles were also manually searched for relevant publications.

The screening process was the same as that for the clinical evidence (see Section 4.1.3). PICOS criteria describing the relevant population, interventions, comparators, outcomes, and study design were used to determine the relevance of each article (Table 5-1).

Table 5-1. Eligibility criteria used in the economic search strategy

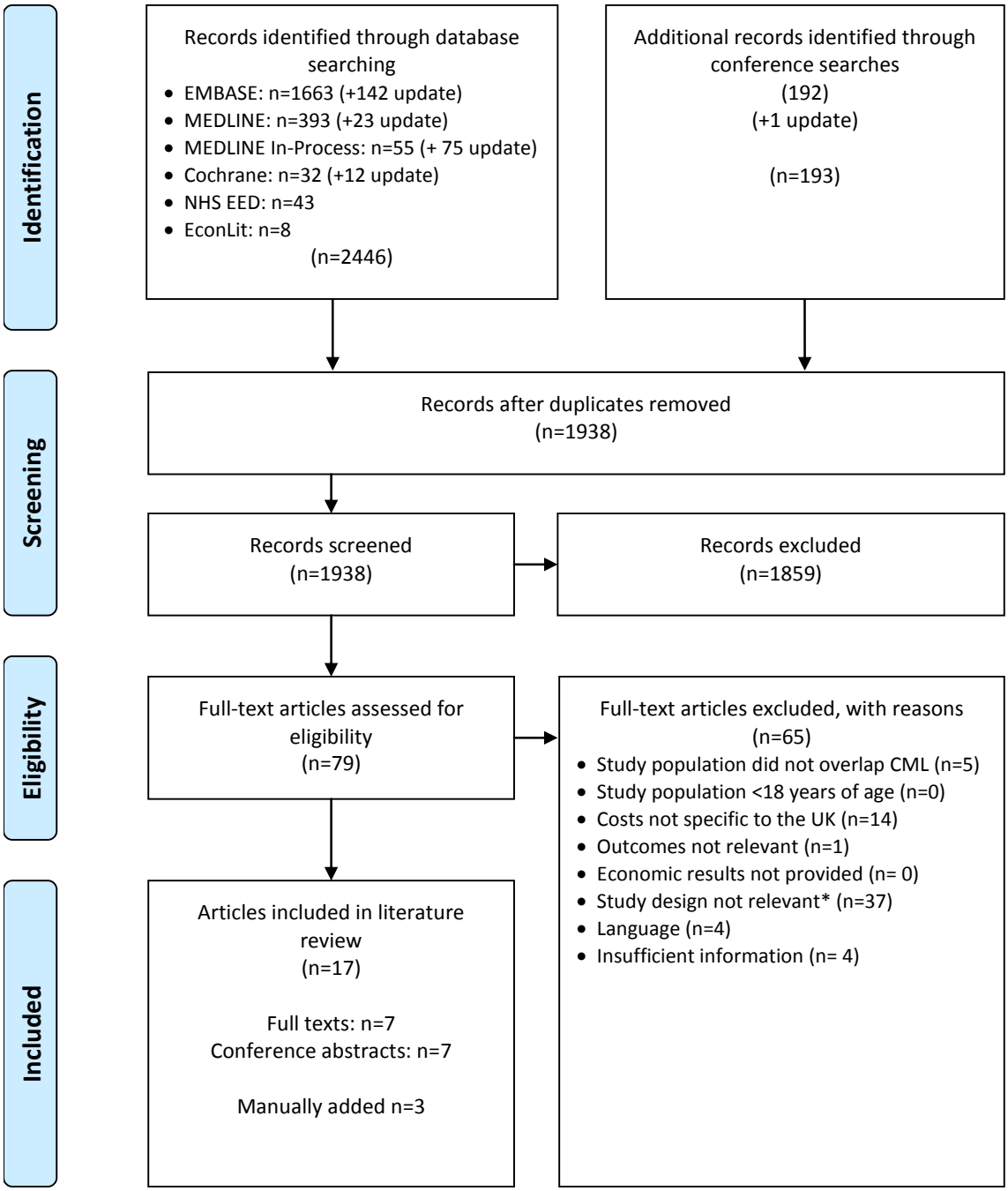
Cost-effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with CML or Ph+ ALL	—
Interventions	• All	—
Comparators	• All	—
Outcomes	• ICERs, QALYs, healthcare resource usage, cost of healthcare resources, modelling methods • Costs specific to the UK	• Studies reporting costs not specific to the UK
Trial design	• Economic evaluations (CEA, CUA, CMA), healthcare resource evaluation studies, healthcare resource economic studies	• Comments, letters, and editorials will be excluded
Language restrictions	• No limitation by language in searches	• Studies in languages other than English excluded during screening

CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CML, chronic myeloid leukaemia; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

After screening the 1951 records identified during the CML searches, a total of 17 articles were included. NICE technology appraisals TA241[92] and TA299[224] were also manually reviewed for relevant data. The process of study selection is presented in detail in Figure 5-1.

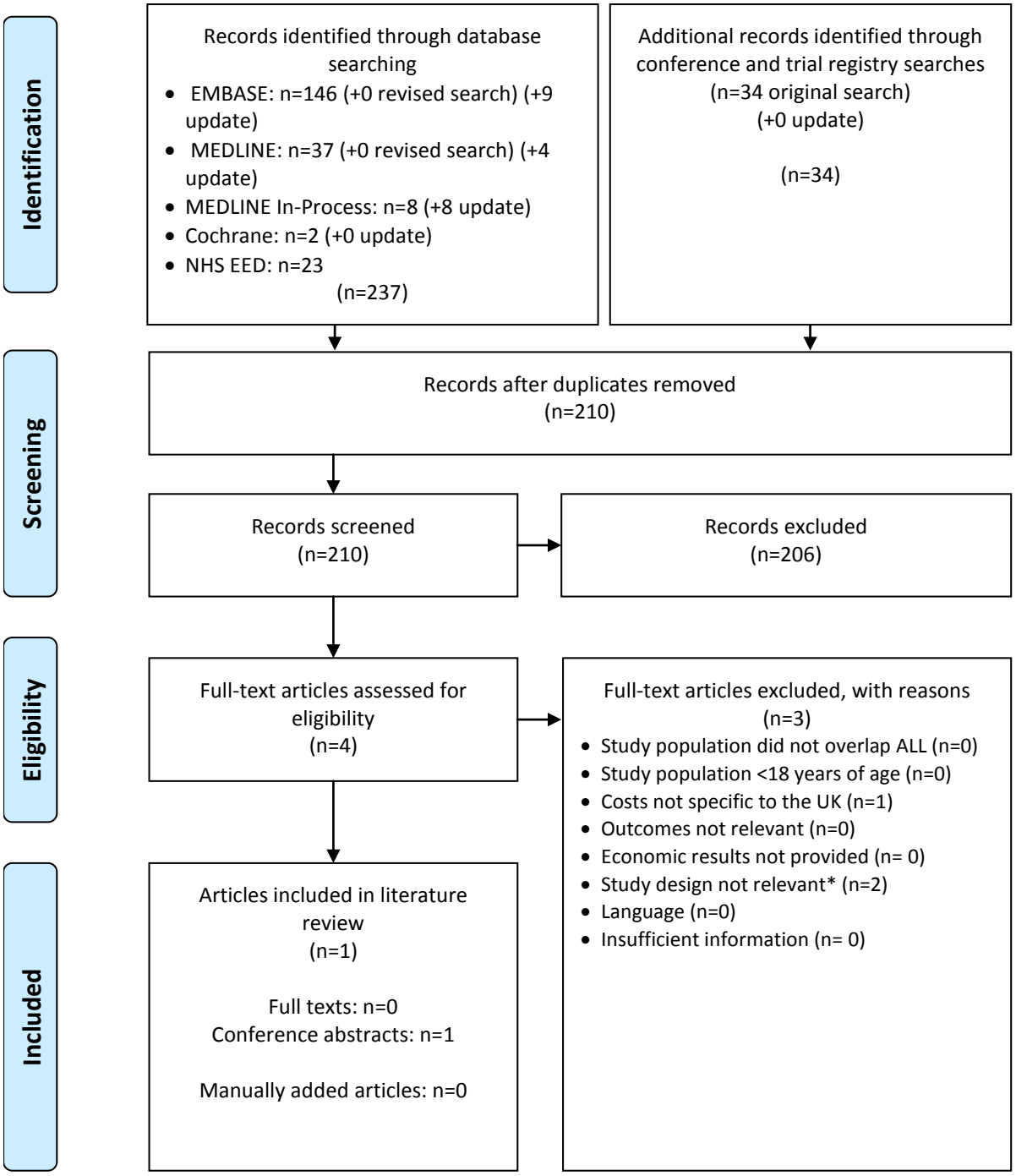
After screening the 210 records identified during the Ph+ ALL searches, one article was included. The process of study selection is presented in detail in Figure 5-2.

Figure 5-1. PRISMA flow diagram for economic evidence in CML



*Reviews, SLRs. In other words, not a cost-based analysis.

Figure 5-2. PRISMA flow diagram for economic evidence in ALL



*Reviews, SLRs. In other words, not a cost-based analysis.

5.1.2 Description of identified studies

Table 5-2 and Table 5-3 provide high-level overviews of the economic studies identified in the CML and Ph+ ALL SLRs, respectively. All studies were conducted from a UK perspective and reported cost results in GBP.

5.1.2.1 CML

No economic analyses for ponatinib were identified; although 12 studies did include a 2G-TKI (dasatinib, nilotinib, or bosutinib) in the evaluation. Allo-SCT was included as a comparator in five of the identified economic evaluations. All but one of the studies was a cost-effectiveness

analysis (CEA)/cost-utility analysis (CUA). The one study that was not CEA/CUA was a resource use survey and associated cost analysis for CML in general.[225]

Of the economic analyses, 13 used a Markov or semi-Markov state-transition model, two used a partitioned survival model, and one used a partitioned survival Markov-type model. Four economic studies included advanced CML at model entry. The remainder were specific to the CP population or did not state the CML phase at model entry.

Three of the analyses were manufacturer models for dasatinib (Bristol-Myers Squibb [BMS]), nilotinib (Novartis), and bosutinib (Pfizer), two of which (dasatinib and nilotinib) were only available as summaries in the Loveman et al. HTA.[168]

The Pfizer model for bosutinib[161] was the only economic analysis identified for inclusion in subsequent modelling as it was the only analysis that evaluated a 3L cohort of patients with CP-CML.

5.1.2.2 Ph+ ALL

The only economic analysis identified in the Ph+ ALL SLR was for ponatinib. Using a Markov cohort model, Iannazzo et al. 2015 assessed the cost-effectiveness in the UK of ponatinib vs BSC after failing dasatinib. In the model, patients who achieved MCyR on ponatinib received allo-SCT in remission.[226]

Table 5-2. Summary list of identified CML cost-effectiveness studies that have relevance to decision-making in England

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
BMS model[168]	2009	To appraise the clinical effectiveness and cost-effectiveness of dasatinib, nilotinib and high-dose imatinib compared with standard-dose imatinib, allo-SCT, hydroxycarbamide, IFN alpha, acute leukaemia-style chemotherapy, and best supportive care, for patients with CML who are resistant to imatinib	40 years; monthly cycles	Any phase of CML (CP, AP, or BP) Age: • CP-CML: 56 years • AP-CML: 56 years • BP-CML: 48 years (myeloid) and 49 years (lymphoid	Discounting not specified *CP-CML* • Dasatinib: 6.425 • Imatinib 400 mg: 1.485 • Imatinib 600 mg: 2.394 • Imatinib 800 mg: 5.910 • Nilotinib: 6.235 • IFN alpha: 1.664 • Bone marrow SCT: 4.738 *AP- and BP-CML* Results NR	Discounting not specified *CP-CML* • Dasatinib: £314,413 • Imatinib 400 mg: £135,326 • Imatinib 600 mg: £173,705 • Imatinib 800 mg: £350,365 • Nilotinib: £318,978 • IFN alpha: £129,292 • Bone marrow SCT: £324,234 *AP- and BP-CML* Results NR	*CP-CML* Dasatinib vs • Imatinib 400 mg: £36,251 • Imatinib 600 mg: £34,907 • Imatinib 800 mg: Dasatinib dominant • Nilotinib: Dasatinib dominant • IFN alpha: £38,877 • Bone marrow SCT: Dasatinib dominant *AP- and BP-CML* Results NR
Dalziel et al. 2004[227]	2002	To evaluate the effectiveness of imatinib as 1L treatment for CML compared with IFN-α, hydroxycarbamide (hydroxyurea), and bone marrow transplantation, and the cost-effectiveness of imatinib compared with IFN-α and hydroxycarbamide	Lifetime (20 years or until death); 3-month cycles	CP Age NR; Adults	Discounted • Imatinib: 7.03 • Hydroxycarbamide: 4.99 • IFN alpha: 5.04 Undiscounted • Imatinib: 7.25 • Hydroxycarbamide: 5.01 • IFN alpha: 5.10	Discounted • Imatinib: £215,684 • Hydroxycarbamide: £38,322 • IFN alpha: £163,581 Undiscounted • Imatinib: £235,403 • Hydroxycarbamide: £46,591 • IFN alpha: £167,052	Discounted • Imatinib vs hydroxycarbamide: £86,934 • IFN alpha vs hydroxycarbamide: £2,505,364 • Imatinib vs IFN alpha: £26,180 Undiscounted • Imatinib vs hydroxycarbamide: £84,100

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
							• IFN alpha vs hydroxycarbamide: £1,293,948 • Imatinib vs IFN alpha: £31,761
Gordois et al. 2003[228]	2001	To evaluate cost-effectiveness of imatinib for AP- and BP-CML compared to conventional therapies	Outcomes were modelled for 5 years from start of treatment; 1-month cycles	AP, BP Age NR	Discounted *AP-CML* • Imatinib: 2.04 • Comparator: -0.04 • *BP-CML* Imatinib: 0.53 • Comparator: -0.05	Discounted *AP-CML* • Imatinib: £78,593 • Comparator: £17,325 *BP-CML* • Imatinib: £35,781 • Comparator: £11,085	Imatinib vs conventional therapy • AP-CML: £29,344 • BP-CML: £42,239
Hoyle et al. 2011[229]	2009/ 2010 (inflated costs)	To estimate the cost-effectiveness of dasatinib and nilotinib compared with high-dose imatinib for people with CP-CML who are resistant to normal-dose imatinib and compared with interferon alpha for people intolerant of imatinib	44 years (patients modelled to age 100); 2-month cycles, with half-cycle corrections	CP Age: 56 years	Discounted *Imatinib resistant* • Dasatinib: 7.846 • Nilotinib: 7.63 • High-dose imatinib: 7.311 *Imatinib intolerant* • Dasatinib: 8.463 • Nilotinib: 7.406 • IFN alpha: 6.229	Discounted *Imatinib resistant* • Dasatinib: £221,325 • Nilotinib: £161,330 • High-dose imatinib: £172,415 *Imatinib intolerant* • Dasatinib: £283,441 • Nilotinib: £222,092 • IFN alpha: £98,818	*Imatinib resistant* • Dasatinib vs high-dose imatinib: £91,499 • Nilotinib vs high-dose imatinib: Nilotinib dominates *Imatinib intolerant* • Dasatinib vs IFN alpha: £82,619 • Nilotinib vs IFN alpha: £104,698
Loveman et al. 2012[168]	2009/ 2010	To evaluate the clinical effectiveness and cost-effectiveness of dasatinib, nilotinib and high-dose imatinib within their licensed indications for the treatment of	Lifetime	CP Age NR	Discounted • Hydroxycarbamide: 2.20 • IFN alpha: 2.20 • Standard-dose imatinib: 2.27 • SCT: 6.35 • High-dose imatinib: 7.31 • Nilotinib: 7.63	Discounted • Hydroxycarbamide: £18,128 • IFN alpha: £34,403 • Standard-dose imatinib: £39,400 • SCT: £305,846	Intervention vs hydroxycarbamide • IFN alpha: £242,448,508 • Standard-dose imatinib: £306,331 • SCT: £69,279

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
		people with CML who are resistant to standard-dose imatinib			• Dasatinib: 7.85	• High-dose imatinib: £172,647 • Nilotinib: £161,667 • Dasatinib £172,473	• High-dose imatinib: £30,229 • Nilotinib: £26,434 • Dasatinib: £27,336
Mealing et al. 2012[230]	NR	To assess the cost-effectiveness of dasatinib versus imatinib in newly diagnosed CML patients	Lifetime; monthly cycles	Phase NR Age NR	Incremental QALYs/patient (95% CI) • Dasatinib vs imatinib: +0.71 (–0.15, 1.68)	Incremental costs (95% CI) • Dasatinib vs imatinib: +£17,646 (–£24,259, £57,947)	• Dasatinib vs imatinib: £24,922
Mildred et al. 2012[231]	2010/ 2011	To evaluate the cost-effectiveness of 1L nilotinib followed by 2L dasatinib compared to 1L imatinib followed by 2L dasatinib for patients newly diagnosed with Ph+ CP-CML	Lifetime	CP Age NR	Incremental discounted QALYs Nilotinib vs imatinib • LYs: +0.35 • QALYs: +0.28	Discounted lifetime costs • Nilotinib: £220,416 • Imatinib: £232,941	• Nilotinib vs imatinib: Dominant
Novartis model[168]	2009/ 2010	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 CP	Lifetime; monthly cycles for first 6 cycles, then 3-month cycles	CP Age: 57 years	Discounting not specified • Nilotinib: 4.51 • High-dose imatinib: 4.28 • SCT/hydroxycarbamide: 3.18	Discounting not specified • Nilotinib: £139,216 • High-dose imatinib: £146,234 • SCT/hydroxycarbamide: £80,933	Intervention vs high-dose imatinib • Nilotinib: –£30,513 (Dominant) • SCT/hydroxycarbamide: £44,028
Padula et al. 2014[232]	2013	To analyse the cost-effectiveness of treating all CP-CML with imatinib initially compared to physician-choice between imatinib or	5 years	CP Age NR	• Step-therapy: 2.864 • Physician-choice: 2.879	• Step-therapy: £62,388 • Physician-choice: £71,268	• Step-therapy vs physician-choice: £592,000

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
		the 2G-TKIs dasatinib or nilotinib					
Pavey et al. 2012[167]	2011/ 2012	To determine the cost-effectiveness of 1L treatment for newly diagnosed Ph+ CML with dasatinib or nilotinib or imatinib (standard dose), using each of the three treatments as comparators	50 years, or age 107 years, at which time all people have died; 3-month cycles	CP Age: 57 years	Discounted Scenario 1: cumulative survival without 2L nilotinib • Imatinib – then hydroxycarbamide/ SCT: 9.0 • Nilotinib – then hydroxycarbamide/ SCT: 9.4 • Dasatinib – then hydroxycarbamide/ SCT: 9.2 Scenario 2: cumulative survival without 2L nilotinib – simplified method • Imatinib – then hydroxycarbamide/ SCT: 9.0 • Nilotinib – then hydroxycarbamide/ SCT: 9.7 • Dasatinib – then hydroxycarbamide/ SCT: 9.3 Scenario 3: cumulative survival with 2L nilotinib • Nilotinib – then hydroxycarbamide/ SCT: 9.4	Discounted Scenario 1: cumulative survival without 2L nilotinib • Imatinib – then hydroxycarbamide/ SCT: £159,000 • Nilotinib – then hydroxycarbamide/ SCT: £170,000 • Dasatinib – then hydroxycarbamide/ SCT: £224,000 Scenario 2: cumulative survival without 2L nilotinib – simplified method • Imatinib – then hydroxycarbamide/ SCT: £159,000 • Nilotinib – then hydroxycarbamide/ SCT: £172,000 • Dasatinib – then hydroxycarbamide/ SCT: £225,000 Scenario 3: cumulative survival with 2L nilotinib • Nilotinib – then hydroxycarbamide/ SCT: £170,000	Scenario 1: cumulative survival without 2L nilotinib • Imatinib – then hydroxycarbamide/ SCT: NA • Nilotinib – then hydroxycarbamide/ SCT: £25,000 • Dasatinib – then hydroxycarbamide/ SCT: Dominated by nilotinib Scenario 2: cumulative survival without 2L nilotinib – simplified method • Imatinib – then hydroxycarbamide/ SCT: NA • Nilotinib – then hydroxycarbamide/ SCT: £20,000 • Dasatinib – then hydroxycarbamide/ SCT: Dominated by nilotinib Scenario 3: cumulative survival with 2L nilotinib • Nilotinib – then hydroxycarbamide/ SCT: NA • Imatinib – then nilotinib: £192,000

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
					• Imatinib – then nilotinib: 9.5 • Dasatinib – then nilotinib: 9.7 Scenario 4: cumulative survival with 2L nilotinib – simplified method • Nilotinib – then hydroxycarbamide/ SCT: 9.1 • Imatinib – then nilotinib: 9.5 • Dasatinib – then nilotinib: 9.7	• Imatinib – then nilotinib: £188,000 • Dasatinib – then nilotinib: £252,000 Scenario 4: cumulative survival with 2L nilotinib – simplified method • Nilotinib – then hydroxycarbamide/ SCT: £166,000 • Imatinib – then nilotinib: £188,000 • Dasatinib – then nilotinib: £253,000	• Dasatinib – then nilotinib: £450,000 Scenario 4: cumulative survival with 2L nilotinib – simplified method • Nilotinib – then hydroxycarbamide/ SCT: NA • Imatinib – then nilotinib: £46,000 • Dasatinib – then nilotinib: £301,000
Pfizer model[161]	NR	NR	Lifetime (50 years); monthly cycles	CP (CP model) AP (AP model) BP (BP model) Age: • CP-CML: 54 years • AP-CML: 50 years • BP-CML: 47 years	Discounted *CP-CML* • Bosutinib: 6.25 • Hydroxycarbamide: 2.43 • SCT: 3.70 • IFN alpha: 2.42 *AP-CML* • Bosutinib: 2.76 • Hydroxycarbamide: 0.90 • SCT: 1.96 *BP-CML* • Bosutinib: 0.54 • Hydroxycarbamide: 0.46 • SCT: 1.28	Discounted *CP-CML* • Bosutinib: NR (CiC) • Hydroxycarbamide: £29,473 • SCT: £171,539 • IFN alpha: £38,268 *AP-CML* • Bosutinib: NR (CiC) • Hydroxycarbamide: £26,078 • SCT: £178,093 *BP-CML* • Bosutinib: NR (CiC)	*CP-CML* • Bosutinib vs IFN alpha: NR (CiC) • Bosutinib vs hydroxycarbamide: NR (CiC) • SCT vs bosutinib: Dominated • SCT vs hydroxycarbamide: £111,511 • IFN alpha vs bosutinib: Dominated • IFN alpha vs hydroxycarbamide: Dominated *AP-CML*

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
						• Hydroxycarbamide: £14,170 • SCT: £200,526	• Bosutinib vs hydroxycarbamide: NR (CiC) • SCT vs bosutinib: Dominated • SCT vs hydroxycarbamide: £142,982 *BP-CML* • Bosutinib vs hydroxycarbamide: NR (CiC) • SCT vs bosutinib: NR (CiC) • SCT vs hydroxycarbamide: £186,265
Rogers et al. 2012[82]	2009/ 2010	To estimate the cost-effectiveness, in terms of ICER per QALY of dasatinib and nilotinib against relevant comparators for: 1. People in CP-CML who develop resistance to imatinib, dasatinib, or nilotinib compared with high-dose imatinib 2. People in CP-CML who are intolerant of imatinib, dasatinib, or nilotinib compared with IFN	44 years; 2-month cycles	CP Age: 56 years (assumed)	Discounted *Imatinib-resistant patients* • Dasatinib: 7.85 • Nilotinib: 7.63 • High-dose imatinib: 7.31 *Imatinib-intolerant patients* • Dasatinib: 8.46 • Nilotinib: 7.41 • IFN-α: 6.23	Discounted *Imatinib-resistant patients* • Dasatinib: £221,325 • Nilotinib: £161,330 • High-dose imatinib: £172,415 *Imatinib-intolerant patients* • Dasatinib: £283,441 • Nilotinib: £222,092 • IFN-α: £98,818	*Imatinib-resistant patients* • Dasatinib vs nilotinib: £277,698 • Nilotinib dominates high-dose imatinib *Imatinib-intolerant patients* • Nilotinib extendedly dominated by IFN and dasatinib • Dasatinib vs IFN: £82,600

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
Szabo et al. 2009[225]	2008	To calculate UK-specific resource use and cost estimates associated with the treatment of CML	NA	Phase and age NA	NA	NA	NA
Taylor et al. 2011a[233]	NR	To estimate lifetime costs and health outcomes associated with dasatinib treatment of chronic-phase imatinib-resistant CML	Lifetime	CP Age NR	Discounting not specified • Dasatinib: 6.425 • Imatinib 400 mg: 1.485 • Imatinib 600 mg: 2.394 • Imatinib 800 mg: 5.910 • Nilotinib: 6.235 • IFN alpha: 1.664 • Bone marrow transplant: 4.738	Discounting not specified • Dasatinib: £314,413 • Imatinib 400 mg: £135,326 • Imatinib 600 mg: £173,705 • Imatinib 800 mg: £350,365 • Nilotinib: £228,576 • Interferon alpha: £6764 • Bone marrow transplant: £302,937	Dasatinib vs: • Imatinib 400 mg: £36,251 • Imatinib 600 mg: £34,907 • Imatinib 800 mg: Dominant • Nilotinib: Dominant • Interferon alpha: £38,877 • Bone marrow transplant: Dominant
Taylor et al. 2011b[234]	NR	To estimate the lifetime costs and health outcomes associated with dasatinib in the treatment of imatinib-resistant CML patients who are in AP or BP	Lifetime	AP or BP Age NR	Discounting not specified *AP-CML* • Dasatinib: 2.603 • Imatinib 600 mg: 0.583 • Imatinib 800 mg: 0.583 • Nilotinib: 1.697 • Bone marrow transplant: 2.861 *BP-CML* • Dasatinib: 0.485 • Imatinib 600 mg: 0.240 • Imatinib 800 mg: 0.240 • Bone marrow transplant: 1.757	Discounting not specified *AP-CML* • Dasatinib: £170,478 • Imatinib 600 mg: £88,949 • Imatinib 800 mg: £96,552 • Nilotinib: £141,128 • Bone marrow transplant: £230,277 *BP-CML* • Dasatinib: £105,103 • Imatinib 600 mg: £108,306; • Imatinib 800 mg: £115,123	*AP-CML* Dasatinib vs: • Imatinib 600 mg: £40,357 • Imatinib 800 mg: £36,594 • Nilotinib: £32,405 • Bone marrow transplant: £231,650 *BP-CML* Dasatinib vs: • Imatinib 600 mg: Dominant • Imatinib 800 mg: Dominant

Publication	Costing year	Objective	Time horizon	CML disease phase and patient age at model entry	QALYs (intervention, comparator)	Costs (currency), (intervention, comparator)	ICER (per QALY gained)
						• Bone marrow transplant: £173,892	• Bone marrow transplant: £54,093
Taylor et al. 2012[235]	NR	To estimate the lifetime costs and benefits associated with dasatinib and imatinib in patients with CML	Lifetime; 1-month cycles	NR Age NR	Incremental QALYs • Dasatinib vs imatinib: +3.53	Incremental costs • Dasatinib vs imatinib: +£90,800	• Dasatinib vs imatinib: £25,700
Warren et al. 2004[236]	2001	To estimate the incremental cost-utility of imatinib compared with hydroxycarbamide (hydroxyurea) in patients with CP-CML for whom 1L treatment with IFN alpha failed to produce a response	Lifetime; 1-month cycles	CP Age: 53 years	Discounted • Imatinib: 5.95 • Hydroxycarbamide: 3.49	Discounted • Imatinib: £110,103 • Hydroxycarbamide: £15,566	• Imatinib vs IFN alpha: £38,468

1L, first line; 2L, second line; 3L, third line; AE, adverse event; AP, accelerated phase; BMS, Bristol-Myers Squibb; BP, blast phase; CIC, commercial in confidence; CP, chronic phase; CT, computed tomography; DAT, daunorubicin, cytarabine arabinoside, and 6-Tioguanine; GP, general practitioner; HRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; IFN, interferon; NA, not applicable; NR, not reported; QALY, quality-adjusted life-year; SCT, stem cell transplantation.

Table 5-3. Summary list of identified ALL cost-effectiveness study that has relevance to decision-making in England

Publication	Costing year	Objective	Patient population	LYs	QALYs	Costs	ICERs per LY gained	ICERs per QALY gained
Iannazzo et al. 2015[226]	2014	To conduct a CEA for patients with Ph+ ALL and R/I to dasatinib, comparing ponatinib (followed by allo-SCT in patients who achieve MCyR) vs BSC, from the UK NHS perspective	Patients with Ph+ ALL who have failed a previous course of dasatinib (PACE study subgroup)	Discounted • Ponatinib + allo-SCT: 4.14 • BSC: 0.32	Discounted • Ponatinib + allo-SCT: 2.57 • BSC: 0.09	Discounted • Ponatinib + allo-SCT: £88,553 • BSC: £21,208	Ponatinib vs BSC • £17,600	Ponatinib vs BSC • £27,200

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; LY, life-years; MCyR, major cytogenetic response; NHS, National Health Service; Ph+, Philadelphia chromosome–positive; QALY, quality-adjusted life-year; R/I, resistant/intolerant; —, not reported.

5.1.3 Quality assessment of relevant identified studies

Quality assessment of the relevant studies (the Pfizer model for bosutinib and Iannazzo et al. 2015) was conducted independently by two researchers, with disagreements resolved by a third researcher.

Quality assessment was performed using the checklist for assessing economic evaluations outlined in the CRD guidance,[160] which was originally adapted from Drummond et al. (1996).[237] See Appendix 12: Quality assessment of cost-effectiveness studies for details of the quality assessment.

5.2 Overview of economic analyses

There are no head-to-head clinical trials comparing efficacy and healthcare resource utilisation with ponatinib compared to relevant comparators used in England within the indicated population. In the absence of head-to-head trial data, three cost-effectiveness models were constructed to estimate the cost-effectiveness of ponatinib compared to relevant interventions in patients with CP-CML, AP- or BP-CML, and Ph+ ALL. Section 5.3 describes the economic model, considering only patients who start ponatinib (or comparator) treatment in the CP-CML disease stage; the adaptations of the models for the AP-/BP-CML and Ph+ ALL populations are reported separately, see Sections 5.4 (AP-/BP-CML) and 5.5 (Ph+ ALL) .

Each economic analysis is a fully incremental CUA.

5.2.1 Curve-fitting methodology for model outcomes

For the three models (CP-CML, AP-/BP-CML, and Ph+ ALL) similar methods were used to extrapolate model outcomes from data:

5.2.1.1 Ponatinib

A key strength of these models is their use of the detailed IPD from the PACE trial to extrapolate outcomes for patients receiving ponatinib. Curve fitting to the IPD was performed using parametric survival analysis on these patient-level data. The following main parametric functions were assessed for goodness of fit: exponential, Weibull, Gompertz, log-logistic, and log-normal. The goodness of the fit of these functions was assessed with the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics.

5.2.1.2 Other comparators

As IPD were unavailable for comparators other than ponatinib, curve fitting was performed on published data. Where KM plots for the outcome of interest were available in a published reference, these were digitised to estimate the probability estimates for the outcome at time points along the KM curves. This step was unnecessary for data that were reported in tabular format. In either case, these data were imported into Excel, where the inbuilt Solver® function was used to derive the parameter values by minimising the sum of squared errors (SSE) between these data and predicted survival curves. The same main parametric functions were assessed for goodness of fit as for ponatinib (exponential, Weibull, Gompertz, log-logistic, and log-normal).

5.3 De novo analysis – CP-CML

5.3.1 Methodology

5.3.1.1 Patient population

The target population in the economic model is consistent with that defined in the NICE scope, as follows:[164]

> Adults with CP-CML whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

This target population is consistent with the patient population indicated in the approved EU label (see Section 2.2.2) and the subjects in the ponatinib clinical study programme. Specifically, the target population of the economic analysis is patients in the 3L treatment setting, reflecting the anticipated place in therapy of ponatinib—post-imatinib and a 2G-TKI. Consistent with SmPC guidance[22] and ponatinib efficacy data from the PACE trial,[238] the base case reflects all 3L patients, including those with and without any mutation at baseline, including T315I; having a mutation is not a pre-requisite for ponatinib use.[22] Not stratifying the model cohort by T315I-mutation status is appropriate since, as shown in the multivariate analysis by Mauro et al. 2012,[238] the presence of the T315I mutation does not predict treatment response to ponatinib. Despite these considerations, it should be noted that only patients with the T315I mutation can currently receive ponatinib through the CDF, highlighting the current inequity of access to this breakthrough treatment. The core assumption that the presence of the T315I mutation does not predict treatment response with ponatinib was validated by a clinical expert, Dr Richard Clark of the Haematology Department at the Royal Liverpool University Hospital (henceforth referred to as "the clinical expert").

To mimic the clinical course of CML, patients enter the CP-CML model in the CP phase, after which they can remain in CP or progress to AP- and BP-CML. A separate model has been developed for patients who start treatment in the AP- or BP-CML stages (see Section 5.4).

5.3.1.2 Baseline characteristics of the simulated population

5.3.1.2.1 Source data

A MAIC of ponatinib vs bosutinib was conducted to provide a more robust comparison of data than a naïve comparison; results of the MAIC were used to inform the economic analysis. Traditional approaches to mixed treatment comparison or network meta-analysis were not feasible given that the PACE and the bosutinib phase 1/2 trials were single-arm studies. Baseline characteristics available for the indirect comparison of bosutinib vs ponatinib were sex, median age, race, duration of CML, T315I mutation status, and ECOG performance status. Reported medians were interpreted, for matching purposes, as a binary characteristic (eg, median age of 53.0 years was transformed into a binary variable age >53.0 years, with a frequency of 50%). Matching would ideally be based on clinically relevant risk factors that impact relative treatment effects; however, there is no well-established procedure regarding how risk factors to be matched should be identified; therefore, all variables that were available for inclusion in the analysis were used. IPD from the PACE trial were used to match the baseline characteristics of patients on ponatinib to the baseline characteristics of patients in the bosutinib phase 1/2 trial. Using this approach, individual patients treated with ponatinib in the PACE study were assigned weights such that: (1) the weighted mean baseline characteristics in PACE exactly matched those reported for patients treated with bosutinib and, (2) each patient's weight was equal to his or her estimated odds of being treated with bosutinib versus ponatinib. Weights meeting these conditions were obtained from a logistic regression model for the propensity of being treated with bosutinib vs ponatinib, with individual patient values for all matched-on baseline characteristics included as predictors. The methods and results of the MAIC are presented in Sections 4.10.2–4.10.15 (and in Appendix 18: Matching-adjusted indirect comparison). It should be noted that the effect of the adjustment produced by the MAIC analysis is toward a reduction of response rates for ponatinib (ie, adjusted response rates were lower). To this extent the adoption of the MAIC analysis (rather than a naïve comparison) could be seen as a step towards a more conservative cost-effectiveness analysis.

The baseline characteristics of the modelled population used in the simulation are derived from the CP-CML cohort in the PACE study after adjustment in the MAIC (Table 5-4).

Table 5-4. Baseline characteristics of the modelled CP-CML population*

Parameter	Value	Source
Initial age (years)	54.50	MAIC analysis
Proportion of males	44.9%	MAIC analysis

MAIC, matching-adjusted indirect comparison.

*See Section 4.10 for the description of the MAIC analysis; the results of the MAIC are reported in Section 4.10.15.

5.3.1.3 Model structure

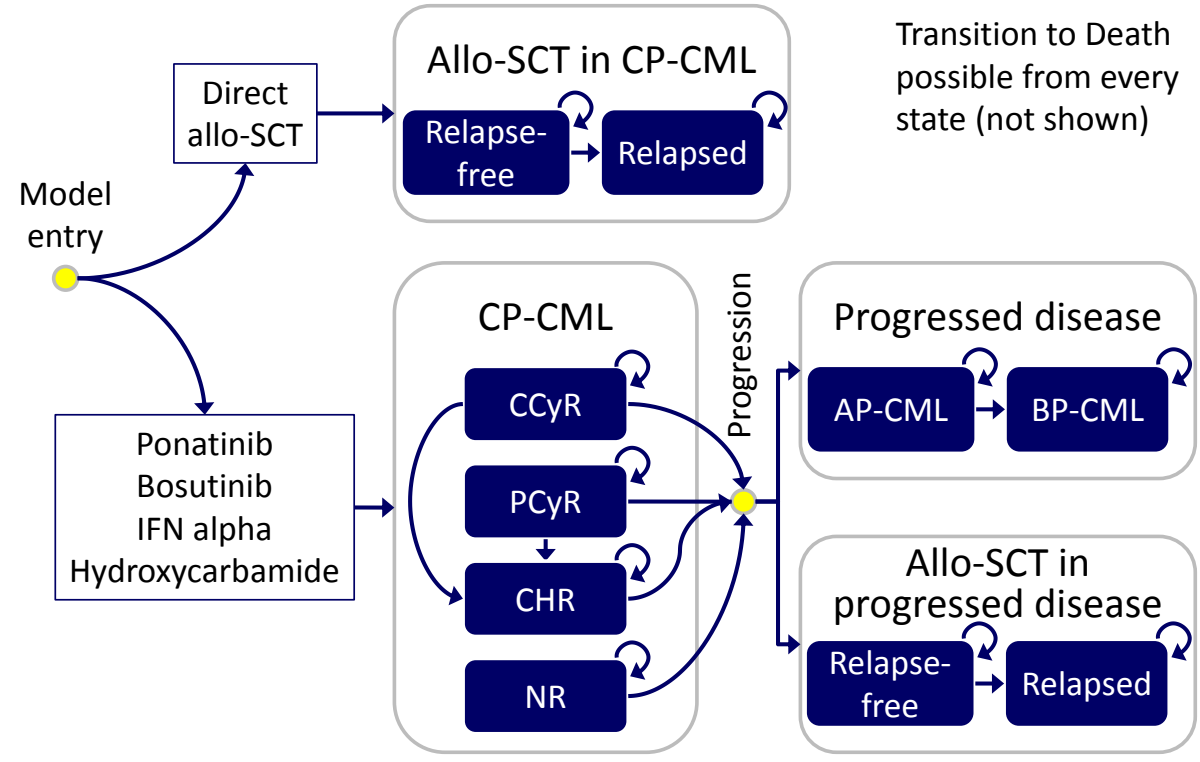
No economic models for ponatinib in the indication population have been published. We therefore developed a de novo cost-effectiveness model based on previously developed models for the treatment of patients with CP-CML,[239] and in conformity with requirements of NICE as expressed in its Guide to the methods of technology appraisal.[158]

The model was built in Microsoft Excel® (Microsoft Corporation, Redmond, WA), and incorporates several user-modifiable variables allowing customisation of the model for different countries. The contents of this report refer specifically to the English adaptation of the cost-effectiveness model, in which parameters have been set in accordance with the latest guidance for conducting pharmacoeconomic submissions from NICE.[158]

Based on a review of previous economic models,[240] the structure of the model was designed as a conventional state transition (Markov) model with three CML health states (Figure 5-3):[241]

- CP-CML, which incorporates 4 substates corresponding to response category (CCyR, PCyR, CHR, NR)
- Progressed disease with AP-CML and BP-CML as substates (ie, patients unsuitable for allo-SCT)
- Progressed disease treated with allo-SCT with relapse and relapse-free substates

Figure 5-3. Schematic representation of the CP-CML model health states



Allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; IFN alpha: interferon alpha; NR, no response; PCyR, partial cytogenetic response.

Disease response is accounted for within each living state. In the CP-CML health states, disease response is categorised according to presence/absence of cytogenetic or haematologic response. In the progressed CML health state post–allo-SCT, patients can remain clear of

disease or experience relapse. Patients with advanced CML do not receive allo-SCT can be in either AP- or BP-CML. As such, there are several transitions possible within a given time cycle: a live patient can either remain in their present health state, change response category, progress to the next-most-severe phase of CML and receive allo-SCT, progress and not receive allo-SCT, or die. Death is possible in any state and, as such, is not represented in Figure 5-3.

The CML health states are applicable to all comparators except allo-SCT. Since allo-SCT can result in cure, following allo-SCT patients could be considered as no longer having CML. Consequently, in the model the use of allo-SCT is modelled as a unique health state with patients being in either the relapse-free or relapsed substate (Figure 5-3).

5.3.1.3.1 CP-CML to progressed CML

Regardless of treatment option, all patients enter the Markov model in the CP-CML health state, having failed to respond to prior treatment (ie, are not already in remission at study entry). Patients with CP-CML either receive pharmacologic treatment or undergo direct allo-SCT. Distribution among response rates (CCyR, PCyR, CHR, and non-response [NR]) occurs during the first cycle. Thereafter, during any given cycle, patients can either remain in their current health state, die, transition into the progressed-disease state (non–allo-SCT CP-CML patients only) or experience relapse (allo-SCT patients). Each pharmacologic treatment option elicits treatment responses in accordance with published response rates; except ponatinib, in which responses rates are obtained from the MAIC analysis based on IPD from the PACE trial (Sections 4.10.2–4.10.15). Duration of response—obtained from the literature for each comparator and from the MAIC for ponatinib—was used to determine when patients transition from CCyR/PCyR to CHR. The method used to model response rates is described in Section 5.3.2.1.1.

Progression to AP-CML was modelled via a surrogate relationship based on specific disease response within CP-CML, categorised as follows:

- Complete cytogenetic response (CCyR)
- Partial cytogenetic response (PCyR)
- Complete haematologic response (CHR)
- No response (NR)

The core assumption that response to TKI is the most important prognostic factor in CP-CML, irrespective of the TKI used, was validated by the clinical expert and is in agreement with the 2013 ELN recommendations.[47] In addition, this approach is consistent with that used in the dasatinib technology appraisal submission to NICE,[242] which was generally accepted by the evidence review group.[82] The probability of progression from each response category was modelled based on published data (see Section 5.3.2.1.2).

The probability of death in the CP-CML health state is assumed to be equivalent across all treatments and is assumed to be the same as that of the general population, supported by evidence showing no disease-specific excess mortality in this early stage of CML.[132] Hence, mortality rates of the English general population have been applied.[243]

5.3.1.3.2 Progressed CML

In patients with progressed CML who are suitable candidates for allo-SCT, the costs and benefits accrued post–allo-SCT are estimated. Patients with progressed CML who receive allo-SCT are assumed to be in one of two health states: in remission or relapsed. All individuals in the allo-SCT arm accrue the cost of the operation during the first model cycle and follow-up costs throughout the first year (ie, first four model cycles), with lower follow-up costs in years 2 and 3; the cost in year 3 is applied in all subsequent years until relapse or death. Patients in remission are considered as no longer having CML, and those who relapse revert to pharmacologic-based options for the treatment of CML. Parametric functions were used to model both OS and relapse-free survival (RFS). Because the cohort starting age is 54.50 years and allo-SCT is usually offered to younger patients (eg, 44 years was reported in Jabbour et al. [2011]), an adjustment factor was applied to the survival function (which was based on the allo-SCT mortality data) to

ensure that the probability of dying due to allo-SCT in each cycle was not lower than the mortality risk in the general population.

In patients with progressed CML who are unsuitable candidates for allo-SCT, the costs and benefits associated with background therapy (assumed to comprise 20% imatinib, 20% hydroxycarbamide, 20% dasatinib, 20% nilotinib, and 20% bosutinib, based on a survey of clinical experts in the UK)[48] are estimated. All individuals enter this health state in AP. During any given cycle, patients can either remain in AP, progress to BP, or die, with transitions being determined by PFS and OS data derived from the literature as described in Section 5.3.2.1.3.

Events occurring in the progressed CML health state are independent of the initial treatment allocation. Hence, the only source of a differential across treatments in terms of intervention-specific costs and benefits accrued in AP-CML and BP-CML is the time at which patients transition to the progressed CML state, which is a function of their time-to-progression in CP-CML.

As patients enter the progressed CML state at different time points, the costs and benefits accrued in the health substates need to be discounted accordingly. To fully account for this impact, a "double discounting" approach is used. Initially, discounted costs and QALYs are calculated for the time horizon within the progressed CML health state. These values are applied to all patients in each health state within the submodels. Secondly, the patients entering the progressed CML state in each cycle are assigned discounted costs and QALYs from the time at which they progressed back to $t = 0$, the first model cycle in which all patients are in CP-CML. This calculation therefore captures the different times at which patients enter the progressed CML health state.

5.3.1.4 Features and justification of the de novo analysis

5.3.1.4.1 Perspective

In accordance with the NICE guide to the methods of technology appraisal, the reference-case CUA adopts the payer perspective for costs, specifically that that of the NHS and Personal Social Services (PSS).[158] The NHS/PSS perspective includes direct medical costs and allo-SCT follow-up costs.

The perspective on outcomes is that of the most relevant direct health effects on patients, namely survival and HRQoL (as a function of CML health states and adverse effects of treatment), in order to generate QALY outcomes.

5.3.1.4.2 Time horizon

To capture all important differences in costs or outcomes between the technologies being compared, the time horizon of the CUA is the duration of the simulated patient cohort's lifetime. The model employs 3-month Markov cycles with a half-cycle correction, and costs and outcomes are accrued within these cycles across the overall model time horizon. A 3-month cycle parallels the length of the ponatinib response evaluation period described in the SmPC, and is short enough to allow fitting of curves; a half-cycle correction was adopted because the cycle length is relatively long. The starting age of all patients entering the model is 54.50 years, based on baseline characteristics in the PACE trial after weighting in the matching-adjusted indirect comparison (MAIC analysis, Section 4.10; Appendix 18: Matching-adjusted indirect comparison) to match those in the bosutinib study by Khoury et al. 2012.[8]

5.3.1.4.3 Discount rate

In the base-case analysis, both costs and benefits are discounted at 3.5% per annum as recommended by NICE.[158] Discount rates of 0% and 6% were used in sensitivity analyses.

5.3.1.4.4 Outcome measures

The primary and secondary outcomes of this analysis are cost per QALY gained and cost per life-year gained (LYG), respectively.

Table 5-5 summarises the features of the CP-CML de novo analysis. The chosen values were in accordance with the NICE guide to the methods of technology appraisal.[158]

Table 5-5. Features of the CP-CML de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (maximum of 400 cycles, up to 100 years)	To capture all important differences in costs or outcomes between the technologies being compared[158]
Were health effects measured in QALYs; if not, what was used?	QALY and LYG	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY[164] For completeness, the analysis evaluates incremental LYGs
Discount of 3.5% for utilities and costs	3.5%	3.5% per annum as recommended by NICE[158] Discount rates of 0% and 6% were used in sensitivity analyses
Perspective (NHS/PSS)	NHS/PSS	In accordance with the NICE guide to the methods of technology appraisal,[158] the reference-case CUA adopts the payer perspective for costs

CUA, cost-utility analysis; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.

5.3.1.5 Intervention technology and comparators

5.3.1.5.1 Ponatinib

The modelling of ponatinib reflects the decision problem defined by NICE. Ponatinib has marketing authorisation in the EU for treating adult patients with CP-, AP-, or BP-CML, who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.[22] Ponatinib is included in the treatment pathways for patients who are R/I to dasatinib or nilotinib in the most recent key clinical practice guidelines, namely the 2013 update of the ELN recommendations for CML management[47] and the 2016 update of the NCCN CML guidelines.[1]

Ponatinib is currently available to patients with the T315I mutation in England through the CDF.[89] The model does not address patients with the T315I mutation separately from those who are R/I to 2G-TKIs as high response rates to ponatinib have been demonstrated in PACE regardless of mutation status[238] and this approach underlies the current inequity in CDF access to ponatinib between patients with the T315I mutation and those who fall within the indication but do not have this mutation.

5.3.1.5.2 Comparators

The comparators included in the CUA are those defined in the NICE scope, namely the 2G-TKI bosutinib, allo-SCT, interferon alpha, and hydroxycarbamide.

Bosutinib has marketing authorisation in the EU for treating patients with Ph+ CML who were previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.[7] NICE recommends bosutinib as an option, within its marketing authorisation, if the company provides bosutinib with the discount agreed in the PAS (as revised in 2016).[93] As with ponatinib, bosutinib is included in the treatment pathways for patients who are R/I to dasatinib or nilotinib in the 2013 ELN recommendations for CML management[47] and the 2016 NCCN CML guidelines.[1]

Compared with ponatinib, bosutinib provides only modest benefit to heavily pre-treated patients with CML: for achieved CCyR, the best response with bosutinib was 24.1% (Khoury et al. 2012),[8] while the CCyR rate in the PACE trial was 65% (Hochhaus et al. 2015),[24] and after matching PACE IPD to bosutinib baseline characteristics the CCyR rate with ponatinib was calculated to be 61.3% (MAIC comparison; Section 4.10.15). In addition to the modest clinical evidence

supporting bosutinib, there are other reasons to not consider bosutinib as an appropriate comparator for ponatinib:

- Whereas the ponatinib label notes that ponatinib is recommended for patients with the T315I mutation, the bosutinib label explains that bosutinib has limited activity against this mutation, and therefore clinical activity of bosutinib in patients with the T315I mutation is not expected.[7, 22] The MAIC analysis, carried out to inform the ponatinib response rates applied in the economic model, adjusted for differences in the proportions of patients with the T315I mutation enrolled in the PACE trial and the bosutinib study (see Section 4.10.15).
- The CML indications for ponatinib and bosutinib are not directly comparable with respect to TKI resistance and intolerance. That is, bosutinib is indicated for patients who have been previously treated with ≥1 TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, which differs from the more detailed wording of the ponatinib indication (ie, adults with CP-CML whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation).[7, 22]
- Only limited data are available to support bosutinib in patients with an "unmet medical need", defined in the bosutinib EPAR as patients for whom either dasatinib or nilotinib may not be considered suitable treatment after failure of the other 2G-TKI due to a pre-existing medical condition, TKI intolerance, or mutation which would be expected to confer resistance to that therapy, as well as patients who have received prior imatinib only but for whom neither dasatinib nor nilotinib may be considered a suitable treatment for the above referenced reasons.[36] In the bosutinib study upon which the conditional approval is based, among patients with CP-CML, only 21 met these criteria for unmet medical need.[102]

The other pharmacologic comparators included in the NICE scope are hydroxycarbamide and interferon alpha. Hydroxycarbamide is a conventional chemotherapeutic drug (ie, non-TKI), which clinical expert opinion suggests may be used as palliative therapy although it does not prevent or significantly delay the progression towards advanced phases of CML.[244] Interferon alpha was displaced as a CML therapy by the discovery of TKIs,[244] and current clinical practice guidelines recommend it only in rare instances when a TKI cannot be used.[47] Consequently, interferon alpha is rarely used in clinical practice for CML in England, as noted by the NICE appraisal committee in the bosutinib evaluation.[93] Allo-SCT is also included as a nonpharmacologic comparator. The ELN guidelines state that, for patients in CP-CML, it is reasonable to reserve transplant for those who are R/I to at least one 2G-TKI.[47]

5.3.1.6 Treatment continuation rule

The model applies a stopping rule for patients on ponatinib who have not achieved at least CHR by 3 months. For patients responding to treatment, a discontinuation probability is derived from the parametric on-treatment survival analysis on patient-level data from the PACE study (for ponatinib) and from an exponential fit on the median on-treatment survival data (8.3 months) for bosutinib (Khoury et al. 2012).[8] When a TKI is discontinued, we assume BSC is started and continued until progression or death. Allo-SCT is modelled as a one-time event and therefore the treatment continuation rule does not apply.

5.3.1.7 Summary of the de novo analysis

The CP-CML model characteristics are summarised in Table 5-6.

Table 5-6. Summary of CP-CML model characteristics

Component	Description
Population	Adults with CP-CML R/I to imatinib and either dasatinib or nilotinib
Comparators	Bosutinib Hydroxycarbamide IFN alpha Allo-SCT
Perspective	NHS/PSS
Cycle length	3 months (half-cycle correction)
Time horizon	Cohort lifetime (maximum of 400 cycles, up to 100 years)
Starting age	54.50 years
Discount rate per annum: costs	3.5%
Discount rate per annum: benefits	3.5%
Outcome measures generated	Cost/QALYs gained Cost/LYG

Allo-SCT, allogeneic haematopoietic stem cell transplantation; CML, chronic myeloid leukaemia; CP, chronic phase; IFN alpha, interferon alpha; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life-year; R/I, resistant or intolerant.

5.3.2 Clinical parameters and variables

5.3.2.1 Clinical data sources

5.3.2.1.1 Effectiveness data

As dictated by the PFS data (see Section 5.3.2.1.2), response was modelled for the following categories of best response:

- CCyR
- PCyR
- CHR
- NR

To align with the PFS data, the definition of best response was set such that, for example, if a patient experiences a CHR followed by a PCyR then they will only be included in the PCyR category. Patients who did not achieve a CCyR, PCyR, or CHR were assumed to be non-responders (NR). For both ponatinib and bosutinib cytogenetic and haematologic responses in each category were calculated excluding those patients who already had that response at baseline.

5.3.2.1.1.1 Ponatinib

Response rates for ponatinib (Table 5-7) were obtained from the most recent PACE study IPD (data cut-off, 3 August 2015), after adjustment in the MAIC to match patient baseline characteristics in the pivotal bosutinib trial (see Sections 4.10 and 5.3.1.2; Appendix 18: Matching-adjusted indirect comparison). In order to align with the comparator evidence, the rates used in the base-case analysis were based on patients who had failed 2 prior TKIs. PACE was identified in the clinical SLR (Section 4.11; Table 4-7 [study design], Table 4-10 [baseline characteristics], and Table 4-13 [outcomes]).

Table 5-7. Best response to ponatinib (3 August 2015 follow-up; source: PACE clinical trial data, adjusted in MAIC)*

	Response rate, %	
Best response	**Unadjusted**	**Adjusted in MAIC**
CCyR	64.95%	61.34%
PCyR	6.19%	8.46%
CHR	17.53%	18.19%
NR	11.34%	12.01%

CCyR, complete cytogenetic response; CHR, complete haematologic response; MAIC, matching-adjusted indirect comparison; NR, non-response; PCyR = partial cytogenetic response.

*See Section 4.10 for the description of the MAIC analysis; the results of the MAIC are reported in Section 4.10.15.

5.3.2.1.1.2 Bosutinib

Data for modelling response to bosutinib following failure of another 2G-TKI were derived from a phase 1/2, open-label, two-part study by Khoury et al., identified in the clinical SLR (see Section 4.11; Table 4-7 [study design], Table 4-10 [baseline characteristics], and Table 4-13 [outcomes]).[8] The second part of this study evaluated the efficacy and safety of bosutinib (500 mg/day) across multiple CP-CML patient subpopulations. The response rates applied in the model were those for the total population (N=118), comprising patients who had failed imatinib as well as either dasatinib or nilotinib (n=114), and patients who had failed imatinib, dasatinib, and nilotinib (n=4). Response rates incorporated in the model for bosutinib are presented in Table 5-8.

Table 5-8. Best response to bosutinib (source: Khoury et al. 2012)[8]

Best response	Response rate*, %
CCyR	24.07%
PCyR	8.33%
CHR	37.93%
NR	29.66%

CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, non-response; PCyR, partial cytogenetic response.

*Response rates for bosutinib are not adjusted for in the MAIC. The analysis only adjusts ponatinib response rates through matching patient baseline characteristics between studies.

5.3.2.1.1.3 Interferon alpha

When designing our SLR for CML (prior to receipt of the pre-invitation draft scope in June 2016), we did not include interferon alpha as a comparator because it is rarely used to treat CML in the UK and is not part of the NICE blood and bone marrow cancers pathway.[18, 47, 82] In the bosutinib appraisal, it was also the conclusion of the committee that interferon alpha is not used in clinical practice in England and Wales.[93] Nevertheless, to align with the decision problem, we added interferon alpha as a comparator in the economic analysis.

We assume that CCyR and PCyR do not occur with interferon alpha and that the only response categories applicable to patients on this therapy are CHR or NR. The median overall CHR on interferon alpha applied in the model is 47%, as reported in the HTA by Dalziel et al. 2004 based on results of interferon alpha vs hydroxycarbamide trials in which patients either had no prior treatment or were previously treated with hydroxycarbamide.[227] We therefore assume a NR rate of 53%. Dalziel et al. 2004 was identified in the economic SLR (Section 5.1.2) and has been cited in previous HTAs (eg, Loveman et al. 2012,[168] Rogers et al. 2012,[82] and Pavey et al 2012)[167].

5.3.2.1.1.4 Hydroxycarbamide

No studies for hydroxycarbamide in the post–2G-TKI setting were identified in the clinical SLR. In the absence of response data for hydroxycarbamide in patients who received prior 2G-TKI therapy, CHR rates were obtained from Dalziel et al. 2004.[227] In addition, due to the absence of comprehensive data, indirect treatment comparisons were not possible between ponatinib and hydroxycarbamide (or interferon alpha).

Based on the median response rate across two studies identified in a SLR by Dalziel et al. 2004,[227] it was assumed that 41% of patients receiving hydroxycarbamide will achieve a CHR and the remaining 59% will be non-responders; cytogenetic responses were assumed not to occur with this therapy.

5.3.2.1.1.5 Allo-SCT

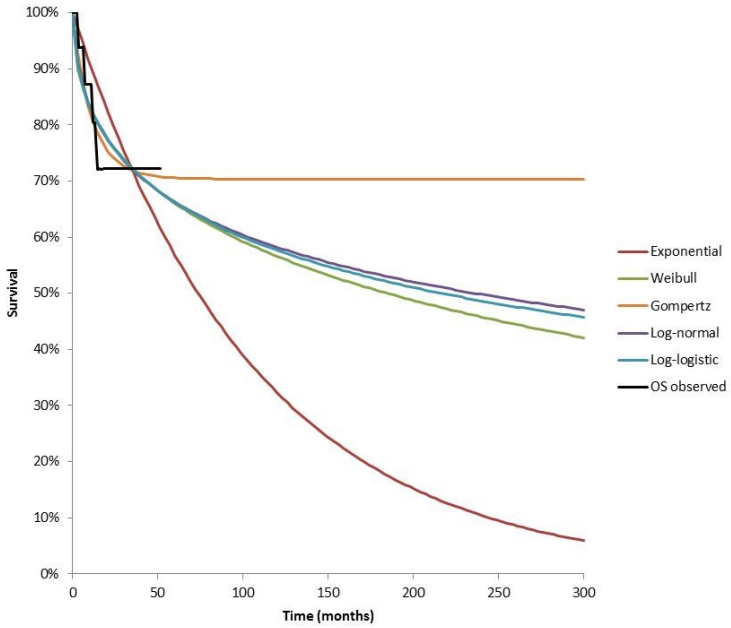
5.3.2.1.1.5.1 Overall survival

The observational study by Jabbour et al. 2011, identified in the SLR, was considered the most suitable study to provide data on OS post–allo-SCT; the study evaluates survival outcomes following allo-SCT stratified by CML disease stage for 47 patients with CML.[144] For further justification on including Jabbour et al. in the submission, refer to Section 4.11.2. Study details are provided see Section 4.11; Table 4-7 [study design], Table 4-10 [baseline characteristics], and Table 4-13 [outcomes]).

An OS function was extrapolated from the published survival graph as described in Section 5.2.1.2. Based on the formal goodness of fit estimates and visual inspection of the long-term projections of these curves (Figure 5-4 and Figure 5-5), an exponential model was selected for inclusion in the economic evaluation for both CP-CML and AP-CML (the Gompertz function provided best fit, but the exponential function was selected because all other functions yielded an unrealistic OS after allo-SCT). While data extrapolated over the long-term carry uncertainty, the clinical plausibility of the median OS predicted with the exponential fit (ie, 6 years in CP after failing ≥2 TKIs and 3.8 years in AP after failing ≥3 TKIs) were validated by the clinical expert. To address the uncertainty with using the exponential fit, a scenario analysis was carried out using the best fit (see Section 5.3.7.8.9). Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

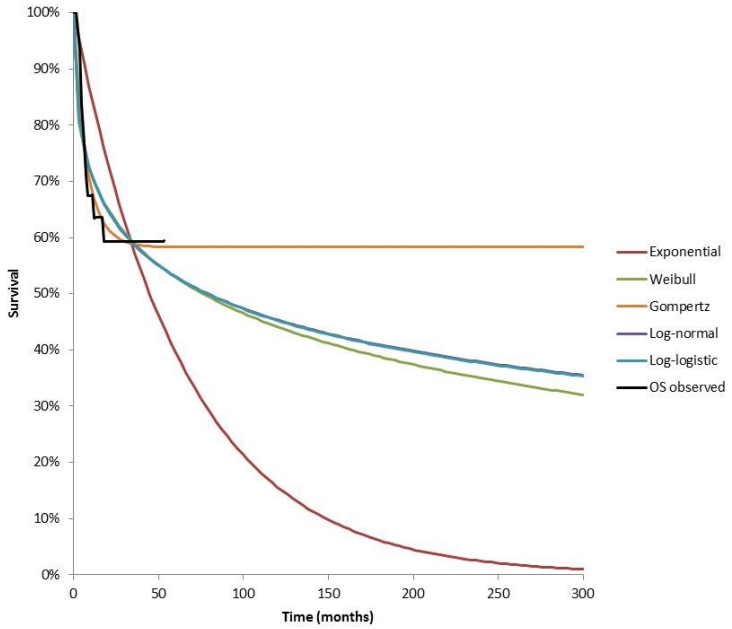
A comparison of original and fitted data is presented in Figure 5-4 and Figure 5-5. In order to maintain clinical plausibility, population mortality estimates were used in the modelling of allo-SCT–based death, with the rule applied that survival in allo-SCT patients can never be better than the age-equivalent survival rate in the general population. Hence, during each model cycle, the mortality probability derived using the exponential function is compared to that derived using English life table data[243] and the larger of the two numbers is used in the model.

Figure 5-4. Comparison of observed (source: Jabbour et al. 2011)[144] and fitted OS data for allo-SCT in patients with CP-CML



Allo-SCT, allogeneic haematopoietic stem cell transplantation; CML, chronic myeloid leukaemia; CP, chronic phase; OS, overall survival.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

Figure 5-5. Comparison of observed (source: Jabbour et al. 2011)[144] and fitted OS data for allo-SCT in patients with AP-CML



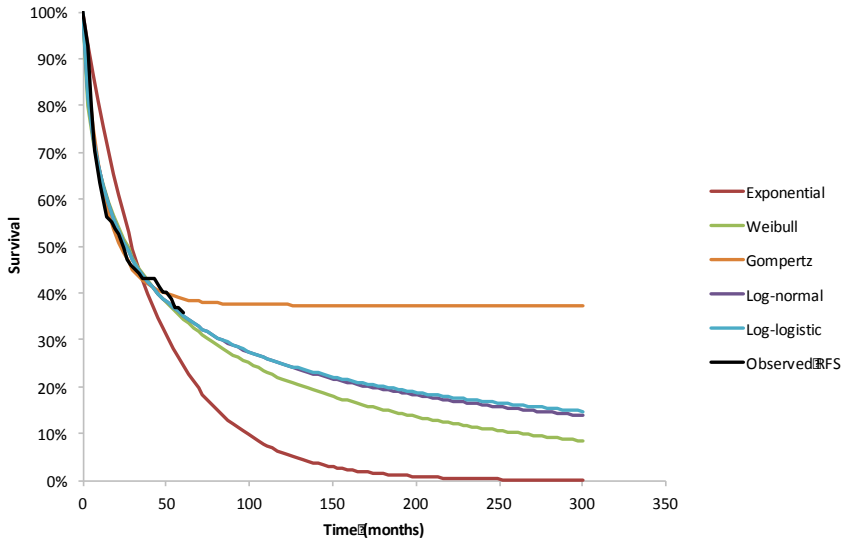
Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, advanced phase; CML, chronic myeloid leukaemia; OS, overall survival.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

5.3.2.1.1.5.2 Relapse-free survival

No studies reporting RFS following allo-SCT in the post–2G-TKI setting were identified in the clinical SLR. In the absence of RFS data for allo-SCT in patients who received prior 2G-TKI therapy, data on leukaemia relapse were extracted from a study by Craddock et al. 2000 of 189 UK patients in CP, of which 60 patients (32%) had previously relapsed, with a minimum follow-up of 3 years.[245] Craddock et al. 2000 was identified in the economic SLR search but not the clinical SLR because the PICOS criterion for patient population in the economic search was broader. That is, the search strategy focussed on a more comprehensive patient population that was not limited to patients who were R/I to prior TKI therapy. Although Craddock et al. 2000 did not meet inclusion criteria based on study design, data from this study were used in the model in the absence of alternative sources.

A similar curve-fitting process to that described above for allo-SCT OS was undertaken for RFS, with a Gompertz model being selected. The comparison of observed and fitted data is presented in Figure 5-6.

Figure 5-6. Comparison of observed (source: Craddock et al. 2000)[245] and fitted relapse-free data (allo-SCT only)



Allo-SCT, allogeneic haematopoietic stem cell transplantation; RFS, relapse-free survival.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

5.3.2.1.2 Progression-free survival: CP-CML to progressed disease

5.3.2.1.2.1 Data sources

The model requires values for the following survival measures for patients' post–2G-TKI therapy:

- Long-term data for both PFS
- PFS data stratified by clinical response category (cytogenetic or haematologic)

No suitable studies were identified in the SLR that provided relevant data in this patient population. Data from the PACE trial were inadequate to derive PFS because only 9/267 (3.4%) patients with CP-CML transformed to AP-CML (5 patients) or BP-CML (4 patients).[25] Instead, PFS data were extrapolated from recent appraisals by NICE of dasatinib and nilotinib in patients who are R/I to imatinib.[168]

PFS data were derived from the BMS-034 study, a randomised open-label phase 3 study of dasatinib in patients with imatinib-resistant or -intolerant CP-CML, as reported by the Southampton Health Technology Assessments Centre (SHTAC).[168] PFS data stratified by best response by 12 months were obtained for the 167 patients in this study who were administered the licenced CP-CML dose (100 mg QD), as shown in Table 5-9.

Table 5-9. Progression to AP-/BP-CML stratified by best response (source: Loveman et al. 2012)[168]

	Best response			
Month	**NR, %**	**CHR, %**	**PCyR, %**	**CCyR, %**
0	100.0	100.0	100.0	100.0
6	30.0	94.9	100.0	100.0
12	30.0	84.1	94.4	98.2
18	30.0	77.7	83.3	98.2
24	30.0	63.6	83.3	94.2
30	30.0	55.9	83.3	94.2
36	30.0	38.7	77.8	94.2
42	25.8	25.8	71.3	94.2
48	24.1	25.8	59.4	94.2

AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; MCyR, major cytogenetic response; NR, non-response; PCyR, partial cytogenetic response.

5.3.2.1.2.2 Model parameterisation

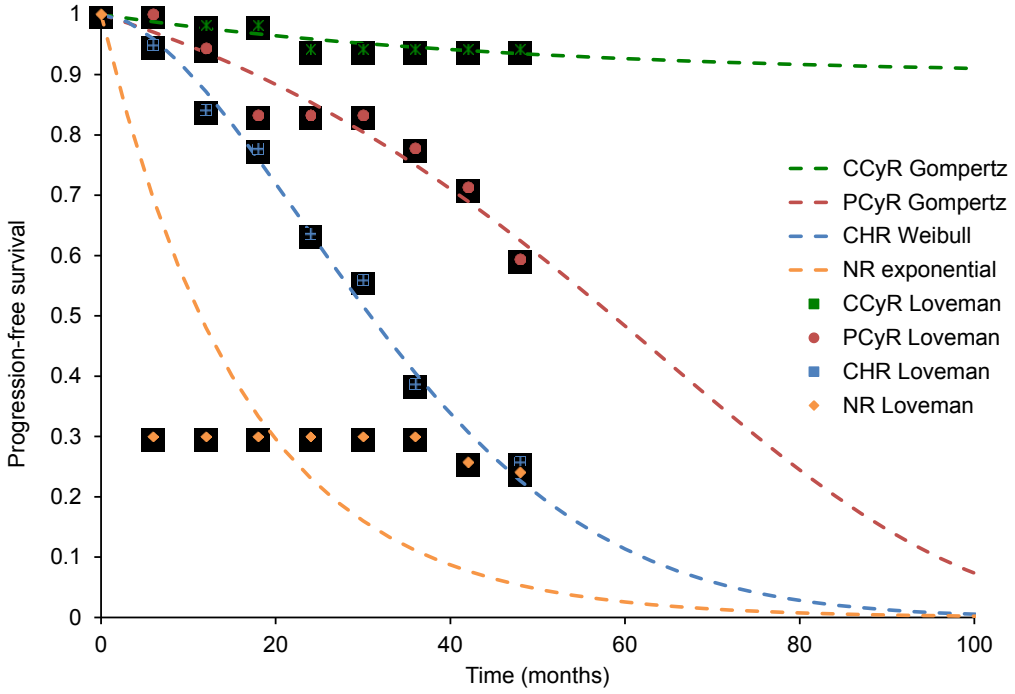
For modelling purposes, the relationship between response and progression was assumed to be independent of the line of therapy, so the data obtained from the post-imatinib BMS-034 study were assumed to apply to post–2G-TKI patients.

To estimate a continuous function of disease progression out of the CP-CML state, the data reported in Table 5-9 were extrapolated as described in Section 5.2.1.2. Based on the observed fit of the survival functions to the data presented in Table 5-9, as well as the clinical plausibility of the extrapolated portion of the survival curves, the following distributions were selected for modelling progression to AP-CML from each response category:

- CCyR: Gompertz
- PCyR: Gompertz
- CHR: Weibull
- NR: exponential

A comparison of observed and fitted data is provided in Figure 5-7.

Figure 5-7. Comparison of the BMS-034 study data and the fitted parametric functions



CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, non-response; PCyR, partial cytogenetic response.

The best fit for all response-based PFS data (CCyR, PCyR, CHR) was selected on the basis of minimising the SSE between the data reported in Loveman et al.[168] and the predicted survival curve. For NR, the exponential function was selected based on clinical plausibility.

The time-dependent probabilities of transitioning from CP-CML to AP-CML in a given cycle for each response category were estimated as 1 minus the ratio of the survivor function at the end of the cycle to the survivor function at the beginning of the cycle.[241]

This approach to modelling time in CP-CML assumes the probability of remaining in the CP-CML health state is independent of treatment within a given response category. This renders the response profile of each treatment the driver of outcomes through the assumed surrogate relationship between response and progression. This approach to modelling outcomes in CP-CML is common practice, and has been adopted in previous CML technology appraisals.[82]

In addition to the probability of progression associated with each response category, duration of response associated with each TKI was calculated. To obtain the duration of response for each TKI, data from the PACE study (ponatinib) and published literature (bosutinib; 48-month update of the phase 1/2 study, Gambacorti-Passerini et al. 2014)[186] were used. These data are biased in favour of bosutinib, however, because the maintenance of response is based on overall response in the bosutinib trial, including achieved response and maintained baseline response. Unlike the bosutinib data, the duration of response with ponatinib reflects only the maintenance of achieved response in patients who were not already responders at study baseline. Duration of response, defined as the time spent in cytogenetic response (CCyR or PCyR), was extrapolated for ponatinib through parametric survival analysis on patient-level data (adjusted based on the MAIC analysis) from PACE as described in Section 5.2.1.1. For bosutinib the duration of response was extrapolated through parametric fitting from published survival-on-response curves as described in Section 5.2.1.2 (Figure 5-8). From the fitted function, the probability of transitioning from CCyR and PCyR to CHR was derived, with the assumption that upon loss of cytogenetic response, haematologic response is retained.

Figure 5-8. Parametric extrapolation of duration of response data for ponatinib (source: PACE data cut-off, 3 August 2015; MAIC; Gambacorti-Passerini et al. 2014)[186]

CCyR, complete cytogenetic response; MAIC, matching-adjusted indirect comparison; PCyR, partial cytogenetic response.

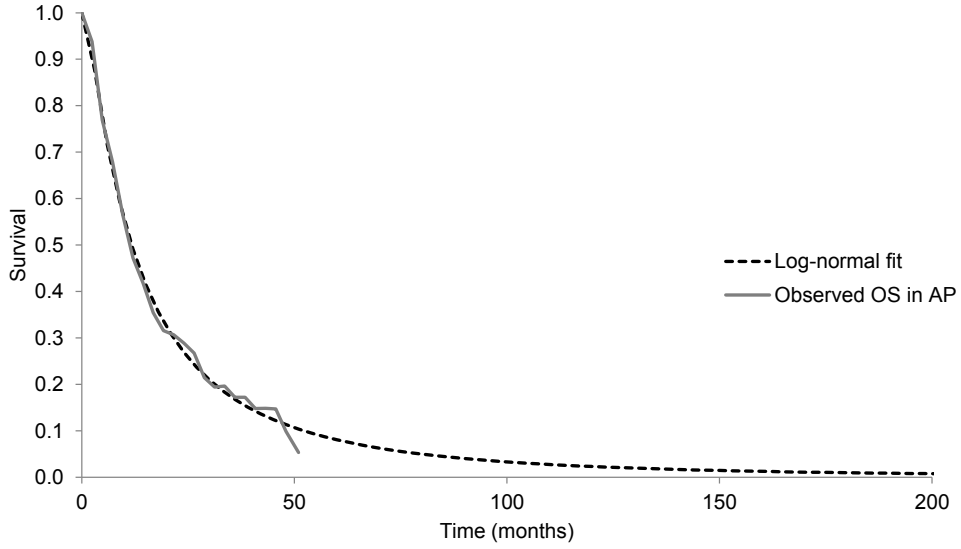
5.3.2.1.3 Progression-free and overall survival: Progressed CML unsuitable for allo-SCT

No suitable studies in the post–2G-TKI setting were identified to provide PFS and OS data following progression to AP-CML. Kantarjian et al. 2007, identified in the SLR prior to filtering for post–2G-TKI studies, and thus not included in the clinical effectiveness section of the submission pertaining to the indicated population, nonetheless provided applicable data for PFS/OS in progressed CML in the post-imatinib setting (see Sections 4.1.4, 4.1.6, and 4.11; Appendix 16: Complete list of included studies identified in the SLR).

In progressed disease, treatment is interrupted and PFS and OS following progression to AP-CML are drug-treatment–independent. Long-term outcomes in AP-CML and BP-CML were modelled based on data reported by Kantarjian et al. 2007 for 420 patients with CML post-imatinib failure (resistance/recurrence in 374; toxicities in 46).[29] Based on an extrapolation from the survival curves for AP- and BP-CML in this study, the mean PFS for patients in AP-CML was set at 9.16 months.

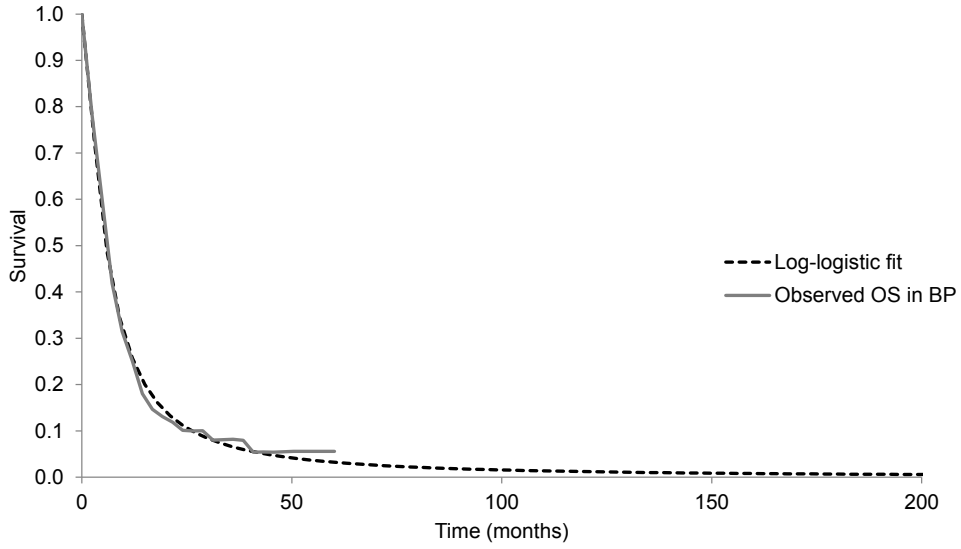
OS functions were extrapolated as described in Section 5.2.1.2. The best-fitting curves (in terms of minimising the SSE) were the log-normal distribution for OS in AP-CML and the log-logistic distribution for OS in BP-CML (see Figure 5-9 and Figure 5-10).

Figure 5-9. Comparison of observed (KM curve; source: Kantarjian et al. 2007)[29] and fitted OS data for AP-CML



AP, accelerated phase; CML, chronic myeloid leukaemia; KM, Kaplan–Meier; OS, overall survival.

Figure 5-10. Comparison of observed (KM curve; source: Kantarjian et al. 2007)[29] and fitted OS data for BP-CML



BP, blast phase; CML, chronic myeloid leukaemia; KM, Kaplan–Meier; OS, overall survival.

5.3.2.1.4 Mortality

Patients are at risk of both CML-related and all-cause death in all health states in the model. As stated earlier, each patient in the CP-CML health state is assumed to have an equivalent baseline risk of death to an age- and gender-matched member of the general public. This mortality risk is modelled based on the average age (54.50 years) and gender distribution (44.9% male) in the CP-CML patients in the PACE trial after adjustment in the MAIC, and on English national statistics.[243] The core assumption that there is no excess mortality (compared to the general population) in CP-CML due to the disease itself and that the excess mortality of CML is due to progression to advanced phases of the disease was validated by the clinical expert.

CML-related mortality in AP-CML and BP-CML is modelled through the PFS and OS data from Kantarjian et al. (2007).[29] Death from other causes was not modelled in either state as it is captured in the OS curve from this study.

5.3.2.1.5 Time to response

Time to response is considered in the model. In the PACE study, median time to MCyR on ponatinib was less than 3 months in CP-CML (Cortes et al. 2013).[9] In the model, allocation of patients to response categories therefore occurs in the first cycle. Patients who do not achieve CHR in CP discontinue ponatinib per SmPC guidance.[22]

5.3.2.1.6 Time-on-treatment

In order to capture the differential timing between patients discontinuing treatment and progression to AP-CML, and hence to accurately estimate treatment costs, a time-on-treatment analysis was conducted, as described below in Sections 5.3.2.1.6.1–5.3.2.1.6.3. The data were derived from the PACE trial (data cut-off, 3 August 2015) for ponatinib. The time-on-treatment for bosutinib was derived based on the mean time-on-treatment reported in the clinical literature.

Our base-case analysis applies the surrogate survival approach, where the benefit of treatment is expressed in terms of levels of response (that correlate with the probability of progression). However, we used a time-on-treatment curve to determine the probability of discontinuing the treatment during the simulation. The maintenance-of-response curves and the time-on-treatment curves are applied independently during the simulation. This may result in simulated cases of patients who discontinued the treatment but do not suffer any consequence in terms of loss of response. To avoid the simulation of such an indiscriminate benefit beyond treatment discontinuation, in the base-case analysis, it was assumed that only patients who had achieved CCyR maintained response after TKI discontinuation. All other response cohorts (PCyR, CHR, and NR) lose benefit upon treatment discontinuation and accrue the PFS rate of hydroxycarbamide.

5.3.2.1.6.1 Source data: PACE

The time-on-treatment was calculated using a time-to-event approach, measuring the risk of treatment discontinuation over time. To calculate the time-on-treatment for each patient, the time from first dose to the date of the last dose was calculated and converted into months. Patients were censored if they continued treatment after the study end date.

In order to align this element of the model with the overall modelling approach, separate analyses were conducted for each of the key best-response categories.

5.3.2.1.6.2 Analysis

To enable estimation of time-on-treatment beyond the PACE follow-up duration, five parametric distributions (exponential, Weibull, Gompertz, log-logistic, and log-normal) were considered for predicting time-on-treatment. To adjust for the differences in time-on-treatment between best-response categories, dummy variables for CCyR, PCyR, and CHR were included as covariates with NR modelled as the baseline. The fit of each model was assessed through investigation of AIC and BIC statistics. Although a log-logistic model had the best fit, based on the AIC and BIC statistics, the exponential function was chosen to model time-on-treatment adjusting for best response for consistency with the function used for bosutinib. In accordance with the approved ponatinib SmPC,[22] the base-case analysis considers ponatinib interruption if no CHR is achieved. In this case, treatment is halted after 3 months (ie, in the next cycle) for patients who do not demonstrate a haematologic response while on ponatinib.

5.3.2.1.6.3 Comparator time-on-treatment

The time-on-treatment for the model comparators was calculated by extrapolating an exponential curve from the median duration of treatment because the exponential function is the only parametric curve that can be fit using only a single parameter (in this instance, median duration of treatment). Data from Khoury et al. 2012 provided the median time-on-treatment of 8.30 months for bosutinib, over a median follow-up 28.5 months.[8] Time-on- treatment is not modelled

for the hydroxycarbamide or interferon alpha comparators because these interventions are given as BSC and patients are expected to stay on treatment indefinitely. Time on treatment is not a relevant variable for allo-SCT, as a one-time procedure.

5.3.2.2 Transition probabilities

Transition probabilities that are used in the CP-CML model are described below. All probabilities, with the exception of the mortality of the general population, are derived from survivor functions extrapolated from clinical data. The time-dependent probabilities of transitioning between states were in general estimated as 1 minus the ratio of the survivor function at the end of the cycle to the survivor function at the beginning of the cycle.

- **Loss of response** (ie, transition from the CCyR and PCyR substates to CHR). The duration of the response is a function of the treatment (this is not applicable to comparators hydroxycarbamide and interferon alpha as their CCyR and PCyR rates are assumed to be zero). As explained in Section 5.3.2.1.2.2, two survivor functions (depicting the fraction of the cohort which retains response over time) were obtained for ponatinib (one for CCyR and one for PCyR) through parametric survival analysis on patient-level data from the PACE study (adjusted based on the MAIC analysis). For bosutinib, a single survivor function, assumed to be valid for both CCyR and PCyR, was extrapolated through parametric fitting from published survival-on-response curves.
- **Relapse (in Allo-SCT in CP-CML and Allo-SCT in Progressed Disease states)**. A survivor function, describing the fraction of patients remaining free from relapse over time, was extrapolated through parametric fitting from published curves in Craddock et al. 2000,[245] as described in Section 5.3.2.1.1.5. In the absence of relevant data, the same function was assumed valid for both the Allo-SCT in CP-CML and Allo-SCT in Progressed Disease states.
- **Discontinuation of TKI treatment**. The probability of discontinuing the active treatment before progression is applied to ponatinib and to bosutinib, as described in Section 5.3.2.1.6. This probability does not directly determine a state transition in the Markov model, but rather is used to accurately estimate treatment costs. However, since it was assumed that only patients who had achieved CCyR maintained response after TKI interruption, the event of discontinuation in the PCyR substate determines a transition to the CHR substate. Four survivor functions depicting the fraction of the cohort which remains on treatment over time were obtained for ponatinib (for CCyR, PCyR, CHR and NR response categories) through parametric survival analysis on patient-level data from the PACE study. For bosutinib, a single survivor function, calculated by extrapolating an exponential curve from the median duration of treatment reported in the literature, was assumed valid for all four of the best-response categories.
- **Progression to AP-CML** (ie, transition from the CP-CML state to progressed disease). The probability of progression for patients in CCyR, PCyR, CHR and NR substates is not dependent on the treatment. The source of the data is BMS-034 study, and for each response category a parametric function was obtained to describe the fraction of patients remaining free from progression at each time (survivor function) as described in Section 5.3.2.1.2.2. Since death is normally considered as a censoring event when presenting PFS data, the actual probabilities used in the model at each cycle were obtained by subtracting the probability of death from progression probability at the same cycle.
- **Progression to BP-CML** (ie, transition from the AP-CML substate to BP-CML [in the Progressed Disease state]). As described in Section 5.3.2.1.3, no suitable studies in the post–2G-TKI setting were identified to provide PFS data following progression to AP-CML. The mean PFS for patients in AP-CML of 9.16 months was estimated as the difference from the mean OS in AP-CML and BP-CML calculated with the survivor functions extrapolated from Kantarjian et al. 2007.[29] Finally, a survivor function, depicting the fraction of the cohort remaining free from progression to BP-CML over time, was calculated by extrapolating an exponential curve from the mean PFS.
- **Death (from CP-CML)**. Probability of death in CP-CML is extracted at each cycle from the mortality table of males and females in the general population. The overall background

mortality rate in the model was weighted by the gender mix in the simulated population (44.9% males). Mortality rates were converted into death probabilities. The population begins the simulation at an age of 54.5 years and the corresponding death probability is extracted at each model cycle to account for the ageing of the cohort.[243]

- **Death (from Progressed Disease state).** Two survivor functions (for AP-CML and BP-CML respectively) were extrapolated through parametric fitting from published OS curves in Kantarjian et al. 2007,[29] as described in Section 5.3.2.1.3.
- **Death (from Allo-SCT in CP-CML and Allo-SCT in Progressed Disease states)**. Two survivor functions (for OS after allo-SCT in CP-CML and in progressed disease, respectively) were extrapolated through parametric fitting from published OS curves in Jabbour et al. 2011,[144] as described in Section 5.3.2.1.1.5. To avoid unrealistic estimate of the OS, the model controls at each cycle that the survival probability derived from the allo-SCT literature is not higher than the survival probability of the general population with the corresponding age.

5.3.2.3 Evidence that (transition) probabilities may change over time for the treatment effect, condition or disease

The change over time of transition probabilities was captured as described in the previous Section 5.3.2.2.

5.3.2.4 Clinical expert assessment of the applicability or approximation of clinical parameters

Core assumptions of the economic analysis have been validated by a clinical expert in England. Two clinical experts were approach and one expert participated, Dr Richard Clark, Professor of Haematology at the University of Liverpool. The clinical expert was given a questionnaire of main assumptions of the economic analysis and his opinions were collected by telephone interview.[246] Main assumptions validated were T315I stratification (5.3.1.1), distribution of time on different ponatinib doses (5.3.4.5.2), progression from CP to AP (5.3.1.3.1), mortality in CP-CML (5.3.2.1.4), OS on ponatinib in CP (5.3.6.3), and OS after allo-SCT in CP and AP (5.3.2.1.1.5).

The key assumption in the model that progression to AP is a function of response to TKI therapy is also supported by clinical expert response in the UK HCP survey: 91.7% of respondents agreed that PFS would be dependent on the control of the disease at the time of treatment discontinuation.[48]

5.3.3 Measurement and valuation of health effects

5.3.3.1 Health-related quality-of-life data from clinical trials

Only one study identified in the clinical SLR reported results of HRQoL assessments. This study was a retrospective observational study of ponatinib use in Israeli patients. Physicians ranked patient quality of life using a 1–5 scale. As this was a conference abstract, few additional details were provided. This study is not considered consistent with the reference case for several reasons including the narrow patient population, the observational nature of the study, the use of physician respondents, the lack of additional data, and failure to use a tool from which utilities could be derived (eg, the EuroQoL Five Dimensions Questionnaire [EQ-5D]).[181] The PACE trial did not evaluate HRQoL and as such no HRQoL data associated with ponatinib were available for patients participating in this phase 2 clinical trial.

5.3.3.2 Mapping

Not applicable; health utilities from the literature were identified in a distinct SLR designed specifically to capture relevant data for modelling. See Section 5.3.3.3 for more details.

5.3.3.3 Health-related quality-of-life studies

As with the clinical and economic search strategies, the HRQoL portion of the SLR was designed to identify relevant evidence published from January 2000–January 2016. An updated search

was conducted in July 2016. The SLR was conducted in accordance with the requirements of NICE[158, 159] and the CRD guidance.[160]

Bibliographic databases were searched using the predefined search strategies outlined in Appendix 13: Search strategy for measurement and valuation of health effects. The search strategies were adapted from those described in the STA for bosutinib.[161] The searches were designed to be broad to ensure adequate sensitivity.

Searches were conducted in EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and Cochrane CENTRAL and HTA using Ovid®; NHS EED using the University of York CRD database; and EconLit using ProQuest.

In addition to bibliographic databases, abstracts from the following conferences were searched from 2013–present: ISPOR, ASCO, ASH, and EHA. Review articles were also manually searched for relevant publications.

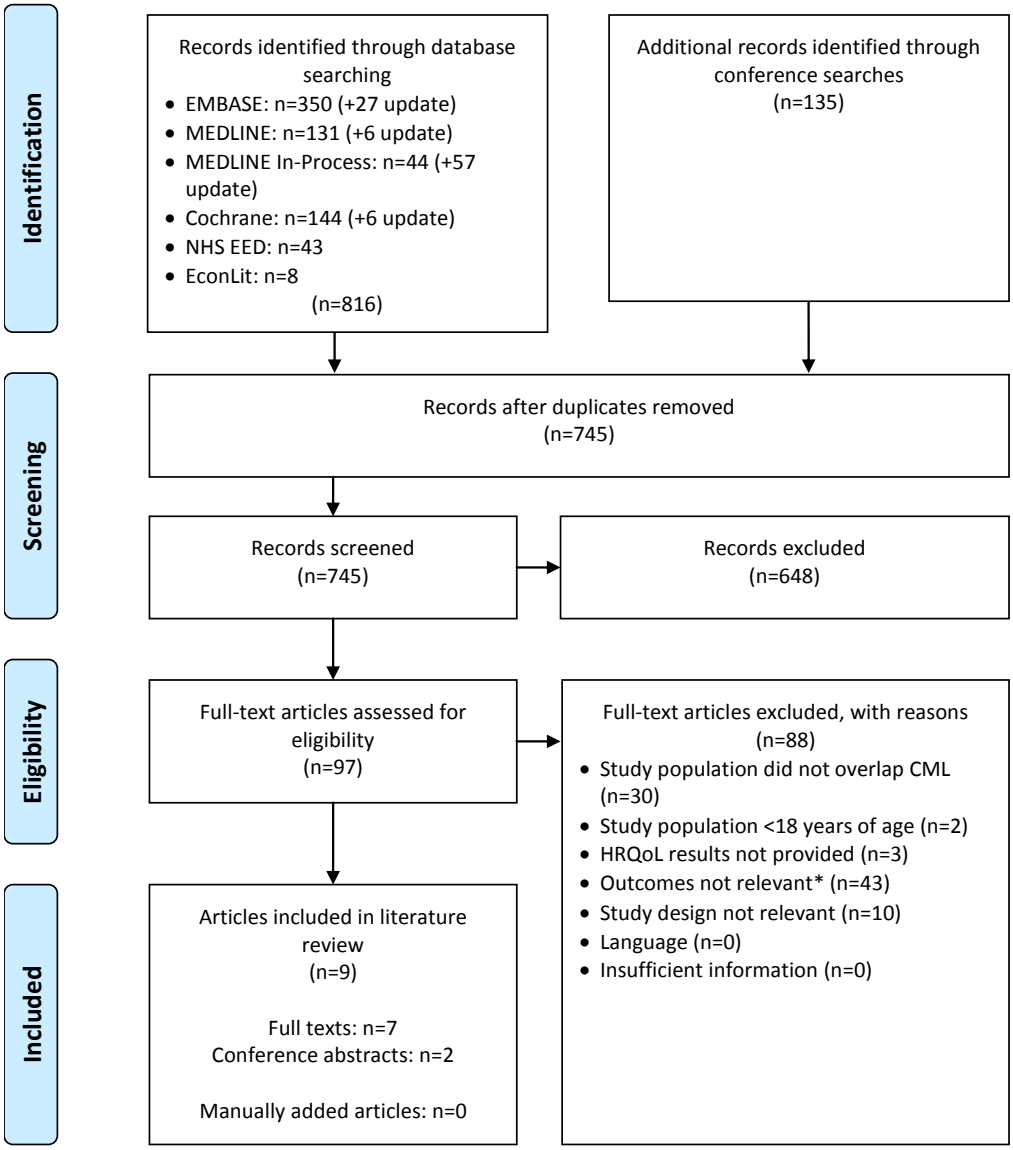
The screening process was same as that for the clinical evidence (see Section 4.1.3). PICOS criteria describing the relevant population, interventions, comparators, outcomes, and study design were used to determine the relevance of each article (Table 5-10).

Table 5-10. Eligibility criteria used in the HRQoL search strategy

HRQoL evidence	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with CML • Studies reporting data from surveys of the general public if focused on CML	—
Interventions	• All	—
Comparators	• All	—
Outcomes of interest	• Utility values, health state information	• Studies reporting only HRQoL data obtained with generic or disease-specific HRQoL instruments (eg, specific HRQoL scores)
Study design of interest	• Utility studies or HRQoL studies that report health state information	• Randomised controlled trials that report HRQoL endpoints and validation studies of HRQoL instruments • Comments, letters, and editorials
Language restrictions	• No limitation by language in searches	• Studies in languages other than English excluded during screening

After screening the 745 records identified during the CML searches, a total of 9 articles were included. The process of study selection is presented in detail in Figure 5-11.

Figure 5-11. PRISMA flow diagram for relevant HRQoL evidence in CML



CML, chronic myeloid leukaemia.

*Did not report utilities or health state information.

5.3.3.4 Details of HRQoL studies

Table 5-11 provides details of the HRQoL studies identified in the SLR. Of the eight studies reporting health utilities or health state information, four were conducted from a UK perspective. Overall, three studies used the choice-based time-trade-off (TTO) approach to determining utilities (two of which also evaluated the standard gamble [SG] approach), while the remainder used the EQ-5D. Three studies were conducted in the general public, four were conducted in patients in the clinical trial setting, and one was conducted in patients in the real-world setting.

Studies using the ED-Q5 (Table 5-11) were not considered applicable as they only provided treatment-specific utility values (imatinib, interferon alpha, TKIs, SCT). According to NICE guidance, the valuation of HRQoL in patients should be based on a "valuation of public preferences from a representative sample of the UK population using a choice-based method". Based on this guidance, the two studies conducted by Guest et al.[247, 248] and the study by Szabo et al. 2010[249] were considered the most relevant sources of utilities for inclusion in the model. Since the Guest et al. studies specifically evaluated the CP-CML health state, Szabo et al., which provided utilities for all CML phases as well as treatment failure due to SAEs, was used in the model. Table 5-12 details the methods and results of Szabo et al.

Table 5-11. Summary list of published HRQoL studies identified as potentially relevant in the CML SLR

Publication	Objective	Region	Respondents	Type of analysis	Utility provided for treatment/disease?
Guest et al. 2014[247]	To estimate preference values among members of the general public for individual health states associated with CML	UK	General public	TTO and SG	Disease
Guest et al. 2012[248]	To estimate preference values for the individual health states which relate to the different levels of response, as experienced within CP only	UK	General public	TTO and SG	Disease
Hahn et al. 2003[250]	To compare the QoL in patients receiving either imatinib or IFN alpha plus LDAC in an international phase 3 study	International	Patients (IRIS study)	EQ-5D	Imatinib IFN alpha + LDAC
Kuo et al. 2014[251]	To evaluate QoL of CML patients	US	Patients (Huntsman Cancer Institute)	EQ-5D-5L	SCT TKIs (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib)
Szabo et al. 2010[249]	To estimate TTO preference values for standardised CML health states that consider disease stage and responsiveness to treatment	Australia, Canada, US, UK	General public	TTO	Disease (CP, AP, BP)
Whiteley et al. 2013[252]	To evaluate the effect of bosutinib on health utilities in patients with CML after failure with imatinib	NR (used UK tariff)	Patients (phase 1/2 bosutinib study)	EQ-5D	Bosutinib
Whiteley et al. 2016[253]	To examine the effect of bosutinib on HRQoL in patients with advanced phase CML (AP and BP) after imatinib treatment failure	NR	Patients (phase 1/2 bosutinib study)	EQ-5D	Bosutinib
Reed et al. 2004[254]	To estimate the incremental cost-effectiveness of imatinib compared with IFN + LDAC as 1L treatment for patients with newly diagnosed CP-CML	International	Patients (IRIS study)	EQ-5D	Imatinib IFN alpha + LDAC
Dalziel et al. 2004[227]	To evaluate the effectiveness of imatinib as 1L treatment for CML compared with IFN alpha, hydroxycarbamide (hydroxyurea), and bone marrow transplantation, and the cost-effectiveness of imatinib compared with IFN alpha and hydroxycarbamide	UK	Patients (IRIS study)	EQ-5D	Imatinib IFN alpha Hydroxycarbamide Mercaptopurine

1L, first line; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; EQ-5D, EuroQoL Five Dimensions Questionnaire; IFN, interferon; LDAC, low-dose cytarabine; NR, not reported; QoL, quality of life; SCT, stem cell transplantation; SG, standard gamble; TTO, time-trade-off.

Table 5-12. Details of the relevant HRQoL study identified in the SLR

Publication	Szabo et al. 2010[249]
Population	General public (without CML) Age, mean: 44.9 years
Recruitment	Newspaper advertising, July 2006 to November 2007
Intervention and comparators	NA
N	357 (97 from UK)
Response rates	95% (5% omitted)
Health states	CP responding to treatment CP not responding to treatment AP responding to treatment AP not responding to treatment BP responding to treatment BP not responding to treatment Treatment withdrawal due to SAEs
Adverse reactions	NA
Health states appropriate?	Yes
Method of elicitation	One-on-one interview using health state descriptions (no HRQoL tool)
Method of valuation	Choice-based
Mapping	NA
Consistency with reference case	Not EQ-5D, but direct TTO from sample of UK population
Appropriate for CEA?	Yes (UK population, choice-based method, all phases of CML)
Results	Mean utilities for UK population (95% CI) • CP responding to treatment: 0.91 (0.89, 0.94) • CP not responding to treatment: 0.73 (0.69, 0.78) • AP responding to treatment: 0.78 (0.74, 0.82) • AP not responding to treatment: 0.53 (0.48, 0.58) • BP responding to treatment: 0.56 (0.52, 0.6) • BP not responding to treatment: 0.29 (0.24, 0.33) • Treatment withdrawal due to SAEs: 0.52 (0.46, 0.58)
Uncertainty around results	Participants may not have been broadly representative of population (recruited from one city in each country). The effect on QoL of treatment-related toxicities that did not result in treatment withdrawal was not considered. Mean utility values by TTO may overestimate true preferences as the duration of living in the health state was considered independent of the individual's utility value (preferences have been shown to decline with increasing duration of the health state).

AP, accelerated phase; BP, blast phase; CEA, cost-effectiveness analysis; CML, chronic myeloid leukaemia; CP, chronic phase; HRQoL, health-related quality of life; NA, not applicable; SAE, serious adverse event; TTO, time trade-off.

5.3.3.5 Key differences between values derived from the literature and those reported in or mapped from the clinical trials

Not applicable; mapping from clinical trials was not performed.

5.3.3.6 Adverse reactions

No studies have described the impact of ponatinib TEAEs on patient HRQoL. A lack of patient-specified HRQoL data is true of many rare disease.[255] It is, nevertheless, known that AEs associated with treatment can impact a patient's wellbeing and lead to treatment discontinuation.[8, 9] The impact of AEs on disease specific HRQoL is modelled in the economic analysis using values obtained from the UK general population. As reported by Szabo et al. 2010, treatment withdrawal due to SAE was associated with a TTO utility (95%) of 0.52 (0.46, 0.58).[249] This data was used to inform the health utilities for AEs (see Section 5.3.3.7.2.1).

5.3.3.7 Health-related quality-of-life data used in cost-effectiveness analysis

The impact of CML on patients' HRQoL was modelled as a decrement from that of an age-matched member of the general population.

5.3.3.7.1 Population norms

During each cycle, the model generates age-adjusted EQ-5D norm-based scores, using UK population norms reported by Kind et al. (1999; Table 5-13).[256] These data are reported in 10-year bands and so linear interpolation was used to generate the interim values where no data exist.

Table 5-13. EQ-5D population norm by sex and age bands (source: Kind et al. 1999)[256]

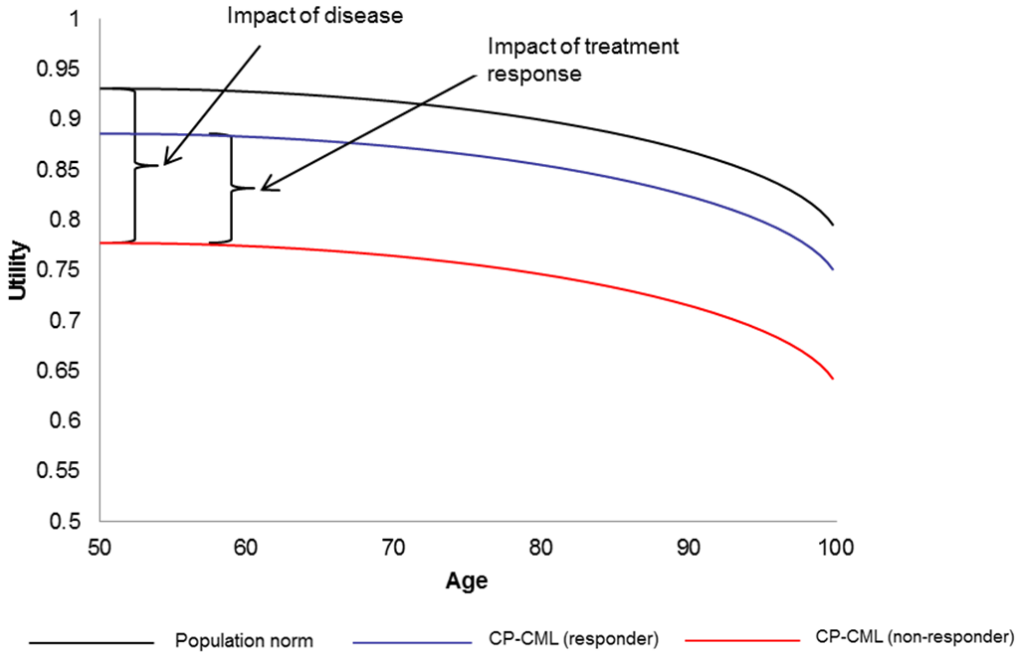
Age category (years)	Males	Females
Under 25	0.94	0.94
25–34	0.93	0.93
35–44	0.91	0.91
45–54	0.84	0.85
55–64	0.78	0.81
65–74	0.78	0.78
≥75	0.75	0.71

5.3.3.7.2 Utility decrements

5.3.3.7.2.1 CML health states and AEs

From the age-adjusted baseline, disease-phase–specific utility decrements associated with each health state are applied to model the impact of CML. Figure 5-12 presents this approach, showing both the impact of disease and treatment response as described below.

Figure 5-12. HRQoL modelling approach



CML, chronic myeloid leukaemia; CP, chronic phase; HRQoL, health-related quality of life.

Disease-specific utility decrements incorporated into the model were derived from Szabo et al. 2010.[249]

Szabo et al. reported utility values elicited using time trade-off (TTO) methods from 339 members of the general public in the UK (n=97), the US (n=74), Canada (n=89), and Australia (n=79) for all relevant health states, namely CP-CML, AP-CML, and BP-CML. Utility values for CP-CML used in the model were stratified by response status (response, no response; Table 5-14). Szabo et al. also elicited valuations for AEs serious enough to require treatment withdrawal.

Table 5-14. Absolute health utilities for response categories (source: Szabo et al. 2010; Table 5-12)[249]

	CP-CML				
Study	Response	Non-response	AP-CML	BP-CML	Adverse event
Szabo et al.	0.91	0.73	0.53	0.29	0.52

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase.

The utility decrements available in the model are reported in Table 5-15; as previously mentioned, the English adaptation employs the values derived for UK respondents from Szabo et al.[249] Since the utility estimate for CP-CML responders in Szabo et al. exceeds the population norm for people aged 60 years, no utility decrement is assigned to this health state in the model.

Table 5-15. Utility decrements used in the economic model (sources: Szabo et al. 2010, Table 5-12; Kind et al. 1999,Table 5-13)[249, 256]

Health state	Utility decrement
CP-CML (responder)	0.000
CP-CML (non-responder)	0.116
AP-CML	0.316
BP-CML	0.556
Adverse event	0.326

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase.

For the purpose of assigning utilities in the model, responders are defined as patients achieving CCyR, consistent with previous CML technology appraisals.[168]

5.3.3.7.2.2 Allo-SCT

Individuals who undergo allo-SCT can expect to spend an extended period in specialist hospital care, be exposed to a myriad of infections arising from their weakened immune system, and may well be anxious about their condition, all of which would impair their HRQoL. The utility decrement associated with allo-SCT in different model cycles (Table 5-16) was calculated from HRQoL scores reported for the peri-operative period by van Agthoven et al. 2001,[257] and for the long-term period by Loveman et al. 2012,[168] adjusted using the population norms obtained from Kind et al. 1999.[256]

Table 5-16. Allo-SCT utility values

Time period post allo-SCT (model cycle)	Utility value	Decrement	Source
1	0.55	0.296	van Agthoven et al. (2001),[257] population norms
2	0.63	0.216	Assumption: midpoint of peri-operative and long-term estimate
3+	0.71	0.136	Loveman et al. (2012)[168], population norms
Post-relapse	0.59	0.260	Kantarjian et al. 2002[258] and Olavarria et al. 2003,[259]

Allo-SCT, allogeneic haematopoietic stem cell transplantation.

In the absence of published utility data for leukaemia relapse in CML patients, a single utility decrement for this health state was calculated from the utilities modelled for the patients described above and the proportion of patients in each CML phase following relapse. Estimates

of the latter proportions were derived from studies of imatinib use for patients with relapse reported by Kantarjian et al. 2002[258] and Olavarria et al. 2003,[259] yielding values of 36% of patients in CP-CML, 30% in AP-CML, and 34% in BP-CML. These percentages were multiplied by the respective utility decrements reported in Table 5-15, to obtain a utility decrement of 0.260 for the post-relapse state.

5.3.3.8 HRQoL over time

Within each health state, HRQoL was assumed to decrease as a function of increasing patient age. For each health state, the impact of CML on patients' HRQoL was modelled as a decrement from that of an age-matched member of the general population (see Section 5.3.3.7; Table 5-13).[256] Therefore, age-adjusted decrements over time are taken into account for all patients in the model.

Over time, a patient may progress from CP-CML to AP- and then BP-CML, with HRQoL worsening with advancing disease phase (see Section 5.3.3.7; Table 5-14).[249] The model assumes no effect of HRQoL in CP-CML patients responding to treatment, while patients with CP-CML not responding to treatment experience impaired HRQoL.[249] Therefore, for CP-CML patients who lose their response to treatment over time, the model takes into account the utility decrement associated with loss of response.

5.3.3.9 Comparison of baseline HRQoL and utility values for each health state

All patients enter the model in the CP-CML health state and thus all initially have the same HRQoL. Patients can then respond to treatment, progress, or undergo allo-SCT. Different utility values are applied depending on a patient's clinical course (see Table 5-14); utilities are applied as a disutility to the age-specific utility of the population norms (see Table 5-13).

5.3.3.10 Adjustment of utility values for cost-effectiveness analysis

Health state utility values are norm-based and adjusted for age-specific EQ-5D–based utility scores in the UK general population (see Section 5.3.3.7.1).[256]

5.3.3.11 Health effects found in the literature or clinical trials

Scarce data on HRQoL scores are available for patients with CML; no studies have evaluated HRQoL in patients treated with ponatinib. Szabo et al. 2010 reported utility values for AP-CML and BP-CML in response, in addition to the utility values for AP-and BP-CML without response as used in the model.[249] The utility values for response in these two health states were not incorporated into the model because cytogenetic and haematologic response categories were not attributed to AP- or BP-CML. AEs modelled in the economic analyses were of Grade 3/4 in severity (ie, those most likely associated with HRQoL decrement and cost); milder AEs were not considered because of a lack of data on the magnitude of the potential HRQoL impact of mild AEs in these patients. Due to fewer bosutinib AE data, inputs to the model were limited to data from published literature.

5.3.3.12 Summary of chosen utility values

Table 5-17. Summary of utility values for cost-effectiveness analysis

State	Utility value†: mean	95% CI	Reference in submission (section and page number)	Justification
CP-CML (with response)	0.91	0.89, 0.94	Section 5.3.3.4 Table 5-12, p140	Utility values elicited using TTO methods from UK respondents[249]
CP-CML (no response)	0.73	0.69, 0.78	Same as above	Utility values elicited using TTO methods from UK respondents[249]
AP-CML	0.53	0.48, 0.58	Same as above	Utility values elicited using TTO methods from UK respondents[249]
BP-CML	0.29	0.24, 0.33	Same as above	Utility values elicited using TTO methods from UK respondents[249]
Treatment withdrawal due to SAEs	0.52	0.46, 0.58	Same as above	Utility values elicited using TTO methods from UK respondents[249]
Allo-SCT cycle 1	0.55	0.44, 0.66	Section 5.3.3.7.2.2 Table 5-16, p142	Peri-operative period by van Agthoven et al. 2001, in patients with refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease[257]
Allo-SCT cycle 2	0.63	0.51, 0.75	Same as above	Assumption. Midpoint of peri-operative and long- term estimate
Allo-SCT cycle 3	0.71	0.57, 0.85	Same as above	Long-term period according to Loveman et al. 2012[168]
Post-relapse	0.59	0.47, 0.70	—	Based on information in Kantarjian et al. 2002;[258] Olavarria et al. 2003[259]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CI, confidence interval; CML, chronic myeloid leukaemia; CP, chronic phase; SAE; serious adverse event; SE, standard error.

†Using age-adjusted baseline utilities, disease-phase–specific utility decrements associated with each health state are applied to model the impact of CML (see Section 5.3.3.7); in the model the utility for CP-CML responders was capped so as not to exceed the population norm.

5.3.3.13 Clinical expert assessment of the applicability or approximation of health state utility values

The applicability of the health state utility values was not validated by clinical experts. We acknowledge that there may be uncertainty in health state utility values applied in the model, and have provided a scenario analysis with utility values from alternative sources (bosutinib STA and Whiteley et al. 2016; Section 5.3.7.8.4).

5.3.4 Cost and healthcare resource use identification, measurement and valuation

5.3.4.1 Parameters used to estimate cost

All parameters used to estimate cost are presented in Table 5-18 and cross-referenced to corresponding sections in the submission. For continuous variables, mean values are presented and used in the analyses. For all variables, measures of precision are detailed.

Resource identification, measurement and valuation studies

5.3.4.2 Identification of cost and healthcare resource use data

Costs were sourced from NHS Reference Costs 2014 to 2015 for monitoring and follow-up, with the exception of palliative care costs, which were sourced from Marie Curie Cancer Care. In the absence of suitable data estimates from the published literature or previous HTAs, an expert survey was conducted to provide relevant and up-to-date healthcare resource use estimates.[48] Twelve clinical experts who were considered to be representative of clinical practice in England and Wales were interviewed: respondents were haematologists actively treating patients with CML across the region, working in distinct clinical practice settings (eg, district general hospitals, teaching hospitals, and centres of excellence). The UK CML survey report is included as an appendix to the submission (see Appendix 14: Cost and healthcare resource identification, measurement, and valuation).

5.3.4.3 Appropriateness of NHS reference costs for costing

The model predominantly uses NHS reference costs. The NHS reference costs are appropriate to use in the economic analysis as they reflect the unit cost of resources used in the management of CML. For allo-SCT, NHS reference costs were not used, because more comprehensive cost data were available from the 2014 report by the UK Stem Cell Strategy Oversight Committee,[260] which provided the cost of allo-SCT, including follow-up costs.

To our knowledge, there are no tariffs for specific CML management that would be more appropriate to use in the model.

5.3.4.4 Clinical expert assessment of the applicability or approximation of cost and healthcare resource use values

A protocol-driven survey of twelve clinical experts in England and Wales was conducted to provide estimates of the healthcare resource use used in the model. None of the experts were affiliated with any contravening agencies and none had undertaken healthcare resource use research in relation to CML during the last 3 months.

The means of the values for resource use reported by the experts were used in the model except for resources that were most frequently stated to be used for only a set number of times; eg, only once at disease progression for bone marrow aspiration. For further details on the study protocol, the clinical expert selection criteria, survey methods and questionnaire, and results, see Appendix 14: Cost and healthcare resource identification, measurement, and valuation.

Intervention and comparators' costs and resource use

The following resource use components were incorporated in the economic model:

- Pharmacologic therapy
- Allo-SCT as a comparator for patients in CP-CML and as a follow-on treatment in patients who progress from CP-CML to AP-/BP-CML
- Monitoring and follow-up care
- AEs
- End-of-life care

Table 5-18. Unit costs associated with the technology in the CP-CML economic model

Item	Ponatinib £ (SE)	Reference in submission	Bosutinib £ (SE)	Reference in submission	Hydroxy-carbamide £ (SE)	Reference in submission	Allo-SCT £ (SE)	Reference in submission
Technology cost	2,525(–) 15 mg-30 tabs pack	Section 5.3.4.5.5 Table 5-21	859.17 (–) 100 mg-28 tablet pack	Section 5.3.4.5.5 Table 5-21	10.47 (–) 500 mg-100 capsule pack	Section 5.3.4.5.5 Table 5-21	60,092* (6,009.21)	Section 5.3.4.6
	5,050.00 (–) 30mg-30 tabs pack	Section 5.3.4.5.5 Table 5-21	3,436.67 (–) (500 mg-28 tablet pack	Section 5.3.4.5.5 Table 5-21	–	–	–	–
	5,050.00 (–) 45mg-30 tabs pack	Section 5.3.4.5.5 Table 5-21	–	–	–	–	–	–
Resource use cost								
Outpatient visits								
Nurse-led	66.42 (6.64)	Section 5.3.4.8 Table 5-23	66.42 (6.64)	Section 5.3.4.8 Table 5-23	66.42 (6.64)	Section 5.3.4.8 Table 5-23	66.42 (6.64)	Section 5.3.4.8 Table 5-23
Haematologist-led	150.38 (15.04)	Section 5.3.4.8 Table 5-23	150.38 (15.04)	Section 5.3.4.8 Table 5-23	150.38 (15.04)	Section 5.3.4.8 Table 5-23	150.38 (15.04)	Section 5.3.4.8 Table 5-23
Tests								
Full blood count	3.01 (0.30)	Section 5.3.4.8 Table 5-23	3.01 (0.30)	Section 5.3.4.8 Table 5-23	3.01 (0.30)	Section 5.3.4.8 Table 5-23	3.01 (0.30)	Section 5.3.4.8 Table 5-23
Cytogenetic analysis	6.99 (0.70)		6.99 (0.70)		6.99 (0.70)		6.99 (0.70)	
Bone marrow aspiration (with biopsy)	517.50 (51.75)	Section 5.3.4.8 Table 5-23	517.50 (51.75)	Section 5.3.4.8 Table 5-23	517.50 (51.75)	Section 5.3.4.8 Table 5-23	517.50 (51.75)	Section 5.3.4.8 Table 5-23
FISH	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23
PCR	25.00 (2.50)	Section 5.3.4.8 Table 5-23ve	25.00 (2.50)	Section 5.3.4.8 Table 5-23ve	25.00 (2.50)	Section 5.3.4.8 Table 5-23ve	25.00 (2.50)	Section 5.3.4.8 Table 5-23ve
Flow cytometry	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23
Cytochemistry analysis	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23
Blood film exam	3.01 (0.30)	Section 5.3.4.8 Table 5-23	3.01 (0.30)	Section 5.3.4.8 Table 5-23	3.01 (0.30)	Section 5.3.4.8 Table 5-23	3.01 (0.30)	Section 5.3.4.8 Table 5-23
Blood chemistry	1.19 (0.12)	Section 5.3.4.8 Table 5-23	1.19 (0.12)	Section 5.3.4.8 Table 5-23	1.19 (0.12)	Section 5.3.4.8 Table 5-23	1.19 (0.12)	Section 5.3.4.8 Table 5-23
Kinase domain mutation*	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23	6.99 (0.70)	Section 5.3.4.8 Table 5-23
Therapies/interventions								
Blood transfusion	121.85 (12.19)	Section 5.3.4.8 Table 5-23	121.85 (12.19)	Section 5.3.4.8 Table 5-23	121.85 (12.19)	Section 5.3.4.8 Table 5-23	121.85 (12.19)	Section 5.3.4.8 Table 5-23

Item	Ponatinib £ (SE)	Reference in submission	Bosutinib £ (SE)	Reference in submission	Hydroxy-carbamide £ (SE)	Reference in submission	Allo-SCT £ (SE)	Reference in submission
Donor lymphocyte transfusion	193.15 (19.32)	Section 5.3.4.8 Table 5-23	193.15 (19.32)	Section 5.3.4.8 Table 5-23	193.15 (19.32)	Section 5.3.4.8 Table 5-23	193.15 (19.32)	Section 5.3.4.8 Table 5-23
Platelet transfusion	193.15 (19.32)	Section 5.3.4.8 Table 5-23	193.15 (19.32)	Section 5.3.4.8 Table 5-23	193.15 (19.32)	Section 5.3.4.8 Table 5-23	193.15 (19.32)	Section 5.3.4.8 Table 5-23
Days in hospital	721.00 (72.10)	Section 5.3.4.8 Table 5-23	721.00 (72.10)	Section 5.3.4.8 Table 5-23	721.00 (72.10)	Section 5.3.4.8 Table 5-23	721.00 (72.10)	Section 5.3.4.8 Table 5-23
Adverse events costs								
Abdominal pain	752.10 (75.21)	Section 5.3.4.10 Table 5-24	752.10 (75.21)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Anaemia	1,827.13 (182.71)	Section 5.3.4.10 Table 5-24	1,827.13 (182.71)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Diarrhoea	801.95 (80.20)	Section 5.3.4.10 Table 5-24	801.95 (80.20)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Hyperglycaemia	1,271.46 (127.15)	Section 5.3.4.10 Table 5-24	1,271.46 (127.15)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Hypophosphataemia	721.00 (72.10)	Section 5.3.4.10 Table 5-24	721.00 (72.10)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Leukocytopaenia	633.26 (63.33)		633.26 (63.33)		0	Section 5.3.4.10	0	Section 5.3.4.10
Lipase increased	721.00 (72.10)	Section 5.3.4.10 Table 5-24	721.00 (72.10)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Neutropaenia	633.26 (63.33)	Section 5.3.4.10 Table 5-24	633.26 (63.33)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Pancreatitis	1,121.98 (112.20)	Section 5.3.4.10 Table 5-24	1,121.98 (112.20)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
ALT elevation	1,121.98 (112.20)	Section 5.3.4.10 Table 5-24	1,121.98 (112.20)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Gamma-glutamyltransferase increased	1,121.98 (112.20)	Section 5.3.4.10 Table 5-24	1,121.98 (112.20)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Thrombocytopaenia	421.74 (42.17)	Section 5.3.4.10 Table 5-24	421.74 (42.17)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10
Serious adverse events†								
Cardiovascular event	2,357.00 (235.70)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10	0	Section 5.3.4.10
Cerebrovascular event	2,962.00 (296.20)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10	0	Section 5.3.4.10
Peripheral vascular event	2,872.00 (287.20)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10	0	Section 5.3.4.10
Venous thromboembolism event	552.00 (235.70)	Section 5.3.4.10 Table 5-24	0	Section 5.3.4.10	0	Section 5.3.4.10	0	Section 5.3.4.10

Item	Ponatinib £ (SE)	Reference in submission	Bosutinib £ (SE)	Reference in submission	Hydroxy-carbamide £ (SE)	Reference in submission	Allo-SCT £ (SE)	Reference in submission
Cardiovascular monitoring† cost	75.19 (7.52)	Section 5.3.4.8.1 Table 5-23	–		–		–	
Cost of palliative care in hospital	463.77 (46.38)	Section 5.3.4.11 Table 5-25	463.77	Section 5.3.4.11 Table 5-25	463.77	Section 5.3.4.11 Table 5-25	463.77	Section 5.3.4.11 Table 5-25
Cost of community palliative care per day	158.23 (15.82)	Section 5.3.4.11 Table 5-25	158.23	Section 5.3.4.11 Table 5-25	158.23	Section 5.3.4.11 Table 5-25	158.23	Section 5.3.4.11 Table 5-25
Total	NA		NA		NA		NA	

Allo-SCT, allogeneic haematopoietic stem cell transplantation; FISH, fluorescence in situ hybridization; NA, not applicable; PAS, patient access scheme; PCR, polymerase chain reaction; SE, standard error.

*Initial cost of allo-SCT procedure; per-cycle follow-up costs (SE) for year 1, 2, and 3 (in remission) are: £12,215 (1,221.47); £3,518 (351.83); and £420 (420.00), respectively. See Section 5.3.4.6.1.

†Serious adverse events and cardiovascular monitoring cost are only applied for ponatinib.

5.3.4.5 Pharmacologic therapy

5.3.4.5.1 Drug dosing

Drug doses used in the model are presented in Table 5-19. The modelled dose of ponatinib is the EMA-approved dosing of 45 mg QD.[22] Dosages for imatinib, dasatinib, nilotinib, and bosutinib are also based on their respective SmPCs. Dasatinib, nilotinib, and imatinib are considered only because they are part of the mix of drugs for background therapy in AP/BP-CML and post–allo-SCT relapse. For nilotinib, the model uses the recommended dose for 2L therapy in all calculations (800 mg daily) as opposed to the dose for newly diagnosed patients (600 mg daily), since patients in the model have previously received TKI treatment and, as such, are assumed not to be newly diagnosed.[51] For hydroxycarbamide, the model employs a mean dose of 2 g per day, as per Loveman et al. 2012.[168]

Table 5-19. Drug doses used in the economic model

Treatment	Dosage	Dose per day
Ponatinib	45 mg QD	45 mg
Dasatinib*	100 mg QD	100 mg
Nilotinib*	400 mg BID	800 mg
Bosutinib	500 mg QD	500 mg
Imatinib	400 mg QD	400 mg
Hydroxycarbamide	2000 mg QD	2000 mg

BID, twice per day; QD = once per day.

*Common values used to model both treatment switching and continuation.

5.3.4.5.2 Relative dose intensity: ponatinib

The relative dose intensity (RDI) is a measure of the differences between the prescribed dose and what is taken in practice (ie, capturing skipped doses and dose modifications), hence modelling treatment costs incorporating RDI supports accurate estimation of the cost of treatment. We used this approach because the price of ponatinib is not linear with tablet dose (ie, the price per mg is not fixed). This approach, however, was not possible for comparators; when the price of a comparator was non-linear, we selected the package that granted the lower price per mg to be conservative.

In the PACE trial, a number of patients experienced dose modification during the course of the study. The PACE data (data cut-off: 3 August 2015) are utilised in the model to quantify the proportion of days on treatment for each ponatinib dose (0 mg, 15 mg, 30 mg, 45 mg) stratified by best-response category, as shown in Table 5-20. These RDI values represent the number of days on a given dose as a percentage of total days on treatment. The average cost of ponatinib weighted by doses is calculated by response category and for the 3L cohort only. The clinical expert agreed that the distribution of the time on treatment in different doses observed in PACE study can be considered a proxy of ponatinib use in clinical practice.[246]

Table 5-20. RDI estimates used in the economic model for ponatinib (3L cohort)

Ponatinib dose (mg per day)	Proportion of days on treatment			
	CCyR	PCyR	CHR	NR
0	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]

CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, non-response; PCyR, partial cytogenetic response.

5.3.4.5.3 Relative dose intensity: 2G-TKIs

In the absence of an alternative source of data for bosutinib, the median dose intensity reported in Khoury et al.[8], 95.6%, was used as a proxy for the mean dose intensity. Mean RDI estimates

for imatinib, dasatinib, and nilotinib when used as background therapy following relapse were 100% (assumption), 100% (Shah et al. 2008),[261] and 99.7% (Kantarjian et al. 2007),[262] respectively.

5.3.4.5.4 Relative dose intensity: hydroxycarbamide

In the absence of data for hydroxycarbamide, RDI was assumed to be 100%.

5.3.4.5.5 Drug acquisition costs

The SKU price for both the 30-mg and 45-mg formulation of ponatinib in England is expected to be £5,050 for a 30 day supply, while the price for the 15-mg formulation is expected to be £2,525 for a 30 day supply; thus, these values are employed in the model. English unit costs for other drugs included in the model were obtained from the British National Formulary (BNF). No biosimilars are available for ponatinib or bosutinib. The unit drug costs used in the model are summarised in Table 5-21.

Table 5-21. Unit drug costs (sources: ARIAD; BNF)

Drug	mg per unit	Units per pack	Cost per pack, £	Source
Ponatinib*	15	30	2,525.50	SKU price
	30	30	5,050.00	
	45	30	5,050.00	
Dasatinib	20	60	1,252.48	BNF[263]
	50	60	2,504.96	
	80	30	2,504.96	
	100	30	2,504.96	
	140	30	2,504.96	
Nilotinib	150	112	2,432.85	BNF[263]
	200	112	2,432.85	
Bosutinib	100	28	859.17	BNF[263]
	500	28	3,436.67	
Imatinib	100	60	918.23	BNF[263]
	400	30	1,836.48	
Hydroxycarbamide	500	100	10.47	BNF[263]

BNF, British National Formulary.

*International units.

As the drug treatments being modelled are administered orally, no drug administration costs are assumed. It is assumed that following TKI treatment discontinuation patients receive hydroxycarbamide, accruing a per-cycle cost of £38.24.

5.3.4.6 Allo-SCT

To reflect the reality that not all patients with progressed disease are deemed suitable for allo-SCT, the proportion of patients in AP-CML or BP-CML receiving allo-SCT was set to 27.3%, based on findings from a survey of clinical experts in the UK (see Appendix 14: Cost and healthcare resource identification, measurement, and valuation).[48]

In the base-case analysis the costs of allo-SCT have been taken from an economic analysis for the UK Stem Cell Strategy Oversight Committee from 2014,[260] which provided both weighted and unweighted costs for up-front running costs, transplantation, and follow up. The figures are based on the methodology of van Agthoven et al. 2002[264] with updated components to reflect UK cord blood transplantation practice, and current costs reported by the Personal Social Services Research Unit (PSSRU).[265] When costs were unavailable they were scaled and converted from the original study to be aligned with the other costs, following a UK NHS perspective. The initial cost included transplant unit personnel and transplantation (which includes the cost of a UK-sourced cord blood donation). Follow-up costs were estimated for 0–2 years after transplantation. Costs were inflated from 2012/13 to 2014/15.

Based on data from the UK Stem Cell Strategy Oversight Committee,[260] the initial cost of the allo-SCT procedure was set at £60,092, regardless of whether the patient initially had CP-CML or had progressed prior to the procedure.

5.3.4.6.1 Costs of allo-SCT in remission

The model incorporates the per-cycle follow-up costs described in Table 5-22.

Table 5-22. Subsequent costs for patients in remission following allo-SCT

Time period post–allo-SCT	Per-cycle cost, £	Source
Year 1	12,215	UK Stem Cell Strategy Oversight Committee[260]
Year 2	3,518	UK Stem Cell Strategy Oversight Committee[260]
Year 3+	420	NICE bosutinib HTA[161]

5.3.4.6.2 Costs of allo-SCT relapse

It is assumed that post-relapse patients have CML, and as such will be treated pharmacologically. The model includes background therapy following relapse, assumed (based on the UK clinical expert survey[48]) to comprise 20% imatinib, 20% hydroxycarbamide, 20% dasatinib, 20% nilotinib, and 20% bosutinib, resulting in a per-cycle cost of £6,375.39. It is assumed that all relapsed patients require the same general follow-up and testing protocol as described for CP-CML non-responders in Section 5.3.4.8 (Table 5-23).

5.3.4.7 Treatment costs: Progressed CML unsuitable for allo-SCT

The data used to estimate the amount of time patients are alive as well as in AP- or BP-CML are reported in Section 5.3.2.1.3. As such, it is important to include treatment costs for the AP- and BP-CML health states in the model to ensure face validity and internal consistency. It is assumed that patients with progressed CML who are ineligible for allo-SCT will receive the same background therapy as those with relapse following allo-SCT (20% imatinib, 20% hydroxycarbamide, 20% dasatinib, 20% nilotinib, 20% bosutinib), and thus also have a per-cycle cost of drug treatment of £6,375.39.

5.3.4.8 Monitoring and follow-up

Resource use associated with monitoring and follow-up was modelled as a function of disease phase and whether or not a patient responds to therapy. For the purposes of stratifying patients, responders were defined as those achieving a CCyR.

5.3.4.8.1 CP-CML (on treatment)

Resource use for patients with CP-CML was derived from the UK clinical expert survey (see Table 5-23; Appendix 14: Cost and healthcare resource identification, measurement, and valuation). It was assumed that resource requirements of a post–2G-TKI population would depend upon the presence/absence of CCyR. Expected resource use was then calculated by weighting these data by the proportion of patients achieving a CCyR for each treatment.

Patient monitoring and follow-up costs are applied to outpatient visits, tests, and interventions subsequent to therapy. Unit costs (Table 5-23) for each component were taken from NHS Reference Costs and other England-specific sources. The per-cycle monitoring and follow-up cost for responding patients with CP-CML is £208.08; for non-responding patients with CP-CML, the cost is £494.90, reflecting the greater intensity of healthcare resource utilisation in non-responders, as shown in Table 5-23. On top of the mentioned monitoring costs, we considered the additional need for cardiovascular monitoring specific to ponatinib treatment. This was accounted for as the cost for a specialist visit every 6 months.

5.3.4.8.2 AP-CML and BP-CML

Patients who progress to AP-CML and BP-CML, by definition, have lost cytogenetic response. The expected monitoring and follow-up resource use of progressed patients was based on the clinical expert survey.[48] Based on the unit costs presented in Table 5-23, the per-cycle cost of monitoring and follow-up in patients with AP- and BP-CML is set to £2,647.56 and £20,319.27,

respectively. The higher cost for patients in BP-CML is accounted for by the longer hospital stay for these patients (26.64 days vs 2.13 for patients in AP-CML).

5.3.4.8.3 Relapse post–allo-SCT in progressed CML

The model assumes that patients with progressed CML can be relapse-free or experience relapse after allo-SCT. We assume that there are no monitoring costs for patients who are relapse-free. The per-cycle monitoring and follow-up costs associated with allo-SCT relapse in progressed CML are assumed to be the same as those for AP-CML (see Section 5.3.4.8.2 above). Moreover, patients who relapse are assumed to be treated with a mix of drugs (20% imatinib, 20% hydroxycarbamide, 20% dasatinib, 20% nilotinib, and 20% bosutinib, based on the UK clinical expert survey).[48]

Table 5-23. Monitoring and follow-up resource use per cycle (source: UK clinical expert survey)[48] and unit costs

Resource	CP-CML		AP/BP-CML	Unit cost, £	Source
	CCyR	No CCyR			
Outpatient visits					
Nurse-led	0.29	0.38	0.51	66.42	NHS Reference Costs 2014 to 2015
Haematologist-led	0.93	1.72	3.63	150.38	NHS Reference Costs 2014 to 2015
Tests					
Full blood count	1.13	1.97	4.38	3.01	NHS Reference Costs 2014 to 2015
Cytogenetic analysis	0.58	0.74	0.90	6.99	NHS Reference Costs 2014 to 2015
Bone marrow aspiration (with biopsy)	0.03	0.30	0.30	517.50	NHS Reference Costs 2014 to 2015
FISH	0.22	0.56	0.13	6.99	NHS Reference Costs 2014 to 2015
PCR	0.79	1.31	1.68	25.00	Szczepura et al. 2006 [49]
Flow cytometry	0.09	0.13	0.45	6.99	NHS Reference Costs 2014 to 2015
Cytochemistry analysis	–	0.05	0.12	6.99	NHS Reference Costs 2014 to 2015
Blood film exam	0.50	1.09	2.19	3.01	NHS Reference Costs 2014 to 2015
Blood chemistry	1.13	1.88	3.15	1.19	NHS Reference Costs 2014 to 2015
Kinase domain mutation*	–	–	0.13	6.99	NHS Reference Costs 2014 to 2015
Therapies/interventions					
Blood transfusion	0.01	0.01	1.98	121.85	NHS Blood and Transplant Price List 2014/15
Donor lymphocyte transfusion	–	–	–	193.15	Assumption: same as platelet transfusion
Platelet transfusion	–	–	0.30	193.15	NHS Blood and Transplant Price List 2014/15
Days in hospital				721.00	Average costs for a hospital day case based on finished consultant episodes (NHS Reference Costs 2014 to 2015)
CP	–	–			
AP			2.13		
BP			26.64		

AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction.

*Once only.

Health-state unit costs and resource use

5.3.4.9 Costs included in each health state

Not applicable. Drug dosages and unit costs did not vary by health state. Resource use associated with monitoring and follow-up was modelled as a function of disease phase and whether or not a patient responds to therapy. Therefore, no costs or resource use specifically associated with health states were included in the cost-effectiveness analysis, with the exception of allo-SCT, which was incorporated in the model as a Markov health state, with costs as described in Section 5.3.4.6.

Adverse reaction unit costs and resource use

5.3.4.10 Costs and resource use for each adverse reaction

AEs included in the model were restricted to Grade 3/4 events occurring in ≥5% of the study population for any given treatment option. Rates for ponatinib were obtained from the PACE CSR, and rates for bosutinib were based on data for patients in a phase 1/2 trial reported by Kantarjian et al. 2014.[184]

The AEs rates used in the model are presented in Table 5-24. In line with a number of recent oncology models, the rate of AEs is applied to the first cycle only on the assumption that such events will happen sooner rather than later. The model also incorporates the assumption that patients experiencing an event have that event only once. In the absence of AEs information for hydroxycarbamide, placeholder values of 0% are employed in the model. AEs rates for allo-SCT are also set to zero, on the assumption that any associated costs would be absorbed into the follow-up costs for allo-SCT.

A consequence of having access to IPD and the CSR for ponatinib but not the other interventions is that rates are known for every event with ponatinib but not the comparators. This results in a bias against ponatinib when modelling TRAEs.

In addition to the events listed in Table 5-24, the rates of SAEs for ponatinib were included, based on the rates in the PACE trial reported in the CSR. Serious cardiovascular, cerebrovascular, peripheral vascular, and venous thromboembolism events were modelled as per-cycle rates in order to capture the long-term impact of treatment: 1.34%, 0.63%, 0.86%, and 0.22%, respectively. In the absence of equivalent long-term data for bosutinib, the rates of these SAEs were set to 0%, the assumption being that any mortality effects would be captured in the background population mortality rate.

The average costs per patient associated with AEs for each CML treatment are summarised in Table 5-24. Cost estimates were taken from NHS reference costs and tariffs.

Table 5-24. AE rates and costs applied in the model (sources: PACE CSR; Kantarjian et al. 2014) and associated costs

Adverse event	Ponatinib[25]	Bosutinib[184]	Unit cost, £	Sources for costs
Abdominal pain	[redacted]	0.00%	752.10	NHS Reference Costs 2014 to 2015
Anaemia	[redacted]	6.78%	1,827.13	NHS 2015/16 Enhanced Tariff Option
Diarrhoea	[redacted]	8.47%	801.95	NHS Reference Costs 2014 to 2015
Hyperglycaemia	[redacted]	0.00%	1,271.46	NHS Reference Costs 2014 to 2015
Hypophosphataemia	[redacted]	0.00%	721.00	Assumption: 1 day in hospital
Leukocytopaenia	[redacted]	0.00%	633.26	Assumption: same as neutropaenia
Lipase increased	[redacted]	0.00%	721.00	Assumption: 1 day in hospital
Neutropaenia	[redacted]	15.25%	633.26	NHS Reference Costs 2014 to 2015
Pancreatitis	[redacted]	0.00%	1,121.98	NHS Reference Costs 2014 to 2015
ALT elevation	[redacted]	5.93%	1,121.98	NHS Reference Costs 2014 to 2015
Gamma-glutamyltransferase increased	[redacted]	0.00%	1,121.98	NHS Reference Costs 2014 to 2015
Thrombocytopaenia	[redacted]	26.27%	421.74	NHS Reference Costs 2014 to 2015
Serious adverse events				
Cardiovascular event	[redacted]	—	2,357.00	NHS 2015/16 Enhanced Tariff Option
Cerebrovascular event	[redacted]	—	2,962.00	NHS 2015/16 Enhanced Tariff Option
Peripheral vascular event	[redacted]	—	2,872.00	NHS 2015/16 Enhanced Tariff Option
Venous thromboembolism event	[redacted]	—	552.00	NHS 2015/16 Enhanced Tariff Option

ALT, alanine aminotransferase.

Miscellaneous unit costs and resource use

5.3.4.11 End-of-life care

To reflect the fact that individuals incur additional resources shortly before death, all patients who die in the model, regardless of treatment option, incur an additional resource use component representing "end of life" care. Based on the UK clinical expert survey,[48] the model incorporates a 21.5-day inpatient stay immediately before death for 51.5% of patients assumed to be treated in hospital and a 17.4-day hospice stay for the 23.1% of patients assumed to be treated in a hospice (Table 5-25); the remaining patients were assumed to die at home. These stays were applied regardless of whether patients were in CP-CML or AP/BP-CML.

Given the distribution of end-of-life stays across hospitals and hospices, and daily palliative care costs of £463.77 and £158.23, respectively (based on information from Marie Curie Cancer Care), the average end-of-life care cost was estimated at £5,765.76 (Table 5-25).

Table 5-25. End-of-life care resource use and costs

	Value	Daily cost, £	Source
In-patient stay, days	21.5	463.77	Marie Curie Cancer Care
Patients treated in hospital, %	51.5	—	Assumption
Hospice stay, days	17.4	158.23	Marie Curie Cancer Care
Patients treated in hospice, %	23.1	—	Assumption
Average end-of-life care cost, £		**5,765.76**	

5.3.5 Summary of base-case de novo analysis inputs and assumptions

5.3.5.1 Summary of base-case de novo analysis inputs

Table 5-26 summarises the variables applied in the economic model. Uncertainty regarding the parameter values was addressed via sensitivity analyses, as described below in Section 5.3.7.

Table 5-26. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
Clinical Inputs				
Allo-SCT suitability after progression	0.27250 (–)	–	5.3.4.6	UK HCP Survey, Q7
CCyR rate				
Bosutinib	0.24074 (Table 5-8)	–	5.3.2.1.1.2	Khoury et al. 2012
Ponatinib	0.61340 (Table 5-7)	–	5.3.2.1.1.1	MAIC analysis
CHR rate				
Bosutinib	0.37931 (Table 5-8)	–	5.3.2.1.1.2	Khoury et al. 2012
Hydroxycarbamide	0.41000 (–)	–	5.3.2.1.1.4	Dalziel et al. 2004
IFN alpha	0.47000 (–)	–	5.3.2.1.1.3	Dalziel et al. 2004
Ponatinib	0.18190 (Table 5-7)	–	5.3.2.1.1.1	MAIC analysis
Duration of response				
Bosutinib	– (Figure 5-8)	Log-normal	5.3.2.1.2.2	Gambacorti-Passerini et al. 2014
Ponatinib	– (Figure 5-8)	Gompertz	5.3.2.1.2.2	MAIC analysis
Mean PFS in AP phase, months	9.16004 (–)	–	5.3.2.1.3	Derived from Kantarjian et al. 2007
Median time on treatment				
Bosutinib	8.30000 (–)	–	5.3.2.1.6.3	Khoury et al. 2012
NR rate		–		
Bosutinib	0.29662 (Table 5-8)	–	5.3.2.1.1.2	Residual calculation
Hydroxycarbamide	0.59000 (–)	–	5.3.2.1.1.4	Residual calculation

Variable	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
IFN alpha	0.53000 (–)	–	5.3.2.1.1.3	Residual calculation
Ponatinib	0.12010 (Table 5-7)	–	5.3.2.1.1.1	MAIC analysis
Overall survival				
OS in AP	– (Figure 5-9)	Log-normal	5.3.2.1.3	Kantarjian et al. 2007
OS in BP	– (Figure 5-10)	Log-logistic	5.3.2.1.3	Kantarjian et al. 2007
OS post–allo-SCT in CP	– (Figure 5-4)	Exponential	5.3.2.1.1.5.1	Jabbour et al. 2011
OS post–allo-SCT in AP	– (Figure 5-5)	Exponential	5.3.2.1.1.5.1	Jabbour et al. 2011
PCyR rate				
Bosutinib	0.08333 (Table 5-8)	–	5.3.2.1.1.2	Khoury et al. 2012
Ponatinib	0.08460 (Table 5-7)	–	5.3.2.1.1.1	MAIC analysis
Progression-free survival				
In CCyR	– (Figure 5-7)	Gompertz	5.3.2.1.2.2	Loveman et al. 2012
In PCyR	– (Figure 5-7	Gompertz	5.3.2.1.2.2	Loveman et al. 2012
In CHR	– (Figure 5-7	Weibull	5.3.2.1.2.2	Loveman et al. 2012
In NR	– (Figure 5-7	Exponential	5.3.2.1.2.2	Loveman et al. 2012
Relapse-free survival post–allo-SCT	– (Figure 5-6)	Gompertz	5.3.2.1.1.5.2	Craddock et al. 2000
Time-on-treatment				
CCyR	– (–)	Exponential	5.3.2.1.6	PACE CSR
PCyR	– (–)	Exponential	5.3.2.1.6	PACE CSR
CHR	– (–)	Exponential	5.3.2.1.6	PACE CSR
Economic Inputs				
Adverse event unit cost	(Table 5-24)			
Abdominal pain	752.10	–	5.3.4.10	NHS Reference Costs 2014 to 2015
ALT elevation	1121.98	–	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Anaemia	1827.13	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Cardiovascular event	2357.00	–	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Cerebrovascular event	2962.00	–	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Diarrhoea	801.95	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Gamma-glutamyltransferase increased	1121.98	–	5.3.4.10	Assumption: 1 day in hospital
Hyperglycaemia	1271.46	–	5.3.4.10	Assumption: same as neutropaenia
Hypophosphatemia	721.00	–	5.3.4.10	Assumption: 1 day in hospital
Leukocytopaenia	633.26	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Lipase increased	721.00	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Neutropaenia	633.26	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Pancreatitis	1121.98	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Peripheral vascular event	2872.00	–	5.3.4.10	NHS 2015/16 Enhanced Tariff Option

Variable	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
Thrombocytopaenia	421.74	–	5.3.4.10	NHS Reference Costs 2014 to 2015
Venous thromboembolism event	552.00	–	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Allo-SCT initial cost, £	60092.13 (–)	–	5.3.4.6	UK Stem Cell Strategy Oversight Committee
Cost of community palliative care per day, £	158.23 (Table 5-25)	–	5.3.4.11	Marie Curie Cancer Care
Cost of palliative care in hospital per day, £	463.77 (Table 5-25)	–	5.3.4.11	Marie Curie Cancer Care
Discount rate costs	3.50% (Table 5-5)	–	–	NICE
Discount rate outcomes	3.50% (Table 5-5)	–	–	NICE
EOL hospice days	17.40 (Table 5-25)	–	5.3.4.11	UK Survey, Q13
EOL hospital days	21.50 (Table 5-25)	–	5.3.4.11	UK Survey, Q13
EOL, proportion being treated in hospice	0.23 (Table 5-25)	–	5.3.4.11	UK Survey, Q13
EOL, proportion being treated in hospital	0.51 (Table 5-25)	–	5.3.4.11	UK Survey, Q13
Per-cycle cost, £				
Bosutinib	10714.40 (–)	–	–	–
Dasatinib	7624.47 (–)	–	–	–
Hydroxycarbamide	38.24 (–)	–	–	–
Imatinib	5589.73 (–)	–	–	–
IFN alpha	6832.91 (–)	–	–	–
Nilotinib	7910.11 (–)	–	–	–
Ponatinib in CCyR	[redacted]	–	–	–
Ponatinib in CHR	[redacted]	–	–	–
Ponatinib in NR	[redacted]	–	–	–
Ponatinib in PCyR	[redacted]	–	–	–
CV monitoring with ponatinib	75.19 (–)	–	–	Assumed 0.5 visits per cycle; same cost as haematologist visit (Table 5-23)
Follow-up after allo-SCT, y1	12214.71 (Table 5-22)	–	5.3.4.6.1	UK Stem Cell Strategy Oversight Committee
Follow-up after allo-SCT, y2	3518.25 (Table 5-22)	–	5.3.4.6.1	UK Stem Cell Strategy Oversight Committee
Follow-up after allo-SCT, y3+	420.00 (Table 5-22)	–	5.3.4.6.1	Bosutinib NICE HTA
Treatment post discontinuation	38.24 (–)	–	5.3.4.5.5	Assumed BSC is hydroxycarbamide
Treatment AP/BP patients not receiving allo-SCT	6375.39 (–)	–	5.3.4.7	Assumption based on UK HCP Survey: 20% imatinib, 20% hydroxycarbamide, 20% dasatinib, 20% nilotinib, and 20% bosutinib
Treatment post–allo-SCT relapse	6375.39 (–)	–	5.3.4.6.2	
Per-cycle resource use with:	(Table 5-23)			
CCyR in CP: Blood chemistry	1.130000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Blood film exam	0.500000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Blood transfusion	0.010000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Bone marrow aspiration	0.030000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Complete blood count	1.130000	–	5.3.4.8	UK Survey, Q6

Variable	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
CCyR in CP: Cytogenetic analysis	0.580000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: FISH	0.220000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Flow Cytometry	0.090000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Haematologist-led outpatient visit	0.930000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: Nurse-led outpatient visit	0.290000	–	5.3.4.8	UK Survey, Q6
CCyR in CP: PCR	0.790000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: blood chemistry	1.88000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: blood film exam	1.09000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: blood transfusion	0.01000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: bone marrow aspiration	0.30000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: complete blood count	1.97000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: cytochemistry analysis	0.05000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: cytogenetic analysis	0.74000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: FISH	0.56000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: flow cytometry	0.13000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: haematologist-led outpatient visit	1.72000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: kinase domain mutation analysis	0.00000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: nurse-led outpatient visit	0.38000	–	5.3.4.8	UK Survey, Q6
No CCyR in CP: PCR	1.31000	–	5.3.4.8	UK Survey, Q6
No response in AP/BP: blood chemistry	3.15	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: blood film exam	2.19	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: blood transfusion	1.98	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: bone marrow aspiration	0.30	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: complete blood count	4.38	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: cytochemistry analysis	0.12	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: cytogenetic analysis	0.90	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: donor lymphocyte transfusion	0.00	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: FISH	0.13	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: flow cytometry	0.45	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)

Variable	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
No response in AP/BP: haematologist-led outpatient visit	3.63	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: kinase domain mutation analysis	0.13	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: nurse-led outpatient visit	0.51	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: PCR	1.68	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP/BP: platelet transfusion	0.30	–	5.3.4.8	UK Survey, Q8 (AP resources assumed)
No response in AP: hospital days	2.13	–	5.3.4.8	UK Survey, Q8 (general ward+ ICU)
No response in BP: hospital days	26.64	–	5.3.4.8	UK Survey, Q10 (general ward+ ICU)
Resource unit cost, £	(Table 5-23)			
Blood chemistry	1.19	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Blood film exam	3.01	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Blood transfusion	121.85	–	5.3.4.8	NHS Blood and Transplant Price List 2014/15
Bone marrow aspiration	517.50	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Complete blood count	3.01	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Cytochemistry analysis	6.99	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Cytogenetic analysis	6.99	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Donor lymphocyte transfusion	193.15	–	5.3.4.8	Assumed same as platelet transfusion
FISH	6.99	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Flow Cytometry	6.99	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Haematologist-led outpatient visit	150.38	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Hospital days	721.00	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Kinase domain mutation analysis	6.99	–	5.3.4.8	NHS Reference Costs 2014 to 2015
Nurse-led outpatient visit	66.42	–	5.3.4.8	NHS Blood and Transplant Price List 2014/15
PCR	25.00	–	5.3.4.8	Szczepura et al. 2006
Platelet transfusion	193.15	–	5.3.4.8	NHS Blood and Transplant Price List 2014/15
HRQoL Inputs / AEs				
Cumulative incidence	(Table 5-24)			
Abdominal pain ponatinib	[redacted]	–	5.3.4.8	PACE study CSR - Table 14.3.1.3.1.2.6
ALT elevation bosutinib	[redacted]	–	5.3.4.8	Kantarjian et al. 2014
ALT elevation ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Anaemia bosutinib	[redacted]	–	5.3.4.8	Kantarjian et al. 2014
Anaemia ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Diarrhoea bosutinib	[redacted]	–	5.3.4.8	Kantarjian et al. 2014

Variable	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
Gamma-glutamyltransferase increased ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Leukocytopaenia ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Lipase increased ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Neutropaenia bosutinib	[redacted]	–	5.3.4.8	Kantarjian et al. 2014
Neutropaenia ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Pancreatitis ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Thrombocytopaenia bosutinib	[redacted]	–	5.3.4.8	Kantarjian et al. 2014
Thrombocytopaenia ponatinib	[redacted]	–	5.3.4.8	PACE study CSR -
Per-cycle probability (ponatinib only)	(Table 5-24)			
Cardiovascular event	[redacted]	–	5.3.4.10	PACE study CSR - Section 14.3.5 Other Safety Measurements, Table 2.2
Cerebrovascular event	[redacted]	–	5.3.4.10	
Peripheral vascular event	[redacted]	–	5.3.4.10	
Venous thromboembolism event	[redacted]	–	5.3.4.10	
Population norm utility	(Table 5-13)			
Females <25 years	0.94000	–	5.3.3.7.1	Kind et al. 1999
Females 25-34 years	0.93000	–	5.3.3.7.1	Kind et al. 1999
Females 35-44 years	0.91000	–	5.3.3.7.1	Kind et al. 1999
Females 45-54 years	0.85000	–	5.3.3.7.1	Kind et al. 1999
Females 55-64 years	0.81000	–	5.3.3.7.1	Kind et al. 1999
Females 65-74 years	0.78000	–	5.3.3.7.1	Kind et al. 1999
Females ≥75 years	0.71000	–	5.3.3.7.1	Kind et al. 1999
Males <25 years	0.94000	–	5.3.3.7.1	Kind et al. 1999
Males 25-34 years	0.93000	–	5.3.3.7.1	Kind et al. 1999
Males 35-44 years	0.91000	–	5.3.3.7.1	Kind et al. 1999
Males 45-54 years	0.84000	–	5.3.3.7.1	Kind et al. 1999
Males 55-64 years	0.78000	–	5.3.3.7.1	Kind et al. 1999
Males 65-74 years	0.78000	–	5.3.3.7.1	Kind et al. 1999
Males ≥75 years	0.75000	–	5.3.3.7.1	Kind et al. 1999
Utility	(Table 5-14 and Table 5-16)			
During a SAE	0.52000	–	5.3.3.7.2.1	Szabo et al. 2010
In AP	0.53000	–	5.3.3.7.2.1	Szabo et al. 2010
In BP	0.29000	–	5.3.3.7.2.1	Szabo et al. 2010
In CP with response	0.91000	–	5.3.3.7.2.1	Szabo et al. 2010
In CP without response	0.73000	–	5.3.3.7.2.1	Szabo et al. 2010
In cycle 1 after allo-SCT	0.55000	–	5.3.3.7.2.2	van Agthoven et al. 2001 population norms
In cycle 2 after allo-SCT	0.63000	–	5.3.3.7.2.2	Assumption: midpoint of peri-operative and long-term estimate
In cycle 3 after allo-SCT	0.71000	–	5.3.3.7.2.2	Loveman et al. 2012, population norms
Post-relapse after allo-SCT	0.58520	–	5.3.3.7.2.2	Kantarjian et al. 2002 and Olavarria et al. 2003

Allo-SCT, allogeneic haematopoietic stem cell transplantation; ALT, alanine aminotransferase; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; CSR, clinical study report; EOL, end of life; FISH, fluorescence in situ hybridization; ICU, intensive care unit; IFN alpha, interferon alpha; MAIC, matching-adjusted indirect comparison; NR, non-response; OS, overall survival; PFS, progression-free survival; PCR, polymerase chain reaction; PCyR, partial cytogenetic response; SAE, serious adverse event; SCT, stem cell transplantation.

5.3.5.2 Assumptions

Table 5-27 summarises the main assumptions in the economic analysis.

Table 5-27. Summary of main assumptions and justifications in the CP-CML model

Assumption	Justification
The cost of ponatinib is calculated with the % of time on different doses, from the PACE study	The unit pricing of ponatinib is not linear with dose, so the relative-dose intensity approach is unfeasible. Moreover for other drugs that also don't have linear unit pricing we conservatively assume that the cost is determined by the package that yields the lowest price/mg
Time-on-treatment for ponatinib is simulated with an exponential function, regardless of the function providing the best fit in the parametric survival analysis	This assumption was adopted because selecting the best-fit function would have introduced bias against ponatinib given that available time-on-treatment data for TKI comparators are median values, which necessitate adopting an exponential function
Response to TKI is the most important prognostic factor in CP-CML, irrespective of the TKI used	Validated by clinical expert and in agreement with the 2013 ELN recommendations[47]
OS with allo-SCT is simulated with an exponential function regardless of the goodness of the fit of other functions	Based on the plausibility of the extrapolated portion of the curve (the other functions conferred an implausible OS); validated by clinical expert
The probability of death in the CP-CML health state is assumed to be equivalent across all treatments and reflects mortality rates in the English general population[243]	Based on the literature (Sasaki et al. 2015)[132]; validated by clinical expert
Patients with progressed CML who receive allo-SCT are assumed to be in one of two health states: in remission or relapsed	Based on a survey of clinical experts in the UK[48]
It was assumed that 41% of patients receiving hydroxycarbamide will achieve a CHR, and the remaining 59% will be non-responders; stronger responses were assumed not to occur with this therapy	Based on the overall median CHR reported by Dalziel et al. 2004[227]
The relationship between response and progression was assumed to be independent of the line of therapy, so the data obtained from the post-imatinib BMS-034 study were assumed to apply to post–2G-TKI patients	Approach used in prior HTAs (eg, Loveman et al. 2012)[168]
Probability of remaining in the CP-CML health state is independent of treatment within a given response category	Approach is common practice and has been adopted in previous CML technology appraisals (eg, Rogers et al. 2012)[82]
The presence of the T315I mutation does not predict treatment response with ponatinib	Based on the literature (Mauro et al. 2012);[238] validated by clinical expert
Only patients who achieve CCyR maintain response after TKI discontinuation	Only patients who discontinue treatment in CCyR are in a different clinical state with a reduced burden of cancer than at the beginning of therapy, and are therefore in a better position to survive
When patients discontinue a TKI (with the exception of CCyR patients) they are assumed to get the response rates of BSC (ie, they are re-distributed along CHR and NR states according to the figures specific to BSC)	PCyR and CHR are not optimal targeted responses for 2L TKI therapy after imatinib failure.[47] Therefore, patients who fail to achieve a CCyR are not considered to be in a better position to survive with BSC than had patients received BSC earlier in the treatment pathway
Resource requirements of a post–2G-TKI population would depend upon the presence/absence of CCyR	Based on a survey of clinical experts in the UK[48]
The rate of AEs is applied to the first cycle only on the assumption that such events will happen sooner rather than later	Common practice; in line with recent oncology models
AE rates for hydroxycarbamide set to zero	Absence of AEs information for hydroxycarbamide

Assumption	Justification
AE rates for allo-SCT set to zero	Associated costs would be absorbed into the follow-up costs for allo-SCT
For bosutinib, hydroxycarbamide, and allo-SCT, the rates of SAEs (cardiovascular, cerebrovascular, peripheral vascular, and venous thromboembolism events) were set to 0%	In the absence of equivalent long-term data for bosutinib, the assumption was that any mortality effects would be captured in the background population mortality rate
The model incorporates a 21.5-day inpatient stay immediately before death for 51.5% of patients assumed to be treated in hospital and a 17.4-day hospice stay for the 23.1% of patients assumed to be treated in a hospice; the remaining patients were assumed to die at home	Based on a survey of clinical experts in the UK[48]
Drug administration costs were set to zero	It is assumed that treatments administered orally require no drug administration costs
Post-relapse patients have CML and are treated pharmacologically	Based on a survey of clinical experts in the UK;[48] 2013 ELN treatment recommendations[47]
Patients with progressed CML who are ineligible for allo-SCT will receive the same background therapy as those with relapse following allo-SCT (20% imatinib, 20% hydroxycarbamide, 20% dasatinib, 20% nilotinib, 20% bosutinib)	Based on a survey of clinical experts in the UK[48] For relapse after allo-SCT most clinical experts stated they would consider using any of the five TKIs (imatinib, nilotinib, dasatinib, bosutinib, and ponatinib). For patients progressed to AP and ineligible for allo-SCT, the majority of patients are estimated by the clinical experts to be given a previously unused TKI. In the economic model ponatinib was substituted with hydroxycarbamide to be conservative and an even distribution among treatment options was assumed.
Utility decrement associated with allo-SCT in model cycle 2 is the midpoint of peri-operative and long-term estimate	In the absence of data, the best estimate for model cycle 2 was the midpoint of the peri-operative period by van Agthoven et al. 2001,[257] and the long-term period by Loveman et al. 2012[168]

2G, second-generation; AE, adverse event; allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; ELN, European LeukemiaNet; NR, no response; OS, overall survival; SAEs, serious adverse events; TKI, tyrosine kinase inhibitor.

5.3.6 Base-case results

5.3.6.1 Results of the analysis

Sections 5.3.6.2 to 5.3.6.6 provide the results for the de novo base-case analysis.

Base-case incremental cost effectiveness analysis results

5.3.6.2 Cost-effectiveness

The incremental cost-effectiveness ratio (ICER) results for ponatinib compared with each comparator in terms of LYG and QALYs, from the NHS/PSS direct medical perspective (ie, the payer perspective), are presented in Table 5-28. [redacted].

Table 5-28. Base-case cost-effectiveness results (discounted, per person): direct medical perspective

	Total costs (£)	Total LYG (Disc)	Total QALYs (Disc)	Incremental costs (£) (ponatinib vs)	Incremental LYG (ponatinib vs)	Incremental QALYs (ponatinib vs)	ICER (£/LYG)	ICER (£/QALYs)
Interferon alpha	188.917.38	4.02	2.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide	136,666.02	3.95	2.24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	150,810.61	6.09	4.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	209,257.69	6.74	3.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–

Allo-SCT, allogeneic haematopoietic stem cell transplantation; Disc, discounted; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year; Undisc, undiscounted.

Clinical outcomes from the model

5.3.6.3 Outcomes from the model vs clinically important outcomes

Figure 5-13 shows that the CP-CML model (assuming a 0% rate of allo-SCT after progression) does not predict an excess survival benefit over the long term compared with the OS data from the PACE trial. Indeed, the model is conservative with respect to ponatinib, as the OS benefit is underestimated beginning at year 3, with data from the PACE study showing higher survival compared to the model.

Figure 5-13. Face validity comparison between model-predicted OS and the PACE study (Hochhaus et al. 2015)[24]

OS, overall survival.

5.3.6.4 Markov trace

The Markov traces for the CP-CML economic analysis are presented in Appendix 19: Markov traces – CP-CML economic model.

5.3.6.5 QALYs accrued over time

Table 5-29 presents the QALYs for each health state accrued in the CP-CML economic analysis. In the CP health state, ponatinib accrues the most QALYs. The key driver of benefits with ponatinib in CP is superior effectiveness (higher and more durable cytogenetic response rates);[8, 9] hence, patients will spend longer in the CP health on ponatinib than on bosutinib, interferon alpha, or hydroxycarbamide.

Table 5-29. QALYS accrued in the CP-CML economic analysis

	Health state			Total	
	CP	**AP/BP**	**Allo-SCT**	**Undisc**	**Disc**
Interferon alpha	1.42	0.36	0.84	2.63	2.30
Hydroxy-carbamide	1.36	0.36	0.84	2.57	2.24
Bosutinib	4.53	0.31	0.72	5.55	4.00
Allo-SCT	0.00	0.00	5.07	5.07	3.93
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AP, accelerated phase; BP, blast phase; CP, chronic phase; Disc, discounted; QALY, quality-adjusted life-year; Undisc, undiscounted.

Note: Undiscounted totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

QALYs for each health state accrued over time for each comparator in the CP-CML economic analysis are presented in Appendix 20: QALYS over time – CP-CML economic model.

Disaggregated results of the base case incremental cost effectiveness analysis

5.3.6.6 Disaggregated QALYs, LYGs, and costs

5.3.6.6.1 QALYs and life-years gained

A summary of the treatment-specific deterministic survival and quality-adjusted survival estimates resulting from the analysis is presented in Table 5-30. Of the two TKI drug therapies being compared, ponatinib is associated with the largest increase in both OS and QALYs. Compared to bosutinib, treatment with ponatinib is predicted to improve survival (undiscounted) by almost [redacted]. After discounting future health benefits and costs, ponatinib achieved an estimated [redacted]. Ponatinib was also the TKI associated with the highest proportion of LYG and QALYs accrued within the CP-CML health state. Ponatinib was estimated to produce an additional [redacted]. In contrast, allo-SCT was associated with higher gains of undiscounted and discounted LYs than bosutinib, whilst hydroxycarbamide yielded lower OS and QALYs than any other comparator. The key driver of increased overall and quality-adjusted survival with ponatinib is superior effectiveness in terms of response: ponatinib has demonstrated higher response rates than comparators and responses are maintained for years in most patients, particularly in patients who remain in the CP health state.[8, 9] Thus, due to the superior efficacy of ponatinib, patients will remain alive in the CP health state longer than with bosutinib, interferon alpha, or hydroxycarbamide.

Table 5-30. LYG and QALY outcomes

	LYG					QALY				
			Allo-	Total				Allo-	Total	
	CP	AP/BP	SCT	Undisc	Disc	CP	AP/BP	SCT	Undisc	Disc
Interferon alpha	2.06	1.22	1.45	4.72	4.02	1.42	0.36	0.84	2.63	2.30
Hydroxy-carbamide	1.97	1.22	1.45	4.64	3.95	1.36	0.36	0.84	2.57	2.24
Bosutinib	6.11	1.04	1.24	8.38	6.09	4.53	0.31	0.72	5.55	4.00
Allo-SCT	0.00	0.00	8.77	8.77	6.74	0.00	0.00	5.07	5.07	3.93
Ponatinib	[redacted]									

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CP, chronic phase; Disc, discounted; LYG, life-year gained; QALY, quality-adjusted life-year; Undisc, undiscounted.

Table 5-31 and Table 5-32 list the incremental disaggregated QALYs and LYG by health state results for ponatinib vs each comparator.

Table 5-31. Summary of QALY gain by health state (discounted)

Health state	QALY ponatinib	QALY comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs interferon alpha					
CP	[redacted]	1.34	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	0.30	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.66	[redacted]	[redacted]	[redacted]
Total	[redacted]	2.30	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide					
CP	[redacted]	1.28	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	0.30	[redacted]	[redacted]	[redacted]

Health state	QALY ponatinib	QALY comparator	Increment	Absolute increment	% absolute increment
Allo-SCT	[redacted]	0.66	[redacted]	[redacted]	[redacted]
Total	[redacted]	2.24	[redacted]	[redacted]	[redacted]
Ponatinib vs bosutinib					
CP	[redacted]	3.18	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	0.25	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.56	[redacted]	[redacted]	[redacted]
Total	[redacted]	4.00	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT					
CP	[redacted]	-	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	-	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	3.93	[redacted]	[redacted]	[redacted]
Total	[redacted]	3.93	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CP, chronic phase; QALY, quality-adjusted life-year. Table was 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

Table 5-32. Summary of LYG gain by health state (discounted)

Health state	LYG ponatinib	LYG comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs interferon alpha					
CP	[redacted]	1.93	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	0.96	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	1.13	[redacted]	[redacted]	[redacted]
Total	[redacted]	4.02	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide					
CP	[redacted]	1.85	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	0.96	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	1.14	[redacted]	[redacted]	[redacted]
Total	[redacted]	3.95	[redacted]	[redacted]	[redacted]
Ponatinib vs bosutinib					
CP	[redacted]	4.32	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	0.81	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.96	[redacted]	[redacted]	[redacted]
Total	[redacted]	6.09	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT					
CP	[redacted]	-	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	-	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	6.74	[redacted]	[redacted]	[redacted]
Total	[redacted]	6.74	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CP, chronic phase; LYG, life-year gained. 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

5.3.6.6.2 Costs

Of the pharmacologic treatments under consideration, ponatinib has the highest main drug cost (Table 5-33), which contributes to its elevated overall cost in comparison with other pharmacologic comparators. A key driver of higher costs with ponatinib is a longer time-on-treatment as opposed to a higher cost of acquisition. In the CP-CML economic model, compared with ponatinib, the bosutinib time-on-treatment is very short (0.76 years on bosutinib vs 4.45 years on ponatinib). In this disease, a short time-on-treatment reflects a failure to achieve the

goals of therapy, because the two main reasons that patients typically discontinue treatment are lack of efficacy (eg, failure to achieve response or inability to maintain response) and intolerable side effects. The long duration of treatment observed in patients receiving ponatinib therefore indicates that this breakthrough therapy is both effective and well tolerated, with patients maintaining response and remaining in the CP-CML state.[24] Notably, the incremental costs with ponatinib are substantially offset by a reduction in costs associated with other drugs, allo-SCT, monitoring and follow-up, and end-of-life care, which reflects the fact that ponatinib maintains patients in the unprogressed CP-CML health state longer than either bosutinib or hydroxycarbamide. The apparently higher AE-related costs for ponatinib reflect the availability of more AE data for ponatinib rather than a genuinely higher rate of adverse events compared to the other drug treatments.

Overall, ponatinib is associated with a higher cost than the allo-SCT comparator, mainly as a consequence of patients successfully maintaining response on ponatinib for a long duration, thus incurring ongoing costs for the drug and for monitoring and follow-up.[144]

Table 5-33. Cost results (discounted)

Cost, £	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide	Interferon alpha
Main drug	[redacted]	31,697.92	-	283.32	52,826.43
Other drugs	19,753.48	33,924.63	93,694.36	39,459.41	39,324.51
Allo-SCT*	12,039.49	21,414.92	103,904.11	25,317.42	25,230.87
Monitoring/follow-up	40,618.38	58,817.78	7,273.24	66,692.30	66,636.44
Adverse events	1,992.59	461.80	-	-	-
End-of-life	3,508.53	4,493.56	4,385.98	4,913.57	4,899.14
Total	[redacted]	150,810.61	209,257.69	136,666.02	188,917.38

Allo-SCT, allogeneic haematopoietic stem cell transplantation.

*Includes costs associated with procedure and relapse.

Table 5-34 summarises the costs by health state to identify which health states are responsible for most differences in costs between ponatinib and the comparators. It can readily be seen that the majority of the incremental costs with ponatinib are accrued in the CP health state, reflecting the ability of ponatinib to provide high and sustained rates of response and reduce the rate of disease progression.

Table 5-34. Summary of cost by health state (discounted)

Health state	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs interferon alpha					
CP	[redacted]	56,704	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	84,651	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	47,562	[redacted]	[redacted]	[redacted]
Total	[redacted]	188,917	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide					
CP	[redacted]	3,999	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	84,942	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	47,725	[redacted]	[redacted]	[redacted]
Total	[redacted]	136,666	[redacted]	[redacted]	[redacted]
Ponatinib vs bosutinib					
CP	[redacted]	38,594	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	71,849	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	40,368	[redacted]	[redacted]	[redacted]
Total	[redacted]	150,811	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT					
CP	[redacted]	-	[redacted]	[redacted]	[redacted]
AP/BP	[redacted]	-	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	209,258	[redacted]	[redacted]	[redacted]

Health state	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Total	[redacted]	209,258	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CP, chronic phase. 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places , due to rounding error.

Table 5-35 summarises the predicted resource use by category of cost for ponatinib vs each comparator.

Table 5-35. Summary of predicted resource use by category of cost (discounted)

Resource use	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs interferon alpha					
Main drug	[redacted]	52,826	[redacted]	[redacted]	[redacted]
Other drugs	19,753	39,325	-19,571	19,571	[redacted]
Allo-SCT*	12,039	25,231	-13,191	13,191	[redacted]
Monitoring/ follow-up	40,618	66,636	-26,018	26,018	[redacted]
Adverse events	1,993	-	1,993	1,993	[redacted]
End-of-life	3,509	4,899	-1,391	1,391	[redacted]
Total	[redacted]	188,917	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide					
Main drug	[redacted]	283	[redacted]	[redacted]	[redacted]
Other drugs	19,753	39,459	-19,706	19,706	[redacted]
Allo-SCT*	12,039	25,317	-13,278	13,278	[redacted]
Monitoring/ follow-up	40,618	66,692	-26,074	26,074	[redacted]
Adverse events	1,993	-	1,993	1,993	[redacted]
End-of-life	3,509	4,914	-1,405	1,405	[redacted]
Total	[redacted]	136,666	[redacted]	[redacted]	[redacted]
Ponatinib vs bosutinib					
Main drug	[redacted]	31,698	[redacted]	[redacted]	[redacted]
Other drugs	19,753	33,925	-14,171	14,171	[redacted]
Allo-SCT*	12,039	21,415	-9,375	9,375	[redacted]
Monitoring/ follow-up	40,618	58,818	-18,199	18,199	[redacted]
Adverse events	1,993	462	1,531	1,531	[redacted]
End-of-life	3,509	4,494	-985	985	[redacted]
Total	[redacted]	150,811	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT					
Main drug	[redacted]	-	[redacted]	[redacted]	[redacted]
Other drugs	19,753	93,694	-73,941	73,941	[redacted]
Allo-SCT*	12,039	103,904	-91,865	91,865	[redacted]
Monitoring/ follow-up	40,618	7,273	33,345	33,345	[redacted]
Adverse events	1,993	-	1,993	1,993	[redacted]
End-of-life	3,509	4,386	-877	877	[redacted]
Total	[redacted]	209,258	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation. 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.

*Includes costs associated with procedure and relapse.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places , due to rounding error.

5.3.7 Sensitivity analyses

Probabilistic sensitivity analysis

5.3.7.1 Measure of decision uncertainty

To address the uncertainty in the parameters used within the model, a probabilistic sensitivity analysis (PSA) was implemented. The PSA was performed on the comparison between ponatinib vs bosutinib, since this was the comparison yielding the highest ICER.

5.3.7.2 Parameter distributions

The parameters and their corresponding distributions that were used in the PSA are presented in Table 5-36. The beta distribution for response rates was normalised in order to have all response categories sum to 1. For duration of response and time on treatment of ponatinib, the PSA was obtained by applying the Cholesky decomposition method on the covariance matrix obtained directly from the parametric survival analysis of patient-level data. For all other parameters, the distribution used was Beta (for parameters whose possible values are constrained between 0 and 1) or Gamma. The distributions were calculated with the mean values (base case) and the standard error (SE). Where the SE was not available, it was either estimated from the 95% CI or assumed as 10% of the mean. Mean results were calculated from the 1000 simulations in this analysis.

Table 5-36. PSA distributions

Parameter	Distribution
Adverse event rates	Beta
Allo-SCT suitability	Gamma
Costs	Gamma
HRQoL	Beta
Number of days in hospital per treatment course	Gamma
OS curve-fitting parameters	Gamma
PFS curve-fitting parameters	Gamma
Proportion treated in hospital/hospice at end of life	Beta
Resource use rates	Gamma
Response duration	Gamma
Response rates	Beta (normalised)
Duration of response (ponatinib)	Cholesky decomposition
Duration of response (bosutinib)	Gamma
Time on treatment (ponatinib)	Cholesky decomposition
Time on treatment (bosutinib)	Gamma

Allo-SCT, allogeneic haematopoietic stem cell transplantation; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis.

5.3.7.3 Results of probabilistic sensitivity analysis

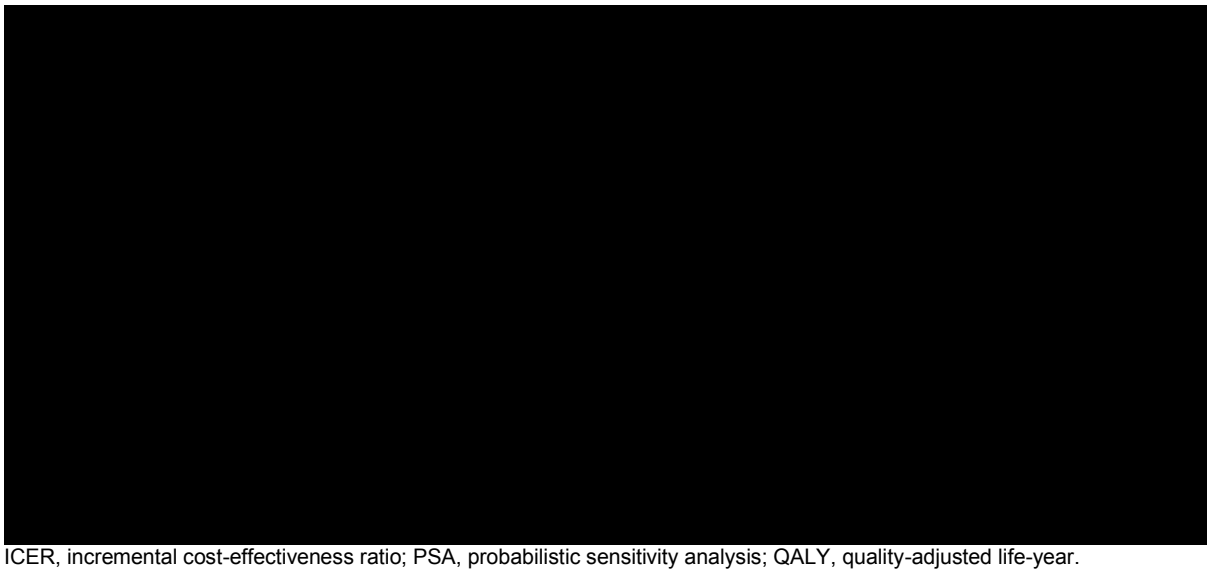
Table 5-37 reports the 95% CI for incremental costs, QALYs, and ICERs for ponatinib vs bosutinib.

Table 5-37. 95% CI for costs, QALYs, and ICERs

	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]

Figure 5-14 shows the incremental costs and QALYs derived from the 1000 simulations of the PSA for ponatinib vs bosutinib. This graph demonstrates that most simulations are generally consistent with the mean result; there are few extreme values.

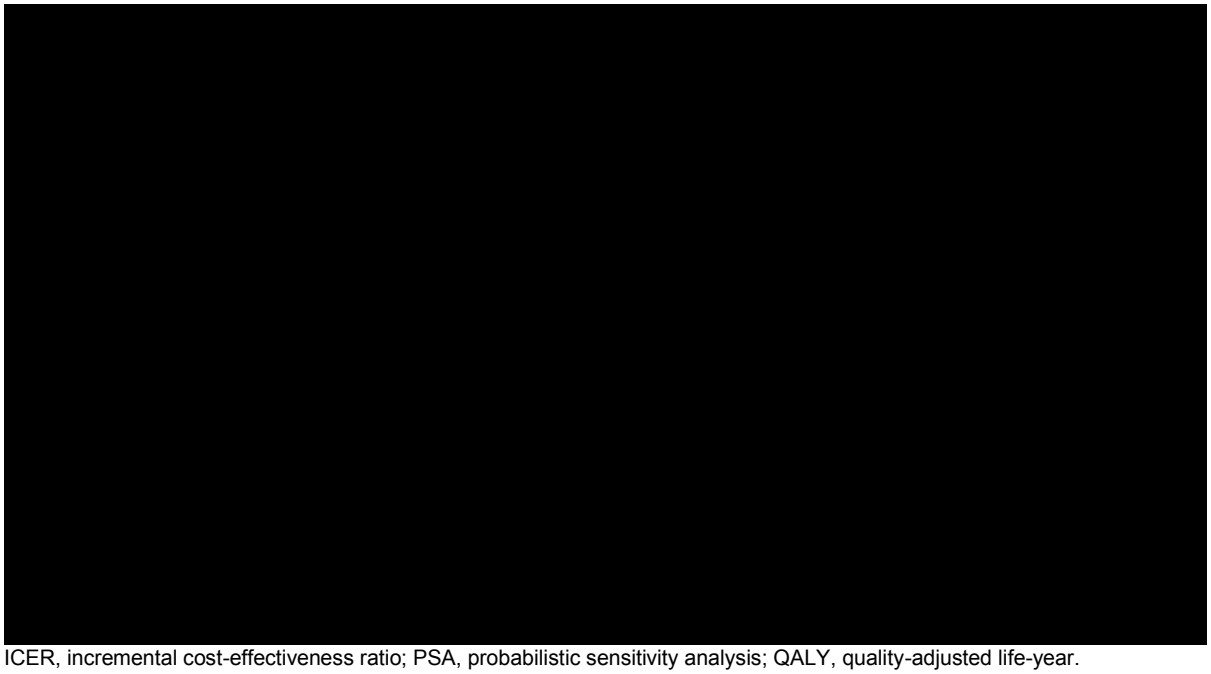
Figure 5-14. Results of 1000 simulations in the PSA for the ICER of ponatinib vs bosutinib



ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 5-15 shows the cost-effectiveness acceptability curve derived from the PSA. As can be seen, at an ICER threshold of approximately £25,000, over [redacted]% of simulations will be cost-effective. At a willingness-to-pay (WTP) threshold of ≤£20,000, [redacted]% of iterations were cost-effective and at a WTP threshold of ≤£30,000, [redacted]% of iterations were cost-effective.

Figure 5-15. Cost-effectiveness acceptability curve in the PSA for the ICER of ponatinib vs bosutinib



ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

5.3.7.4 ICER results from base-case vs PSA

Results of the PSA were consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values.

Deterministic sensitivity analysis

5.3.7.5 Parameters

In order to assess the impact of each of the inputs on the overall result, a univariate analysis was conducted to identify the parameters with greatest influence on the model results. Each parameter selected was set to upper and lower values, holding all other parameters constant, to understand how sensitive the ICER is to changes in the inputs. The upper and lower values for over 200 parameters, as shown in Table 5-38, were set based on the 95% CI or range of the base-case value if directly available, or calculated ±1.96 × the standard error (SE). When neither the 95% CI nor the SE was available, values were varied ±10% of the mean value. For resources for monitoring and follow-up, upper and lower values in the sensitivity analysis were derived from the survey of UK clinical experts.[48] Discount rates of 0% and 6% were also assessed.

Table 5-38. Parameter values in the deterministic sensitivity analysis (parameters with zero for base-case, lower and upper values are not presented)

Parameter	Base case	Method*	Lower value	Upper value
Adverse event unit cost				
Abdominal pain	752.10	±1.96 * SE	604.69	899.51
ALT elevation	1121.98	±1.96 * SE	902.07	1341.89
Anaemia	1827.13	±1.96 * SE	1469.01	2185.25
Cardiovascular event	2357.00	±1.96 * SE	1895.03	2818.97
Cerebrovascular event	2962.00	±1.96 * SE	2381.45	3542.55
Diarrhoea	801.95	±1.96 * SE	644.77	959.13
Gamma-glutamyltransferase increased	1121.98	±1.96 * SE	902.07	1341.89
Hyperglycaemia	1271.46	±1.96 * SE	1022.25	1520.67
Hypophosphatemia	721.00	±1.96 * SE	579.68	862.32
Leukocytopaenia	633.26	±1.96 * SE	509.14	757.38
Lipase increased	721.00	±1.96 * SE	579.68	862.32
Neutropaenia	633.26	±1.96 * SE	509.14	757.38
Pancreatitis	1121.98	±1.96 * SE	902.07	1341.89
Peripheral vascular event	2872.00	±1.96 * SE	2309.09	3434.91
Thrombocytopaenia	421.74	±1.96 * SE	339.08	504.40
Venous thromboembolism event	552.00	±1.96 * SE	443.81	660.19
Allo-SCT initial cost, £	60092.13	±1.96 * SE	48314.08	71870.19
Allo-SCT suitability after progression	0.27250	±1.96 * SE	0.21909	0.32591
CCyR rate				
Bosutinib	0.24074	±1.96 * SE	0.19356	0.28793
Ponatinib	0.61340	±1.96 * SE	0.49317	0.73363
CHR rate				
Bosutinib	0.37931	±1.96 * SE	0.30497	0.45366
Hydroxycarbamide	0.41000	±1.96 * SE	0.32964	0.49036
Interferon alpha	0.47000	±1.96 * SE	0.37788	0.56212
Ponatinib	0.18190	±1.96 * SE	0.14625	0.21755
Cost of community palliative care per day, £	158.23	±1.96 * SE	127.21	189.24
Cost of palliative care in hospital per day, £	463.77	±1.96 * SE	372.87	554.66
Cumulative incidence				
Abdominal pain ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
ALT elevation bosutinib	0.05932	±1.96 * SE	0.04769	0.07095
ALT elevation ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Anaemia bosutinib	0.06780	±1.96 * SE	0.05451	0.08108
Anaemia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Diarrhoea bosutinib	0.08475	±1.96 * SE	0.06814	0.10136
Gamma-glutamyltransferase increased ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Leukocytopaenia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Lipase increased ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Neutropaenia bosutinib	0.15254	±1.96 * SE	0.12264	0.18244
Neutropaenia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Pancreatitis ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Thrombocytopaenia bosutinib	0.26271	±1.96 * SE	0.21122	0.31420
Thrombocytopaenia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Discount rate costs	3.50%	–	0.00%	6.00%
Discount rate outcomes	3.50%	–	0.00%	6.00%
EOL hospice days	17.40	±1.96 * SE	13.99	20.81
EOL hospital days	21.50	±1.96 * SE	17.29	25.71
EOL, proportion being treated in hospice	0.23	Range	0.04	0.50

Parameter	Base case	Method*	Lower value	Upper value
EOL, proportion being treated in hospital	0.51	Range	0.01	0.90
Mean PFS in AP phase, months	9.16004	±1.96 * SE	7.36467	10.95540
Median time on treatment				
Bosutinib	8.30000	±1.96 * SE	6.67320	9.92680
NR rate				
Bosutinib	0.29662	±1.96 * SE	0.23848	0.35475
Hydroxycarbamide	0.59000	±1.96 * SE	0.47436	0.70564
Interferon alpha	0.53000	±1.96 * SE	0.42612	0.63388
Ponatinib	0.12010	±1.96 * SE	0.09656	0.14364
PCyR rate				
Bosutinib	0.08333	±1.96 * SE	0.06700	0.09967
Ponatinib	0.08460	±1.96 * SE	0.06802	0.10118
Per-cycle cost, £				
Bosutinib	10714.40	±1.96 * SE	8614.38	12814.42
Dasatinib	7624.47	±1.96 * SE	6130.08	9118.87
Hydroxycarbamide	38.24	±1.96 * SE	30.75	45.74
Imatinib	5589.73	±1.96 * SE	4494.14	6685.31
Interferon alpha	6832.91	±1.96 * SE	5493.66	8172.17
Nilotinib	7910.11	±1.96 * SE	6359.73	9460.50
Ponatinib in CCyR	[redacted]	±1.96 * SE	[redacted]	[redacted]
Ponatinib in CHR	[redacted]	±1.96 * SE	[redacted]	[redacted]
Ponatinib in NR	[redacted]	±1.96 * SE	[redacted]	[redacted]
Ponatinib in PCyR	[redacted]	±1.96 * SE	[redacted]	[redacted]
CV monitoring with ponatinib	75.19	±1.96 * SE	60.45	89.93
Follow-up after allo-SCT, y1	12214.71	±1.96 * SE	9820.63	14608.79
Follow-up after allo-SCT, y2	3518.25	±1.96 * SE	2828.67	4207.83
Follow-up after allo-SCT, y3+	420.00	±1.96 * SE	337.68	502.32
Treatment post discontinuation	38.24	±1.96 * SE	30.75	45.74
Treatment AP/BP patients not receiving allo-SCT	6375.39	±1.96 * SE	5125.81	7624.97
Treatment post allo-SCT relapse	6375.39	±1.96 * SE	5125.81	7624.97
Per-cycle probability (ponatinib only)				
Cardiovascular event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Cerebrovascular event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Peripheral vascular event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Venous thromboembolism event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Per-cycle resource use with:				
CCyR in CP: Blood chemistry	1.130000	HCP survey	0.500000	3.000000
CCyR in CP: Blood film exam	0.500000	HCP survey	0.000000	1.000000
CCyR in CP: Blood transfusion	0.010000	HCP survey	0.000000	0.125000
CCyR in CP: Bone marrow aspiration	0.030000	HCP survey	0.000000	0.250000
CCyR in CP: Complete blood count	1.130000	HCP survey	0.500000	3.000000
CCyR in CP: Cytogenetic analysis	0.580000	HCP survey	0.000000	3.000000
CCyR in CP: FISH	0.220000	HCP survey	0.000000	1.000000
CCyR in CP: Flow Cytometry	0.090000	HCP survey	0.000000	1.000000
CCyR in CP: Haematologist-led outpatient visit	0.930000	HCP survey	0.000000	2.140000
CCyR in CP: Nurse-led outpatient visit	0.290000	HCP survey	0.000000	1.000000
CCyR in CP: PCR	0.790000	HCP survey	0.000000	1.000000
No CCyR in CP: blood chemistry	1.88000	HCP survey	0.75000	3.00000
No CCyR in CP: blood film exam	1.09000	HCP survey	0.00000	3.00000
No CCyR in CP: blood transfusion	0.01000	HCP survey	0.00000	0.12500
No CCyR in CP: bone marrow aspiration	0.30000	HCP survey	0.00000	1.00000
No CCyR in CP: complete blood count	1.97000	HCP survey	0.75000	3.00000
No CCyR in CP: cytochemistry analysis	0.05000	HCP survey	0.00000	0.50000
No CCyR in CP: cytogenetic analysis	0.74000	HCP survey	0.00000	2.17000
No CCyR in CP: FISH	0.56000	HCP survey	0.00000	2.17000
No CCyR in CP: flow cytometry	0.13000	HCP survey	0.00000	1.00000
No CCyR in CP: haematologist-led outpatient visit	1.72000	HCP survey	0.75000	2.17000
No CCyR in CP: kinase domain mutation analysis	0.00000	HCP survey	0.00000	1.00000
No CCyR in CP: nurse-led outpatient visit	0.38000	HCP survey	0.00000	2.00000
No CCyR in CP: PCR	1.31000	HCP survey	0.00000	2.17000
No response in AP/BP: blood chemistry	3.15	HCP survey	0.00	6.00
No response in AP/BP: blood film exam	2.19	HCP survey	0.00	6.00
No response in AP/BP: blood transfusion	1.98	HCP survey	0.00	6.00
No response in AP/BP: bone marrow aspiration	0.30	HCP survey	0.00	0.99
No response in AP/BP: complete blood count	4.38	HCP survey	1.62	6.00
No response in AP/BP: cytochemistry analysis	0.12	HCP survey	0.00	0.99

Parameter	Base case	Method*	Lower value	Upper value
No response in AP/BP: cytogenetic analysis	0.90	HCP survey	0.00	3.00
No response in AP/BP: donor lymphocyte transfusion	0.00	HCP survey	0.00	0.00
No response in AP/BP: FISH	0.13	HCP survey	0.00	3.00
No response in AP/BP: flow cytometry	0.45	HCP survey	0.00	2.16
No response in AP/BP: haematologist-led outpatient visit	3.63	HCP survey	1.62	6.00
No response in AP/BP: kinase domain mutation analysis	0.13	HCP survey	0.00	0.50
No response in AP/BP: nurse-led outpatient visit	0.51	HCP survey	0.00	6.00
No response in AP/BP: PCR	1.68	HCP survey	0.00	3.00
No response in AP/BP: platelet transfusion	0.30	HCP survey	0.00	3.00
No response in AP: hospital days	2.13	HCP survey	0.00	12.51
No response in BP: hospital days	26.64	HCP survey	0.90	87.00
Population norm utility				
Females <25 years	0.94000	±1.96 * SE	0.75576	1.00000
Females 25-34 years	0.93000	±1.96 * SE	0.74772	1.00000
Females 35-44 years	0.91000	±1.96 * SE	0.73164	1.00000
Females 45-54 years	0.85000	±1.96 * SE	0.68340	1.00000
Females 55-64 years	0.81000	±1.96 * SE	0.65124	0.96876
Females 65-74 years	0.78000	±1.96 * SE	0.62712	0.93288
Females ≥75 years	0.71000	±1.96 * SE	0.57084	0.84916
Males <25 years	0.94000	±1.96 * SE	0.75576	1.00000
Males 25-34 years	0.93000	±1.96 * SE	0.74772	1.00000
Males 35-44 years	0.91000	±1.96 * SE	0.73164	1.00000
Males 45-54 years	0.84000	±1.96 * SE	0.67536	1.00000
Males 55-64 years	0.78000	±1.96 * SE	0.62712	0.93288
Males 65-74 years	0.78000	±1.96 * SE	0.62712	0.93288
Males ≥75 years	0.75000	±1.96 * SE	0.60300	0.89700
Resource unit cost, £				
Blood chemistry	1.19	±1.96 * SE	0.96	1.42
Blood film exam	3.01	±1.96 * SE	2.42	3.60
Blood transfusion	121.85	±1.96 * SE	97.97	145.73
Bone marrow aspiration	517.50	±1.96 * SE	416.07	618.93
Complete blood count	3.01	±1.96 * SE	2.42	3.60
Cytochemistry analysis	6.99	±1.96 * SE	5.62	8.36
Cytogenetic analysis	6.99	±1.96 * SE	5.62	8.36
Donor lymphocyte transfusion	193.15	±1.96 * SE	155.29	231.01
FISH	6.99	±1.96 * SE	5.62	8.36
Flow Cytometry	6.99	±1.96 * SE	5.62	8.36
Haematologist-led outpatient visit	150.38	±1.96 * SE	120.91	179.85
Hospital days	721.00	±1.96 * SE	579.68	862.32
Kinase domain mutation analysis	6.99	±1.96 * SE	5.62	8.36
Nurse-led outpatient visit	66.42	±1.96 * SE	53.40	79.44
PCR	25.00	±1.96 * SE	20.10	29.90
Platelet transfusion	193.15	±1.96 * SE	155.29	231.01
Utility				
During a SAE	0.52000	95% CI	0.46000	0.58000
In AP	0.53000	95% CI	0.48000	0.58000
In BP	0.29000	95% CI	0.24000	0.33000
In CP with response	0.91000	95% CI	0.89000	0.94000
In CP without response	0.73000	95% CI	0.69000	0.78000
In cycle 1 after allo-SCT	0.55000	±1.96 * SE	0.44220	0.65780
In cycle 2 after allo-SCT	0.63000	±1.96 * SE	0.50652	0.75348
In cycle 3 after allo-SCT	0.71000	±1.96 * SE	0.57084	0.84916
Post-relapse after allo-SCT	0.58520	±1.96 * SE	0.47050	0.69990

Allo-SCT, allogeneic haematopoietic stem cell transplantation; ALT, alanine aminotransferase; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CI confidence interval; CML, chronic myeloid leukaemia; CP, chronic phase; EOL, end of life; FISH, fluorescence in situ hybridization; HCP, healthcare practitioner; NR, non-response; PFS, progression-free survival; PCR, polymerase chain reaction; PCyR, partial cytogenetic response; SAE, serious adverse event; SCT, stem cell transplantation; SE, standard error.

*SE was set to 10% base-case value for these inputs.

5.3.7.6 Results of deterministic sensitivity analysis

Results of the univariate sensitivity analysis are presented as a tornado plot (Figure 5-16) for the pairwise comparison of ponatinib vs bosutinib. The analysis was run on all model parameters. From this plot, it is apparent that the ICERs are most sensitive to changes in the discount rate on outcomes and costs, hospital days for patients in BP-CML, and the cost of ponatinib in CCyR. Parameters that are not presented in the plot have minimal or negligible effect on the analysis. The relative efficacy was captured by varying response rates in the one-way sensitivity analysis (OWSA) (Figure 5-16). ICERs were also sensitive to CCyR (ponatinib and bosutinib), CHR (ponatinib and bosutinib), and NR (bosutinib).

[177]

Figure 5-16: Tornado plot displaying the most influential parameters for the ICER of ponatinib vs bosutinib

AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CP, chronic phase; ICER, incremental cost-effectiveness ratio; NR, non-response; QALY, quality-adjusted life-year.

5.3.7.7 Sensitivity analysis of technology prices

Sensitivity analyses of technology prices were incorporated in the one-way and probabilistic sensitivity analyses in terms of per-cycle costs, as described above.

5.3.7.8 Scenario analyses

5.3.7.8.1 Uncertainty on effectiveness (-25% CCyR)

This scenario addresses the uncertainty around the estimation of the effectiveness of ponatinib. Response rates applied in the CP-CML are derived from the MAIC, an established statistical process that attempts to minimise the inherent biases of naïve indirect comparison. Regardless, uncertainty of the effectiveness data still remains, mainly due to differences in the design of the single-arm trials. Moreover, as in every statistical method based on a propensity score regression, there is potential bias due to unobserved confounders. To address this uncertainty, an arbitrary 25% reduction of the number of ponatinib patients achieving a best response of CCyR is tested as a worst possible case. Since the mutually exclusive best-response rates must sum to 100%, the same 25% of patients is added to the PCyR category (Table 5-39).

Table 5-39. Model inputs for uncertainty on CCyR scenario analysis

Response	Base-case analysis Ponatinib rates	Base-case analysis Ponatinib rates	Scenario analysis Ponatinib rates
CCyR	61.34%	24.07%	46.1%
PCyR	8.46%	8.33%	23.80%
CHR	18.19%	37.93%	18.19%
NR	12.01%	29.66%	12.01%

CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, no response; PCyR, partial haematologic response.

5.3.7.8.2 Fourth-line CP-CML

In the base-case analysis, the population is defined as CP-CML patients who received 2 prior TKIs (3L). All input data and statistics from the PACE study are based on this subpopulation (n=97).

The base case reflects the targeted place in therapy for ponatinib—third line after treatment failure with imatinib and either nilotinib or dasatinib, if used through the CDF. Although not supported by strong scientific evidence, in clinical practice 2G-TKIs are sometimes used sequentially. It is therefore possible that ponatinib might be considered in the 4L setting. We discourage this placement in the clinical pathway of care due to the loss of benefit relative to its use as a 3L treatment. The unmet medical need for patients who fail imatinib and a 2G-TKI is high and there is little evidence to support the sequential use of 2G-TKIs (including bosutinib) as an effective strategy for patients with CML who are R/I to prior therapy. Sequential use of nilotinib and dasatinib is not an approved indication for either of these drugs[17, 51] and only a minority of patients in the phase 1/2 bosutinib trial (ie, n=21, 3L CP-CML) met the criteria for the “unmet medical need” subpopulation defined by the EMA.[102] Bosutinib was thus only granted a “conditional approval” in 2013 with additional efficacy data needed to confirm the benefit of bosutinib in the intended indication.[36] In comparison, the study population of the PACE trial reflects the ponatinib indication, for use after failure of one 2G-TKI, and support the efficacy of ponatinib in the 3L setting (since imatinib is standard 1L therapy and would thus be used before the [subsequently failed] 2G-TKI).[9]

For completeness, we have carried out a scenario analysis to evaluate the cost-effectiveness of ponatinib in the population of CP-CML patients who received at least 3 prior TKIs (3 TKIs n=142; 4 TKIs n=12). Table 5-40 compares the model inputs of the 4L scenario analysis with the base case. The comparators for ponatinib are BSC and allo-SCT. The results of the 4L scenario analysis are presented in Table 5-45.

Table 5-40. Model inputs for 4L scenario analysis

Parameter	Base case	4L scenario analysis
Population characteristics		
Initial age (years)	54.5	59.9
Proportion of males	44.9%	52.6%
Response rates		
CCyR rate	61.34%	44.16%
PCyR rate	8.46%	5.84%
CHR rate	18.19%	24.68%
NR rate	12.01%	25.32%
Functions		
Duration of response	Gompertz function	Exponential function
Time-on-treatment		
Undiscounted LY in CP-CML, on-treatment	4.44	3.00
Time with doses		
Proportion of days on treatment, %	[redacted]	[redacted]

4L, fourth-line; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; LY, life-year; NR, no response; PCyR, partial haematologic response.

5.3.7.8.3 Cost of allo-SCT

In the base case, the initial cost of allo-SCT and the follow-up costs for years 1 and 2 were based on data from the UK Stem Cell Strategy Oversight Committee.[260] We carried out a scenario analysis using the same source for allo-SCT costs as in bosutinib NICE submission. In the bosutinib submission, allo-SCT costs were sourced from a NHS Blood and Transplant publication, inflated to 2012/2013 (bosutinib NICE submission, page 145).[161] For follow-up year 3, as reported in the bosutinib STA, patients are assumed to receive 100 mg ciclosporin twice daily at a monthly cost of £140, resulting in a per-cycle follow-up cost of £420. This last value was also used in the base case analysis. Table 5-41 compares the model inputs. Table 5-45 presents the results of the cost of allo-SCT scenario analysis.

Table 5-41. Model input for cost of allo-SCT scenario analysis

	Base case	Cost of allo-SCT scenario analysis
Allo-SCT initial cost (£)	60,092	76,560
Per-cycle follow-up cost after allo-SCT (£)		
Year 1	12,215	2,133
Year 2	3,518	292
Year 3	420	420

Allo-SCT, allogeneic haematopoietic stem cell transplantation.

5.3.7.8.4 HRQoL utility

In the base-case analysis the utilities are derived from Szabo et al. 2010 (UK cohort data),[249] van Agthoven et al. 2001,[257] Loveman et al. 2012,[168] Kantarjian et al. 2002,[258] and Olavarria et al. 2003.[259] We carried out two scenarios analyses: one using the utility values obtained from the

bosutinib NICE submission,[161] and the other with utilities for the advanced CML population in the bosutinib clinical trial as reported by Whiteley et al. 2016.[253]

In the first utility scenario analysis, we used the values from the bosutinib NICE submission,[161] which were derived from the previous NICE appraisals TA251[90] (reported in Hoyle et al. 2011)[266] and TA241[92] (reported in Loveman et al. 2012[168] and Rogers et al. 2012[82]). 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 et al. 2004[254] and used by Dalziel et al. 2004[227] in a previous HTA of imatinib for CML. In the second scenario analysis, we tested the use of utilities for the advanced phase of CML from the bosutinib clinical trial reported by Whiteley et al. 2016.[253] The values we considered are those recorded for AP and BP patients at baseline because the paper did not report the single mean utilities for the efficacy assessment period of the trial.

Table 5-42 compares the model inputs. Table 5-45 presents the results of the HRQoL utility scenario analysis.

Table 5-42. Model inputs for HRQoL utility scenario analyses

	Base case		Bosutinib NICE STA utility values scenario analysis		Whiteley et al. 2016 utility values scenario analysis	
Utilities	**Value**	**Source**	**Value**	**Source**	**Value**	**Source**
CP-CML						
CCyR	0.91	Szabo et al. 2010, UK cohort	0.85	Bosutinib NICE submission	0.91	As in base case
No CCyR	0.73	Szabo et al. 2010, UK cohort	0.85	Bosutinib NICE submission	0.73	As in base case
AP-CML	0.53	Szabo et al. 2010, UK cohort	0.73	Bosutinib NICE submission	0.78	Whiteley et al. 2016
BP-CML	0.29	Szabo et al. 2010, UK cohort	0.52	Bosutinib NICE submission	0.66	Whiteley et al. 2016
AE	0.52	Szabo et al. 2010, UK cohort	0.52	Same as in base case	0.52	As in base case
Allo-SCT						
Cycle 1	0.55	van Agthoven et al 2001	0.71	Bosutinib NICE submission	0.55	As in base case
Cycle 2	0.63	Assumption. Midpoint of peri-operative and long term estimate	0.71	Bosutinib NICE submission	0.63	As in base case
Cycle 3	0.71	Loveman et al. 2012	0.71	Bosutinib NICE submission	0.71	As in base case
Post-relapse	0.59	Based on information in Kantarjian et al. 2002; Olavarria et al. 2003	0.59	Same as in base case	0.59	As in base case

AE, adverse event; Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; HRQoL, health-related quality-of-life.

5.3.7.8.5 Bosutinib price

A scenario analysis on the price of bosutinib was carried out after the bosutinib pack price was recalculated to obtain the same daily cost as imatinib (£61.22/day). Table 5-43 compares the model inputs. Table 5-45 presents the results of the bosutinib price scenario analysis.

Table 5-43. Model inputs for bosutinib price scenario analysis

Bosutinib price	mg per unit	Units per pack	Base-case price (£)	Scenario price (£)
Tablet	100	28	859.17	342.83
Tablet	500	28	3,436.67	1,714.16

5.3.7.8.6 Trial-based mortality

The base case employs a surrogate survival approach where a benefit beyond treatment discontinuation is assumed, but only for patients who are in CCyR at treatment discontinuation. This approach assumes a post-treatment benefit with ponatinib.

A scenario analysis on OS was carried out to address the uncertainty in the assumption of benefit beyond treatment discontinuation in CCyR. In the base case, the background mortality was set to that of the UK general population by age and sex. In the trial-based mortality scenario, we estimated the mortality of patients who achieved CCyR in the PACE and then discontinued treatment (7 deaths among 26 patients over 4 years). We assumed a constant risk of death (ie, an exponential survival function). This mortality substituted the background mortality in the base case for patients who achieve CCyR and interrupt TKI treatment (ponatinib or bosutinib) before they progress. Table 5-45 presents the ICER results reflecting the increased mortality in CCyR after treatment discontinuation in this scenario analysis. In the trial-based mortality scenario, OS on ponatinib is 11.12 years.

5.3.7.8.7 Discount rate outcomes

As survival can theoretically be extended beyond 30 years if patients remain in CP-CML, the discount rate of 1.5% is applied as suggested in the NICE Guide to the methods of technology appraisal.[158]

5.3.7.8.8 Background mortality

A scenario is tested with background mortality increased by a factor of 1.5.

5.3.7.8.9 Fitting functions

Scenario analyses were carried out to test the impact of alternative fitting functions for time-on-treatment with ponatinib and OS for allo-SCT in CP-CML and in AP-CML, where the base-case choice was made based on considerations different from the best fit. Table 5-44 compares the model inputs. Additional scenarios were tested for other key functions (ie, duration of response and PFS) using different fitting functions that provided a similarly good fit. Table 5-45 presents the ICER results of the fitting functions scenario analyses.

Table 5-44. Model inputs for fitting functions scenario analyses

Function	Base case		Fitting functions scenario analyses	
Duration of response ponatinib	Gompertz	Best fit	Log-logistic	Second best fit
Duration of response bosutinib	Gompertz	Best fit	Log-logistic	Second best fit
PFS with CCyR	Gompertz	Best fit	Log-normal	Second best fit
PFS with PCyR	Gompertz	Best fit	Weibull	Second best fit
PFS with CHR	Weibull	Best fit	Gompertz	Second best fit

Function	Base case		Fitting functions scenario analyses	
OS for allo-SCT in CP-CML	Exponential	Only function that does not yield an unrealistic OS	Gompertz	Best fit
OS for allo-SCT in AP-CML	Exponential	Only function that does not yield an unrealistic OS	Gompertz	Best fit

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; NR, no response; PCyR, partial haematologic response; PFS, progression-free survival; OS, overall survival; ToT, time-on-treatment.

5.3.7.9 Summary of sensitivity analysis results

5.3.7.9.1 Summary of deterministic and probabilistic sensitivity analyses

Deterministic sensitivity analyses reveal that the parameters most strongly influencing the results include discount rates, the cost of ponatinib, hospital days for patients in BP-CML, and the CCyR rate with ponatinib and bosutinib. Cost-effectiveness results for ponatinib compared with bosutinib in the PSA were similar to those in the base-case analysis.

5.3.7.9.2 Scenario analyses results—Impact on ICER

Table 5-45 reports the scenario analyses impact on ICERs. Most scenario analyses yielded similar ICERs to those obtained in the base-case analysis. The scenario analyses that produced the highest ICERs was that in which ponatinib was used in 4L instead of 3L, the scenario using trial-based mortality, and . However, in both of these cases, ICERs remained well below £35,000/QALY even for the comparison that yielded the highest ICER, and in all other scenario analyses ICERs were below £30,000/QALY.

Table 5-45. Scenario analyses ICER results

Scenario	ICER (£/QALY) for ponatinib vs			
	Bosutinib	Allo-SCT	Hydroxycarbamide	Interferon alpha
Base case	[redacted]	[redacted]	[redacted]	[redacted]
–25% CCyR	[redacted]	[redacted]	[redacted]	[redacted]
4L CP-CML	[redacted]	[redacted]	[redacted]	[redacted]
Cost of allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]
HRQoL utility				
Bosutinib STA	[redacted]	[redacted]	[redacted]	[redacted]
Whiteley et al.	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib price	[redacted]	[redacted]	[redacted]	[redacted]
Trial-based mortality	[redacted]	[redacted]	[redacted]	[redacted]
1.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]
Background mortality +1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Fitting functions				
DoR, ponatinib	[redacted]	[redacted]	[redacted]	[redacted]
DoR, bosutinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS with CCyR	[redacted]	[redacted]	[redacted]	[redacted]
PFS with PCyR	[redacted]	[redacted]	[redacted]	[redacted]
PFS with CHR	[redacted]	[redacted]	[redacted]	[redacted]
OS for allo-SCT in CP-CML	[redacted]	[redacted]	[redacted]	[redacted]
OS for allo-SCT in AP-CML	[redacted]	[redacted]	[redacted]	[redacted]

4L, fourth-line; allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; CML, chronic myeloid leukaemia; CP, chronic phase; DoR, duration of response; HRQoL, health-related quality-of-life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; OS, overall survival.

5.4 De novo analysis – AP/BP-CML

5.4.1 Methodology

5.4.1.1 Patient population

As with the cost-effectiveness analysis for CP-CML (see Section 5.3.1), the target population in the AB/BP-CML economic model is consistent with that defined in the NICE scope[164]—that is, the patient population indicated in the approved EU label (see Section 2.2.2) and the subjects in the ponatinib clinical study programme. Whereas all patients in the CP-CML economic model commence treatment in the CP-CML health state (though they may subsequently progress to AP- and/or BP-CML), the patients in the AP/BP-CML model initiate treatment in either AP-CML or BP-CML.

5.4.1.1.1 Baseline characteristics of the simulated population

The baseline characteristics of the modelled population used in the simulation are derived from those patients in the AP/BP-CML cohort in the PACE study who had received at least two prior TKIs—ie, subjects in 3L and 4L (Table 5-46).

Table 5-46. Baseline characteristics of the modelled AP-/BP-CML population

Parameter	Value		Source
	AP-CML	BP-CML	
Initial age (years)	54.6	50.4	PACE
Proportion of males	41.8%	60.0%	**PACE**

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia.

5.4.1.2 Model structure – AP/BP-CML

The de novo AP/BP-CML cost-effectiveness model was developed based on previously developed models for the treatment of patients with CML,[239] and in conformity with requirements of NICE as expressed in its Guide to the methods of technology appraisal.[158]

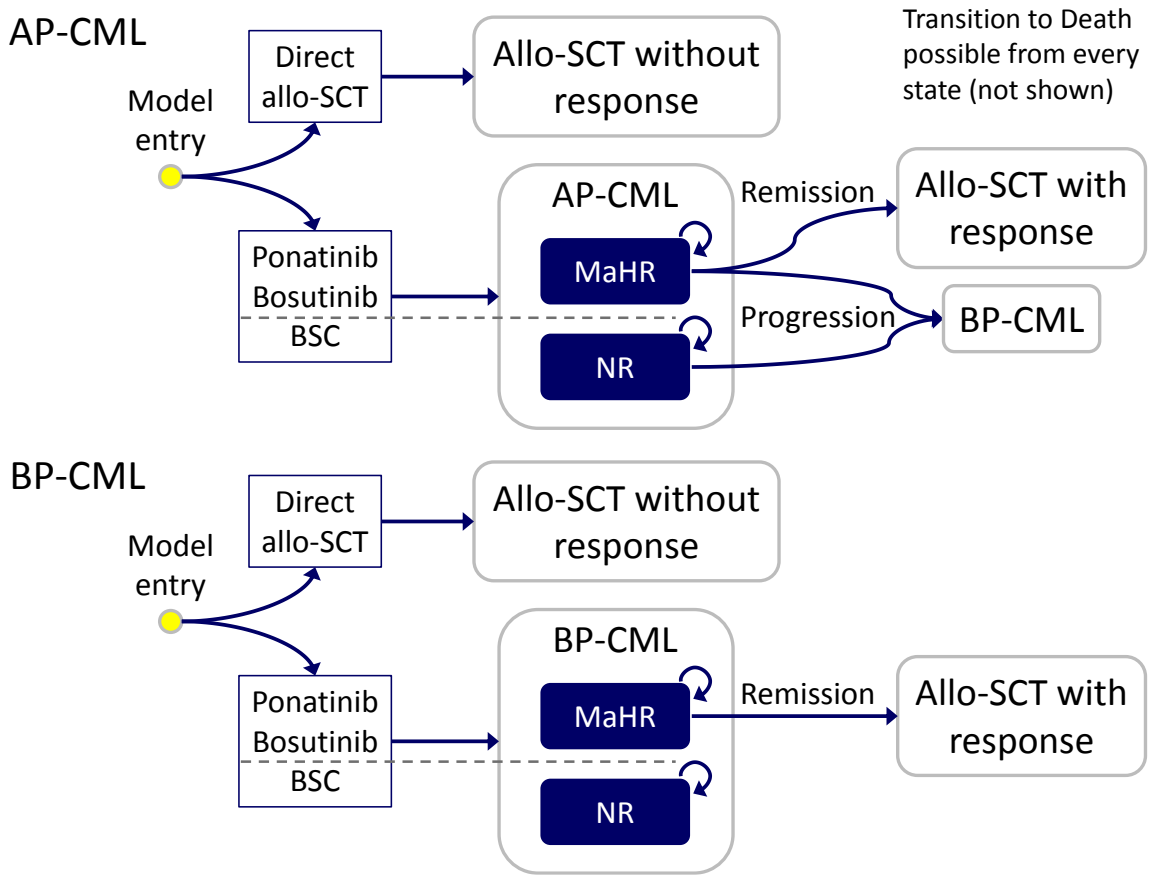
As for the CP-CML model, the AP/BP-CML cost-effectiveness analysis was performed using a Markov model constructed in Microsoft Excel®. Model parameters have been set in accordance with the latest guidance for conducting pharmacoeconomic submissions from NICE.[158]

Within a given time cycle in the Markov model (3 months), a patient can either remain in their present health state, transition to the next state in the respective pathway, or die. Patients enter the model either in AP-CML or BP-CML (Figure 5-17). Those who proceed directly to allo-SCT enter the health state of allo-SCT without response (ie, remission was not induced prior to the procedure). Patients who receive TKI treatment in the AP-CML or BP-CML health states can either achieve a major haematologic response (MaHR; considered a proxy measure for remission) or fail to respond (NR). Among patients initially receiving TKI treatment, only those who achieve a MaHR are considered eligible to receive allo-SCT. Whether or not MaHR is achieved is determined in the first time cycle, which is realistic given that the median time to MaHR in PACE was 3 weeks for patients in AP-CML and 4.1 weeks for patients in BP-CML.[9] It is assumed that patients cannot achieve a MaHR on BSC.

Patients who achieve remission in the first cycle of TKI therapy and receive allo-SCT enter the health state of allo-SCT with response, which is assigned different outcomes than allo-SCT without response, to reflect the improved outcomes associated with being in remission before transplant.

Patients in AP-CML and MaHR may relapse and progress to BP-CML; patients in AP-CML and NR may also progress to BP-CML. As BP-CML is the final health state in progressed disease, no further disease progression is possible for nonresponders in BP-CML. Patients who enter the model in BP-CML may achieve a MaHR on TKI therapy, whereas those who enter the model in AP-CML and subsequently progress to BP-CML cannot subsequently achieve a MaHR because they have already failed to respond to ponatinib or bosutinib while in the AP state.

Figure 5-17. Schematic representation of the AP/BP-CML model health states



Allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; MaHR, major haematologic response; NR, no response.

Note: dashed line indicates that patients receiving BSC cannot achieve MaHR, and thus remain nonresponders; patients receiving ponatinib or bosutinib can either achieve MaHR or be nonresponders.

5.4.1.3 Features and justification of the de novo analysis

Table 5-47 summarises the features of the AP/BP-CML de novo analysis. The chosen values were in accordance with the NICE guide to the methods of technology appraisal.

Table 5-47. Features of the AP/BP-CML de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (maximum of 400 cycles, up to 100 years)	To capture all important differences in costs or outcomes between the technologies being compared[158]
Were health effects measured in QALYs; if not, what was used?	QALY and LYG	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY[164] For completeness, the analysis evaluates incremental LYGs
Discount of 3.5% for utilities and costs	3.5%	3.5% per annum as recommended by NICE[158] Discount rates of 0% and 6% were used in sensitivity analyses
Perspective (NHS/PSS)	NHS/PSS	In accordance with the NICE guide to the methods of technology appraisal,[158] the reference-case CUA adopts the payer perspective for costs

CUA, cost-utility analysis; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life year.

5.4.1.4 Intervention technology and comparators

5.4.1.4.1 Ponatinib

As summarised in Section 5.3.1.5.1 above, ponatinib has marketing authorisation in the EU for treating patients with adult patients with CP-, AP-, or BP-CML, who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.[22] Thus, patients initiating treatment in AP- or BP-CML are eligible for ponatinib as incorporated in the AP/BP-CML model, in which patients who achieve remission on ponatinib receive allo-SCT. See Section 5.3.1.5.1 for further details.

5.4.1.4.2 Comparators

The comparators listed for CML in the NICE scope are bosutinib, allo-SCT, hydroxycarbamide, and interferon alpha; however, this list is not stratified by CML disease stage. Patients with advanced CML who are eligible for ponatinib are assumed to have exhausted TKI treatment with imatinib, nilotinib, and/or dasatinib. The ELN guidelines state that TKI-pretreated patients who have progressed from CP-CML should receive one of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients.[47] As such, the main comparators in the AP/BP-CML analysis are direct allo-SCT, and bosutinib (followed by allo-SCT for patients achieving remission).

Hydroxycarbamide is also incorporated as a direct comparator in the model, where it is considered as BSC to manage patients with advanced disease until death. Since hydroxycarbamide is incapable of significantly modifying the disease course,[244] the model assumes patients receiving BSC cannot achieve MaHR.

Although listed in the NICE scope as a comparator in CML, interferon alpha is not included as a treatment option in the AP/BP-CML model, as there is no evidence of its effectiveness in AP- or BP-CML. Exclusion of interferon alpha was also adopted in the prior bosutinib submission to NICE; the Evidence Review Group recognized this as a reasonable assumption in their report.[224]

5.4.1.5 Treatment continuation rule

The model assumes that patients receiving ponatinib may discontinue treatment if they do not achieve MaHR. Time-on-treatment estimates are used to determine the discontinuation of active treatment with ponatinib, based on data from PACE. Time-on-treatment estimates are also considered for bosutinib, based on Gambacorti-Passerini et al. 2015, which reports the results of the bosutinib phase 1/2 trial for patients with advanced CML (AP/BP).[185] A treatment continuation rule has not been assumed for BSC, which is continued until death, and does not apply to allo-SCT as explained in Section 5.3.1.6.

5.4.1.6 Summary of the de novo analysis

The AP-/BP-CML model characteristics are summarised in Table 5-6.

Table 5-48. Summary of AP-/BP-CML model characteristics

Component	Description
Population	Adults with AP-/BP-CML R/I to imatinib and either dasatinib or nilotinib
Comparators	Bosutinib BSC (hydroxycarbamide) Allo-SCT
Perspective	NHS/PSS
Cycle length	3 months (with half-cycle correction)
Time horizon	Cohort lifetime (maximum of 400 cycles, up to 100 years)
Starting age, years	AP-CML: 54.6 BP-CML: 50.4
Discount rate per annum: costs	3.5%
Discount rate per annum: benefits	3.5%
Outcome measures generated	Cost/QALYs gained Cost/LYG

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life-year; R/I, resistant or intolerant.

5.4.2 Clinical parameters and variables

5.4.2.1 Clinical data sources

5.4.2.1.1 Effectiveness data

5.4.2.1.1.1 Haematologic response

Response to active treatment was modelled to determine OS, PFS, and the transition to allo-SCT. MaHR was assumed as a proxy of disease remission—in other words, the best possible condition for patients to undergo a transplant. As explained in Section 5.4.1.2, MaHR was relevant only for TKI therapy (ie, ponatinib and bosutinib).

MaHR rates for patients with AP- and BP-CML treated with ponatinib were obtained from the most recent PACE study data (Table 5-49).[25] The MaHR rates used in the analysis were based on patients who had received at least two prior TKIs. MaHR was defined as the proportion of patients who achieved a CHR or who had no evidence of leukaemia after initiation of study treatment. Notably, only patients who achieved MaHR on ponatinib were counted as responders; those already in remission at baseline were classified as nonresponders since they only maintained response rather than improved response.

Table 5-49. Haematologic response to ponatinib and bosutinib

	MaHR rate		
	AP-CML	**BP-CML**	**Source**
Ponatinib	55.7%	31.7%	PACE[25]
Bosutinib*	29.2%	4.3%	Gambacorti-Passerini et al. 2015[185]

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; MaHR, major haematologic response; OHR, overall haematologic response rate.
*OHR applied for bosutinib.

MaHR rate reported by Gambacorti-Passerini et al. 2015 includes both achieved MaHR and previously achieved MaHR maintained from baseline.[185] Therefore, OHR rate was applied for bosutinib in the model. The rationale for this choice is that the definitions of MaHR and OHR largely overlap, though the more stringent criteria required for MaHR make it more difficult to achieve. MaHR is defined as CHR + no evidence of leukaemia. OHR is defined as CHR + no evidence of leukaemia + minor haematologic response + return to CP (if applicable).[9, 185]

MaHR rates for bosutinib (Table 5-49) were derived from Gambacorti-Passerini et al. 2015.[185] As was the case for patients on ponatinib, patients receiving bosutinib in this study who were already in remission at baseline and maintained response were not considered to be responders.

5.4.2.1.1.2 Overall survival

5.4.2.1.1.2.1 TKI therapy

OS data for patients with AP-CML and BP-CML who had or had not reached MaHR were derived from the PACE study data. For patients who achieved MaHR, mortality observed on ponatinib treatment in the PACE trial was applied in the first cycle only, as patients in the model reaching this response stop ponatinib treatment and proceed to allo-SCT within the first cycle. It was assumed that OS would depend on haematologic response, independently of which TKI yielded MaHR; therefore, the same function based on PACE was applied to both ponatinib and bosutinib. A parametric survival analysis was performed on PACE patient-level data as described in Section 5.2.1.1. Five parametric models were estimated (Weibull, Gompertz, exponential, log-normal, and log-logistic), with a dummy variable for MaHR included as covariate with NR modelled as the baseline. For both AP- and BP-CML, best fit was provided by the log-normal function for OS without MaHR (Figure 5-18).

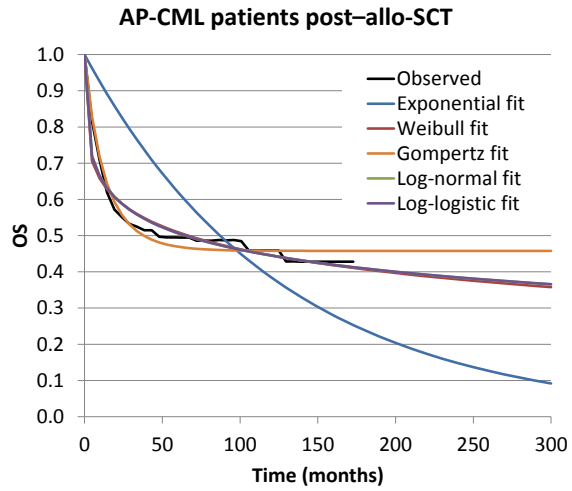
Figure 5-18. Observed (source: PACE[25]) and fitted OS data for AP-CML and BP-CML patients without MaHR

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; MaHR, major haematologic response; OS, overall survival.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.[25]

5.4.2.1.1.2.2 Allo-SCT

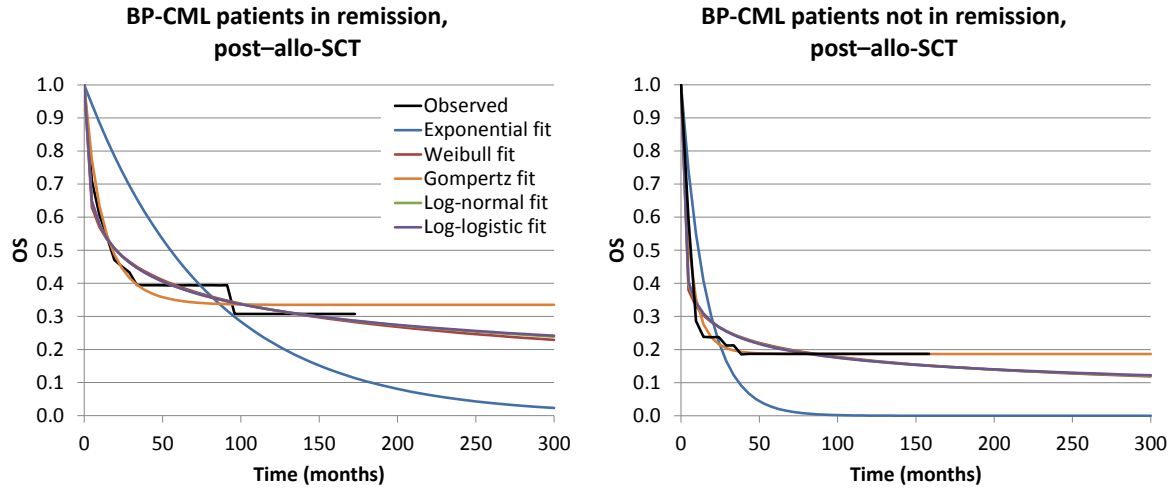
Data on OS of CML patients after allo-SCT were obtained from a study by Radich (2010).[267] This publication reported long-term OS data post–allo-SCT stratified by disease phase from patients receiving allografts at the Fred Hutchinson Cancer Research Center from 1995 to 2010. Survival curves for patients with AP-CML (125 patients), BP-CML in remission (62 patients), and BP-CML without remission (44 patients) were provided in the publication. The three curves were digitized and fitted with parametric functions as described in Section 5.2.1.2 (Figure 5-19 and Figure 5-20). The parametric functions that best fit the data were the Gompertz and the log-logistic functions. Application of these functions (Gompertz and log-logistic), however, resulted in unrealistic survival estimates. With a more credible (and conservative) mortality projection, the exponential function was selected for inclusion in the analysis.

Figure 5-19. Observed (source: Radich 2010[267]) and fitted OS data for AP-CML patients post–allo-SCT



Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; CML, chronic myeloid leukaemia; OS, overall survival.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

Figure 5-20. Observed (source: Radich 2010[267]) and fitted OS data for BP-CML patients post–allo-SCT



Allo-SCT, allogeneic haematopoietic stem cell transplantation; BP, blast phase; CML, chronic myeloid leukaemia; OS, overall survival.

In the BP model, survival data from the BP-CML cohort in remission, as described by Radich, were used to inform the probability of death after allo-SCT in patients initially treated with ponatinib or bosutinib (ie, those who enter the model in the BP-CML health state). Survival data from the Radich study describing BP-CML patients not in remission were used to inform the probability of death after direct allo-SCT (ie, for patients who enter the model in the SCT without response health state).

Radich did not report survival after allo-SCT in AP-CML patients by their initial remission state. Given the long life expectancy associated with the AP-CML cohort, it was assumed that the majority of patients were in remission. As a consequence, those data were used to inform the probability of death post–allo-SCT following active treatment in the AP model. To estimate the probability of death for the direct allo-SCT arm in the AP model, the two BP-CML curves were compared, and the obtained ratio was applied to derive a hypothetical KM curve for AP-CML

patients who received allo-SCT without prior remission. This KM curve was fitted with an exponential function.

Considering that the cohort starting age is 54.6 years in the AP model and 50.4 years in the BP model, and that allo-SCT is usually offered to younger patients, an adjustment factor was applied to all of the survival functions to ensure that the probability of dying due to allo-SCT in each cycle is no lower than the mortality risk in the general population.

5.4.2.1.1.2.3 BSC (hydroxycarbamide)

Long-term outcomes in AP-CML and BP-CML patients treated with BSC were modelled based on survival data reported by Kantarjian et al.[29] from a study of 420 patients with CML who had previously failed imatinib, as described above in Section 5.3.2.1.3. Although not explicitly defined in the publication for the AP- and BP-CML groups, other therapies in the CP-CML group included hydroxycarbamide. As such, the OS KM plots for the AP- and BP-CML groups treated with "other therapy" were used to derive survival functions as described in Section 5.2.1.2. As reported in Section 5.3.2.1.3, the log-normal distribution was selected for OS in AP-CML and the log-logistic distribution was selected for OS in BP-CML.

5.4.2.1.1.3 Progression-free survival

5.4.2.1.1.3.1 TKI therapy

The probability of progression from AP-CML to BP-CML was derived from PACE study data for the subgroups of patients who had (first cycle only) and had not achieved MaHR at 6 months. A parametric survival analysis on PACE patient-level data was performed. The best fit for patients who had and had not achieved MaHR was provided by the log-normal function (Figure 5-21).

Figure 5-21. Observed (source: PACE[25]) and fitted PFS data for AP-CML patients with and without MaHR

AP, accelerated phase; CML, chronic myeloid leukaemia; MaHR, major haematologic response; PFS, progression-free survival.

5.4.2.1.1.3.2 BSC (hydroxycarbamide)

No data were available to inform the model on PFS for BSC in AP-CML. In the absence of data, a mean PFS of 9.16 months was assumed, calculated as the difference between the mean OS in AP and the mean OS in BP as derived from Kantarjian et al. (2007).[29] The mean OS values for AP and BP were calculated by fitting parametric functions to the published data, as described in Section 5.3.2.1.3.

5.4.2.1.1.4 Time to response

Time to response is considered in the model. In the PACE study, the median time to MaHR on ponatinib was 3 weeks (AP-CML) and 4 weeks (BP-CML) (Cortes et al. 2013).[9] In the model, patients are allocated to response categories at the start of the simulation. Patients who achieve MaHR in AP or BP will proceed to allo-SCT within the first cycle.

5.4.2.1.1.5 Time on treatment

5.4.2.1.1.5.1 TKI therapy

After the first cycle, patients with a haematologic response undergo allo-SCT. For patients who do not achieve MaHR (ie, nonresponders), time-on-treatment estimates for ponatinib are applied. The probability of discontinuing active treatment in the AP-CML and BP-CML health states was derived from specific time-on-treatment data obtained from the PACE clinical trial data.

Time-on-treatment with ponatinib in patients with AP-CML and BP-CML was modelled using on the PACE study data. Tabulated survivor functions based on to parametric survival analysis of patient-level data provide extrapolation beyond the observed follow-up period as described in Section 5.2.1.1. The log-normal function provided the best fit in AP-CML, while the log-logistic function provided the best fit in BP-CML (Figure 5-22). However, to be consistent with the bosutinib data, the exponential fit was selected for time-on-treatment with ponatinib in both AP- and BP-CML.

Figure 5-22. Observed (source: PACE[25]) and fitted time-on-treatment data for AP- and BP-CML patients treated with ponatinib

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia.

For bosutinib, time-on-treatment was obtained by extrapolating an exponential curve from the median duration of treatment in AP-CML and in BP-CML reported by Gambacorti-Passerini et al. 2015:[185] 10.2 months for patients in AP-CML and 2.8 months for patients in BP-CML.

5.4.2.1.1.5.2 BSC (hydroxycarbamide)

Patients receiving BSC are assumed to stay on treatment until death.

5.4.2.2 Transition probabilities

Transition probabilities used in the AP/BP-CML model are described below. All probabilities are derived from survivor functions extrapolated from clinical data. The time-dependent probabilities of transitioning between states were in general estimated as 1 minus the ratio of the survivor function at the end of the cycle to the survivor function at the beginning of the cycle.

- **Death** (from AP-CML and BP-CML states). Four survivor functions (for OS in AP-CML and in BP-CML with [first-cycle only] and without MaHR, respectively) were obtained through parametric survival analysis on patient-level data from the PACE study. These

functions were applied to both ponatinib and bosutinib. For BSC, as in the CP-CML model, two survivor functions (for AP-CML and BP-CML, respectively) were extrapolated through parametric fitting from published OS curves in Kantarjian et al. 2007.[29]

- **Death** (from allo-SCT with and without response states). Four survivor functions (for OS after allo-SCT in AP-CML and in BP-CML, with and without response, respectively) were extrapolated through parametric fitting from published OS curves in Radich 2010.[267] The curves reported in the original paper relate BP-CML with and without remission and AP-CML. We assumed the AP-CML curve applied to patients in remission, and derived the curve for AP-CML patients without remission from the former, applying the ratio of OS in patients in remission vs OS of those in remission calculated from the BP-CML curves. To avoid unrealistic estimate of the OS, the model controls at each cycle that the death probability derived from the allo-SCT literature is not lower than the death probability of the general population with the corresponding age.
- **Progression to BP-CML**. ie, transition from the AP-CML state to BP-CML. Two survivor functions (for PFS in AP-CML with and without MaHR, respectively) were obtained through parametric survival analysis on patient-level data from the PACE study. These functions were applied to both ponatinib and bosutinib, in the assumption that PFS is a function of the response achieved and not of the specific TKI treatment. For BSC, as in the CP-CML model, the mean PFS for patients in AP-CML of 9.16 months was estimated as the difference from the mean OS in AP-CML and BP-CML calculated with the survivor functions extrapolated from Kantarjian et al. (2007).[29] Subsequently, a survivor function, depicting the fraction of the cohort remaining free from progression to BP-CML over time, was calculated by extrapolating an exponential curve from the mean PFS. Since death is normally considered as a censoring event when presenting PFS data, the actual probabilities used in the model at each cycle were obtained by subtracting the probability of death from progression probability at the same cycle.
- **Discontinuation of TKI treatment.** The probability of discontinuing the active treatment before progression or death is applied to ponatinib and to bosutinib. This probability does not directly determine a state transition in the Markov model, but rather is used to accurately estimate treatment costs. The time-on-treatment functions (depicting the fraction of the cohort which remains on treatment over time) were obtained for ponatinib through parametric survival analysis on patient-level data from the PACE study, and for bosutinib by extrapolating an exponential curve from the median duration of treatment in AP-CML and in BP-CML reported in the literature.

5.4.2.3 Evidence that (transition) probabilities may change over time for the treatment effect, condition or disease

The change over time of transition probabilities was captured in all models and is described in the previous section.

5.4.2.4 Clinical expert assessment of the applicability or approximation of clinical parameters

The core assumption that ponatinib would mainly be used in patients with AP-/BP-CML in order to achieve remission and proceed, for patients in remission, to allo-SCT, was validated by the clinical expert (see 5.3.4).

5.4.3 Measurement and valuation of health effects

Measurement and valuation of health effects in the AP/BP-CML model are fully aligned with the CP-CML model; please see Section 5.3.3 for details.

5.4.4 Cost and healthcare resource use identification, measurement and valuation

5.4.4.1 Parameters used to estimate cost

All parameters used to estimate cost in the AP/BP-CML model are fully aligned with the CP-CML model as previously presented in Table 5-18 of Section 5.3.4.4.

Resource identification, measurement and valuation studies

5.4.4.2 Identification of cost and healthcare resource use data

Please refer to the CP-CML economic analysis (Section 5.3.4.2) for detailed descriptions of how resource use and costs were identified and measured.

5.4.4.3 Appropriateness of NHS reference costs for costing

Please refer to the CP-CML economic analysis (Section 5.3.4.3).

5.4.4.4 Clinical expert assessment of the applicability or approximation of cost and healthcare resource use values

Please refer to the CP-CML economic analysis (Section 5.3.4.4).

Intervention and comparators' costs and resource use

5.4.4.5 Pharmacologic therapies

5.4.4.5.1 Drug dosing

Dosages for ponatinib, bosutinib, and hydroxycarbamide used in the AP/BP model are as presented in Section 5.3.4.5.1 for the CP-CML model.

5.4.4.5.2 Relative dose intensity: ponatinib

RDI was applied to ponatinib dosages in the AP/BP-CML model following the considerations in the CP-CML model as explained in Section 5.3.4.5.2. PACE data (data cut-off: 3 August 2015) for patients in AP- and BP-CML are utilised in the AP/BP-CML model, as shown in Table 5-50.

Table 5-50. RDI estimates used in the AP/BP-CML economic model for ponatinib

Ponatinib dose (mg per day)	Proportion of days on treatment	
	AP-CML	BP-CML
0	[redacted]	[redacted]
15	[redacted]	[redacted]
30	[redacted]	[redacted]
45	[redacted]	[redacted]

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; RDI, relative dose intensity.

5.4.4.5.3 Relative dose intensity: bosutinib

In the absence of data on mean dose intensity for bosutinib, the median dose intensity reported in Khoury et al.,[8] 95.6%, was used as a proxy for bosutinib RDI.

5.4.4.5.4 Relative dose intensity: hydroxycarbamide

As for the CP-CML model, in the absence of data for hydroxycarbamide, RDI was assumed to be 100% in the AP/BP-CML model.

5.4.4.5.5 Drug acquisition costs

Drug unit prices for ponatinib, bosutinib, and hydroxycarbamide used in the AP/BP model are as presented in Section 5.3.4.5.5 for the CP-CML model.

5.4.4.6 Allo-SCT

Initial procedure costs and follow-up costs for allo-SCT in the AP/BP-CML model are the same as those in the CP-CML model (see Section 5.3.4.6). As a simplifying assumption for the AP/BP-

CML model in the absence of data in this patient population, 100, 100% of patients who achieve MaHR in their first cycle of TKI therapy receive allo-SCT. Since the AP/BP-CML model does not incorporate relapse after allo-SCT, there are no associated treatment costs for post–allo-SCT relapse.

5.4.4.7 Monitoring and follow-up

Monitoring and follow-up healthcare resource use and associated costs in the AP/BP-CML model are identical to those applied in the CP-CML model for patients who progress to AP/BP-CML, as presented above in Table 5-23. These parameters yield per-cycle monitoring and follow-up costs of £2,648 in AP-CML and £20,319 in BP-CML.

Health-state unit costs and resource use

5.4.4.8 Costs included in each health state

Not applicable. See Section 5.3.4.9 of the CP-CML economic section.

Adverse reaction unit costs and resource use

5.4.4.9 Costs and resource use for each adverse reaction

Costs associated with AEs were modelled for TKI therapy only, in the absence of AE data for hydroxycarbamide. The AE rates associated with ponatinib and bosutinib in AP- and BP-CML, and associated average costs per patient, are summarised in Table 5-51. As in the CP-CML model, SAEs were applied only to ponatinib in the absence of equivalent long-term bosutinib safety data (see Section 5.3.4.10). Cost estimates were taken from NHS reference costs and tariffs.

Table 5-51. AE rates and costs applied in the AP/BP-CML model (sources: PACE CSR[25]; Gambacorti-Passerini et al. 2015[185]) and associated costs

	Ponatinib		Bosutinib			
Adverse event	**AP-CML**	**BP-CML**	**AP-CML**	**BP-CML**	**Unit cost, £**	**Sources for costs**
Anaemia	[redacted]	[redacted]	32.91%	20.31%	1,827.13	NHS 2015/16 Enhanced Tariff Option
Leukocytopaenia	[redacted]	[redacted]	6.33%	18.75%	633.26	Assumption: same as neutropaenia
Lipase increased	[redacted]	[redacted]	–	–	721.00	Assumption: 1 day in hospital
Neutropaenia	[redacted]	[redacted]	17.72%	25.00%	633.26	NHS Reference Costs 2014 to 2015
Pancreatitis	[redacted]	[redacted]	–	–	1,121.98	NHS Reference Costs 2014 to 2015
ALT elevation	[redacted]	[redacted]	7.59%	–	1,121.98	NHS Reference Costs 2014 to 2015
Thrombocytopaenia	[redacted]	[redacted]	44.30%	35.94%	421.74	NHS Reference Costs 2014 to 2015
Serious adverse events						
Cardiovascular event	[redacted]	[redacted]	–	–	2,357.00	NHS 2015/16 Enhanced Tariff Option
Cerebrovascular event	[redacted]	[redacted]	–	–	2,962.00	NHS 2015/16 Enhanced Tariff Option
Peripheral vascular event	[redacted]	[redacted]	–	–	2,872.00	NHS 2015/16 Enhanced Tariff Option
Venous thromboembolism event	[redacted]	[redacted]	–	–	552.00	NHS 2015/16 Enhanced Tariff Option

AE, adverse event; ALT, alanine aminotransferase.

Note: only AEs applied in the AP/BP-CML model are included in this table.

Miscellaneous unit costs and resource use

5.4.4.10 End-of-life care

All parameters for end-of-life care in the AP/BP-CML model were identical to those in the CP-CML model, as presented in Section 5.3.4.11, and thus yielded the same average end-of-life care cost of £5,765.76.

5.4.5 Summary of base-case de novo analysis inputs and assumptions

5.4.5.1 Summary of base-case de novo analysis inputs

Table 5-52 summarises the variables applied in the economic model. Uncertainty regarding the parameter values was addressed via sensitivity analyses, as described below in Section 5.4.7.

Table 5-52. Summary of variables applied in the economic model

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Lower value	Upper value	Reference to section	Source
Clinical Inputs						
MaHR rate in AP	(Table 5-49)					
Bosutinib*	0.29167	–	0.23450	0.34883	5.4.2.1.1.1	Gambacorti-Passerini et al. 2015
Ponatinib	0.55700	–	0.44783	0.66617	5.4.2.1.1.1	PACE study CSR
MaHR rate in BP		–				
Bosutinib*	0.04348	–	0.03496	0.05200	5.4.2.1.1.1	Gambacorti-Passerini et al. 2015
Ponatinib	0.31670	–	0.25463	0.37877	5.4.2.1.1.1	Dalziel et al. 2004
Mean PFS with BSC in AP phase, months	9.1600 (Figure 5-9)	–	7.36464	10.95536	5.3.2.1.3	Derived from Kantarjian et al. 2007
Overall survival						
OS in AP	– (Figure 5-18)	Log-normal	–	–	5.4.2.1.1.2.1	PACE study CSR
OS in BP	– (Figure 5-18)	Log-normal	–	–	5.4.2.1.1.2.1	PACE study CSR
OS post–allo-SCT in AP with remission	– (Figure 5-19)	Exponential	–	–	5.4.2.1.1.2.2	Radich 2010
OS post–allo-SCT in AP without remission	– (Figure 5-19)	Exponential	–	–	5.4.2.1.1.2.2	Derived from Radich 2010
OS post–allo-SCT in BP with remission	– (Figure 5-20)	Exponential	–	–	5.4.2.1.1.2.2	Radich 2010
OS post–allo-SCT in BP without remission	– (Figure 5-20)	Exponential	–	–	5.4.2.1.1.2.2	Radich 2010
Progression-free survival						
PFS in AP with TKI therapy	– (Figure 5-21)	Log-normal	–	–	5.4.2.1.1.3.1	PACE study CSR
PFS in AP with BSC, months	9.160 (–)	–	7.36464	10.95536	5.4.2.1.1.3.2	Kantarjian et al. 2007
Time-on-treatment, months		–				
Bosutinib in AP, median	10.2 (–)	–	8.20080	12.19920	5.4.2.1.1.5.1	Gambacorti-Passerini et al. 2015
Bosutinib in BP, median	2.8 (–)	–	2.25120	3.34880	5.4.2.1.1.5.1	Gambacorti-Passerini et al. 2015

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Lower value	Upper value	Reference to section	Source
Ponatinib in AP	– (Figure 5-22)	Exponential	–	–	5.4.2.1.1.5.1	PACE CSR
Ponatinib in BP	– (Figure 5-22)	Exponential	–	–	5.4.2.1.1.5.1	PACE CSR
Economic Inputs						
Adverse event unit cost	(Table 5-24)					
ALT elevation	1121.98	–	902.07	1341.89	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Anaemia	1827.13	–	1469.01	2185.25	5.3.4.10	NHS Reference Costs 2014 to 2015
Cardiovascular event	2357.00	–	1895.03	2818.97	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Cerebrovascular event	2962.00	–	2381.45	3542.55	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Leukocytopaenia	633.26	–	509.14	757.38	5.3.4.10	NHS Reference Costs 2014 to 2015
Lipase increased	721.00	–	579.68	862.32	5.3.4.10	NHS Reference Costs 2014 to 2015
Neutropaenia	633.26	–	509.14	757.38	5.3.4.10	NHS Reference Costs 2014 to 2015
Pancreatitis	1121.98	–	902.07	1341.89	5.3.4.10	NHS Reference Costs 2014 to 2015
Peripheral vascular event	2872.00	–	2309.09	3434.91	5.3.4.10	NHS 2015/16 Enhanced Tariff Option
Thrombocytopaenia	421.74	–	339.08	504.40	5.3.4.10	NHS Reference Costs 2014 to 2015
Venous thromboembolism	552.00	–	443.81	660.19	5.3.4.10	NHS 2015/16 Enhanced Tariff
Allo-SCT initial cost, £	60092.13 (–)	–	48314.08	71870.19	5.3.4.6	UK Stem Cell Strategy Oversight Committee
Cost of community palliative care per day, £	158.23 (Table 5-25)	–	127.21	189.24	5.3.4.11	Marie Curie Cancer Care
Cost of palliative care in hospital per day, £	463.77 (Table 5-25)	–	372.87	554.66	5.3.4.11	Marie Curie Cancer Care
Discount rate costs	3.50% (Table 5-47)	–	0.00%	6.00%	–	NICE
Discount rate outcomes	3.50% (Table 5-47	–	0.00%	6.00%	–	NICE
EOL hospice days	17.40 (Table 5-25)	–	13.99	20.81	5.3.4.11	UK Survey, Q13
EOL hospital days	21.50 (Table 5-25)	–	17.29	25.71	5.3.4.11	UK Survey, Q13
EOL, proportion being treated in hospice	0.23 (Table 5-25)	–	0.04	0.50	5.3.4.11	UK Survey, Q13
EOL, proportion being treated in hospital	0.51 (Table 5-25)	–	0.01	0.90	5.3.4.11	UK Survey, Q13
Per-cycle cost, £						
Bosutinib	10714.40 (–)	–	8614.38	12814.42	–	–
Hydroxycarbamide	38.24 (–)	–	30.75	45.74	–	–
Ponatinib in AP	[redacted]	–	[redacted]	[redacted]	–	–
Ponatinib in BP	[redacted]	–	[redacted]	[redacted]	–	–

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Lower value	Upper value	Reference to section	Source
CV monitoring with ponatinib	75.19 (–)	–	60.45	89.93	–	Assumed 0.5 visits per cycle; same cost as haematologist visit
Follow-up after allo-SCT, y1	12214.71 (Table 5-22)	–	9820.63	14608.79	5.3.4.6.1	UK Stem Cell Strategy Oversight Committee
Follow-up after allo-SCT, y2	3518.25 (Table 5-22)	–	2828.67	4207.83	5.3.4.6.1	UK Stem Cell Strategy Oversight Committee
Follow-up after allo-SCT, y3+	420.00 (Table 5-22)	–	337.68	502.32	5.3.4.6.1	Bosutinib NICE HTA
Treatment post discontinuation	38.24 (–)	–	30.75	45.74	5.3.4.5.5	Assumed BSC is hydroxycarbamide
Per-cycle resource use with:	(Table 5-24)					
AP/BP: blood chemistry	3.15	–	0.00	6.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: blood film exam	2.19	–	0.00	6.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: blood transfusion	1.98	–	0.00	6.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: bone marrow aspiration	0.30	–	0.00	0.99	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: complete blood count	4.38	–	1.62	6.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: cytochemistry analysis	0.12	–	0.00	0.99	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: cytogenetic analysis	0.90	–	0.00	3.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: donor lymphocyte transfusion	0.00	–	0.00	0.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: FISH	0.13	–	0.00	3.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: flow cytometry	0.45	–	0.00	2.16	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: haematologist-led outpatient visit	3.63	–	1.62	6.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: kinase domain mutation analysis	0.13	–	0.00	0.50	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: nurse-led outpatient visit	0.51	–	0.00	6.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: PCR	1.68	–	0.00	3.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP/BP: platelet transfusion	0.30	–	0.00	3.00	5.3.4.8	UK Survey, Q8 (AP resources assumed)
AP: hospital days	2.13	–	0.00	12.51	5.3.4.8	UK Survey, Q8 (general ward+ ICU)
BP: hospital days	26.64	–	0.90	87.00	5.3.4.8	UK Survey, Q10 (general ward+ ICU)
Resource unit cost, £	(Table 5-23)	–				
Blood chemistry	1.19	–	0.96	1.42	5.3.4.8	NHS Reference Costs 2014 to 2015
Blood film exam	3.01	–	2.42	3.60	5.3.4.8	NHS Reference Costs 2014 to 2015
Blood transfusion	121.85	–	97.97	145.73	5.3.4.8	NHS Blood and Transplant Price List 2014/15

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Lower value	Upper value	Reference to section	Source
Bone marrow aspiration	517.50	–	416.07	618.93	5.3.4.8	NHS Reference Costs 2014 to 2015
Complete blood count	3.01	–	2.42	3.60	5.3.4.8	NHS Reference Costs 2014 to 2015
Cytochemistry analysis	6.99	–	5.62	8.36	5.3.4.8	NHS Reference Costs 2014 to 2015
Cytogenetic analysis	6.99	–	5.62	8.36	5.3.4.8	NHS Reference Costs 2014 to 2015
Donor lymphocyte transfusion	193.15	–	155.29	231.01	5.3.4.8	Assumed same as platelet transfusion
FISH	6.99	–	5.62	8.36	5.3.4.8	NHS Reference Costs 2014 to 2015
Flow Cytometry	6.99	–	5.62	8.36	5.3.4.8	NHS Reference Costs 2014 to 2015
Haematologist-led outpatient visit	150.38	–	120.91	179.85	5.3.4.8	NHS Reference Costs 2014 to 2015
Hospital days	721.00	–	579.68	862.32	5.3.4.8	NHS Reference Costs 2014 to 2015
Kinase domain mutation analysis	6.99	–	5.62	8.36	5.3.4.8	NHS Reference Costs 2014 to 2015
Nurse-led outpatient visit	66.42	–	53.40	79.44	5.3.4.8	NHS Blood and Transplant Price List 2014/15
PCR	25.00	–	20.10	29.90	5.3.4.8	Szczepura et al. 2006
Platelet transfusion	193.15	–	155.29	231.01	5.3.4.8	NHS Blood and Transplant Price List 2014/15
HRQoL Inputs / AEs						
Cumulative incidence, AP	(Table 5-51)					
ALT elevation bosutinib	[redacted]		[redacted]	[redacted]	5.4.4.9	Gambacorti-Passerini et al. 2015
Anaemia bosutinib	0.32911	–	0.26461	0.39362	5.4.4.9	Gambacorti-Passerini et al. 2015
Anaemia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Leukocytopaenia bosutinib	0.06329	–	0.05089	0.07570	5.4.4.9	PACE study CSR
Leukocytopaenia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Lipase increased ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Neutropaenia bosutinib	0.17722	–	0.14248	0.21195	5.4.4.9	Gambacorti-Passerini et al. 2015
Neutropaenia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Pancreatitis ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Thrombocytopaenia bosutinib	0.44304	–	0.35620	0.52987	5.4.4.9	Gambacorti-Passerini et al. 2015
Thrombocytopaenia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Cumulative incidence, BP	(Table 5-51)					
Anaemia bosutinib	0.20313	–	0.16331	0.24294	5.4.4.9	Gambacorti-Passerini et al. 2015
Anaemia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Leukocytopaenia bosutinib	0.18750	–	0.15075	0.22425	5.4.4.9	PACE study CSR

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Lower value	Upper value	Reference to section	Source
Lipase increased ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Neutropaenia bosutinib	0.25000	–	0.20100	0.29900	5.4.4.9	Gambacorti-Passerini et al. 2015
Neutropaenia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Thrombocytopaenia bosutinib	0.35938	–	0.28894	0.42981	5.4.4.9	Gambacorti-Passerini et al. 2015
Thrombocytopaenia ponatinib	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Per-cycle probability (ponatinib only)	(Table 5-51)					
Cardiovascular event, AP	[redacted]	–	[redacted]	[redacted]	5.4.4.9	PACE study CSR
Cardiovascular event, BP	[redacted]	–	[redacted]	[redacted]	5.4.4.9	
Cerebrovascular event, AP	[redacted]	–	[redacted]	[redacted]	5.4.4.9	
Peripheral vascular event, AP	[redacted]	–	[redacted]	[redacted]	5.4.4.9	
Peripheral vascular event, BP	[redacted]	–	[redacted]	[redacted]	5.4.4.9	
Venous thromboembolism event, AP	[redacted]	–	[redacted]	[redacted]	5.4.4.9	
Population norm utility	(Table 5-13)					
Females <25 years	0.94000	–	0.75576	1.00000	5.3.3.7.1	Kind et al. 1999
Females 25-34 years	0.93000	–	0.74772	1.00000	5.3.3.7.1	Kind et al. 1999
Females 35-44 years	0.91000	–	0.73164	1.00000	5.3.3.7.1	Kind et al. 1999
Females 45-54 years	0.85000	–	0.68340	1.00000	5.3.3.7.1	Kind et al. 1999
Females 55-64 years	0.81000	–	0.65124	0.96876	5.3.3.7.1	Kind et al. 1999
Females 65-74 years	0.78000	–	0.62712	0.93288	5.3.3.7.1	Kind et al. 1999
Females ≥75 years	0.71000	–	0.57084	0.84916	5.3.3.7.1	Kind et al. 1999
Males <25 years	0.94000	–	0.75576	1.00000	5.3.3.7.1	Kind et al. 1999
Males 25-34 years	0.93000	–	0.74772	1.00000	5.3.3.7.1	Kind et al. 1999
Males 35-44 years	0.91000	–	0.73164	1.00000	5.3.3.7.1	Kind et al. 1999
Males 45-54 years	0.84000	–	0.67536	1.00000	5.3.3.7.1	Kind et al. 1999
Males 55-64 years	0.78000	–	0.62712	0.93288	5.3.3.7.1	Kind et al. 1999
Males 65-74 years	0.78000	–	0.62712	0.93288	5.3.3.7.1	Kind et al. 1999
Males ≥75 years	0.75000	–	0.60300	0.89700	5.3.3.7.1	Kind et al. 1999
Utility	(Table 5-14 and Table 5-16)					
During an AE	0.52000	–	0.46000	0.58000	5.3.3.7.2.1	Szabo et al. 2010

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Lower value	Upper value	Reference to section	Source
In AP	0.53000	–	0.48000	0.58000	5.3.3.7.2.1	Szabo et al. 2010
In BP	0.29000	–	0.24000	0.33000	5.3.3.7.2.1	Szabo et al. 2010
In cycle 1 after allo-SCT	0.55000	–	0.44220	0.65780	5.3.3.7.2.2	van Agthoven et al. 2001 population norms
In cycle 2 after allo-SCT	0.63000	–	0.50652	0.75348	5.3.3.7.2.2	Assumption: midpoint of peri-operative and long-term estimate
In cycle 3 after allo-SCT	0.71000	–	0.57084	0.84916	5.3.3.7.2.2	Loveman et al. 2012, population norms
Post-relapse after allo-SCT	0.58520	–	0.47050	0.69990	5.3.3.7.2.2	Kantarjian et al. 2002 and Olavarria et al. 2003

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AE, adverse event; ALT, alanine aminotransferase; AP, accelerated phase; BP, blast phase; CSR, clinical study report; EOL, end of life; FISH, fluorescence in situ hybridization; ICU, intensive care unit; MaHR, major haematologic response; OS, overall survival; PFS, progression-free survival; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.
*OHR for bosutinib was used as a proxy for MaHR; the definitions of MaHR and OHR largely overlap, though the more stringent criteria required for MaHR make it more difficult to achieve (MaHR is defined as CHR + NEL whereas OHR is defined as CHR + NEL + minor haematologic response + return to CP [if applicable]).[9, 185]

5.4.5.2 Assumptions

Table 5-53 summarises the main assumptions in the economic analysis.

Table 5-53. Summary of main assumptions and justifications in the AP-/BP-CML model

Assumption	Justification
Patients who achieve a MaHR do so in the first Markov time cycle	Median time to MaHR in PACE was 3 weeks for patients in AP-CML and 4.1 weeks for patients in BP-CML[9]
All patients who achieve a MaHR proceed to allo-SCT	ELN guidelines recommend TKI-pretreated patients who have progressed from CP-CML should receive one of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients[47]
Patients receiving BSC (hydroxycarbamide) do not achieve a MaHR	It is established that hydroxycarbamide does not significantly influence the disease course[244]
The cost of ponatinib is calculated with the % of time on different doses, from the PACE study	The unit pricing of ponatinib is not linear with dose, so the relative-dose intensity approach is unfeasible. Moreover for other drugs that also don't have linear unit pricing we conservatively assume that the cost is determined by the package that yields the lowest price/mg
Time-on-treatment for ponatinib is simulated with an exponential function, regardless of the function providing the best fit in the parametric survival analysis	This assumption was adopted because selecting the best-fit function would have introduced bias against ponatinib given that available time-on-treatment data for bosutinib are median values, which necessitate adopting an exponential function
OS with allo-SCT is simulated with an exponential function regardless of the goodness of the fit of other functions	Based on the plausibility of the extrapolated portion of the curve (the other functions conferred an implausible OS)
Patients with progressed CML who receive allo-SCT are assumed to be in one of two health states: in remission or relapsed	Based on a survey of clinical experts in the UK[48]

Assumption	Justification
PACE OS and PFS data is applied to bosutinib	The relationship between MaHR and OS/PFS is independent of the drug used
The rate of AEs is applied to the first cycle only on the assumption that such events will happen sooner rather than later	Common practice; in line with recent oncology models
AE rates for hydroxycarbamide set to zero	Absence of AE information for hydroxycarbamide
AE rates for allo-SCT set to zero	Associated costs would be absorbed into the follow-up costs for allo-SCT
For bosutinib, hydroxycarbamide, and allo-SCT, the rates of SAEs (cardiovascular, cerebrovascular, peripheral vascular, and venous thromboembolism events) were set to 0%	In the absence of equivalent long-term data for bosutinib, the assumption was that any mortality effects would be captured in the background population mortality rate
The model incorporates a 21.5-day inpatient stay immediately before death for 51.5% of patients assumed to be treated in hospital and a 17.4-day hospice stay for the 23.1% of patients assumed to be treated in a hospice; the remaining patients were assumed to die at home	Based on a survey of clinical experts in the UK[48]
Drug administration costs were set to zero	It is assumed that treatments administered orally require no drug administration costs
Utility decrement associated with allo-SCT in model cycle 2 is the midpoint of peri-operative and long-term estimate	In the absence of data, the best estimate for model cycle 2 was the midpoint of the peri-operative period by van Agthoven et al. 2001,[257] and the long-term period by Loveman et al. 2012[168]

2G, second-generation; AE, adverse event; allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; CP, chronic phase; ELN, European LeukemiaNet; MaHR, major haematologic response; NR, no response; OS, overall survival; TKI, tyrosine kinase inhibitor.

5.4.6 Base-case results

5.4.6.1 Results of the analysis

Sections 5.3.6.2 to 5.3.6.6 provide the results for the de novo base-case analysis.

Base-case incremental cost effectiveness analysis results

5.4.6.2 Cost-effectiveness

The incremental cost-effectiveness ratio (ICER) results for ponatinib compared with each comparator in terms of LYG and QALYs, from the NHS/PSS direct medical perspective (ie, the payer perspective), are presented in Table 5-54. For patients entering the model in AP-CML or BP-CML, ponatinib yielded more LYs and QALYs than any comparator. Ponatinib also incurred lower total cost than bosutinib in AP-CML and both hydroxycarbamide and allo-SCT in BP-CML, and was thus dominant in those comparisons. While ponatinib added costs overall in the other comparisons, ICERs remained well below the acceptability threshold even for non–end-of-life interventions, ranging from [redacted].

Table 5-54. Base-case cost-effectiveness results (discounted, per person): direct medical perspective

Disease state Ponatinib vs	Total costs (£)	Total LYG (Disc)	Total QALYs (Disc)	Incremental costs (£) (ponatinib vs)	Incremental LYG (ponatinib vs)	Incremental QALYs (ponatinib vs)	ICER (£/LYG)	ICER (£/QALYs)
AP-CML								
Hydroxycarbamide	82,532	1.60	0.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	150,957	5.04	2.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	116,635	2.87	1.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]					
BP-CML								
Hydroxycarbamide	86,958	1.00	0.28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	63,424	0.77	0.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	103,748	1.27	0.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]					

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; Disc, discounted; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year.

Clinical outcomes from the model

5.4.6.3 Outcomes from the model vs clinically important outcomes

While no formal analysis of face validity was undertaken for the AP/BP-CML model (given the much smaller patient population in comparison with CP-CML), all key outcome parameters were based on the best available data, as described in Section 5.4.2.1.1.

5.4.6.4 Markov trace

The Markov traces for the AP-/BP-CML economic analysis are presented in Appendix 21: Markov traces – AP/BP-CML economic model

5.4.6.5 QALYs accrued over time

QALYs for each health state accrued over time for each comparator in the AP-/BP-CML economic analysis are presented in Appendix 22: QALYS over time – AP/BP-CML economic model.

Disaggregated results of the base case incremental cost effectiveness analysis

5.4.6.6 Disaggregated QALYs, LYGs, and costs

5.4.6.6.1 QALYs and life-years gained

A summary of the treatment-specific deterministic survival and quality-adjusted survival estimates resulting from the analysis is presented in Table 5-55. Of the two TKI drug therapies being compared, ponatinib is associated with the largest increase in both OS and QALYs. Compared to bosutinib, treatment with ponatinib is predicted to increase real life (undiscounted) by [redacted]. The LYG with bosutinib is less than those with hydroxycarbamide, suggesting an overestimation of survival with BSC (possibly due to limitations in the data source for BSC), which would be conservative for the comparison between ponatinib and BSC.

[redacted], and retained a large survival and QALY advantage over allo-SCT in BP-CML. While ponatinib yielded more OS and QALYs than hydroxycarbamide in all cases, bosutinib yielded fewer LYs than hydroxycarbamide in BP-CML. In the model, allo-SCT is the key driver of OS for patients with BP-CML who achieve MaHR on ponatinib. Higher rates of achieved MaHR with ponatinib mean more patients with BP-CML reach a state in which they can proceed to allo-SCT. The lower rate of achieved response with bosutinib explains the poorer performance in BP-CML with this 2G-TKI than with hydroxycarbamide.

Table 5-55. Survival and QALY results

	LYG					QALY				
	AP-CML	BP-CML	Allo-SCT	Total		AP-CML	BP-CML	Allo-SCT	Total	
				Undisc	Disc				Undisc	Disc
AP-CML										
Hydroxy-carbamide	0.77	1.14	0.00	1.91	1.60	0.39	0.26	0.00	0.65	0.58
Bosutinib	2.45	1.29	3.03	6.77	5.04	1.17	0.28	1.96	3.41	2.62
Allo-SCT	0.00	0.00	3.20	3.20	2.87	0.00	0.00	2.08	2.08	1.86
Ponatinib	[redacted]									
BP-CML										
Hydroxy-carbamide	–	1.16	0.00	1.16	1.00	–	0.32	0.00	0.32	0.28
Bosutinib	–	0.56	0.29	0.85	0.77	–	0.22	0.20	0.42	0.37
Allo-SCT	–	0.00	1.34	1.34	1.27	–	0.00	0.90	0.90	0.85
Ponatinib	[redacted]									

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; Disc, discounted; LYG, life-year gained; QALY, quality-adjusted life-year; Undisc, undiscounted.

Table 5-56 and Table 5-57 list the incremental disaggregated QALYs and LYG by health state results for ponatinib vs each comparator. Notably, patients who receive ponatinib in either AP- or BP-CML spend a longer time alive in the post–allo-SCT health state compared with patients who receive direct allo-SCT without first achieving remission, demonstrating the value of first achieving MaHR with ponatinib to help to optimise transplant outcomes. This is not the case for bosutinib, which yields fewer LYs and QALYs post-allo-SCT than does direct allo-SCT. As a comparator, hydroxycarbamide is unable to achieve MaHR allowing patients to receive allo-SCT, and thus all LYs and QALYs for this form of BSC are accrued in advanced disease health states.

Table 5-56. Summary of QALY gain by health state (discounted)

	AP-CML					BP-CML				
Health state	QALY ponatinib	QALY comparator	Increment	Absolute increment	% absolute increment	QALY ponatinib	QALY comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs bosutinib										
AP	[redacted]	0.98	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BP	[redacted]	0.18	[redacted]	[redacted]	[redacted]	[redacted]	0.21	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	1.46	[redacted]	[redacted]	[redacted]	[redacted]	0.16	[redacted]	[redacted]	[redacted]
Total	[redacted]	2.62	[redacted]	[redacted]	[redacted]	[redacted]	0.37	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide										
AP	[redacted]	0.38	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BP	[redacted]	0.20	[redacted]	[redacted]	[redacted]	[redacted]	0.28	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Total	[redacted]	0.58	[redacted]	[redacted]	[redacted]	[redacted]	0.28	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT										
AP	[redacted]	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BP	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	1.86	[redacted]	[redacted]	[redacted]	[redacted]	0.85	[redacted]	[redacted]	[redacted]
Total	[redacted]	1.86	[redacted]	[redacted]	[redacted]	[redacted]	0.85	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; QALY, quality-adjusted life-year. Table was 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

Table 5-57. Summary of LYG gain by health state (discounted)

	AP-CML					BP-CML				
Health state	LYG ponatinib	LYG comparator	Increment	Absolute increment	% absolute increment	LYG ponatinib	LYG comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs bosutinib										
AP	[redacted]	2.03	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BP	[redacted]	0.76	[redacted]	[redacted]	[redacted]	[redacted]	0.54	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	2.24	[redacted]	[redacted]	[redacted]	[redacted]	0.24	[redacted]	[redacted]	[redacted]
Total	[redacted]	5.04	[redacted]	[redacted]	[redacted]	[redacted]	0.77	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide										
AP	[redacted]	0.75	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BP	[redacted]	0.85	[redacted]	[redacted]	[redacted]	[redacted]	1.00	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.00	[redacted]	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Total	[redacted]	1.60	[redacted]	[redacted]	[redacted]	[redacted]	1.00	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT										
AP	[redacted]	0	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BP	[redacted]	0	[redacted]	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	2.87	[redacted]	[redacted]	[redacted]	[redacted]	1.27	[redacted]	[redacted]	[redacted]
Total	[redacted]	2.87	[redacted]	[redacted]	[redacted]	[redacted]	1.27	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; LYG, life-year gained. 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

5.4.6.6.2 Costs

Examination of the disaggregated cost results (Table 5-58) reveals that, [redacted]. This is due to the much higher MaHR rate with ponatinib compared with bosutinib, which results in a higher percentage of ponatinib patients rapidly receiving allo-SCT and thus no longer consuming TKI therapy. While this means that spending on allo-SCT is higher for patients treated with ponatinib than with bosutinib, this should be considered in the context of more patients becoming eligible for potentially curative transplant— the treatment recommended in clinical practice guidelines for patients with advanced CML. Table 5-58 also shows substantial cost offsets for ponatinib in terms of reduced monitoring and follow-up costs compared with bosutinib.

Table 5-58. Cost results (discounted)

Cost, £	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
AP-CML				
TKI	[redacted]	25,696	–	–
Other drugs	256	336	–	244
Allo-SCT	67,970	35,592	111,486	–
Monitoring/follow-up	52,809	83,595	–	76,886
Adverse events	778	1,017	–	–
End-of-life	4,516	4,721	5,149	5,401
Total	[redacted]	150,957	116,635	82,532
BP-CML				
TKI	[redacted]	8,320	–	–
Other drugs	48	52	–	153
Allo-SCT	37,024	5,083	98,283	–
Monitoring/follow-up	34,063	43,612	–	81,286
Adverse events	707	793	–	–
End-of-life	5,293	5,564	5,465	5,519
Total	[redacted]	63,424	103,748	86,958

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

Table 5-59 summarises the costs by health state to identify which health states are responsible for most differences in costs between ponatinib and the comparators.

Table 5-59. Summary of cost by health state (discounted)

	AP-CML					BP-CML				
Health state	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs bosutinib										
AP	[redacted]	50,446	[redacted]	[redacted]	[redacted]	–	–	–	–	–
BP	[redacted]	62,887	[redacted]	[redacted]	[redacted]	[redacted]	57,445	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	37,624	[redacted]	[redacted]	[redacted]	[redacted]	5,979	[redacted]	[redacted]	[redacted]
Total	[redacted]	150,957	[redacted]	[redacted]	[redacted]	[redacted]	63,424	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide										
AP	[redacted]	11,005	[redacted]	[redacted]	[redacted]	–	–	–	–	–
BP	[redacted]	71,527	[redacted]	[redacted]	[redacted]	[redacted]	86,958	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	–	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]	[redacted]
Total	[redacted]	82,532	[redacted]	[redacted]	[redacted]	[redacted]	86,958	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT										
AP	[redacted]	–	[redacted]	[redacted]	[redacted]	–	–	–	–	–
BP	[redacted]	–	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	116,635	[redacted]	[redacted]	[redacted]	[redacted]	103,748	[redacted]	[redacted]	[redacted]
Total	[redacted]	116,635	[redacted]	[redacted]	[redacted]	[redacted]	103,748	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia. 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

Table 5-60 summarises the predicted resource use by category of cost for ponatinib vs each comparator. When evaluating these results, it is important to recognise that whereas comprehensive long-term AE data were available for ponatinib, these were lacking for the comparators, and thus the inclusion of costs for a wider range of AEs with ponatinib is a conservative method that biases the cost results against it.

Table 5-60. Summary of predicted resource use by category of cost (discounted)

	AP-CML					BP-CML				
Resource use	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs bosutinib										
Main drug	[redacted]	25,696	[redacted]	[redacted]	[redacted]	[redacted]	8,320	[redacted]	[redacted]	[redacted]
Other drugs	256	336	-80	80	[redacted]	48	52	-4	4	[redacted]
Allo-SCT*	67,970	35,592	32,378	32,378	[redacted]	37,024	5,083	31,941	31,941	[redacted]
Monitoring/ follow-up	52,809	83,595	-30,786	30,786	[redacted]	34,063	43,612	-9,549	9,549	[redacted]
Adverse events	778	1,017	-239	239	[redacted]	707	793	-86	86	[redacted]
End-of-life	4,516	4,721	-205	205	[redacted]	5,293	5,564	-271	271	[redacted]
Total	[redacted]	150,957	[redacted]	[redacted]	[redacted]	[redacted]	63,424	[redacted]	[redacted]	[redacted]
Ponatinib vs hydroxycarbamide										
Main drug	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Other drugs	256	244	12	12	[redacted]	48	153	-105	105	[redacted]
Allo-SCT*	67,970	-	67,970	67,970	[redacted]	37,024	-	37,024	37,024	[redacted]
Monitoring/ follow-up	52,809	76,886	-24,077	24,077	[redacted]	34,063	81,286	-47,223	47,223	[redacted]
Adverse events	778	-	778	778	[redacted]	707	-	707	707	[redacted]
End-of-life	4,516	5,401	-885	885	[redacted]	5,293	5,519	-226	226	[redacted]
Total	[redacted]	82,532	[redacted]	[redacted]	[redacted]	[redacted]	86,958	[redacted]	[redacted]	[redacted]
Ponatinib vs allo-SCT										
Main drug	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Other drugs	256	-	256	256	[redacted]	48	-	48	48	[redacted]
Allo-SCT*	67,970	111,486	-43,516	43,516	[redacted]	37,024	98,283	-61,258	61,258	[redacted]
Monitoring/ follow-up	52,809	-	52,809	52,809	[redacted]	34,063	-	34,063	34,063	[redacted]
Adverse events	778	-	778	778	[redacted]	707	-	707	707	[redacted]
End-of-life	4,516	5,149	-633	633	[redacted]	5,293	5,465	-172	172	[redacted]
Total	[redacted]	116,635	[redacted]	[redacted]	[redacted]	[redacted]	103,748	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia. 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.

*Includes costs associated with procedure and relapse.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

5.4.7 Sensitivity analyses

Probabilistic sensitivity analysis

5.4.7.1 Measure of decision uncertainty

To address the uncertainty in the parameters used within the model, a PSA was implemented.

5.4.7.2 Parameter distributions

The parameters and their corresponding distributions that were used in the PSA are presented in Table 5-36.

Table 5-61. PSA distributions

Parameter	Distribution
Adverse event rates	Beta
Costs	Gamma
HRQoL	Beta
Number of days in hospital per treatment course	Gamma
OS curve-fitting parameters (active treatment)	Cholesky decomposition
OS with BSC	Gamma
OS in allo-SCT	Gamma
PFS curve-fitting parameters	Cholesky decomposition
Proportion treated in hospital/hospice at end of life	Gamma
Resource use rates	Gamma
Response rates	Beta
Time on treatment (ponatinib)	Cholesky decomposition
Time on treatment (bosutinib)	Gamma

Allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis.

5.4.7.3 Results of probabilistic sensitivity analysis

Results are presented for the comparison of ponatinib vs bosutinib in AP-CML (which accounts for the majority of patients starting treatment with these TKIs in advanced CML). Table 5-37 reports the 95% CI for incremental costs, QALYs, and ICERs.

Table 5-62. 95% CI for costs, QALYs, and ICERs

	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]

Figure 5-23 shows the incremental costs and QALYs derived from the 1000 simulations of the PSA for ponatinib vs bosutinib. This graph demonstrates that most simulations are generally consistent with the mean result, with ponatinib both more effective and less costly than bosutinib.

Figure 5-23. Results of 1000 simulations in the PSA for the ICER of ponatinib vs bosutinib

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 5-24 shows the cost-effectiveness acceptability curve derived from the PSA. Reflecting the dominance of ponatinib over bosutinib in the vast majority of iterations, even at the lowest WTP threshold ponatinib would be considered cost-effective in more than [redacted]% of iterations.

Figure 5-24. Cost-effectiveness acceptability curve in the PSA for the ICER of ponatinib vs bosutinib

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

5.4.7.4 ICER results from base-case vs PSA

Results of the PSA were consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values.

Deterministic sensitivity analysis

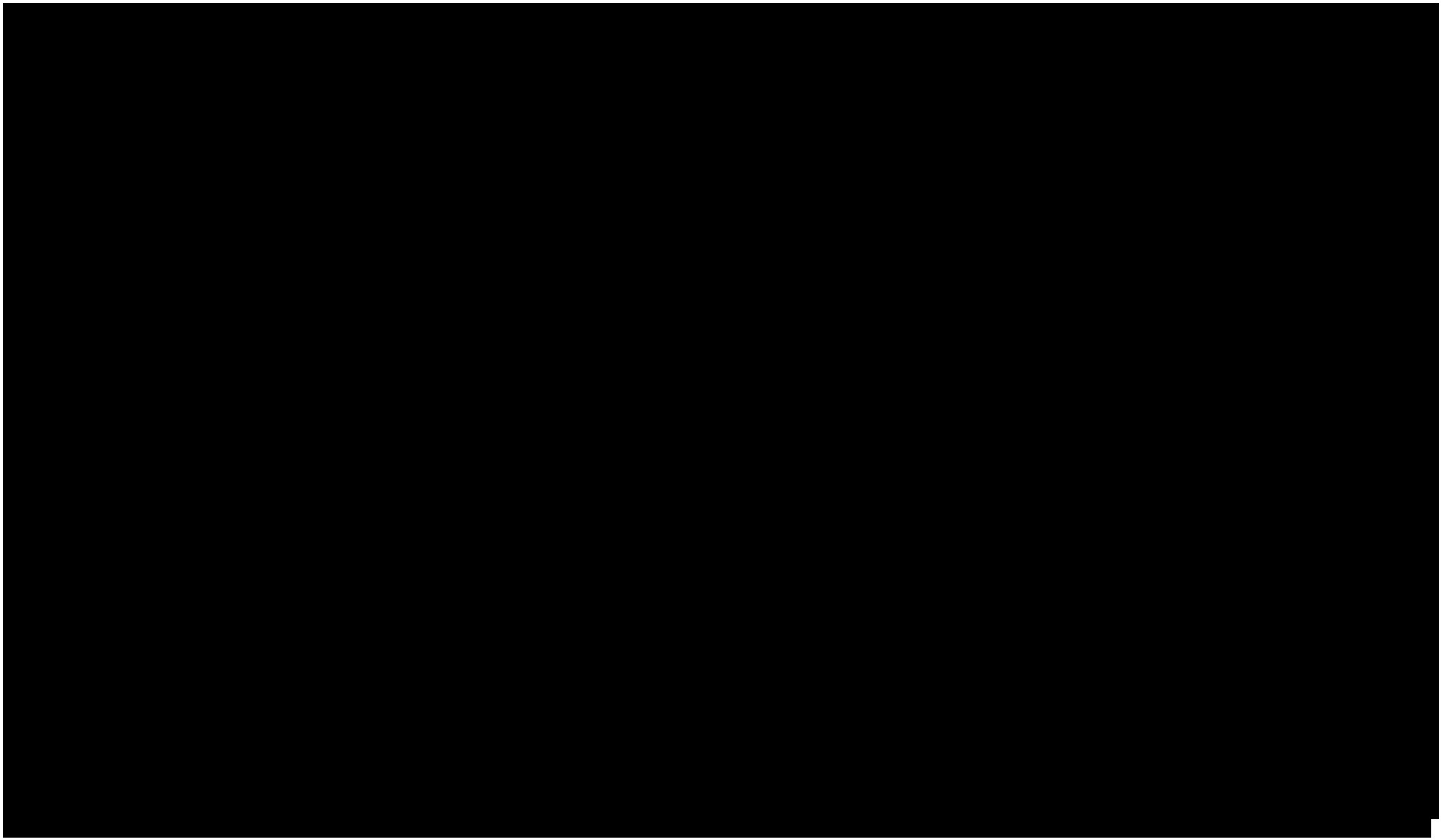
5.4.7.5 Parameters

A univariate analysis was conducted following the same procedures described for the CP-CML model in Section 5.3.7.5. The upper and lower values for the parameters in this deterministic sensitivity analysis are reported in Table 5-52.

5.4.7.6 Results of deterministic sensitivity analysis

Results of the univariate sensitivity analysis are presented as a tornado plot (Figure 5-25) for the pairwise comparison of ponatinib vs bosutinib. The analysis was run on all model parameters. Variation in the relative efficacy of the comparators was captured by varying response rates for each drug in the OWSA. From this plot, it is apparent that the ICERs are most sensitive to changes in the days in hospital, the discount rate on costs, and the MaHR rate with ponatinib in AP (Figure 5-16). The MaHR rate with bosutinib in AP influences the ICER, but to a lesser degree than the rate with ponatinib. Ponatinib remains dominant in all OWSA scenarios except the days in hospital in BP, where the upper range ICER is [redacted].

Figure 5-25: Tornado plot displaying the most influential parameters for the ICER of ponatinib vs bosutinib



AP, accelerated phase; BP, blast phase; ICER, incremental cost-effectiveness ratio; M&FU, monitoring and follow-up; MaHR, major haematologic response; QALY, quality-adjusted life-year; SCT, stem cell transplant; ToT, time on treatment.

5.4.7.7 Sensitivity analysis of technology prices

Sensitivity analyses of technology prices were incorporated in the one-way and probabilistic sensitivity analyses in terms of per-cycle costs, as described above.

5.4.7.8 Scenario analysis

No scenario analyses were carried out. For scenario analyses in CP-CML, please refer to Section 5.3.7.8.

5.4.7.9 Summary of sensitivity analysis results

5.4.7.9.1 Summary of deterministic and probabilistic sensitivity analyses

Deterministic sensitivity analyses reveal that the parameters most strongly influencing the results include discount rates, the cost of ponatinib, hospital days for patients in BP-CML, and the CCyR rate with ponatinib and bosutinib. Cost-effectiveness results for ponatinib compared with bosutinib in the PSA were similar to those in the base-case analysis.

5.5 De novo analysis – Ph+ ALL

5.5.1 Methodology

5.5.1.1 Patient population

The target population in the Ph+ ALL economic model is consistent with that defined in the NICE scope[164]—that is, the patient population indicated in the approved EU label (see Section 2.2.2) and the subjects in the ponatinib clinical study programme.

5.5.1.1.1 Baseline characteristics of the simulated population

The baseline characteristics of the modelled population used in the simulation is derived from the Ph+ ALL cohort in the PACE study (Table 5-63).

Table 5-63. Baseline characteristics of the modelled Ph+ ALL population

Parameter	Value	Source
Initial age (years)	53.03	PACE Study
Proportion of males	62.5%	PACE Study

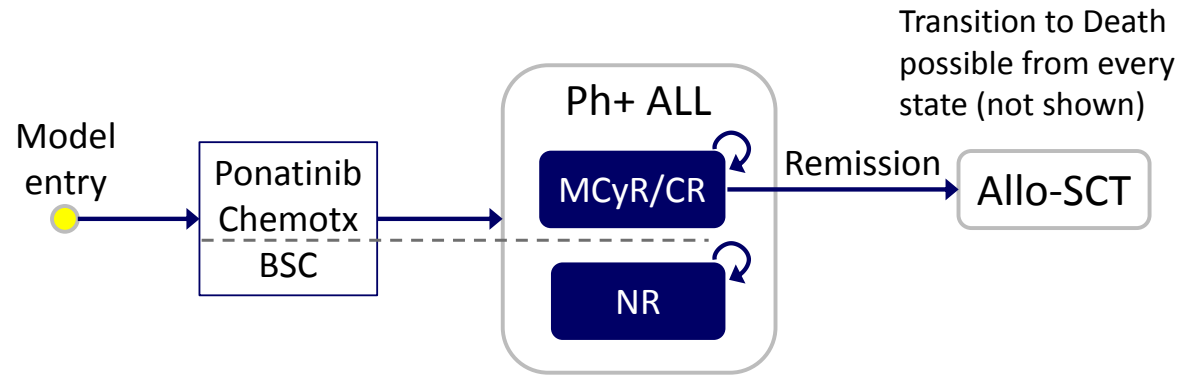
5.5.1.2 Model structure – Ph+ ALL

The *de novo* cost-effectiveness model for Ph+ ALL was developed to conform to requirements of NICE as expressed in its Guide to Methods of Technology Appraisal.[158] The model was built following the same principles of model design described above for the CP-CML and AP/BP-CML models.

The structure of the model was designed as a conventional state transition (Markov) model with two health states (Figure 5-26):

- Ph+ ALL, which incorporates two substates corresponding to response category (in remission and no remission) for patients treated with ponatinib, induction chemotherapy, or BSC
- Allo-SCT (for patients who achieve remission with treatment)

Figure 5-26. Schematic representation of the Ph+ ALL model health states



ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; chemotx, chemotherapy; CR, complete remission; MCyR, major cytogenetic response; NR, non-response; Ph+, Philadelphia chromosome–positive.

Note: dashed line indicates that patients receiving BSC cannot achieve MaHR, and thus remain nonresponders; patients receiving ponatinib or chemotherapy can either achieve MCyR or be nonresponders.

As shown in Figure 5-26, patients with Ph+ ALL enter the Markov cohort model in the Ph+ ALL health state. In this health state, disease response is categorised according to the presence/absence of cytogenetic response, with MCyR a proxy measure of remission with ponatinib (based on response rates from the PACE study)[9] and complete remission a proxy measure of remission with induction chemotherapy (per Tavernier et al. 2007)[133]. Upon achieving treatment-induced remission in the first cycle, patients are treated with allo-SCT. It is assumed that BSC cannot induce remission.

In the base-case analysis, the duration of treatment with ponatinib is 6 weeks before allo-SCT (given the half-cycle correction). Patients who do not achieve remission, and therefore do not receive allo-SCT, are treated with BSC until death. Death is possible in any state and, as such, is not represented in Figure 5-26. The model provides the option to continue treatment beyond 3 months for patients who do not achieve MCyR while on ponatinib; time-on-treatment estimates determine the point at which ponatinib is discontinued.

5.5.1.3 Features and justification of the de novo analysis

Table 5-64 summarises the features of the Ph+ ALL de novo analysis. The chosen values were in accordance with the NICE guide to the methods of technology appraisal.

Table 5-64. Features of the Ph+ ALL de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime(maximum of 400 cycles, up to 100 years)	To capture all important differences in costs or outcomes between the technologies being compared[158]
Were health effects measured in QALYs; if not, what was used?	QALY and LYG	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY[164] For completeness, the analysis evaluates incremental LYGs
Discount of 3.5% for utilities and costs	3.5%	3.5% per annum as recommended by NICE[158] Discount rates of 0% and 6% were used in sensitivity analyses
Perspective (NHS/PSS)	NHS/PSS	In accordance with the NICE guide to the methods of technology appraisal,[158] the reference-case CUA adopts the payer perspective for costs

CUA, cost-utility analysis; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.

5.5.1.4 Intervention technology and comparators

5.5.1.4.1 Ponatinib

The intervention evaluated in the Ph+ ALL economic analysis is one 45-mg tablet of ponatinib administered orally once daily. This is aligned with the SmPC-recommended starting dose of 45 mg QD.[22] Treatment with ponatinib is modelled for one 3-month cycle (Cycle 1); patients who achieve MCyR are then treated with allo-SCT. That is, allo-SCT is incorporated into the model as a follow-on treatment for patients who achieve remission with ponatinib. Hence, the model demonstrates the use of ponatinib as a "bridge" to allo-SCT. If a patient fails to demonstrate a MCyR response within the first model cycle, treatment is discontinued per SmPC guidance.[22]

5.5.1.4.2 Comparators

The comparator for Ph+ ALL included in the NICE scope is established clinical management without ponatinib (including but not limited to BSC), as shown in Table 5-65. Other than ponatinib, imatinib and dasatinib are the only TKI treatments indicated for the treatment of Ph+ ALL. However, as ponatinib is indicated in patients who are R/I to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, neither imatinib nor dasatinib can be considered as a comparator in this analysis.

Table 5-65. Established clinical management comparators in the Ph+ ALL economic model

Comparator	Regimen	Justification
Patients suitable for allo-SCT		
Induction chemotherapy + allo-SCT	LALA-94 Hyper-CVAD FLAG-IDA	Most common chemotherapy protocols used to induce remission prior to allo-SCT
BSC	6-week course of vincristine and prednisone	Palliative regimen used for patients with ALL (Pagano et al. 2000)[30]
Patients unsuitable for allo-SCT		
BSC	6-week course of vincristine and prednisone	Palliative regimen used for patients with ALL (Pagano et al. 2000)[30]

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care.

Comparator data for induction chemotherapy was obtained from Tavernier et al. 2007,[133] a prospective observational study of 421 relapsed patients who were enrolled in the LALA-94 trial. Tavernier et al. was identified in the Ph+ ALL SLR and provides the most comprehensive data for reinduction chemotherapy followed by allo-SCT in patients with ALL after first relapse. This study reports both outcomes of reinduction therapy by salvage regimen (data available for Ph+ ALL) and OS in CR2 following allo-SCT.[133] Reinduction chemotherapy regimens for patients with relapsed Ph+ ALL included LALA-94, hyper-CVAD, and FLAG-IDA.

BSC was used as a comparator to ponatinib in patients who were both suitable for allo-SCT and unsuitable for transplantation. BSC was used indefinitely in both situations, regardless of whether a patient was suitable/unsuitable for allo-SCT, to assess the cost-effectiveness of ponatinib when used as a bridge to transplant or when used in patients eligible for transplantation. Comparator data for BSC come from Pagano et al. (2000),[30] a single-centre, retrospective analysis of treatment in ALL patients. The palliative BSC regimen used in this study consisted of a 6-week course of vincristine and prednisone, which was incorporated into the model.

5.5.1.5 Treatment continuation rule

The model applies a stopping rule for patients on ponatinib who have not responded to treatment by 3 months, as described previously in the de novo CP-CML economic analysis (see Section 5.3.1.6).Induction chemotherapy is only administered for 6 weeks. When a TKI or chemotherapy is discontinued, we assume BSC is started and continued until progression or death.

5.5.1.6 Summary of the de novo analysis

The Ph+ ALL model characteristics are summarised in Table 5-6.

Table 5-66. Summary of Ph+ ALL model characteristics

Component	Description
Population	Adults with Ph+ ALL R/I to imatinib and dasatinib
Comparators	Chemotherapy BSC
Perspective	NHS/PSS
Cycle length	3 months; half-cycle correction applied
Time horizon	Cohort lifetime (maximum 400 cycles; up to 100 years)
Starting age	53.03 years
Discount rate per annum: costs	3.5%
Discount rate per annum: benefits	3.5%
Outcome measures generated	Cost/QALYs gained Cost/LYG

Allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; LYG, life-year gained; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life-year.

5.5.2 Clinical parameters and variables

5.5.2.1 Clinical data sources

5.5.2.1.1 Effectiveness data

5.5.2.1.1.1 Response rates

Response to ponatinib treatment was modelled to determine the transition to the allo-SCT state. Response rates for ponatinib (Table 5-67) were obtained from the most recent PACE study IPD of all patients with Ph+ ALL (n=32) (data cut-off, 3 August 2015). PACE was identified in the clinical SLR (see Section 4.1.1; Table 4-7[study design], Table 4-10 [baseline characteristics], and Table 4-13 [outcomes]).

MCyR was assumed as a proxy of disease remission—in other words, the best possible condition for patients to undergo a transplant. MCyR rate for patients with Ph+ ALL treated with ponatinib (47%) was obtained from the PACE study (Table 5-67).[9] The MCyR rate used in the base-case analysis was based on IPD from the population who were R/I to either dasatinib or nilotinib, or those with the T315I mutation (ie, all Ph+ ALL patients in the PACE dataset). We assume response to treatment is instantaneous. This is supported by evidence for PACE study, where the reported median time to MCyR in patients with Ph+ ALL was 1 month (Cortes et al. 2013).[9] Thus, the achievement of response and consequent transition to allo-SCT is simulated within the first cycle of the model.

Data for modelling response to induction chemotherapy in patients with relapsed ALL were derived from a prospective observation study by Tavernier et al. 2007,[133] identified in the clinical SLR (see Section 4.1.1; Table 4-7 [study design], Table 4-10 [baseline characteristics], and Table 4-13 [outcomes]). Tavernier et al. 2007 was selected as the data are in line with other published studies and the rate of remission with salvage treatment was reported for patients with Ph+ ALL (see Section 4.11.2)

In the absence of MCyR data in this publication, CR was used as the proxy for remission. The response rate to induction chemotherapy in patients with Ph+ ALL was 37% (Table 5-67).[133]

Table 5-67. Cytogenetic response (ponatinib) and complete remission (induction chemotherapy) rates applied in the model

Parameter	Ponatinib	Chemotherapy	BSC	Source
Remission (MCyR)	46.88%	–	–	PACE study
Remission (CR)		37.04	–	Tavernier 2007

BSC, best supportive care; CR, complete remission; MCyR, major cytogenetic response.

5.5.2.1.1.2 Overall survival

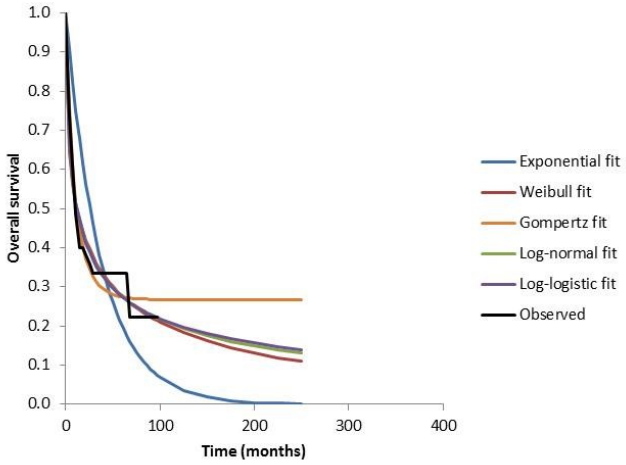
The OS data for patients with Ph+ ALL treated with ponatinib who had or had not reached MCyR were derived from the PACE trial data. A parametric survival analysis was performed on PACE patient-level data, as described in Section 5.2.1.1. Five parametric models were estimated (Weibull, Gompertz, exponential, log-normal, and log-logistic) with a MCyR as a covariate. The AIC and BIC criteria were not in agreement, as the AIC indicated the Gompertz, while the BIC indicated the exponential. The exponential fit was the most plausible and conservative among the two fittings and was thus selected (Figure 5-27).

Figure 5-27. Comparison of observed (source: PACE study) and fitted OS data for patients with Ph+ ALL with and without MCyR

ALL, acute lymphoblastic leukaemia; MCyR, major cytogenetic response; OS, overall survival; Ph+, Philadelphia chromosome–positive.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

In the model, patients are treated with allo-SCT after achieving remission induced by ponatinib or induction chemotherapy. The OS in Ph+ ALL patients after allo-SCT was obtained from the study published by Tavernier et al., which reported results from 421 patients with ALL (81 with Ph+ ALL) who experienced a relapse on first-line therapy.[133] Clinical evidence supports that the overall patient data from this study (across Ph mutation status) are reasonably representative of Ph+ ALL with respect to post–allo-SCT outcomes in that Ph+ ALL is not a risk factor for lower survival post–allo-SCT (Cornelissen et al. 2001)[201] and Ph+ disease status does not influence OS in patients undergoing allo-SCT (Tekgunduz et al. 2016).[209] The publication provided the KM curve for OS of the subgroup of patients allografted after achieving a second remission (61 patients, median OS: 10.4 months). The OS derived from the KM curve (SCT in remission, Figure 5-28) was applied in the simulation of allo-SCT following response to ponatinib or induction chemotherapy. The best fit for the data was provided by the log-logistic function, which was used to extrapolate OS for allo-SCT in patients in remission.

Figure 5-28. Comparison of observed (source: Tavernier et al. 2007)[133] and fitted OS data for patients in remission



OS, overall survival.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

No studies reporting OS with BSC in patients with Ph+ ALL R/I to prior therapy were identified in the clinical SLR. The OS in Ph+ ALL patients treated with palliative chemotherapy was based on clinical evidence derived from a single-centre retrospective study in ALL by Pagano et al. 2000 (identified in a targeted literature search).[30] This study reports a median OS of 2.6 months for patients receiving BSC. This value was used to derive an exponential function and calculate a per-cycle probability of 0.5508.

5.5.2.1.1.3 Time to response

Time to response is implicitly considered in the model as patients who achieve MCyR proceed to allo-SCT within the first cycle. The rationale for this is that in the PACE study the median time to MCyR on ponatinib was less than 1 month for patients with Ph+ ALL (Cortes et al. 2013).[9] In the model, patients are allocated to response categories at the start of the simulation and patients who achieve MCyR proceed to allo-SCT at 6 weeks (due to the half-cycle model correction).

5.5.2.1.1.4 Time-on-treatment

In order to capture the differential timing between treatment discontinuation and disease progression, which is necessary for an accurate estimation of treatment costs, time-on-treatment data were included in the model. The probability of discontinuing active ponatinib treatment was derived from specific time-on-treatment data obtained from the PACE clinical trial data.

Time-on-treatment with ponatinib in patients with Ph+ ALL was modelled from the PACE trial data as described in Section 5.2.1.1. The log-logistic function provided the best fit (Figure 5-29)..

Figure 5-29. Observed and fitted time-on-treatment data for Ph+ ALL patients treated with ponatinib

ALL, acute lymphoblastic leukaemia; Ph+, Philadelphia chromosome–positive.
Formal goodness of fit estimates are shown in Appendix 25: Parametric survival analysis and curve fitting.

5.5.2.2 Transition probabilities

Transition probabilities used in the Ph+ ALL model are described below. All probabilities are derived from survivor functions extrapolated from clinical data. The time-dependent probabilities of transitioning between states were in general estimated as 1 minus the ratio of the survivor function at the end of the cycle to the survivor function at the beginning of the cycle.

- **Death** (from the Ph+ ALL state). Two survivor functions (for OS in Ph+ ALL with and without MCyR, respectively) were obtained for ponatinib through parametric survival analysis on patient-level data from the PACE study. For BSC, a survivor functions was obtained by extrapolating an exponential curve from published median OS in Pagano et al. 2000. For induction chemotherapy it was assumed, in the case of no remission, the same OS of BSC.
- **Death** (from allo-SCT state). A survivor function (for OS after allo-SCT) was extrapolated through parametric fitting from published OS curves in Tavernier et al. 2007.
- **Discontinuation of TKI treatment.** The probability of discontinuing the active treatment before death is applied to ponatinib. This probability is not directly determining a state transition in the Markov model, and it is rather used to accurately estimate treatment costs. Two survivor functions (depicting the fraction of the cohort which remains on treatment over time) were obtained for ponatinib (with and without MCyR, respectively) through parametric survival analysis on patient-level data from the PACE study. After the discontinuation of ponatinib, the administration of the BSC (fixed course of 6-weeks palliative chemotherapy) is assumed. For induction chemotherapy it is assumed a fixed course of 6 weeks, and no subsequent drug administration is conservatively assumed.

5.5.2.3 Evidence that (transition) probabilities may change over time for the treatment effect, condition or disease

The change over time of transition probabilities was captured in all models and is described in the previous section.

5.5.2.4 Clinical expert assessment of the applicability or approximation of clinical parameters

The applicability of clinical parameters was not validated by clinical experts. The economic model, however, is the final outcome of a thorough development process during which key experts in the field, including health economists, have extensively reviewed it, as described in Section 5.7.

5.5.3 Measurement and valuation of health effects

5.5.3.1 Health-related quality-of-life data from clinical trials

The PACE trial did not evaluate HRQoL and as such no HRQoL data associated with ponatinib were available for patients of the phase 2 clinical trial.

5.5.3.2 Mapping

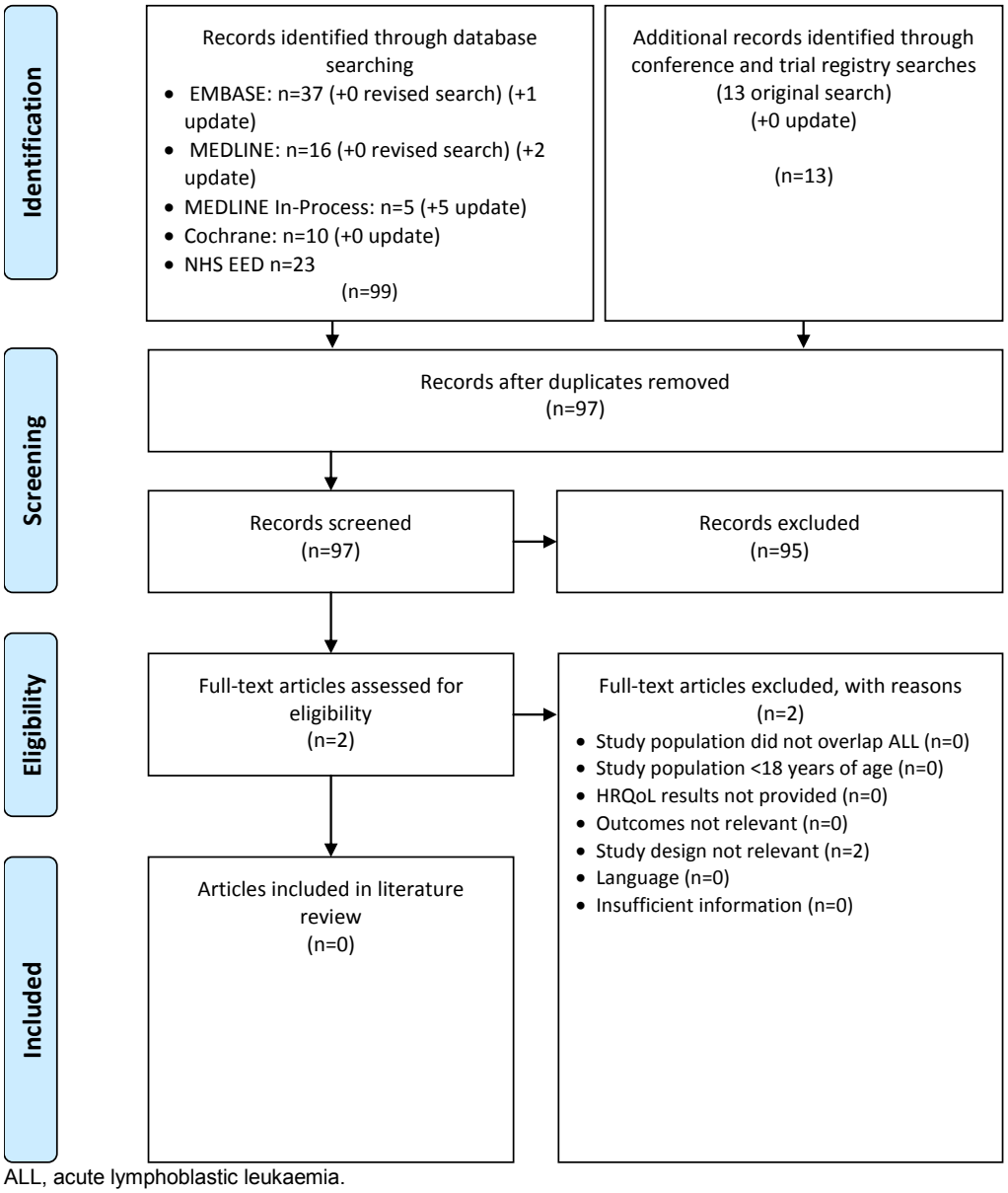
Not applicable; mapping from clinical trials was not performed.

5.5.3.3 Health-related quality-of-life studies

As with the clinical and economic search strategies, the HRQoL portion of the SLR was designed to identify relevant evidence published from January 2000–February 2016, with an updated search conducted in July 2016. The search strategy and PICOS criteria for the HRQoL portion of the Ph+ ALL SLR were the same as for the CML SLR, as described in Section 5.3.3.3, with the exception that the patient population was that of Ph+ ALL instead.

After screening the 97 records identified, none were found to be relevant, and so no articles were included. The process of study selection is presented in detail in Figure 5-30.

Figure 5-30. PRISMA flow diagram for relevant HRQoL evidence in Ph+ ALL



ALL, acute lymphoblastic leukaemia.

In the absence of HRQoL data in Ph+ ALL, the utilities used in the CML economic analysis were also used in the Ph+ ALL economic model (see Sections 5.3.3.4–5.3.3.12), with the exception of post-relapse utility, which was not applied in the Ph+ ALL mode. Briefly, during each cycle, the model generates age-adjusted EQ-5D norm-based scores, using UK population norms reported by Kind et al. (1999; Table 5-13).[256] These data are reported in 10-year bands and so linear interpolation was used to generate the interim values where no data exist. Disease-specific utilities incorporated into the model were derived from Szabo et al. 2010.[249] In the absence of data specific for ALL, the same utilities used for patients with BP-CML were used in this model (see Table 5-14 and Table 5-15). For the purpose of assigning utilities in the model, responders are defined as patients achieving MCyR(ponatinib) or complete remission (induction chemotherapy).

The allo-SCT utility values were the same as those used in the CP-CML model (see 5.3.3.7.2.2).

5.5.4 Cost and healthcare resource use identification, measurement and valuation

5.5.4.1 Parameters used to estimate cost

The following resource use components were incorporated into the economic model: pharmacologic therapy, allo-SCT, monitoring and follow-up care, AEs, end-of-life care. All parameters used to estimate cost in the Ph+ ALL model are aligned with the CP-CML model as previously presented in Table 5-18., with the exception of costs associated with induction chemotherapy and BSC, which are detailed in Table 5-68.

Table 5-68. Unit costs associated with the induction chemotherapy and BSC in the Ph+ ALL economic model

Item	Induction chemotherapy (6-week course) £ (SE)	Reference in submission	BSC (6-week course) £ (SE)	Reference in submission
Technology cost	17,999.73 (1799.97)	Section 5.5.4.5 Table 5-70	4,063.87 (406.39)	Section 5.5.4.5 Table 5-70
Supportive therapy				
Day in hospital	714.64 (–)	Section 5.5.4.5	–	–
Total	NA		NA	

Allo-SCT, allogeneic haematopoietic stem cell transplantation; FISH, fluorescence in situ hybridization; NA, not applicable; PCR, polymerase chain reaction; SE, standard error.

Resource identification, measurement and valuation studies

5.5.4.2 Identification of cost and healthcare resource use data

Please refer to the CP-CML economic analysis (Section 5.3.4.2) for detailed descriptions of how resource use and costs were identified and measured. The NICE TA399 (Azacitidine)[268] was used to inform resource use and cost for supportive therapy during a 6-week course of induction chemotherapy. The source for BSC, a 6-week course of palliative chemotherapy, was an Italian study by Pagano et al. 2000 [30]

5.5.4.3 Appropriateness of NHS reference costs for costing

Please refer to the CP-CML economic analysis (Section 5.3.4.3).

5.5.4.4 Clinical expert assessment of the applicability or approximation of cost and healthcare resource use values

Please refer to the CP-CML economic analysis (Section 5.3.4.4).

Intervention and comparators' costs and resource use

5.5.4.5 Pharmacologic therapies

Table 5-69 outlines the unit drug costs considered in the model. The ponatinib SmPC recommends a starting dose of 45 mg once daily, with optional dose reduction at the treating physician's discretion.[22] Induction chemotherapy was assumed to follow the three most common regimens based on clinician advice: LALA-94, hyper-CVAD, and FLAG-IDA treatment protocols. We assumed a uniform distribution, with equal proportions of patients (33%) receiving each regimen.

Table 5-69. Unit drug costs for Ph+ ALL

Drug	Daily dose	mg per unit	Units per pack	Cost per pack (€)	Daily cost (€)
Ponatinib	15	15	30	2,525.00	84.17
	30	15	30	5,050.00	168.33
	45	45	30	5,050.00	168.33
	Daily dose	**mg per unit**	**Units per pack**	**Cost per pack (€)**	**Cost per mg**
Induction chemotherapy	500	5	100.00	500	0.04
Cytarabine	20	1	121.85	20	6.09
Mitoxantrone	1,000	1	85.00	1,000	0.09
Methotrexate IV	5	5	30.00	5	1.20
Methotrexate IT	10,000	5	3065.00	10,000	0.06
Asparaginase	2	1	26.66	2	13.33
Vincristine	25	56	40.00	25	0.03
Prednisolone	500	1	9.66	500	0.02
Cyclophosphamide IV	50	1	131.75	50	2.64
Daunorubicin	10	1	165.98	10	16.60
Idarubicin	50	1	103.00	50	2.06
Doxorubicin	50	1	155.00	50	3.10
Fludarabine	30	5	263.52	30	1.76
Filgrastim (million units)	500	5	100.00	500	0.04
BSC					
Vincristine (non-proprietary)	—*	56	40.00	2	0.03
Prednisolone (non-proprietary)	40 mg/m^2	1	9.66	25	0.02

Source: BNF[263]
*Vincristine dose is 1.5mg/m^2 weekly.

To account for the potential for dosage variation in clinical practice, the model incorporates ponatinib dosing data from the PACE clinical study (see Table 5-70). The cost of induction chemotherapy and BSC was applied to the first cycle only.

Table 5-70. Products, proportion of time spent on each dose in the trial, and resulting cost per treatment

Treatment	Proportion of time patients in the trial spent on each dose	Cost of treatment (€ per cycle)	Source
Ponatinib	[redacted]	[redacted]	PACE study; ARIAD Pharmaceuticals
Induction chemotherapy (6-week course)	—	17,999.73*	BNF[263]
BSC (6-week course)	—	4,063.87*	Pagano et al. 2000[30]

BNF; British National Formulary; BSC, best supportive care; QD, once per day.
*Cost applied during first cycle only.

Supportive therapy

Supportive therapy during the 6-week course of induction chemotherapy was based on the NICE TA399 (azacitidine), which reported 13.91 hospital days per month at a daily cost of £714.64.[268]

Additional costs incurred by patients receiving palliative chemotherapy were assumed to be zero. Blood and platelet transfusions and inpatient hospital days during a 6-week palliative care treatment period were included as monitoring and follow-up costs for all patients.[30]

5.5.4.6 Allo-SCT

The Ph+ ALL model incorporates the same initial cost of allo-SCT and per-cycle follow-up costs as in CP-CML, described in Section 5.3.4.6.

5.5.4.7 Monitoring and follow-up

Resource use associated with monitoring and follow-up was modelled as a function of whether or not a patient responds to therapy. For the purposes of stratifying patients, responders were defined as those achieving a MCyR. Resource use for patients with Ph+ ALL with/without response was assumed to be the same as in CP-CML with response/BP-CML, respectively; resource use was derived from the UK clinical expert survey (see Table 5-23; Appendix 14: Cost and healthcare resource identification, measurement, and valuation). Patient monitoring and follow-up costs are applied to outpatient visits, tests, and interventions subsequent to therapy and are fully aligned with CP-CML model. Unit costs (Table 5-23) for each component were taken from NHS Reference Costs and other England-specific sources. The per-cycle monitoring and follow-up cost for responding patients with Ph+ ALL is £208.08; for non-responding patients with Ph+ ALL, the cost is £4,862.23, reflecting the greater intensity of healthcare resource utilisation in non-responders.

Health-state unit costs and resource use

5.5.4.8 Costs included in each health state

Not applicable. Drug dosages and unit costs did not vary by health state. Resource use associated with monitoring and follow-up was modelled as a function of disease phase and whether or not a patient responds to therapy.

Adverse reaction unit costs and resource use

5.5.4.9 Costs and resource use for each adverse reaction

AEs included in the model were restricted to Grade 3/4 events occurring in ≥5% of the study population for any given treatment option. Rates for ponatinib were obtained from the PACE CSR, and rates. The AE rates and costs applied in the Ph+ ALL model are summarised in Table 5-71. Cost estimates were taken from NHS reference costs and tariffs. In the absence of AEs information for induction chemotherapy and BSC, placeholder values of 0% are employed in the model.

Table 5-71. AE rates and costs applied in the model (source: PACE CSR) and associated costs

Adverse event	Ponatinib	Unit cost, £	Sources for costs
Abdominal pain	[redacted]	752.10	NHS Reference Costs 2014 to 2015
Anaemia	[redacted]	1,827.13	NHS 2015/16 Enhanced Tariff Option
Diarrhoea	[redacted]	801.95	NHS Reference Costs 2014 to 2015
Hypophosphataemia	[redacted]	721.00	Assumption: 1 day in hospital
Leukocytopaenia	[redacted]	633.26	Assumption: same as neutropaenia
Lipase increased	[redacted]	721.00	Assumption: 1 day in hospital
Neutropaenia	[redacted]	633.26	NHS Reference Costs 2014 to 2015
Pancreatitis	[redacted]	1,121.98	NHS Reference Costs 2014 to 2015
Thrombocytopaenia	[redacted]	421.74	NHS Reference Costs 2014 to 2015
Serious adverse events			
Cardiovascular event	[redacted]	2,357.00	NHS 2015/16 Enhanced Tariff Option
Cerebrovascular event	[redacted]	2,962.00	NHS 2015/16 Enhanced Tariff Option
Peripheral vascular event	[redacted]	2,872.00	NHS 2015/16 Enhanced Tariff Option
Venous thromboembolism event	[redacted]	552.00	NHS 2015/16 Enhanced Tariff Option

ALT, alanine aminotransferase.

Miscellaneous unit costs and resource use

5.5.4.10 End-of-life care

End-of-life care resource use and costs are assumed to be the same as in the CP-CML economic model (see 5.3.4.11), as shown in Table 5-72.

Table 5-72. End-of-life care resource use and costs

	Value	Daily cost, £	Source
In-patient stay, days	21.5	463.77	Marie Curie Cancer Care[269] 2009 costs inflated to 2014/15
Patients treated in hospital, %	51.5	—	Assumed same as in acute phases of leukaemia
Hospice stay, days	17.4	158.23	Marie Curie Cancer Care[269] 2009 costs inflated to 2014/15
Patients treated in hospice, %	23.1	—	Assumed same as in acute phases of leukaemia
Average end-of-life care cost, £		**5,765.76**	

CML. chronic myeloid leukaemia.

5.5.5 Summary of base-case de novo analysis inputs and assumptions

5.5.5.1 Summary of base-case de novo analysis inputs

Base-case inputs that are fully aligned with the CP-CML economic analysis are shown in Table 5-26. All other variables applied to the Ph+ ALL economic model are summarised in Table 5-73. Uncertainty regarding the parameter values was addressed via sensitivity analyses, as described below in Section 5.5.7.

Table 5-73. Summary of variables applied in the economic model

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
Clinical Inputs				
Remission rate				

Parameter	Value (reference to appropriate table or figure in submission)	Function used for extrapolation	Reference to section	Source
Induction chemotherapy (CR)	0.37037 (Table 5-67)	–	5.5.2.1.1.1	Tavernier et al. 2007
Ponatinib (MCyR)	0.46875 (Table 5-67)	–	5.5.2.1.1.1	PACE study
Overall survival				
OS in allo-SCT	– (Figure 5-28)	Log-logistic	5.5.2.1.1.2	Tavernier et al. 2007
OS in BSC, months	2.6 (–)		5.5.2.1.1.2	Pagano et al. 2000
OS in Ph+ ALL with ponatinib	– (Figure 5-27)	Exponential	5.5.2.1.1.2	PACE study
Time-on-treatment				
ponatinib	– (Figure 5-29)	Log-logistic	5.5.2.1.1.4	PACE study
Economic Inputs				
Per-cycle cost, £				
BSC	4,063.87 (Table 5-70)	–	5.5.4.5	–
Induction chemotherapy	17,999.73 (Table 5-70)	–	5.5.4.5	–
Ponatinib	[redacted]	–	5.5.4.5	–
HRQoL Inputs / AEs				
Cumulative incidence	(Table 5-71)			
Abdominal pain ponatinib	[redacted]	–	5.5.4.9	PACE study CSR - Table 14.3.1.8.2.10.2
Anaemia ponatinib	[redacted]	–	5.5.4.9	PACE study CSR -
Lipase increased ponatinib	[redacted]	–	5.5.4.9	PACE study CSR -
Neutropaenia ponatinib	[redacted]	–	5.5.4.9	PACE study CSR -
Febrile neutropaenia ponatinib	[redacted]	–	5.5.4.9	PACE study CSR -
Thrombocytopaenia ponatinib	[redacted]	–	5.5.4.9	PACE study CSR -
Per-cycle probability (ponatinib only)	(Table 5-71)			
Cardiovascular event	[redacted]	–	–	PACE study CSR - Section 14.3.5 Other Safety Measurements, Table 2.2
Cerebrovascular event		–	–	
Peripheral vascular event		–	5.5.4.9	
Venous thromboembolism event		–	5.5.4.9	

AEs, adverse events; ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; CSR, clinical study report; HRQoL, health-related quality of life; MCyR, major cytogenetic response; OS, overall survival; Ph+, Philadelphia chromosome–positive.

5.5.5.2 Assumptions

Base-case inputs that are fully aligned with the CP-CML economic analysis are justified as shown in Table 5-52.Table 5-74 summarises the main assumptions in the economic analysis.

Table 5-74. Summary of main assumptions and justifications in the Ph+ ALL model

Assumption	Justification
Treatment response was assumed to be instantaneous	Based on a median time to MCyR of 1 month reported in Cortes et al. 2013[9]
BSC consists of weekly administration of vincristine is 1.5 mg/m^2 and daily methylprednisolone is 40 mg/m^2 for 6 weeks; an average body surface of 1.69 m^2 is assumed	As considered by Pagano et al. 2000[30]

Assumption	Justification
Equal proportions of patients (33%) receive one of the following induction chemotherapy regimen: LALA-94, hyper-CVAD, or FLAG-IDA	Induction chemotherapy protocols as reported in Tavernier et al. 2007[133]
All patients with a MCyR response with ponatinib / induction chemotherapy undergo allo-SCT	For patients who achieve complete remission and are suitable candidates for transplantation, allo-SCT is considered to be the best therapeutic option[28]
Monitoring cost was the same as for CP-CML response and BP-CML without response	These costs were used in the absence of data specific to Ph+ ALL.
The same utilities used for patients with BP-CML were used for patients with Ph+ ALL, derived from Szabo et al. 2010[249]	Absence of data specific for ALL; survival in BP is generally only a few month, as in Ph+ ALL, and BP health state utilities are the closest approximation for health state utilities in acute leukaemia
Quality of life reduction associated with AEs is applied in the first model cycle only	Based on the assumptions that AEs happen sooner rather than later and that patients experience an event only once
AE rates are set to 0 for induction chemotherapy and BSC	Based on a lack of clinical evidence for comparators most conservative assumption

AE, adverse event; ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; BP, blast phase; CML, chronic myeloid leukaemia; MCyR, major cytogenetic response; Ph+, Philadelphia chromosome–positive.

5.5.6 Base-case results

5.5.6.1 Results of the analysis

Base-case incremental cost effectiveness analysis results

5.5.6.2 Cost-effectiveness

The ICER results for ponatinib compared with each comparator in terms of LYG and QALYs, from the NHS/PSS direct medical perspective, are presented in Table 5-75. For patients receiving allo-SCT in remission, ponatinib compared with induction chemotherapy yields an incremental cost-effectiveness of [redacted].

Table 5-75. Base-case cost-effectiveness results (discounted, per person): direct medical perspective

	Total costs (£)	Total LYG (Disc)	Total QALYs (Disc)	Incremental costs (£) (ponatinib vs)	Incremental LYG (ponatinib vs)	Incremental QALYs (ponatinib vs)	ICER (£/LYG)	ICER (£/QALYs)
Patients suitable for allo-SCT								
Induction chemotherapy	69,180.82	2.96	1.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	15,982.70	0.32	0.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Patients unsuitable for allo-SCT								
BSC	15,982.70	0.32	0.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–

Allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; Disc, discounted; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year; Undisc, undiscounted.

Clinical outcomes from the model

5.5.6.3 Outcomes from the model vs clinically important outcomes

While no formal analysis of face validity was undertaken for the AP/BP-CML model (given the much smaller patient population in comparison with CP-CML), all key outcome parameters were based on the best available data.

5.5.6.4 Markov trace

The Markov traces for the Ph+ ALL economic analysis are presented in Appendix 23: Markov traces – Ph+ ALL economic model.

5.5.6.5 QALYs accrued over time

QALYs for each health state accrued over time for each comparator in the Ph+ ALL economic analysis are presented in Appendix 24: QALYS over time – Ph+ ALL economic model.

Disaggregated results of the base case incremental cost effectiveness analysis

5.5.6.6 Disaggregated QALYs, LYGs, and costs

5.5.6.6.1 QALYs and life-years gained

A summary of the treatment-specific deterministic survival and quality-adjusted survival estimates resulting from the analysis is presented in Table 5-55. Of the therapies being compared, ponatinib is associated with the largest increase in both OS and QALYs, with the greatest benefit seen in patients who proceed to allo-SCT in remission. Compared to induction chemotherapy, treatment with ponatinib is predicted to increase real life (undiscounted) by [redacted]. BSC yielded lower OS and QALYs than any other comparator.

Table 5-76. Survival and QALY results

	LYG				QALY			
			Total				Total	
	Ph+ ALL	Allo-SCT	Undisc	Disc	Ph+ ALL	Allo-SCT	Undisc	Disc
Patients suitable for allo-SCT								
Induction chemotherapy	0.25	6.19	6.44	2.96	0.09	3.88	3.96	1.84
BSC	0.33	0.00	0.33	0.32	0.10	0.00	0.10	0.09
Ponatinib	[redacted]							
Patients unsuitable for allo-SCT								
BSC	0.33	0.00	0.33	0.32	0.10	0.00	0.10	0.09
Ponatinib	[redacted]							

Allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; Disc, discounted; LYG, life-year gained; QALY, quality-adjusted life-year; Undisc, undiscounted.

Table 5-77 and Table 5-78 list the incremental disaggregated QALYs and LYG by health state results for ponatinib vs each comparator.

Table 5-77. Summary of QALY gain by health state (discounted)

Health state	QALY ponatinib	QALY comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs induction chemotherapy					
Ph+ ALL	[redacted]	0.08	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	1.75	[redacted]	[redacted]	[redacted]
Total	[redacted]	1.84	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC					
Ph+ ALL	[redacted]	0.09	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.00	[redacted]	[redacted]	[redacted]
Total	[redacted]	0.09	[redacted]	[redacted]	[redacted]

Health state	QALY ponatinib	QALY comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs BSC (patients unsuitable for allo-SCT)					
Ph+ ALL	[redacted]	0.09	[redacted]	[redacted]	[redacted]
Allo-SCT	-	-	-	-	-
Total	[redacted]	0.09	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; Ph+, Philadelphia chromosome–positive; QALY, quality-adjusted life-year. Table was 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

Table 5-78. Summary of LYG gain by health state (discounted)

Health state	LYG ponatinib	LYG comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs induction chemotherapy					
Ph+ ALL	[redacted]	0.25	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	2.71	[redacted]	[redacted]	[redacted]
Total	[redacted]	2.96	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC					
Ph+ ALL	[redacted]	0.32	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0.00	[redacted]	[redacted]	[redacted]
Total	[redacted]	0.32	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC (patients unsuitable for allo-SCT)					
Ph+ ALL	[redacted]	0.32	[redacted]	[redacted]	[redacted]
Allo-SCT	-	-	-	-	-
Total	[redacted]	0.32	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; Ph+, Philadelphia chromosome–positive; LYG, life-year gained. 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.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

5.5.6.6.2 Costs

Of the pharmacologic treatments under consideration, ponatinib has the highest main drug cost (Table 5-79). The TKI cost of ponatinib for patients unsuitable for allo-SCT is twice that of ponatinib treatment for patients who achieve remission and proceed to allo-SCT as these patients remain on treatment longer than patients who receive transplantation. The total cost of ponatinib is only marginally higher than the cost of induction chemotherapy. The apparently higher AE-related costs for ponatinib reflect the availability of more AE data for ponatinib rather than a genuinely higher rate of AEs compared to the other treatments.

Table 5-79. Cost results (discounted)

Cost, £	Ponatinib	Induction chemotherapy	BSC	Ponatinib (patients unsuitable for allo-SCT)
Main drug	[redacted]	0.00	0	[redacted]
Other drugs	1,020.81	17,845.59	4,029.07	2,189.92
Allo-SCT*	53,413.70	42,203.41	0.00	0.00
Monitoring/follow-up	6,904.64	4,005.64	6,301.23	7,608.61
Adverse events	568.27	0.00	0.00	663.92
End-of-life	4,951.22	5,126.17	5,652.40	5,478.40
Total	[redacted]	69,180.82	15,982.70	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care.

*Includes costs associated with procedure and relapse.

Table 5-80 summarises the costs by health state to identify which health states are responsible for most differences in costs between ponatinib and the comparators.

Table 5-80. Summary of cost by health state (discounted)

Health state	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs induction chemotherapy					
Ph+ ALL	[redacted]	23,484	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	45,696	[redacted]	[redacted]	[redacted]
Total	[redacted]	69,181	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC					
Ph+ ALL	[redacted]	15,983	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	0	[redacted]	[redacted]	[redacted]
Total	[redacted]	15,983	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC (patients unsuitable for allo-SCT)					
Ph+ ALL	[redacted]	15,983	[redacted]	[redacted]	[redacted]
Allo-SCT	-	-	-	-	-
Total	[redacted]	15,983	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care; Ph+, Philadelphia chromosome–positive. 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

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

Table 5-81 summarises the predicted resource use by category of cost for ponatinib vs each comparator.

Table 5-81. Summary of predicted resource use by category of cost (discounted)

Resource use	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Ponatinib vs induction chemotherapy					
Main drug	[redacted]	-	[redacted]	[redacted]	[redacted]
Other drugs	1,021	17,846	-16,825	16,825	[redacted]
Allo-SCT*	53,414	42,203	11,210	11,210	[redacted]
Monitoring/ follow-up	6,905	4,006	2,899	2,899	[redacted]
Adverse events	568	-	568	568	[redacted]
End-of-life	4,951	5,126	-175	175	[redacted]
Total	[redacted]	69,181	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC					
Main drug	[redacted]	-	[redacted]	[redacted]	[redacted]
Other drugs	1,021	4,029	-3,008	3,008	[redacted]
Allo-SCT*	53,414	-	53,414	53,414	[redacted]
Monitoring/ follow-up	6,905	6,301	603	603	[redacted]
Adverse events	568	-	568	568	[redacted]
End-of-life	4,951	5,652	-701	701	[redacted]
Total	[redacted]	15,983	[redacted]	[redacted]	[redacted]
Ponatinib vs BSC (patients unsuitable for allo-SCT)					
Main drug	[redacted]	-	[redacted]	[redacted]	[redacted]
Other drugs	2,190	4,029	-1,839	1,839	[redacted]
Allo-SCT*	-	-	-	-	[redacted]
Monitoring/ follow-up	7,609	6,301	1,307	1,307	[redacted]

Resource use	Cost (£) ponatinib	Cost (£) comparator	Increment	Absolute increment	% absolute increment
Adverse events	664	-	664	664	[redacted]
End-of-life	5,478	5,652	-174	174	[redacted]
Total	[redacted]	15,983	[redacted]	[redacted]	[redacted]

Allo-SCT, allogeneic haematopoietic stem cell transplantation; BSC, best supportive care. 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.

*Includes costs associated with procedure and relapse.

Note: increments and totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

5.5.7 Sensitivity analyses

Probabilistic sensitivity analysis

5.5.7.1 Measure of decision uncertainty

To address the uncertainty in the parameters used within the model, a PSA was implemented. The PSA was performed on the comparison between ponatinib vs induction chemotherapy, since this the main comparator in Ph+ ALL.

5.5.7.2 Parameter distributions

The parameters and their corresponding distributions that were used in the PSA are presented in Table 5-82. For all parameters, the distribution used was Beta (for parameters whose possible values are constrained between 0 and 1), Normal, or Gamma. The distributions were calculated with the mean values (base case) and the standard error (SE). Where the SE was not available, it was assumed as 10% of the mean. Mean results were calculated from the 1000 simulations in this analysis.

Table 5-82. PSA distributions

Parameter	Distribution
Adverse event rates	Beta
Costs	Gamma
HRQoL	Beta
Number of EOL hospital days	Gamma
OS curve-fitting parameters (ponatinib)	Cholesky decomposition
OS curve-fitting parameters (allo-SCT)	Gamma
OS, median (BSC)	Gamma
Proportion treated in hospital/hospice at end of life	Gamma
Resource use rates	Gamma
Response rates	Beta
Time on treatment	Cholesky decomposition

Allo-SCT, allogeneic haematopoietic stem cell transplantation; EOL, end of life, HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis.

5.5.7.3 Results of probabilistic sensitivity analysis

Table 5-37 reports the 95%CI for incremental costs, QALYs, and ICERs.

Table 5-83. 95% CI for costs, QALYs, and ICERs

	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]

Figure 5-31 shows the incremental costs and QALYs derived from the 1000 simulations of the PSA for ponatinib vs induction chemotherapy. This graph demonstrates that most simulations are generally consistent with the base-case ICER.

Figure 5-31. Results of 1000 simulations in the PSA for the ICER of ponatinib vs induction chemotherapy

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 5-32 shows the cost-effectiveness acceptability curve derived from the PSA. As can be seen, at an ICER threshold of approximately £12,000, over [redacted]% of simulations will be cost-effective. At a WTP threshold of ≤£20,000, [redacted]% of iterations were cost-effective and at a WTP threshold of ≤£30,000, [redacted]% of iterations were cost-effective.

Figure 5-32. Cost-effectiveness acceptability curve in the PSA for the ICER of ponatinib vs induction chemotherapy

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

5.5.7.4 ICER results from base-case vs PSA

Results of the PSA were consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values.

Deterministic sensitivity analysis

5.5.7.5 Parameters

In order to assess the impact of each of the inputs on the overall result, a univariate analysis was conducted to identify the parameters with greatest influence on the model results. Each parameter selected was set to extreme values, holding all other parameters constant, to understand how sensitive the ICER is to changes in the inputs. The upper and lower values for parameters fully aligned with the CP-CML model, are shown in Table 5-38. The upper and lower values unique to the Ph+ ALL economic analysis are presented in Table 5-84. Values were set based on the 95% CI of the base-case value if directly available, or calculated ±1.96 × the standard error (SE). If the SE was not available it was assumed as ±10% of the mean value. For resources for monitoring and follow-up, upper and lower values in the sensitivity analysis were derived from the CML survey of UK clinical experts.[48] Discount rates of 0% and 6% were also assessed.

Table 5-84. Parameter values in the deterministic sensitivity analysis (parameters with zero for base-case, lower and upper values are not presented)

Parameter	Base case	Method*	Lower value	Upper value
Cumulative incidence				
Abdominal pain ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Anaemia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Lipase increased ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Neutropaenia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Febrile neutropaenia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Thrombocytopaenia ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Remission rate				
Induction chemotherapy	0.37037	±1.96 * SE	0.29778	0.44296
Ponatinib (MCyR)	0.46875	±1.96 * SE	0.37688	0.56063
Per-cycle cost, £				
BSC	4,063.87	±1.96 * SE	3,267.35	4,860.39
Induction chemotherapy	17,999.73	±1.96 * SE	14471.8	21527.7
Ponatinib	[redacted]	±1.96 * SE	[redacted]	[redacted]
Per-cycle probability (ponatinib only)				
Cardiovascular event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Cerebrovascular event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Peripheral vascular event	[redacted]	±1.96 * SE	[redacted]	[redacted]
Venous thromboembolism event	[redacted]	±1.96 * SE	[redacted]	[redacted]

BSC, best supportive care; MCyR, major cytogenetic response: SE, standard error.

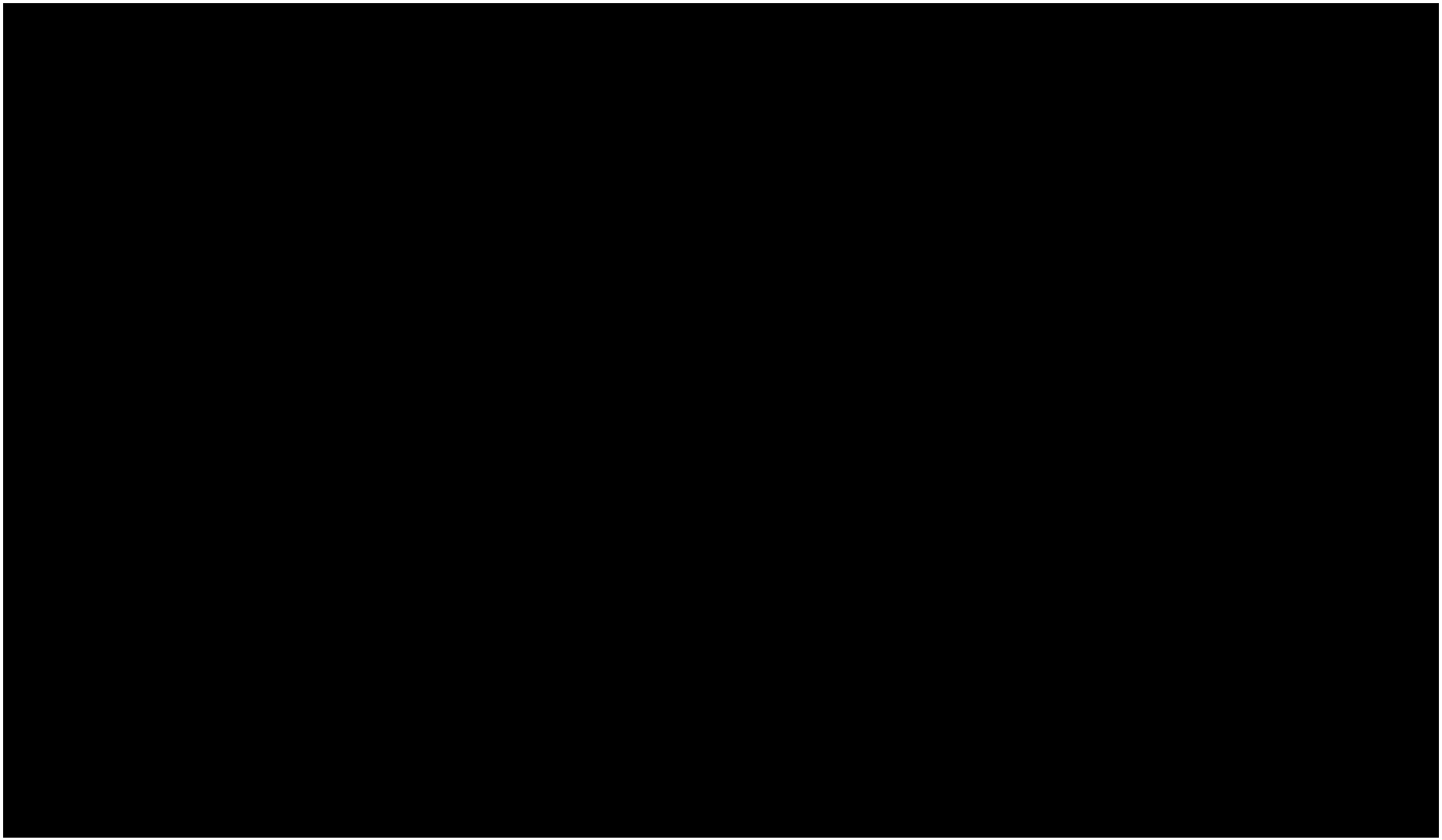
*SE was set to 10% base-case value.

5.5.7.6 Results of deterministic sensitivity analysis

Results of the univariate sensitivity analysis are presented as a tornado plot (Figure 5-33) for the pairwise comparison of ponatinib vs BSC (patients unsuitable for allo-SCT). The analysis was run on all model parameters. The relative efficacy was captured by varying response rates in the OWSA. The ICERs are most sensitive to changes in the cost of ponatinib and response rate with ponatinib. Other influential parameters included the utility value for Ph+ ALL in response and the discount rate for outcomes.

[235]

Figure 5-33: Tornado plot displaying the most influential parameters for the ICER of ponatinib vs BSC (patients unsuitable for allo-SCT)



BSC, best supportive care; EOL, end of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; OS, overall survival; Util, utilities.

5.5.7.7 Sensitivity analysis of technology prices

Sensitivity analyses of technology prices were incorporated in the one-way and probabilistic sensitivity analyses in terms of per-cycle costs, as described above.

5.5.7.8 Scenario analysis

No scenario analyses were carried out.

5.5.7.9 Summary of sensitivity analysis results

5.5.7.9.1 Summary of deterministic and probabilistic sensitivity analyses

Deterministic sensitivity analyses reveal that the parameters most strongly influencing the results include the cost of ponatinib, response rate with ponatinib, utility value for Ph+ ALL in response, and discount rate for outcomes. Cost-effectiveness results for ponatinib compared with induction chemotherapy in the PSA were similar to those in the base-case analysis.

5.6 Subgroup analysis

Not applicable.

5.7 Validation

5.7.1 Validation of de novo cost-effectiveness analysis

Design of the model

For the CP-CML, AP/BP-CML, and Ph+ ALL models, in the stage of model design, the structure of the model, the main assumptions and data sources as well as key features of the model such as health states, time horizon, survival, and quality of life, have been presented and discussed in one advisory board meeting with expert UK health economists who had previously been involved in NICE submission in CML and who authored several publications in this field, as well as in a separate meeting with an eminent UK professor in health economics (February 2014). Their comments were incorporated into model design and the full economic model was developed.

In addition, the following core assumptions of the final CP-CML model were validated by Dr Richard Clark, a Professor of Haematology at the University of Liverpool:[246]

1) Response to TKI is the most important prognostic factor in CP-CML, irrespective of the TKI used.
2) In CML in CP there is no excess mortality (compared to the general population) due to the disease itself and the excess mortality of CML is due to progression to advanced phases of the disease.
3) The presence of T315I mutation does not predict treatment response to ponatinib.
4) Distribution of the time on treatment in different doses observed in PACE study can be considered a proxy of ponatinib use in clinical practice.
5) OS with ponatinib in CP-CML predicted by the model is clinically plausible.
6) Median OS post–allo-SCT in CP and AP predicted in the model is clinically plausible.

Model QC

The accuracy of the calculation performed in the cost-effectiveness models was checked in a number of ways. First, the interim and final results produced by the model were compared with the input data for clinical and economic plausibility. Second, random checks were made on specific elements of the calculation. Finally, the entire model has been revised by a senior health economist not previously involved in the project whose comments and suggestions were incorporated into the model.

A further step of internal validity was performed by comparing the OS predicted by the CP-CML model in the case of ponatinib treatment against the OS recorded in the PACE study and its potential extrapolation (see Section 5.3.6.3).

External review

Due to the market access process followed by the manufacturer of ponatinib, substantially the same design of cost-effectiveness models and clinical input data have been used to support reimbursement applications in a number countries, including Wales and Scotland, Ireland, Canada, Australia, Sweden, Norway, Finland, Italy, Portugal, and Poland, among others. The current models submitted here reflect the outcome of this long revision process, which included review and discussion with local clinical experts, and questions and comments (including the amendments done in response to their questions) received from HTA authorities in many countries.

As a last step, prior to the submission to NICE, the entire submission document, with a predominant focus on the cost-effectiveness sections, has been reviewed by an expert UK health economist previously involved only marginally in the project (to conduct the survey for healthcare resources).

5.8 Interpretation and conclusions of economic evidence

The ponatinib economic models are structurally transparent and clinically relevant tools to estimate the costs and benefits associated with treatment in the post–2G-TKI CML and Ph+ ALL patient populations. Central to the model structure are the assumptions that depth of response is predictive of time to disease progression and that this relationship holds across therapies. Hence, a person who achieves at best a PCyR at one year will have a poorer prognosis than a person who achieves a CCyR. Differences in general prognosis between lines of therapy are incorporated via the probability of an individual achieving a given strength of response. These approaches were validated by an international panel of clinicians, modellers, and reimbursement specialists.

CML

Cost-effectiveness results for ponatinib in CP-CML showed that, compared with the drug comparators, ICERs were below £30,000/QALY for all comparisons. [redacted].

Ponatinib incurred lower total cost than bosutinib in AP-CML and than both hydroxycarbamide and allo-SCT in BP-CML, and was thus dominant in those comparisons. In the other comparisons, ICERs remained well below the acceptability threshold even for non–end-of-life interventions, ranging from [redacted].

Ph+ ALL

For patients receiving allo-SCT in remission, ponatinib yielded an ICER of [redacted].

The cost-effectiveness results for ponatinib in CML and Ph+ ALL should be considered in the context of the high clinical need for an effective 3L treatment, the substantially higher response rates achieved with ponatinib compared to those seen with bosutinib, and the use of ponatinib as a bridge to allo-SCT as clinically appropriate.

A main finding of the model is that ponatinib offers a substantial clinical benefit compared to existing therapy in the target population defined in the EMA-approved indication. The gain of QALYs with ponatinib exceeded that of all comparators. When all clinical inputs are extrapolated over patient lifetime in the CP-CML model, ponatinib was shown to offer an increase in discounted OS of [redacted] compared with bosutinib, and when the discussion is limited to time in the CP-CML disease stage, the use of ponatinib resulted in a substantial increase in time-in-

state. Hence the long-term clinical outlook associated with ponatinib use is highly encouraging. The CP-CML model does not predict an excess benefit (OS), but rather underestimates the benefit starting in year 3 (Figure 5-13). It should be emphasised that many new interventions in oncology are costly but produce relatively small gains in life expectancy or HRQoL in relation to existing treatments;[270] thus, the large increases in QALYs and OS seen with ponatinib in this model are noteworthy. Also notable is the improvement in outcomes predicted following allo-SCT in patients in AP/BP-CML who first achieve remission with ponatinib instead of proceeding directly to allo-SCT.

In terms of cost-utility, the ICERs of ponatinib relative to other treatment can be interpreted as being acceptably cost-effective, given the widespread recognition of the unique circumstances of care for cancer patients who have exhausted other treatment options; several countries have adopted more flexible reimbursement criteria for cancer drugs, accepting treatments with ICERs that may fall above the threshold applied to other diseases.[270] The incremental cost-utility in CP-CML ranges from [redacted]. In AP/BP-CML, ponatinib is in some scenarios dominant over comparators, and highly cost-effective in other comparisons, as it is in Ph+ ALL. These values fall well within the range of cost-effectiveness ratios for numerous interventions (not only in cancer indications) that have been granted reimbursement in England[271] and in other developed countries.[272]

The model revealed that as a result of ponatinib patients remaining within the CP-CML phase for longer than they would have with pharmacologic comparator treatments, costs related to disease progression are reduced compared to the other treatments. Therefore, ponatinib should be viewed as a meaningful addition to the therapeutic options available to reduce the burden of CML on patients, the healthcare system, and society.

5.8.1 Strengths and limitations

The models used in this analysis have a number of strengths and important limitations. The structure was informed by a formal review of previous economic models of CML and was validated in advance of construction by an international panel of clinicians and health technology assessment experts. Access to patient-level data from the pivotal ponatinib clinical trial permitted a detailed approach to modelling key parameters including cytogenetic response category, dose-specific time-on-treatment, and best response rates for ponatinib. Nonetheless, there are some limitations to the analysis undertaken, most of which relate to CML being an orphan disease and thus few patients who have failed or are intolerant to 2G-TKI–based therapy are available for data generation.

A main source of uncertainty in the model is the use of non-comparative data from the PACE trial. A comparative study was not possible for ethical reasons, and both the EMA and FDA confirmed the single-arm study approach during scientific advice meetings in advance of ponatinib's marketing authorisation. Nevertheless, we have attempted to address this limitation by carrying out a MAIC between ponatinib and bosutinib (Section 4.10). Furthermore, multiple sensitivity and scenario analyses were performed to assess the robustness of the base-case cost-effectiveness results; notably, the scenario analysis using a 25% reduction in ponatinib efficacy (CCyR rate) showed that the ICER remained below £30,000/QALY.

Although most clinical inputs for ponatinib were sourced from the PACE study, it was not possible to derive the PFS function from this clinical trial as too few patients progressed to AP-CML (5 patients) or BP-CML (4 patients).[25] Instead, the estimated progression from CP-CML to AP-/BP-CML was based on extrapolation of data from a retrospective analysis of outcomes in patients who were intolerant or resistant to imatinib regimens at a single centre.[29] Although this introduces a discrepancy in patient populations, it reflects a conservative approach, given that a much lower rate of progression was actually observed for patients receiving ponatinib in the PACE study versus the rate used in the model. As a general rule, we have opted for approaches that are conservative to avoid biasing results in favour of ponatinib.

Several key areas of uncertainty have been evaluated in scenario analyses, results of which show that ICERs remain under £30,000/QALYS, and even in the most pessimistic scenarios, ICERs are remarkably low in the context of cancer care cost-effectiveness broadly (Section 5.3.7.9.2).

Benefit beyond treatment discontinuation rationale

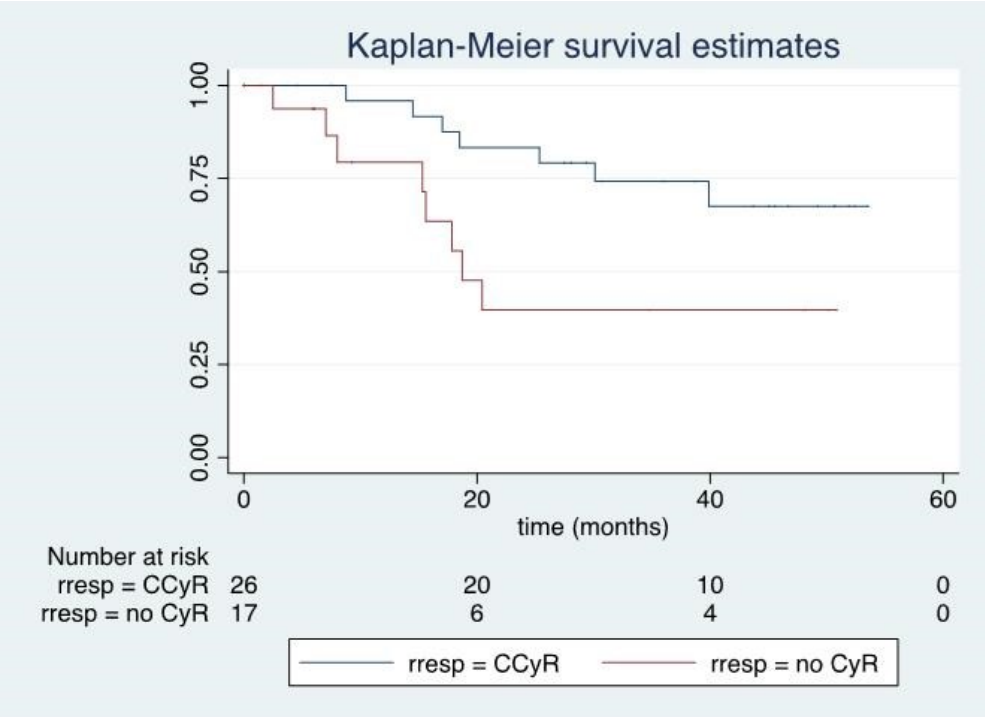
In our model, we assume a benefit beyond treatment discontinuation for patients who achieve CCyR. The issue of benefit beyond TKI treatment discontinuation is addressed in the most realistic way: namely, only patients who achieve a CCyR maintain their response after TKI discontinuation. For all other response categories (PCyR, CHR, and no response) patients who discontinue a TKI adopt the response rates of the BSC comparator. In the base case, although patients with CCyR maintain some benefit beyond treatment discontinuation, it is also true that loss of CCyR is accounted for and that, at loss of CCyR, patients are assumed to follow the PFS trajectory in the CHR response category. Therefore, patients maintain benefit only if CCyR is maintained.

This approach is clinically realistic because, by definition, CCyR indicates that there are no detectable Ph+ metaphases, thus reflecting a level of disease control considered optimal in ELN guidelines.[47] When in CCyR, leukaemic clones can still be present, but at a level below the detection of modern cytogenetic analysis. CCyR doesn't necessarily mean the disease is cured, but it reflects a greatly reduced burden of cancer. This notion aligns with the ELN recommendations defining Ph+ 0% as a targeted 12-month optimal response to 2L TKI therapy after imatinib failure.[47] Once CCyR is achieved, disease control will be easier to maintain—even in the absence of treatment—than it was to achieve. This is possible, for example, because a patient's immune system may contribute to CML control when in this state.[273] Data from imatinib discontinuation studies reveal that patients who maintain a deep molecular response for a long period of time can remain in remission after TKI discontinuation, demonstrating that a clinical benefit beyond treatment discontinuation persists among responders.[274-276] Between 40% and 60% of patients who achieve deep molecular response on 1L imatinib and discontinue treatment remain in remission for years.[273] We acknowledge that these studies that report treatment-free remission post-TKI discontinuation are in patients who have achieved a deep molecular response. However, this evidence is supportive of the assumption that patients who achieve CCyR have a better health status—which allows them to maintain their response following treatment discontinuation and to survive longer on hydroxycarbamide—than had they not achieved CCyR.

In this context, the long time-on-treatment observed with ponatinib is especially relevant, since maintenance of an effective TKI treatment for a prolonged period of time may contribute to the suppression of leukaemic activity. This hypothesis is supported by data from the Stop Imatinib (STIM) trial (Mahon et al. 2010),[277] in which a longer duration of treatment on imatinib predicted improved prognosis; compared with patients on treatment for ≥50 months, those on therapy for <50 months were, after treatment discontinuation, significantly more likely to relapse.[277]

Moreover, maintenance of benefit beyond treatment discontinuation for patients who discontinue in CCyR is directly grounded on clinical evidence from the PACE study. Arbitrarily removing any benefit beyond discontinuation in the model would conflict with observed data and clinical treatment strategies outlined in guidelines. In the PACE trial, patients who discontinued treatment when in CCyR have an OS significantly better than patients who discontinued while not in CCyR (Figure 5-34). In the PACE study, among patients who achieved CCyR and discontinued treatment, the median OS post-treatment discontinuation was not reached. Extrapolating the data yields an OS of approximately 14 years. Among patients without CCyR, the median OS post-treatment discontinuation is slightly less than 5 years, which is similar to OS with hydroxycarbamide in the model ([redacted]). For this reason, loss of benefit beyond treatment discontinuation is simulated in the model for all response cohorts except CCyR.

Figure 5-34. Survival of patients with CP-CML who discontinue 3L treatment by CCyR status* (PACE study data cut-off, 3 Aug 2015)



CCyR, complete cytogenetic response.

*Six patients with PCyR were not included in the analysis because no death events were recorded.

Assuming a benefit beyond treatment discontinuation in this way yields realistic results: in the CP-CML base case, the model predicts a [redacted]. The UK clinical expert haematologist has confirmed that the predicted median OS for ponatinib is clinically plausible.

It should be emphasised that even assuming this benefit beyond treatment discontinuation, our analysis remains conservative with respect to patient outcomes on ponatinib, as the model predicts higher excess mortality than was actually observed in the clinical trial. In the general UK population, in a cohort with the same starting age and gender distribution as in PACE and as simulated in the CP-CML model (54.5 years, 44.9% males), 98.3% of these persons would still be alive after 4 years. In the PACE study, 79.5% of patients with CP-CML treated with two prior TKIs were alive after 4 years;[24] therefore, the excess mortality in the PACE trial with respect to the general population is calculated to be 18.8%. In contrast, in our base-case simulation in the CP-CML economic analysis 70.1% of patients are alive after 4 years; therefore, the excess mortality with respect to the general population is calculated to be 28.2 in the simulation. These calculations show that excess mortality at 4 years is higher in the ponatinib model simulation than what is observed in the clinical trial.

An alternative method to model treatment benefit would be to assume the cumulative survival approach, however, this results in a projection of outcomes that lack face validity and clinical plausibility. With the cumulative survival approach, OS in the model would differ substantially from the observed OS in the PACE study (Figure 5-35). OS with ponatinib and hydroxycarbamide would be 8.09 years ([redacted]). In the PACE study,[24] however, 80% of CP-CML patients are alive at 4 years, and this rate includes patients who discontinue treatment, since patients in the PACE study are followed up for OS after treatment discontinuation (for up to 96 months from the time the last patient was assigned to treatment).[25] In order to have an OS of 8.09 years, when 80% of patients are still alive at 4 years, the survival curve would need to decrease prominently after 4 years. As shown by the lowest curve in Figure 5-35, the observed median 4-year OS in the PACE study would have had to be 60% - much lower than the observed survival in the trial - in order to reach the OS level one would find from the cumulative survival approach.

In addition, the excess mortality rate adopting the cumulative survival approach would be 38.3%, higher than what is observed in the PACE trial and simulated in the economic analysis (18.8% and 28.2%, respectively).

Figure 5-35. OS estimated in the model vs observed in the PACE study CP-CML 3L cohort (Hochhaus et al. 2015)[24]

OS, overall survival.

In conclusion, the CP-CML model does not predict an excess survival benefit over the long term compared with the OS data from the PACE trial. On the contrary, the model is conservative with respect to ponatinib, as the percentage of deaths is overestimated and the OS benefit is underestimated.

6 Assessment of factors relevant to the NHS and other parties

6.1 Overview

Sections 6.2–6.10 provide details on factors relevant to the NHS and other parties and the results of the budget impact analysis.

6.2 Number of people eligible for treatment in England

Table 6-1 presents the number of people eligible for ponatinib in England according to the full marketing authorisation. The number of patients eligible for treatment is assumed to be constant over the next 5 years.

Table 6-1. Number of eligible patients for ponatinib in England

	%	2016	Source
CML			
Incident CML population		631	Office of National Statistics, Cancer Statistics Registrations, England 2014[4]
Ph+ CML	95%	599	Goldman et al. 2009[147]
Treated with 1L TKI (imatinib)		599	Assumption, all patients are treated with imatinib
Failure 1L	36%	216	Kalmanti et al. 2015[148]
Developing T315I during 1L	2%	13	Hughes et al. 2015[149]
Treated with 2L TKI		203	Assumption, all patients are treated with a 2L TKI, except those with T315I mutation
Failure 2L, except progression	48%	95	Kantarjian et al. 2011[111]
Progressing to AP/BP-CML	3%	6	Giles et al. 2013[113]
Total number eligible for ponatinib		**113**	
Ph+ ALL			
Incident ALL population		654	Office of National Statistics, Cancer Statistics Registrations, England 2014[4]
Ph+ ALL	25%	164	Fielding et al. 2007[150]
Treated with 1L TKI (imatinib)		164	Assumption, all patients are treated with imatinib
Failure 1L	30%	49	Lilly et al. 2010[16]
Developing T315I during 1L	13%	6	Pfeifer et al. 2012[154]
Treated with 2L TKI (dasatinib)		43	Assumption, all patients are treated with a 2L TKI, except those with T315I mutation
Failure 2L	62%	26	Lilly et al. 2010[16]
Total number eligible for ponatinib		**33**	

1L, first line; 2L, second line; 3L, third line; ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

Note: The number of patients presented in this table are as calculated by the budget impact model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table, due to rounding error.

6.3 Assumptions that were made about current treatment options and uptake of technologies

Table 6-2 presents the market shares before and in the years after the introduction of ponatinib. For CML, the main current treatment option is allo-SCT, with a minority of patients receiving bosutinib or dasatinib (even though dasatinib is not approved in the target patient population). We do not consider bosutinib as the main comparator to ponatinib for the reasons outlined in the de novo economic analysis (see Section 5.3.1.5.2). Briefly, ponatinib is not comparable to bosutinib due to the low efficacy demonstrated by bosutinib (Khoury et al. 2012)[8] and the lack of robust data in patients with unmet need.[36, 102] Moreover, a proportion of patients treated with ponatinib will be T315I–mutation-positive, and therefore, by definition, not treatable with any other TKI.[7, 22] We assume the market share for ponatinib in CML is [redacted]. It is expected that all ponatinib market share will be captured from allo-SCT, and thus the market share for bosutinib and dasatinib remains constant each year across the 5-year time horizon.

For Ph+ ALL, the current treatment option is induction chemotherapy. We assume a [redacted] uptake of ponatinib in the first year, with the resulting [redacted] market share remaining constant across the time horizon after the introduction.

Table 6-2. Market shares before and in the years after the introduction of ponatinib

	Prior to year 1	Year 1	Year 2	Year 3	Year 4	Year 5
CML						
Ponatinib	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph+ ALL						
Ponatinib	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction chemotherapy	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; CML, chronic myeloid leukaemia; Ph+, Philadelphia chromosome–positive.

6.4 Assumptions about market share in England

Table 6-3 presents the number of patients starting and continuing treatment over the next 5 years. CP-CML is a chronic condition so we assume patients accrue each year. After TKI discontinuation, we assume patients receive BSC. We assume the same discontinuation rate for all TKIs, estimated in an annual probability of [redacted] from PACE patient-level data. In Ph+ ALL, patients do not accrue across years because ponatinib and induction chemotherapy are used as a bridge to transplantation for eligible patients who achieve remission. With ponatinib, patients not responding remain on treatment, but almost all of them discontinue after one year (from PACE patient-level data only [redacted] not responding are on treatment after 12 months).

Table 6-3. Number of patients per treatment over the next 5 years

	Year 1	Year 2	Year 3	Year 4	Year 5
CML					
Potential number of new eligible patients in licence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New patients starting ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated with ponatinib (considering annual interruption)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New patients starting dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated with dasatinib (considering annual interruption rate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New patients starting bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated with bosutinib (considering annual interruption rate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients receiving allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ph+ ALL					
Potential number of new eligible patients in licence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction chemotherapy market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving induction chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; CML, chronic myeloid leukaemia; Ph+, Philadelphia chromosome–positive.

Note: The numbers in the budget impact model carry greater precision than the whole numbers presented in the table. For example, when calculating Ph+ ALL costs, the number of Ph+ ALL patients receiving ponatinib or induction chemotherapy is carried to 6 decimal places.

6.5 Other costs

The costs considered in the budget impact analysis are:

- TKI
- BSC post-TKI discontinuation
- Monitoring and follow-up
- Management of AEs
- Allo-SCT

6.6 Unit costs

All unit costs used in the budget impact analysis were derived from the cost-effectiveness models. Table 6-4 presents the annual costs for each cost considered in the analysis. CML is a chronic condition so patients who do not undergo allo-SCT remain on TKI treatment or, in the event of TKI failure, receive BSC. Monitoring costs are considered for patients who are treated with TKIs; follow-up costs are considered for allo-SCT. In Ph+ ALL, patients who respond to treatment receive allo-SCT. We assume no difference in monitoring for patients who fail to respond to treatment. For patients receiving induction chemotherapy, only one cycle of chemotherapy is administered (6-week course). Patients on ponatinib receive a 6-week course before allo-SCT (half cycle); those who do not respond to treatment remain on ponatinib. In the PACE study, the mean time on treatment of Ph+ ALL patients without MCyR is 3.07 months

(estimated with a log-logistic model fitted to PACE patient-level data). Thus, we assume a single cycle of ponatinib is attributed to patients with no MCyR.

Table 6-4. Annual costs of treatments, monitoring and follow-up, management of AEs, and allo-SCT

	Annual cost (£)
CML	
Cost ponatinib	[redacted]
Cost dasatinib	30,498
Cost bosutinib	42,858
Cost BSC (post-TKI interruption)	153
Monitoring with ponatinib	1,577
Monitoring with dasatinib	1,621
Monitoring with bosutinib	1,703
Monitoring with BSC	1,980
AEs ponatinib (first year)	885
CV AEs ponatinib	305
AEs dasatinib (first year)	588
CV AEs dasatinib	0
AEs bosutinib (first year)	466
CV AEs bosutinib	0
Allo-SCT	60,092
Follow-up post–allo-SCT*	4,143
Ph+ ALL	
Cost ponatinib (with response)	[redacted]
Cost ponatinib (no response)	[redacted]
Cost induction chemotherapy	18,000
AEs ponatinib (first year)	467
CV AEs ponatinib	704
Allo-SCT	60,092

AEs, adverse events; ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; CML, chronic myeloid leukaemia; CV, cardiovascular; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

*Average cost per year over a 4-year period.

6.7 Resource savings

No estimates of resource savings were considered in the budget impact analysis.

6.8 Estimated annual budget impact

Table 6-5 presents the estimated annual budget impact on the NHS in England for the CML and Ph+ ALL indications. For CML, the introduction of ponatinib confers a net savings in years 1 and 2. As ponatinib gains market share and patients accrue on treatment, the budget impact increases marginally from year 3 onwards, rising to [redacted] in year 5. Summed across the model's time horizon, the net budget impact associated with the introduction of ponatinib for CML is projected to be [redacted], representing a 5% increase over the estimated 5-year budget without ponatinib. For Ph+ ALL, ponatinib confers a 1% net savings in each year after its introduction.

Table 6-5. Annual budget impact of ponatinib for CML and Ph+ ALL

	Cost (£)				
	Year 1	Year 2	Year 3	Year 4	Year 5
CML					
Without ponatinib					
Ponatinib	0	0	0	0	0
Other drug	[redacted]				
Monitoring and follow-up					
Management of AEs					
Allo-SCT					
Total					
With ponatinib introduced					
Ponatinib	[redacted]				
Other drug					
Monitoring and follow-up					
Management of AEs					
Allo-SCT					
Total					
Budget impact for CML					
Ph+ ALL					
Without ponatinib					
Ponatinib	[redacted]				
Chemotherapy					
Management of AEs					
Allo-SCT					
Total					
With ponatinib introduced					
Ponatinib	[redacted]				
Chemotherapy					
Management of AEs					
Allo-SCT					
Total					
Budget impact for Ph+ ALL					

AEs, adverse events; ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; CML, chronic myeloid leukaemia; Ph+, Philadelphia chromosome–positive.

6.9 Other opportunities for resource savings

The budget impact calculation for CML does not consider the lower response rates and poorer maintenance of response with bosutinib compared to ponatinib.[8, 9, 24, 186] Bosutinib may therefore be associated with a higher probability of progression—and thus higher costs—representing opportunities for resource savings with ponatinib.

6.10 Budget impact analysis limitations

The budget impact analysis does not consider lower response rates and poorer maintenance of response with bosutinib, which may impact resource utilisation and costs. Other limitations of the analysis are reliance on assumptions 6.3 and 6.4 and uncertainty regarding the market share estimates.

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8 Appendices (Submitted separately from Evidence Submission)

8.1 Appendix 1: SmPC

8.2 Appendix 1: EPAR

8.3 Appendix 1: EPAR procedural steps taken and scientific information after authorisation

8.4 Appendix 2: Search strategies for relevant clinical studies

8.5 Appendix 3: Quality assessment of RCTs

8.6 Appendix 4: Subgroup analysis

8.7 Appendix 5: Search strategy for indirect and mixed treatment comparisons

8.8 Appendix 6: Methods, results, outcomes, and quality assessment of the relevant trials in the indirect or mixed treatment comparison

8.9 Appendix 7: Programming language used in the MAIC analysis

8.10 Appendix 8: Quality assessment of the relevant non-randomised and non-controlled evidence

8.11 Appendix 9: Search strategy for adverse reactions

8.12 Appendix 10: Quality assessment of adverse reaction data

8.13 Appendix 11: Search strategy for cost-effectiveness studies

8.14 Appendix 12: Quality assessment of cost-effectiveness studies

8.15 Appendix 13: Search strategy for measurement and valuation of health effects

8.16 Appendix 14: Cost and healthcare resource identification, measurement, and valuation

8.17 Appendix 15: Checklist of confidential information

8.18 Appendix 16: Complete list of included studies identified in the SLR

8.19 Appendix 17: Complete list of studies excluded in the SLR

8.20 Appendix 18: Matching-adjusted indirect comparison (MAIC)

8.21 Appendix 19: Markov traces – CP-CML economic model

8.22 Appendix 20: QALYS over time – CP-CML economic model

8.23 Appendix 21: Markov traces – AP/BP-CML economic model

8.24 Appendix 22: QALYS over time – AP/BP-CML economic model

8.25 Appendix 23: Markov traces – Ph+ ALL economic model

8.26 Appendix 24: QALYS over time – Ph+ ALL economic model

8.27 Appendix 25: Parametric survival analysis and curve fitting

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Single technology appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Dear Anant,

The Evidence Review Group, School of Health and Related Research (ScHARR) and the technical team at NICE have looked at the submission received on 4 October 2016 from Incyte Corporation In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions **by 5pm on 11 November 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Paling, Technical Lead thomas.paling@nice.org.uk. Any procedural questions should be addressed to Stephanie Yates Project Manager stephanie.yates@nice.org.uk

Yours sincerely

Frances Sutcliffe
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Section A: Clarification on effectiveness data

General

A1. Please provide further details on the clinical pathway of care in England (section 3.3-3.7, company submission [CS]) in particular:

i. Please clarify that the case for the cost-effectiveness of ponatinib is being made only for use in third-line and does not consider use after interventions such as bosutinib.

ii. What treatment(s) would people be expected to receive following ponatinib in clinical practice? Please clarify why it is assumed that dasatinib, nilotinib, bosutinib, imatinib and hydroxycarbamide are used when a patient progressed to AP-CML following use of an intervention (ponatinib, bosutinib etc) in CP-CML but only the use of hydroxycarbamide is assumed following ponatinib treatment in patients with AP-CML.

iii. Please explain why data from a survey of UK clinical experts (p40 and Appendix 14, CS) were not used to calculate the number of patients with CML (section 3.4.2 and section 6.2) that would be eligible to receive ponatinib (within its licence indication) in England?

Literature searching

A2. The searches described in Appendix 2 (section 8.4) use a series of concept combinations to identify relevant citations. Please could you provide further clarification on i) the strengths and limitations of including the concept combinations noted below (in italics) in the search strategy for CML and Ph+ CML (i.e. risk of not identifying all the relevant evidence (Appendix 2, CS))? ii) How many more records would the strategy retrieve without these statements? iii) How did the company investigate the impact of combining these statements on the results retrieved compared to the absence of these statements?

1. Appendix 2 (section 8.4): Search strategies for relevant clinical studies - CML (p1-17). Concept combinations used in the search strategy:

(CML) AND ((imatinib + refractory terms) OR (2^{nd}/3^{rd}/4^{th} line)) AND (intervention OR comparators)

Statement 12, 14 of the EMBASE search strategy and statements 8, 10 of the MEDLINE search strategy (pages 1 and 5):

"(refractory or intoleran or failure* or resistan* or relapse* or pretreated or pre-*

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treated or "previously treated").mp.
((second or third or fourth) adj2 line).mp."

2. Appendix 2 (section 8.4): Search strategies for relevant clinical studies - Ph+ CML (p18-32). Concept combinations used in the search strategy:

(ALL) AND (Philadephia chromosome) AND ((refractory terms) OR (2^{nd}/3^{rd}/4^{th} line)) AND (intervention OR comparators)

Statement 18, 19 of the Embase strategy and 16, 17 of the Medline strategy (pages 19 and 21)

"(refractory or intoleran or failure* or resistan* or relapse* or pretreated or pre-treated or "previously treated").mp.*
((second or third or fourth) adj2 line).mp."

Systematic review process

A3. Please confirm if study selection, data extraction and quality assessment were undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost section. If not, please justify.

A4. Please confirm whether any potentially relevant non-English studies were excluded from the CS (see Table 4-1, CS)? If so, what impact would these have had on the results, if any?

A5. Please explain why health-related quality of life was not an outcome of interest for the systematic literature review of clinical-effectiveness (see Table 4-1, CS).

A6. The study selection process in the PRISMA flow diagrams for clinical evidence in CML (Figure 4-1) and in Ph+ ALL (Figure 4-2) appears confusing. Data are incorrect (e.g. eligibility/included numbers in Figure 4-2) or incomplete (how many studies were included in quantitative/qualitative synthesis for each intervention/comparator in Table 4-1?). Please amend/revise the PRISMA flow diagrams and clarify how these data relate to the information presented in section 4.11.1 of the CS.

A7. In the absence of randomised controlled trial (RCT) evidence, please confirm how many studies (non-randomised and non-controlled evidence), rather than citations, were included in the CML clinical systematic literature review of: i) ponatinib; ii) bosutinib; iii) SCT; iv) best supportive care (including but not limited to hydroxycarbamide)?

Please confirm how many studies (non-randomised and non-controlled evidence), rather than citations, were included in the Ph+ ALL clinical systematic literature review of: i) ponatinib; ii) SCT; iii) best supportive care?

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Quality assessment, data synthesis, analysis

A8. i. Please provide rationale for using the Chambers *et al*. 2009 checklist (which was developed to assess the quality of case-series evidence) to assess the methodological quality of non-RCT studies (section 4.11.7, CS), particularly for single-arm non-comparator clinical trials.

ii. Please clarify why quality assessment was undertaken for each publication (citation) in section 4.11.8 of the CS rather than for each study (conventional practice). For example, Table 4-12 presents conflicting quality scores for included studies e.g. for the PACE study: Cortes et 2013 (graded as 'Good') and Hochhaus 2015 (graded as 'poor').

iii. Please explain why assessment criterion seven (i.e. "were patients recruited consecutively?") for each study 'was not downgraded' as per the instructions in Chambers *et al.* 2009 (i.e. the assessment should either be 'yes' or 'no' not 'unclear'). In addition, was there any attempt to seek clarification from study authors or study sponsors? If not, why? Where applicable, please amend assessments for criterion seven in accordance with the instructions in the Chambers et al. 2009 publication.

A9. Please confirm if blinded outcome assessment was undertaken in the included ponatinib and bosutinib studies. If not, how will this affect the interpretation of the results?

A10. Please provide further details on the number of UK sites and number of UK patients (for all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML who were recruited and participated in: i) NCT00660920 (phase I ponatinib study); ii) PACE/ NCT01207440 (phase II ponatinib study); iii) NCT00261846 (phase I/II bosutinib study).

A11. Please explain why data from the phase I ponatinib study was not used to inform the analyses. Clarify whether all evidence from phases I and II from the bosutinib study was included, and whether the patients in each phase were independent.

A12. Please provide (where applicable) the n/N (%) for all baseline parameter outcomes in Table 4-3 and for all best response rates in Table 4-4 of the CS (p50)

A13. Please provide a tabulated summary of the original and updated PACE study efficacy results (both all lines and for ≥3L separately) for CP-CML, AP-CML,

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BP-CML and Ph+ CML presented in section 4.11.12.1 (p74-75, CS) and 4.11.12.3 (p75-76) including n/N (%) and 95% confidence intervals, where applicable.

A14. Please provide details on the number of patients who were lost-to-follow up in the PACE study (all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML.

A15. Please provide tabulated details (n/N (%) on the number of patients who discontinued study treatment permanently due to adverse events (including deaths related to study treatment) in the PACE study (all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML? What alternative treatments were given to those who stopped study treatment early (all lines and ≥3L separately for CP-CML, AP-CML, BP-CML and Ph+ CML)? Please provide similar data for the bosutinib study.

A16. Please provide details of adherence/compliance to ponatinib in the PACE study. Please provide similar data for the bosutinib study.

A17. Please provide brief details on the terminology criteria used to assess adverse events in the PACE study (e.g. Grade 1, 2, 3 etc.).

A18. For completeness of Table 4-14, Table 4-15, Table 4-16 (p84-85) and Table 4-19 (p94), please provide further details of n/N (%) for any grade, grade 3/4 adverse events (treatment related non-haematological adverse events, haematological treatment related adverse events and vascular occlusive events) in the PACE study (all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML. Please provide similar data for the bosutinib study.

A19. Please clarify whether the decision to classify the 14 patients with AP-CML with major haematologic response at baseline as non-responders is likely to be favourable or unfavourable to ponatinib.

A20. Please clarify why the PACE data could not be re-analysed in order that the major haematologic response data was more comparable with that of bosutinib in AP-CML and CP-CML (see p97, CS)

Matching adjusted indirect comparison (MAIC)

A21. Please comment on the relevance to the NICE decision problem of matching the sample of patients in the PACE study to the sample of patients in the bosutinib study.

A22. Please provide the weights used for each patient within the MAIC analysis and comment on the impact on the results of any extreme weights.

A23. Please comment on why adjustments for differences in patient characteristics

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was not accounted for when analysing AP-CML, BP-CML and adverse events.

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Section B: Clarification on cost-effectiveness data

Clinical parameters used in the model

B1. **Priority Question:** Please clarify why the Guyot approach to reconstructing the individual patient data was not used to estimate survivor functions for published data? (Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012; 1:9). The ERG considers that the method employed of minimising the sum of squares does not estimate parameters and their uncertainty correctly. Please re-estimate all survivor functions and provide updated results.

B2. **Priority Question**: Please provide full incremental analyses for the base case results and for relevant sensitivity or scenario analyses.

B3. **Priority Question**: Please provide full incremental analyses for the PSA results. Show that sufficient samples have been undertaken so that Monte Carlo sampling error is not a problem if pairwise values are compared, or allow simultaneous comparison of all strategies. Such data would be required, if in certain scenarios or when patient access schemes are taken into account, ponatinib becomes less cost-effective than bosutinib.

B4. **Priority Question**: In previous appraisals it has been assumed that it is the level of response that is important for predicting prognoses and that this was independent of the intervention that generated the response. This appears appropriate for CML-, or ALL- related mortality. However, in the submission it is commented that five deaths were assessed as being possibly or probably related to ponatinib treatment (p86). Clarify how this has been taken into account in the modelling.

B5. **Priority Question:** Please comment on whether all patients are expected to lose their response in the future or whether there is a proportion of patients who will maintain their response over their lifetimes.

B6. **Priority Question**: In general, particularly for ponatinib, there is insufficient sample data alone with which to estimate parameters in survivor functions. Please provide the following information for each survivor function that is fitted:

- A plot of each fitted survivor function extrapolated over the lifetime of the patients.
- Include the number of patients at risk when plotting the observed data.
- Comment on the expected hazard of an event over time (e.g. whether it is expected that the hazard of an event will increase, decrease or follow some other relationship over time).

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- Comment on whether it is clinically plausible that there are groups of patients with different baseline characteristics who are likely to be at higher or lower risk of an event
- Comment on the proportion (and associated uncertainty) of patients who are expected to be event-free at some fixed point in the future for each survivor function.

B7. **Priority Question**: Please clarify why sensitivity analyses were not presented to assess the change of the ICER using different parametric fits to the data. For example, a Gompertz distribution has been fitted to the duration of response for ponatinib, but the log-normal and the log-logistic fits have indistinguishable AIC and BIC values but different extrapolations of the data. Please provide a model that allows selection of the candidate parametric distributions.

B8. **Priority Question**: Please amend the model to ensure that PFS is not greater than OS, as occurs in the SCT_AP spreadsheets.

B9. **Priority Question**: For PSA, please clarify why Dirichlet distributions were not used to represent uncertainty about the responses in each category, but instead an arbitrary +/-10% was used. Please amend. Furthermore, please clarify why +/-10% was used for costs when the standard error could be derived from HRG costs.

B10. **Priority Question**: Please clarify how similar the populations are between the ALL patients in PACE and those observed in Pagano 2000. Please clarify the clinical reasons as to why those with no major cytogenetic response with ponatinib treatment are estimated to have a median survival in the region of twice that observed for patients on BSC.

B11. "**Priority Question**: Please clarify why it is assumed in the AP-CML and BP-CML that all patients who get a major haematologic response are eligible for SCT. This contradicts the methodology used in the CP-CML and Ph+ ALL models where a proportion of patients are not assumed to be suitable for allo-SCT"

B12. **Priority Question**: Please clarify why the results for those with Ph+ ALL are divided into those who can and cannot receive allo-SCT whereas the results for CP-CML are combined. Please clarify for CP-CML whether the ICER for ponatinib differs dependent on whether a patient is suitable for allo-SCT in CP-CML (and in AP-CML and BP-CML if it is assumed that not all patients can receive an allo-SCT).

B13. The ERG believes the mortality probability has been calculated incorrectly. The values in columns B and C are believed to be probabilities. As such the first step would be to calculate x '=-(LN(1-D11))/1' and then calculate '=1-exp(-

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x*.25)'. Thus we believe the mortality probability in G11 to be 0.0010630 rather than 0.0010608. It is acknowledged the change will not affect the ICERs greatly, but it would be useful to ascertain whether the method in the submitted model is incorrect.

B14. Please clarify the clinical plausibility of the different adverse events assumed in the CP-CML and the AP/BP-CML models. For instance, is it reasonable to assume that abdominal pain only occurs in patients with CP-CML but not in patients with AP or BP-CML?

B15. Please clarify why all adverse events were believed to have the same HRQoL impact rather than sourcing disutilities for each event separately as has been undertaken for the costs of each adverse event.

B16. Please clarify which distribution was intended to be used for the duration of response to bosutinib. The company submission states that it is the lognormal distribution, based on the sum of squared errors, but the model appears to use the Gompertz distribution.

B17. Please clarify whether it is clinically plausible that the probability of death following allo-SCT is independent of whether a patient has relapsed.

B18. Please clarify whether the assumptions made to calculate the time to progression in the AP-CML phase (in 5.4.2.1.1.3.2) include that everyone moves to BP-CML before dying. If so, clarify whether this contradicts the model assumption that patients can die in AP-CML.

B19. Please clarify how the 26.64 days in hospital per cycle in blast phase were calculated and the 2.13 days in hospital in AP were calculated. The ERG's initial calculations gave fairly similar but different values when using data in 4.3.4.1 in Appendix 14.

B20. Please clarify why the probability of response loss is independent of whether a patient is on or off treatment.

B21. For ALL patients, please clarify why the starting age of the patients is independent of whether the patients are deemed suitable for allo-SCT. Clinical advice to the ERG suggests that the probability of being suitable decreases as a patient ages.

B22. Please clarify whether the negative value associated with the major haematological response covariate in PFS is clinically plausible: this results in the estimated PFS being longer for those without a response than for those with a response. It is acknowledged that the PFS Kaplan-Meier estimates are higher for no-response although these are based on small numbers.

B23. Please amend the calculations derived from the PSA results. The PSA mean should not be the mean of the ICERs. Additionally, the 95% CI on the ICER should be able to distinguish between dominated and dominant negative values and calculated accordingly.

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B24. Please clarify why in the Ph+ ALL model it is assumed that patients cannot die in cycle 0 if they respond to treatment and SCT is an option. Amend the model if this was not intended.

B25. Please clarify the drivers of the models which result in estimated negative QALYs for ponatinib in the PSA analyses run for each of the three models submitted.

B26. Please clarify whether the ICER for ponatinib may change dependent on whether a person had a T315I mutation. Whilst it has been stated that ponatinib does not have differential efficacy based on this mutation, if comparator interventions do then it would be expected that the ICER would be more favourable for ponatinib in the T315I subgroup and less favourable in the non-T315I mutation group.

B27. Please clarify whether there is a possibility for inaccuracy by fitting curves to the data in Table 5-9, and then additionally using the complete haematologic response rates for patients who lose response. If such patients are included in Table 5-9 this would lead to double counting. If double counting is possible, clarify whether this is likely to be favourable or unfavourable to ponatinib.

B28. Please clarify why alternative parametric distributions other than those from the Generalised F family of distributions or the Gompertz distribution have not been used, including fractional polynomials.

B29. Please clarify how the utility decrement of 0.260 for the post-relapse state (p143) was calculated. The ERG could not replicate this value.

B30. Please clarify whether in the CP-CML model it was intended that people with a partial cytogenetic response or MHR who discontinue TKI treatment would be assumed to immediately lose their response, albeit having the possibility of a MHR through subsequent hydroxycarbamide use. This contrasts with those in complete cytogenetic response who are assumed to maintain the response post-TKI discontinuation.

B31. The base case results presented in the submission assumes that ponatinib is not continued if there is no major haematologic response response at 3 months in AP/BP-CML, or are non-responders at 3 months in the CP-CML. Please clarify the impact on the ICER compared to bosutinib if such stopping criteria are applied to bosutinib.

B32. Please clarify whether the separation of duration of ponatinib response data into those with a complete cytogenetic response and those with a partial cytogenetic response, in contrast to duration of bosutinib responses (which is major cytogenetic response), is likely to be favourable or unfavourable to ponatinib.

Resource use & costs

B33. **Priority Question**: Please clarify why it is the half-cycle corrected state values

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that are used in calculating the main drug costs. It is more likely that all people in the state at the beginning of the cycle would receive treatment. Similar logic applies for treatments post continuation, post-SCT relapse and in AP/BP. Please amend the model if this was not intended.

B34. **Priority Question**: Please clarify why it is assumed that treatments used post-SCT failure or in progressed CML (p122) are split equally amongst imatinib, hydroxycarbamide, dasatinib, nilotinib, bosutinib, when this is contrary to evidence provided by the company in Table 27 of Appendix 14. More importantly, the time spent in PFS in AP-CML has been taken from Kantarjian (2007). In this paper 64/84 patients in AP-CML receive 'other treatment' with the remaining 20/84 patients receiving dasatinib or nilotinib. Please amend the model so that the costs represent the treatments used in generating the efficacy data.

B35. **Priority Question**: Please clarify when the SKU price for ponatinib will be confirmed as the list price.

B36. Please tabulate and summarise the HRG costs used within the model so that these can be viewed by the appraisal committee. For example: - Nurse led visit NHS Reference Costs 2014 to 2015 - N10AF (Specialist Nursing, Cancer Related, Adult, Face to face). Presently these only appear in the model which is not typically viewed by the appraisal committee who may want to check the values.

B37. Clinical advice provided to the ERG suggests that, while it is unlikely for ALL, the savings associated with reduced dose intensity could be recouped in CML. Please provide versions of the model that allow the impact on the ICER of being unable to recoup savings based on reduced dose intensity.

B38. Please clarify how sensitive the ICER is to assumptions regarding the split of induction chemotherapies used in ALL, accounting for 1) full packs being used rather than assuming a cost per mg approach and 2) using a distribution of weight rather than a fixed value. Analysis 2 would need to be run in conjunction with Analysis 1 to have an impact.

B39. Please indicate how the costs of the initial SCT and the follow-up costs have been calculated. The numbers reported in the submission do not seem to appear in the provided reference.

Health utility

B40. **Priority Question**: Please clarify why in the CP-CML model the CCyR value was capped at population norm, but the values for other states were left unchanged. This artificially reduces the utility loss of moving from CCyR. Clarify how the results change if the absolute decrements were applied to the population norm values, or if the ratios between the health states were kept constant.

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Section C: Textual clarifications and additional points

General

C1. Please clarify whether major haematologic response (MHA) is more stringent than overall haematologic response (OHR). Multiple times in the text it is said that MHA is more stringent, yet the text (see page 97) also suggests that OHR has to meet the criteria for MHA and additional criteria.

C2. Please clarify whether there is a typo in Table 5-9. The values are likely to be the probability of remaining in the progression free state rather than the probability of progression.

C3. Please clarify that the 0.91 utility value for people in CP-CML with response is not used in the submission, as suggested in Table 5.17. The ERG believes that this value is capped to a population norm value.

C4. Please clarify that it was intended that hyperglycaemia is not included as an adverse event within the model.

C5. Please clarify whether there is a typo in Table 5-62: it is believed that these are the results for BP-CML rather than AP-CML.

C6. Please clarify whether there is a typo in Table 5-68 and that the cost for a day in hospital should be £721 as used in the model and also reported for CML.

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Stephanie Yates
Project Manager, Technology Appraisals Committee C
National Institute for Health and Care Excellence
Tel: 44 (0)161 870 3248

RE: Ponatinib STA, ID 671; Manufacturer response to ERG clarification questions

Dear Stephanie,

Please find below our responses to the ERG clarification questions. Please note that this document contains confidential information that has been redacted. Additionally, there are four appendices accompanying this document that also contain confidential information which has been redacted.

Stephanie, let me take this opportunity to thank you in advance for your support.

Please do not hesitate to contact me should you have any questions.

With my kind regards,

[redacted]
Head of Market Access & Commercial Partnerships
Incyte Biosciences
[redacted]

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Section A: Clarification on effectiveness data

General

A1. *Please provide further details on the clinical pathway of care in England (section 3.3-3.7, company submission [CS]) in particular:*

i. Please clarify that the case for the cost-effectiveness of ponatinib is being made only for use in third-line and does not consider use after interventions such as bosutinib.

The cost-effectiveness analysis was developed to reflect the use of ponatinib in CML within its licensed indication. Specifically, the target population of the economic analysis is patients in the third-line (3L) treatment setting, reflecting the anticipated place in therapy of ponatinib: post-imatinib and a second-line (2G) TKI. This is consistent with SmPC guidance and is supported by ponatinib efficacy data from the PACE trial. It can be anticipated that ponatinib may be used in the fourth line (4L) in some cases. In clinical practice, dasatinib and nilotinib are sometimes used sequentially, although such use is not explicitly approved in their licensed indications. In addition, NICE recommends bosutinib for 3L use. As ponatinib could conceivably be used following either sequential dasatinib and nilotinib or 3L bosutinib, a cost-effectiveness scenario analysis has been provided in the main company submission to demonstrate the cost-efficacy of 4L ponatinib (CS, Table 5-45). Although the ICERs are generally still under the threshold for acceptable cost-effectiveness in the 4L scenario analysis, they are higher compared with the base case (3L ponatinib). These findings are driven by the higher response rates to ponatinib in 3L compared with later lines of therapy and thus confirm the proposed place in therapy of ponatinib—after failure of one 2G-TKI. Delaying the adoption of ponatinib treatment is not beneficial for the patient and provides less value for money for the NHS versus 3L use. In conclusion, ponatinib should be recommended for use within its licensed indication.

ii. What treatment(s) would people be expected to receive following ponatinib in clinical practice? Please clarify why it is assumed that dasatinib, nilotinib, bosutinib, imatinib and hydroxycarbamide are used when a patient progressed to AP-CML following use of an intervention (ponatinib, bosutinib etc) in CP-CML but only the use of hydroxycarbamide is assumed following ponatinib treatment in patients with AP-CML.

In the base case of the CP-CML model, patients who progress to AP do so following treatment with a 3L TKI (ie, ponatinib or bosutinib), not a later line of TKI therapy. It is therefore clinically plausible that any of the remaining TKIs not previously used for treatment could be an option for these patients following progression on ponatinib or bosutinib. In contrast, patients enter the AP-/BP-CML model already in the progressed disease state. The acute phases of CML,

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by definition, require urgent medical intervention. It is assumed that the patient has exhausted available TKIs other than ponatinib, and thus the only remaining comparator treatment options for the patient are hydroxycarbamide or SCT.

iii. *Please explain why data from a survey of UK clinical experts (p40 and Appendix 14, CS) were not used to calculate the number of patients with CML (section 3.4.2 and section 6.2) that would be eligible to receive ponatinib (within its licence indication) in England?*

The survey of UK clinical experts we commissioned was specifically designed to estimate parameters for which actual data are scarce, namely resource use and treatment practice in CML. We considered that experts' clinical experience of ≥3L CML treatment were especially important to capture for those parameters and chose to focus the survey on these areas to fully leverage the time of the survey respondents. In contrast, robust data were available to support an epidemiological calculation of the numbers of patients eligible to receive ponatinib, including data from prior NICE appraisals in the CML area. Therefore, we felt using epidemiology data from robust sources would be a more rigorous approach to calculating the target population size. This lessens the uncertainty that would otherwise arise from an estimate of eligible patients based on expert opinion. In addition, we followed the same methodology and cited several of the same published sources that were used in the bosutinib STA to calculate the number of eligible 3L and 4L patients.

Literature searching

A2. *The searches described in Appendix 2 (section 8.4) use a series of concept combinations to identify relevant citations. Please could you provide further clarification on i) the strengths and limitations of including the concept combinations noted below (in italics) in the search strategy for CML and Ph+ CML (i.e. risk of not identifying all the relevant evidence (Appendix 2, CS))? ii) How many more records would the strategy retrieve without these statements? iii) How did the company investigate the impact of combining these statements on the results retrieved compared to the absence of these statements?*

1. *Appendix 2 (section 8.4): Search strategies for relevant clinical studies - CML (p1-17). Concept combinations used in the search strategy:*

(CML) AND ((imatinib + refractory terms) OR (2nd/3rd/4th line)) AND (intervention OR comparators)

Statement 12, 14 of the EMBASE search strategy and statements 8, 10 of the MEDLINE search strategy (pages 1 and 5):

"(refractory or intoleran or failure* or resistan* or relapse* or pretreated or pre-treated or "previously treated").mp.*
((second or third or fourth) adj2 line).mp."

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2. *Appendix 2 (section 8.4): Search strategies for relevant clinical studies - Ph+ CML (p18-32). Concept combinations used in the search strategy:*

(ALL) AND (Philadephia chromosome) AND ((refractory terms) OR (2nd/3rd/4th line)) AND (intervention OR comparators)

Statement 18, 19 of the Embase strategy and 16, 17 of the Medline strategy (pages 19 and 21)

"(refractory or intoleran or failure* or resistan* or relapse* or pretreated or pre-treated or "previously treated").mp.*
((second or third or fourth) adj2 line).mp."

i. The search strategies were designed to maximise sensitivity to disease state, intervention, and trial design while aligning with the patient population described in the approved ponatinib (Iclusig®) indication. Ponatinib is indicated in adult patients with:

- Chronic phase, accelerated phase, or blast phase CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

- Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

Based on the indication above, a comprehensive list of terms related to resistance and intolerance were developed. To identify appropriate indexing terms, we searched relevant publications and reviewed the MeSH and EMTREE thesauri. To further ensure relevant publications were identified, a concept combination pertaining to line of therapy was included. The bosutinib STA set the precedent for the use of these concept combinations; however, the 'resistance' concept combination developed for the ponatinib searches was broader than that used in the bosutinib SLR. For example, the bosutinib SLR used '(refractory or intoleran* or failure* or resistan*).mp.' whereas the ponatinib STA used all of those terms plus 'relapse* or pretreated or pre-treated or "previously treated"'.

Using these concept combinations in the ponatinib SLR identified publications most relevant to the patient population of interest while allowing the searches to be sufficiently sensitive to trial design. Many of the key trials in this disease area are prospective, single-arm, open-label studies. Currently available pre-tested search filters (eg, from the Scottish Intercollegiate Guidelines Network [SIGN] and the Canadian Agency for Drugs and Technologies in Health [CADTH]) are focused on identifying RCTs and/or observational studies from the literature and not prospective, single-arm, open-label studies. In fact, in a pilot of the SIGN pre-tested search filters for RCTs, observational trials, and

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systematic reviews, we noted that several relevant single-arm, open-label trials were not identified. To ensure we captured as many relevant publications as possible, including those describing key nonrandomised trials, we intentionally broadened the pre-tested search filters to include terms that would identify prospective open-label studies (eg, the terms 'phase' and 'open-label' were included). Piloting the addition of these terms returned several key trials that were not identified with the original pre-tested SIGN search filters. Based on the results of our pilot testing, these modified searches are more robust than those used in prior STAs. One major strength of using a more specific search filter for patient population (ie, the population indicated in the label) is that it allowed time and resources to be focused on the results obtained with the broadened 'Trial design' search filter.

The main limitation of using concept combinations related to patient population is the risk of not identifying key trials. In the pilot phase of the modified search strategies, we compared database search results with a list of key trials that were manually identified from the literature. With the modified search strategies, we identified a majority of the key studies. Furthermore, only 5 relevant publications for both CML and ALL were identified in the manual search of bibliographies and systematic reviews. Thus, incorporating a search filter based on patient population has not limited the SLR results.

In summary, several factors supported the decision to use patient population concept combinations in the SLR strategy, including:

- Alignment with the approved indication
- Few missed records upon piloting of the search strategies
- Precedent set by the bosutinib STA
- Specificity for patient population permitting increased sensitivity for trial design

ii. We reran the EMBASE and MEDLINE searches without the concept combinations noted above for CML and ALL. The difference between running the searches with the concept combinations versus running them without is presented in the table below.

Additional records retrieved with removal of the concept combinations pertaining to patient population

Searches	MEDLINE	EMBASE
CML	+784	+1495
ALL	+59	+105

iii. As noted in part i, the concept combinations were developed based on the approved indication for ponatinib and supported by a precedent set in the bosutinib STA. The appropriateness of this approach was tested by comparing the results of the SLR against a selection of relevant publications manually

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identified from the literature (this was a component of our pilot testing of the search strategies). This test did not indicate an issue with the use of these concept combinations—ie, the SLR did not miss publications as a result of including these terms in the search strategies. Furthermore, upon conducting a formal manual search of bibliographies and systematic reviews as part of the SLR, only 5 additional publications were identified for each of the CML and ALL SLRs. Of these, 3 and 5 publications were considered relevant for the CML and ALL searches, respectively.

Systematic review process

A3. *Please confirm if study selection, data extraction and quality assessment were undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost section. If not, please justify.*

Study selection and quality assessment were conducted by two independent reviewers. Per CRD guidance (CRD's Guidance for Undertaking Reviews in Health Care, 2008; Section 1.3.3.5, pp 29–30), data extraction was conducted by one reviewer and validated by a second reviewer. A standardised electronic data extraction form was used for each literature search.

A4. *Please confirm whether any potentially relevant non-English studies were excluded from the CS (see Table 4-1, CS)? If so, what impact would these have had on the results, if any?*

No potentially relevant non-English studies were excluded from the CS. After reviewing the non-English publications that were excluded in the CML SLR, none met the PICOS eligibility criteria and were in the post–2G-TKI patient population that corresponds to the decision problem. After reviewing the non-English publications excluded in the Ph+ ALL SLR, none met the PICOS eligibility criteria and passed the filtering step for selecting studies in patients who failed at least one prior therapy. We therefore confirm that no potentially relevant non-English studies were excluded from the main evidence submission.

A5. *Please explain why health-related quality of life was not an outcome of interest for the systematic literature review of clinical-effectiveness (see Table 4-1, CS).*

Indeed, we acknowledge the importance of health-related quality of life (HRQoL), and accordingly performed an SLR focussing on HRQoL. Section 5.3.3.3 of the STA details the methodology and the results of the separate HRQoL search strategy. In particular, this search was designed to identify utility values for relevant health states in the literature, to be incorporated in the economic models.

A6. *The study selection process in the PRISMA flow diagrams for clinical evidence in CML (Figure 4-1) and in Ph+ ALL (Figure 4-2) appears confusing. Data are*

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incorrect (e.g. eligibility/included numbers in Figure 4-2) or incomplete (how many studies were included in quantitative/qualitative synthesis for each intervention/comparator in Table 4-1?). Please amend/revise the PRISMA flow diagrams and clarify how these data relate to the information presented in section 4.11.1 of the CS.

Per request, we have reviewed the PRISMA diagrams for clarity, accuracy, and completeness. The PRISMA flow diagrams for CML and Ph+ ALL have been amended to include a box for both qualitative and quantitative syntheses, with results presented by intervention. We have also corrected the data in the Ph+ ALL diagram. To improve clarity, we have moved the manually added articles to the 'Eligibility' box. In this improved version, the difference between the number of articles in the 'Eligibility' box ('Full-text articles assessed' + 'manually added articles') and the number of articles excluded is equal to the number of articles included at study selection. Finally, to provide a comprehensive breakdown of publication type, we have also integrated the manually added articles into the numbers of types of publications included at the study selection phase (eg, full text, conference abstracts, and ClinicalTrials.gov entries).

In the systematic literature search for appropriate clinical data in CML, a total of 280 relevant articles were identified from the bibliographic database and manual searches. The clinical literature search was broad in scope to increase sensitivity (eg, the inclusion criteria included all studies in the second line and beyond, regardless of whether the first-line treatment was a 2G-TKI). Ponatinib is indicated for use in patients with chronic phase, accelerated phase, or blast phase CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. To align with the approved indication for ponatinib, an additional filtering step was conducted to extract only articles providing data in the post–2G-TKI treatment setting. After filtering, a total of 74 articles were deemed relevant. Of these 74 articles, 33 described results from primary studies and 41 were associated with the primary studies (ie, publications reporting subgroup data or long-term follow-up data, etc). Of the 41 associated publications, six were determined to be relevant for further analysis according to the NICE scope. All 39 publications (33 primary and six relevant associated studies) are detailed in Table 4-5 along with reasons for inclusion/exclusion from the economic analysis.

In the systematic literature search in Ph+ ALL, a total of 63 articles were identified in the bibliographic database and manual searches. In an attempt to align with the NICE scope, an additional filtering step was applied to narrow the results to exclude studies in which patients received allo-SCT while in first complete remission. A total of 23 articles were identified as relevant after the additional filtering step. Of these 23 publications in patients with Ph+ ALL who had failed at least one prior therapy, 17 were considered primary studies and six were associated publications (see revised PRISMA diagram Figure 4-2 below). In total, 17 primary studies (including a long-term follow-up publication to one of the primary studies) are detailed in Table 4-6 in the company

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submission along with reasons for inclusion/exclusion.

Figure 4-1. PRISMA flow diagram for clinical evidence in CML

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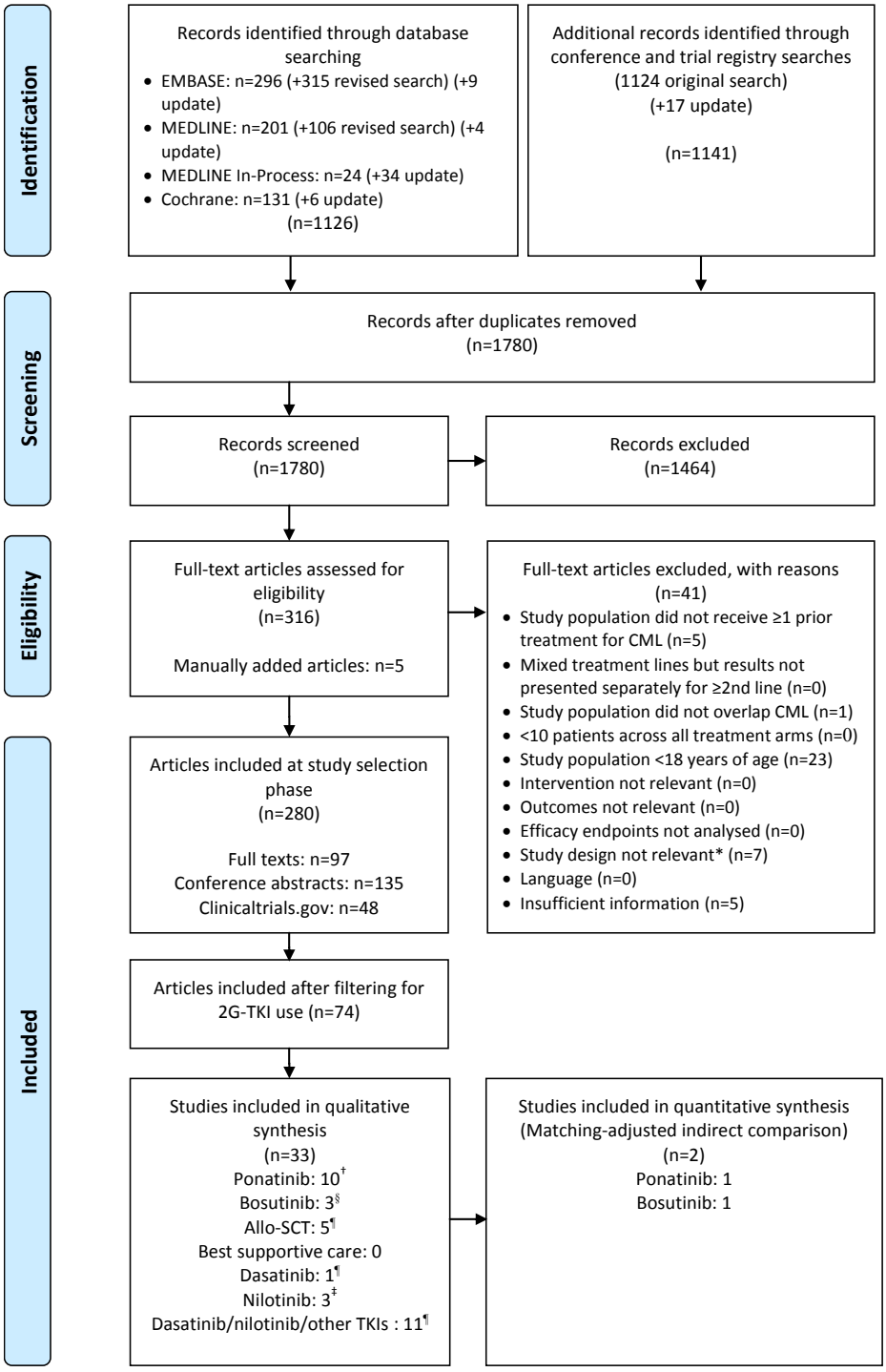

*Reviews, meta-analyses, SLRs, HRQoL studies, epidemiological studies. In other words, not a randomised controlled trial, single-arm trial, or observational study (either retrospective or prospective.
†Three non-RCTs, four observational studies, and three indirect comparison vs comparators.
§Two non-RCTs and one observational study.
¶All studies were observational.
‡Two non-RCTs and one observational study.

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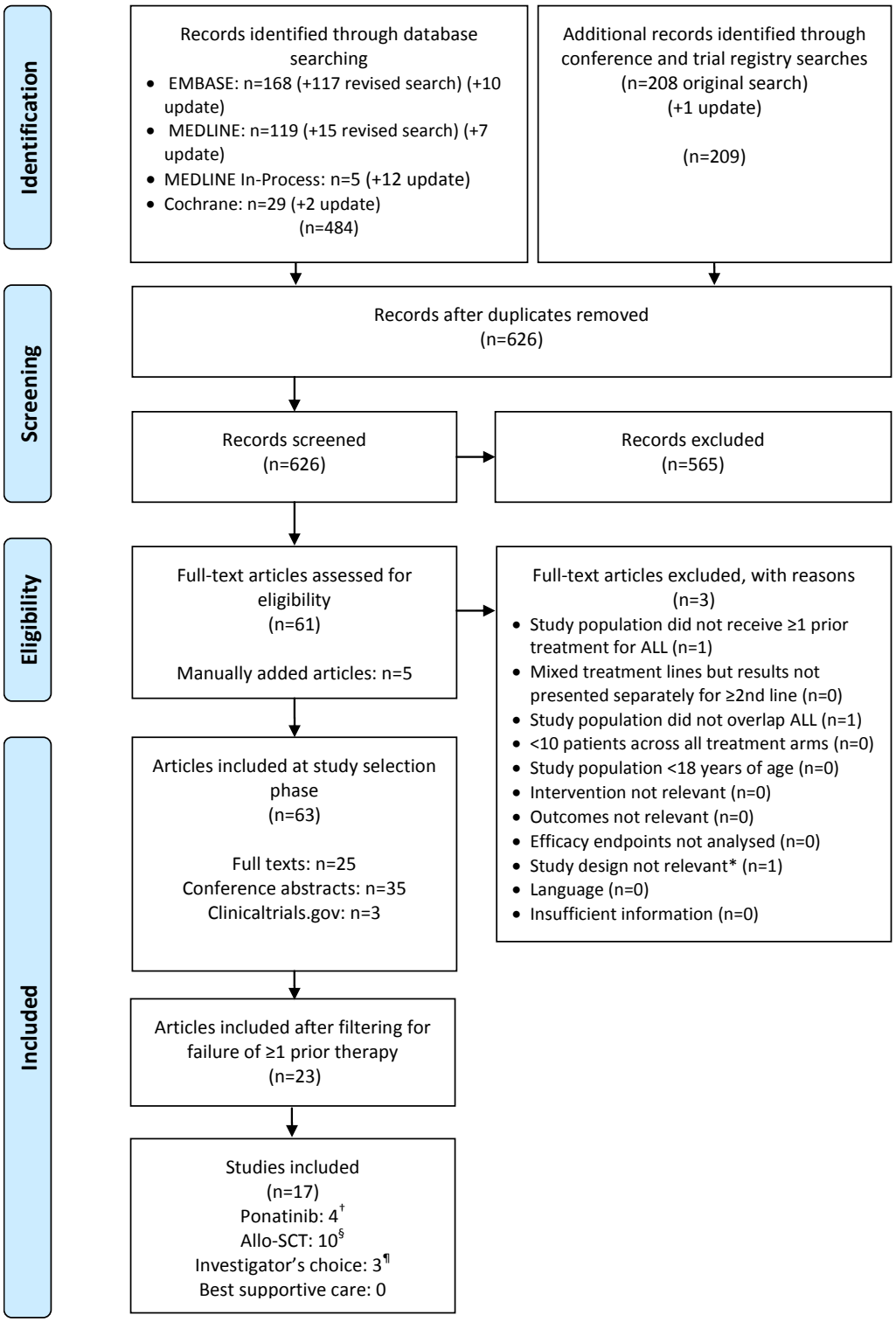
Figure 4-2. PRISMA flow diagram for clinical evidence in Ph+ ALL



†Two non-RCTs, one observational study, and one indirect comparison vs allo-SCT.
§All studies were observational.

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¶All studies were observational.

A7. *In the absence of randomised controlled trial (RCT) evidence, please confirm how many studies (non-randomised and non-controlled evidence), rather than citations, were included in the CML clinical systematic literature review of: i) ponatinib; ii) bosutinib; iii) SCT; iv) best supportive care (including but not limited to hydroxycarbamide)?*

A total of 18 studies focused on ponatinib, bosutinib, and/or allo-SCT were identified in the CML clinical SLR. The breakdown is as follows:

i) Ponatinib: 10 studies (3 non-RCTs, 4 observational, and 3 indirect analyses of ponatinib vs comparators)

ii) Bosutinib: 3 studies (2 non-RCTs and 1 observational)

iii) Allo-SCT: 5 studies (all observational)

iv) Best supportive care: 0 studies

Of these studies, 4 (ponatinib: 2; bosutinib: 1; allo-SCT: 1) were deemed relevant for inclusion in the submission (see Table 4-5 in the STA for further details on inclusion/exclusion). The remaining studies (15) evaluated other TKIs (eg, nilotinib, dasatinib, etc) and, per the NICE scope, were not considered relevant to the decision problem.

Please confirm how many studies (non-randomised and non-controlled evidence), rather than citations, were included in the Ph+ ALL clinical systematic literature review of: i) ponatinib; ii) SCT; iii) best supportive care?

i) Ponatinib: 3 studies (2 non-RCTs and 1 observational)
Indirect comparison ponatinib vs allo-SCT: 1 study

ii) SCT: 10 studies (all observational)
Investigator's choice, including SCT: 3 studies (all observational)

iii) Best supportive care: 0 studies

We acknowledge there is a dearth of comparative clinical evidence to address the decision problem. The evidence base in this submission includes only non-RCTs and observational studies. Head-to-head RCTs are not always feasible in the context of orphan diseases like CML and Ph+ ALL, in particular given the difficulty in recruiting patients who are resistant to and intolerant of prior therapy, as well as the lack of alternative treatments. In this context, when evaluating the efficacy and safety of ponatinib, the EMA, FDA, and other regulators accepted the single-arm design of the PACE study because a controlled study in this late-line setting (ie, ponatinib vs a failed TKI) would have been unethical. Clinical evidence for alternative treatments is equally scarce, and the uncertainty associated with the use of non-comparative studies extends to the comparators selected for this NICE appraisal.

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Quality assessment, data synthesis, analysis

A8. i. *Please provide rationale for using the Chambers et al. 2009 checklist (which was developed to assess the quality of case-series evidence) to assess the methodological quality of non-RCT studies (section 4.11.7, CS), particularly for single-arm non-comparator clinical trials.*

Several of the studies identified for inclusion in the economic analyses were single-arm, open-label trials. In our research on quality assessment tools, we identified tools for assessing the quality of RCTs and nonrandomised observational/cohort studies but none that were designed specifically for prospective, single-arm, open-label trials. Specifically, we considered the Newcastle-Ottawa scale (not applicable as it is specific to case control and cohort studies), the EPOC reviews criteria (not applicable as it is designed for studies with separate treatment groups), the Cochrane Collaboration's tool for assessing risk of bias (not applicable as it is designed for studies with separate treatment groups), and the Downs and Black checklist (not applicable as several questions are specific to studies with separate treatment groups). Certain components of the Downs and Black checklist may have been applicable for our quality appraisal; however, this checklist generates an overall quality score. Both the CRD and the Cochrane Handbook explicitly recommend against the use of tools that yield numerical scores with a preference for tools that 'consider individual aspects of methodological quality' (CRD guidance, page 44; Cochrane Handbook, Section 8.3.3).

As noted in the CRD guidance, choice of quality assessment tool should be guided by study design. Based on the results of our research, we selected the Chambers et al. checklist for quality assessment of the nonrandomised studies in the clinical SLRs. The Chambers et al. checklist is a concise 8-item assessment based on yes/no responses. It generates a quality rating of 'Good', 'Satisfactory', or 'Poor'. Of note, the bosutinib STA also used the Chambers et al. checklist for quality assessment of nonrandomised studies.

ii. *Please clarify why quality assessment was undertaken for each publication (citation) in section 4.11.8 of the CS rather than for each study (conventional practice). For example, Table 4-12 presents conflicting quality scores for included studies e.g. for the PACE study: Cortes et 2013 (graded as 'Good') and Hochhaus 2015 (graded as 'poor').*

Some of the criteria in the Chambers et al. 2009 checklist pertain to the overall study design (eg, prospective patient recruitment), while other criteria are specific to the data analysis performed (eg, follow-up for 90% of patients at baseline). We opted to perform quality assessment on both the primary and the associated studies to ensure that we had assessed these data analysis–

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specific criteria for each set of published data. Note that we address the issue of quality assessment discrepancy between primary and associated articles on page 68 of the STA (eg, Hochhaus 2015 was a conference presentation that received a poor score due to lack of data, which is not unexpected due to reporting constraints associated with this publication format).

iii. *Please explain why assessment criterion seven (i.e. "were patients recruited consecutively?") for each study 'was not downgraded' as per the instructions in Chambers et al. 2009 (i.e. the assessment should either be 'yes' or 'no' not 'unclear'). In addition, was there any attempt to seek clarification from study authors or study sponsors? If not, why? Where applicable, please amend assessments for criterion seven in accordance with the instructions in the Chambers et al. 2009 publication.*

We opted to amend the yes/no categorisation of responses in the Chambers et al. checklist to also include 'unclear' in an effort to avoid penalising studies for poor reporting as opposed to poor conduct. As noted in the CRD guidance (page 53):

> 'Quality of reporting does not necessarily reflect the quality of the underlying methods or data, but when planning quality assessment it is important to decide how to deal with poor reporting. One approach is to assume that if an item is not reported then the criterion has not been met. While this may often be justifiable, there is evidence to suggest that failure to report a method does not necessarily mean it has not been used. Therefore it is important to be accurate and distinguish between failure to report a criterion and failure to meet a criterion. For example, a criterion can be described as being met, not met, or unclear due to inadequate reporting.'

Criterion seven was particularly underreported in the literature with not one study reporting if patients were recruited consecutively. As this was a pivotal criterion for a 'Satisfactory' or 'Good' rating, we opted to apply a revised quality score for those studies that met all other criteria for a 'Good' score. Responding to criterion seven with a 'no' would have been misleading and would have resulted in all studies receiving a 'Poor' rating.

We originally opted to rely solely on the reporting in the publications for the quality assessment to reduce any bias due to access to information (eg, obtaining detailed study conduct information for the ponatinib studies would be easier than for the bosutinib studies). Per the instruction to amend assessments for criterion seven, we directly contacted study authors; however, we have yet to receive a response to our queries for several of the studies. To avoid creating a bias between studies due to inadequate reporting, we have retained the 'unclear' terminology in the Chambers et al. checklist where the publications failed to report the data, as suggested in the CRD guidance. The 'Good*' score has not been modified to 'Poor' in an effort to avoid penalising studies for inadequate reporting.

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A9. *Please confirm if blinded outcome assessment was undertaken in the included ponatinib and bosutinib studies. If not, how will this affect the interpretation of the results?*

Blinded assessment was not undertaken in the ponatinib studies and is not reported in the bosutinib studies. As anti-leukaemic activity was measured by objective response criteria established for the patient's diagnosis, the interpretation of the results will not be affected. Definitions of response criteria are described in Table 9.6 of the AP24534-10-201 Clinical Study Report.[1]

A10. *Please provide further details on the number of UK sites and number of UK patients (for all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML who were recruited and participated in: i) NCT00660920 (phase I ponatinib study); ii) PACE/ NCT01207440 (phase II ponatinib study); iii) NCT00261846 (phase I/II bosutinib study).*

i) NCT00660920 (phase I ponatinib study) was conducted entirely in the United States and no UK centres were involved in this study.

ii) Five UK centres took part in PACE/NCT01207440 (phase II ponatinib study) recruiting 30 patients in total. The number of UK patients receiving ≥3L ponatinib was not reported and the data are not available stratified by line of treatment. The number of UK patients across all lines of therapy is outlined in the table below.

Number of patients who were enrolled in the PACE trial in the UK, across all lines of therapy

CP-CML	AP-CML	BP-CML	Ph+ ALL
28	2	0	0

iii) Two centres took part in NCT00261846 (phase I/II bosutinib study) but the number of UK patients has not been reported by Cortes et al. 2011,[2] Khoury et al. 2012,[3] or in the bosutinib EPAR.[4]

A11. *Please explain why data from the phase I ponatinib study was not used to inform the analyses. Clarify whether all evidence from phases I and II from the bosutinib study was included, and whether the patients in each phase were independent.*

The Phase I ponatinib study was a dose-ranging study. Patients received one of seven dose levels ranging from 2–60 mg. In addition, the study included a mix of diagnoses (CML, Ph+ ALL, AML, myelodysplastic syndrome, multiple myeloma, and myelofibrosis). As such, the Phase I ponatinib study is not entirely relevant to either the recommended dosing or the licenced indication in the approved product label and was not used to inform the analyses.

A total of 571 patients were enrolled in the bosutinib Phase I/II study: 570 patients received at least one dose of study drug. Of these 570 patients, 18

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patients (400 mg: n=3, 500 mg: n=3, and 600 mg: n=12) participated in Part 1 of the study and continued into Part 2.

The evidence for bosutinib (≥3L for CP-CML and AP/BP-CML) presented in the submission includes only the Phase II part of the bosutinib study, with the possible exception of one patient with AP-CML. Part 1 of the bosutinib study (Phase I dose-escalation study) enrolled patients with CP-CML (1 patient had AP-CML) who had previously received only imatinib and had developed resistance to imatinib. Part 2 of the study (Phase II) evaluated the efficacy and safety of bosutinib in CP-CML (≥2L bosutinib) and advanced leukaemia; that is, part 2 enrolled the populations included in the evidence submission—≥3L bosutinib in CP-CML and AP/BP-CML (Khoury et al. 2012, Kantarjian et al. 2014, Gambacorti-Passerini et al. 2015).[3, 5, 6] There are no data on whether the one patient with AP-CML enrolled in phase I participated in the phase II part of the bosutinib study and was thus included in the safety evidence for advanced CML.

A12. *Please provide (where applicable) the n/N (%) for all baseline parameter outcomes in Table 4-3 and for all best response rates in Table 4-4 of the CS (p50).*

The n/N (%) is provided for all baseline parameters and best response rates presented in the tables below. The ponatinib matching-adjusted values for baseline patient characteristsics and best response rates were calculated by applying weights from the matching adjusted indirect comparison (MAIC) analysis; therefore, there are no n/N for these percentages.

Table 4-3. Baseline patient characteristics for bosutinib and ponatinib cohorts included in the MAIC and the matching-adjusted ponatinib cohort

Baseline parameter	Bosutinib Khoury et al 2012[3] (Phase 1/2 trial)	Ponatinib Cortes et al. 2013[7] (IPD PACE)	Ponatinib Matching-adjusted
Number of patients, n	118	97	69*
Median age, n/N (%) >56.0 years	59/118 (50.0)	52/97 (53.6)	– (50.0)
Sex, male, n/N (%)	53/118 (44.9)	52/97 (51.5)	– (44.9)
T315I mutation at study entry, n/N (%)	7/118 (5.9)	30/97 (30.9)	– (5.9)
Race, white, n/N (%)	85/118 (72.0)	77/97 (79.4)	– (72.0)
Median duration of CML, n/N (%) >6.7 years	59/118 (50.0)	41/97 (42.3)	– (50.0)
ECOG PS with 1, n/N (%)	31/117 (26.5)	29/97 (29.9)	– (26.5)

CML, chronic myeloid leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IPD, individual patient data.

*Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.

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Table 4-4. Best response rates before and after the matching with bosutinib characteristics

Best response	Bosutinib Khoury et al. 2012[3] (Phase 1/2 trial)	Ponatinib Cortes et al. 2013[7] (IPD PACE)	Ponatinib Matching-adjusted
Number of patients, n	118	97	69*
CCyR, n/N (%)	26/108 (24.07)	63/97 (64.95)	– (61.34)
PCyR, n/N (%)	9/108 (8.33)	6/97 (6.19)	– (8.46)
CHR, n/N (%)	44/116 (37.93)	17/97 (17.53)	– (18.19)
No response†, n/N (%)	– (29.66)	11/97 (11.34)	– (12.01)

CCyR, complete cytogenetic response; CHR, complete haematologic response; IPD, individual patient data; PCyR, partial cytogenetic response.

*Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights.

†For bosutinib, there is no n/N for the “no response” rate because the value was calculated as 1 minus the other response rates.

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A13. *Please provide a tabulated summary of the original and updated PACE study efficacy results (both all lines and for ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML presented in section 4.11.12.1 (p74-75, CS) and 4.11.12.3 (p75-76) including n/N (%) and 95% confidence intervals, where applicable.*

We have provided tabulated results for the original and updated PACE study efficacy results presented in the aforementioned sections. For completeness and ease of comparison, we have presented below the relevant data from Table 4-13 of the main company submission (eg, 3L and 4L response rates) and some additional data beyond what was originally presented in the main company submission (for example, 5L response rates, maintained MCyR at 3 years, transformation to AP-/BP-CML at 4 years). The 95% CI for MCyR in CP-CML has been corrected in the table below (the 95% CI is 50–62 and not 50–60, as incorrectly stated in the main company submission). We apologise for this typo.

CP-CML: Original and updated PACE study efficacy results

	CP-CML							
	Original efficacy results				Updated efficacy results			
Publication	Cortes et al. 2013[7]				Hochhaus et al. 2015[8]*			
Follow-up	12 months				4 years			
Line of therapy	**All lines**	**3L**	**4L**	**5L**	**All lines**	**3L**	**4L**	**5L**
Number of patients	270†	98§	141§	12	270	97§	142§	12
MCyR, n/N (%) [95% CI]	NR/267 (56) [50–62]	NR/98 (67) [57–76]	NR/141 (45) [37–54]	NR/12 (58) [28–85]	–	NR/97 (71) [NR]	NR/142 (49) [NR]	NR/12 (58) [NR]
CCyR, n/N (%) [95% CI]	NR/267 (46) [NR]	NR/98 (56) [46–66]	NR/141 (39) [31–48]	NR/12 (25) [5–57]	–	NR/97 (65) [NR]	NR/142 (45) [NR]	NR/12 (33) [NR]
MMR, n/N (%) [95% CI]	NR/267 (34) [NR]	NR/98 (36) [26–46]	NR/141 (33) [26–42]	NR/12 (8) [0.2–38]	–	NR/97 (42) [NR]	NR/142 (37) [NR]	NR/12 (8) [NR]

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Median time to MCyR, mo (range)	2.8 (1.6–11.13)	–	–	–	–	–	–	–
Duration of response [median, 95% CI]	1 day to 19.4 months [median not reached, NE]	–	–	–	–	–	–	–
Maintained MCyR , n/N (%) [95% CI]	MCyR at 12 mo NR/NR (91) [85–95]	–	–	–	–	NR/NR (88)‡ [NR]	NR/NR (86)‡ [NR]	NR/NR (25)‡ [NR]
PFS, n/N (%) [median, 95% CI]	NR/267 (80) [not reached, NE]	–	–	–	NR/267 (56) [not reached, NE]	NR/97 (68) [not reached, NE]	NR/142 (52) [not reached, NE]	47-mo PFS NR/12 (11) [11.1 mo, NR]
OS, n/N (%) [median, 95% CI]	NR/267 (94) [not reached, NE]	–	–	–	NR/267 (77) [not reached, NE]	NR/97 (79) [not reached, NE]	NR/142 (80) [not reached, NE]	NR/12 (11) [38.9 mo, NR]
Transforma-tion to AP/BP-CML, n/N (%)	5/267 (1.9)	–	–	–	9/267 (3.4)	–	–	–

3L, third line; 4L, fourth line; 5L, fifth line; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; mo, month; NE, not estimable; PFS, progression-free survival; OS, overall survival.

*Hochhaus et al. 2015 presented at ASH 2015 the results by number of prior TKIs (PPT presentation format); results for “any line” were not reported.

†Three patients with CP-CML were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib).

§One patient was misclassified at the time of the original analysis.
‡Maintained response at 3 years.

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We have provided tabulated results for the original and updated PACE study efficacy results for AP-CML presented in the aforementioned sections. For completeness, we have presented below the relevant data from Table 4-13 of the company submission (eg, 3L and 4L response rates) and additional data beyond what was originally presented in the company submission (for example, 5L response rates, updated response rates by line of therapy).

AP-CML: Original and updated PACE study efficacy results

	AP-CML							
	Original efficacy results				Updated efficacy results			
Publication	Cortes et al. 2013[7]				CSR[1]			
Follow-up	12 months				4 years			
Line of therapy	**All lines**	**3L**	**4L**	**5L**	**All lines**	**3L**	**4L**	**5L**
Number of patients	83	33	44	3	83	33	46	–
MaHR by 6 months, n/N (%) [95% CI]	NR/83 (55) [44–66]	NR/33 (61) [NR]	NR/44 (50) [NR]	2/3 (67) [NR]	[redacted]	[redacted]	[redacted]	–
MCyR, n/N (%) [95% CI]	NR/83 (39) [NR]	NR/33 (42) [NR]	NR/44 (30) [NR]	2/3 (67) [NR]	[redacted]	[redacted]	[redacted]	–
CCyR, n/N (%) [95% CI]	NR/83 (24) [NR]	NR/83 (30) [NR]	NR/33 (16) [NR]	NR/44 (33) [NR]	[redacted]	[redacted]	[redacted]	
MMR, n/N (%) [95% CI]	NR/83 (16) [NR]	NR/33 (24) [NR]	NR/44 (11) [NR]	0/3 (0) [NR]	[redacted]	[redacted]	[redacted]	–

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Median time response, weeks/ months (range)	MaHR: 3 weeks (2–25) MCyR: 3.7 months (0.8–9.7)	–	–	–	[redacted]	–	–	–
Duration of response [median, 95% CI]	MaHR: 1 to 21 months or more [12 months, NR]	–	–	–	[redacted]	–	–	–
Maintained response, n/N (%) [95% CI]	MaHR: NR/NR (48) [NR] MCyR: NR/NR (73) [NR]	–	–	–	[redacted]	–	–	–
PFS, n/N (%) [median, 95% CI]	NR/83 (55) [18 months, NR]	–	–	–	[redacted]	–	–	–
OS, n/N (%) [median, 95% CI]	NR/83 (84) [not reached, NE]	–	–	–	[redacted]	–	–	–

3L, third line; 4L, fourth line; 5L, fifth line; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; mo, month; NE, not estimable; PFS, progression-free survival; OS, overall survival.

Note: Results reported in the CSR include patients who had received imatinib, dasatinib, and/or nilotinib, but not bosutinib.

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We have provided tabulated results for BP-CML and Ph+ ALL below. The original publication by Cortes et al. 2013 did not report the results by prior number of TKIs. For completeness, we have presented below data in addition to what was originally presented in the main company submission (for example, updated BP-CML/Ph+ ALL response rates by line of therapy). In general, updated results from the CSR are reported for the combined BP-CML/Ph+ ALL cohort. For completeness, we also report the 12-month OS for BP-CML as reported by Cortes et al. 2013, which was missing from the main company submission, and note that updated survival results for the combined BP-CML/Ph+ ALL reflect 3-year OS and not 2-year OS as stated in the main company submission.

BP-CML/Ph+ ALL: Original and updated PACE study efficacy results

	BP-CML	Ph+ ALL	Ph+ ALL	BP-CML/Ph+ ALL		
	Original efficacy results		Updated efficacy results	Updated efficacy results		
Publication	**Cortes et al. 2013[7]**		**Cortes et al. 2015[9]**	**CSR[1]**		
Follow-up	12 months		36 months	4 years		
Line of therapy	**All lines**		**All lines**	**All lines**	**3L**	**4L**
Number of patients	BP-CML=62	Ph+ ALL=32	Ph+ ALL=32	94 BP-CML=62 Ph+ ALL=32	38	48
MaHR by 6 months, n/N (%) [95% CI]	NR/NR (31) [20–44]	NR/NR (41) [24–59]	NR	[redacted]	[redacted]	[redacted]

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MCyR, n/N (%) [95% CI]	NR/NR (23) [NR]	NR/NR (47) [NR]	NR	[redacted]	[redacted]	[redacted]
CCyR, n/N (%) [95% CI]	NR/NR (18) [NR]	NR/32 (38) [NR]	NR	–	[redacted]	[redacted]
Median time to MaHR, weeks/months (range)	MaHR: 4.1 weeks (1.7–16.1) MCyR: 1.9 months (0.9–5.5)	MaHR: 2.9 weeks (1.6–24) MCyR: 1 month (0.9–3.7)	NR	–	–	–
Duration of MaHR [median, 95% CI]	MaHR: 1 to 20 months or more [5 months, NR]	MaHR: 2 to 14 months or more [3 months, NR]	NR	–	–	–
Maintained response, n/N (%) [95% CI]	MaHR: NR/NR (42) [NR] MCyR: NR/NR (66) [NR]	MaHR: NR/NR (8) [NR] MCyR: NR/NR (32) [NR]	NR	–	–	–
PFS, n/N (%) [median, 95% CI]	NR/NR (19) [4 months, NR]	NR/NR (7) [3 months, NR]	NR	[redacted]	–	–

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OS, n/N (%) [median; 95% CI]	NR/NR (29) [7 months; NR]	NR/NR (40) [8 months; NR]	NR/NR (16) [NR; NR]	[redacted]	–	–

3L, third line; 4L, fourth line; 5L, fifth line; ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; mo, month; NE, not estimable; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive; OS, overall survival.

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A14. *Please provide details on the number of patients who were lost-to-follow up in the PACE study (all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML.*

The number of patients lost to follow up across all lines of therapy is outlined in the table below.

Number of patients lost to follow up across all lines of therapy

	CP-CML (N=270)	AP-CML (N=85)	BP-CML/ Ph+ ALL (N=94)	Total (N=449)
Lost to follow up, n (%)	9 (3.3)	4 (4.7)	1 (1.1)	14 (3.1)

The number of patients ≥3L lost to follow up was not reported and the data are not available stratified by line of therapy.

A15. *Please provide tabulated details (n/N (%) on the number of patients who discontinued study treatment permanently due to adverse events (including deaths related to study treatment) in the PACE study (all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML? What alternative treatments were given to those who stopped study treatment early (all lines and ≥3L separately for CP-CML, AP-CML, BP-CML and Ph+ CML)? Please provide similar data for the bosutinib study.*

The tables below present the number of patients (stratified by line of treatment, where reported) who discontinued ponatinib or bosutinib permanently due to adverse events and the number of deaths related to study treatment. There are no data available on the alternative treatments given to patients who stopped study treatment early, either in PACE or the bosutinib study.

Number of patients who discontinued ponatinib (any line and ≥3L for CP-CML) (sources: Hochhaus et al. 2015[8] and ponatinib CSR,[1] PACE data cut-off, 3 August 2015)

Ponatinib	CP-CML				AP-CML	BP-CML	Ph+ ALL
Line of therapy	Any line	3L	4L	5L	Any line	Any line	Any line
Number of patients, n	270	97	142	12	85	62	32
Discontinued treatment due to AEs, n (%)	50 (18.5)	18 (19)	25 (18)	4 (33)	10 (11.8)	9 (14.5)	3 (9.4)
Death related to ponatinib, n (%)	2 (0.7)	–	–	–	2 (2.4)	3 (3.2)*	

*Results reported for the combined cohort only.

For completeness, data by line for therapy was derived from patient-level data (PLD) is presented in the table below. The total numbers of patients in the CP-CML and AP-CML cohorts differ from those presented above as the first set of data comes from the entire safety cohort, including patients who were treated

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but not assigned to a cohort. Results derived from PLD did not include patients who were not assigned to a cohort. In addition, the definition for line of therapy derived from PDL included patients who had previously received an unapproved TKI (ie, bosutinib) at the start of study. For this reason, the number of patients with AP-/BP-CML or Ph+ ALL classified as 3L/4L/5L derived from PLD may differ from the numbers presented in the CSR, which reported the results categorised according to number of prior approved TKIs (imatinib, dasatinib, and nilotinib).

Number of patients who discontinued study treatment permanently due to adverse events (PACE study PLD)

	CP-CML			
	Any line	**3L**	**4L**	**5L**
Number of patients	267	97	142	12
Discontinued treatment due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death related to ponatinib, n (%)				
	AP-CML			
	Any line	**3L**	**4L**	**5L**
Number of patients	83	32	44	3
Discontinued treatment due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death related to ponatinib, n (%)				
	BP-CML			
	Any line	**3L**	**4L**	**5L**
Number of patients	62	23	34	3
Discontinued treatment due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death related to ponatinib, n (%)				
	Ph+ ALL			
	Any line	**3L**	**4L**	**5L**
Number of patients	32	14	12	–
Discontinued treatment due to AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death related to ponatinib, n (%)				

Number of patients who discontinued bosutinib (any line and ≥3L) (sources: Kantarjian et al. 2014[6] [CP-CML] and Gambacorti-Passerini et al. 2015[5] [AP/BP/ALL])

Bosutinib	**CP-CML**		**AP-CML**	**BP-CML**	**ALL**
Line of therapy	**2L**	**≥3L**	**Any line**	**Any line**	**Any line**
Number of patients		118	79	64	24
Discontinued treatment due to AEs	64 (22)	29 (25)	24 (30)*	4 (6)*	3 (13)*
Death related to bosutinib	–	1 (0.8)†		2 (1.2)§	

*Data include discontinuations after year 4.
†Lower gastrointestinal haemorrhage with thrombocytopaenia.
§Results reported for the combined cohort only; causes of death were myocardial infarction and acidosis in year 1.
Note: Data from Gambacorti-Passerini et al. 2015 do not breakdown data by 2L vs ≥3L bosutinib treatment.

A16. *Please provide details of adherence/compliance to ponatinib in the PACE study. Please provide similar data for the bosutinib study.*

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Treatment compliance in the PACE study was assessed by use of patient diary cards. The protocol stipulated that patients could receive a reduced dose or a temporary dose interruption to manage AEs, and dose modification guidelines were provided in the protocol. Furthermore, as a result of ongoing analyses and communications with regulatory bodies, general recommendations to reduce the dose were made in October 2013.

A summary of ponatinib dose adjustments by disease group is presented in the table below.

Summary of dose adjustments by disease group (PACE data cut-off, 3 August 2015)[1]

	Ponatinib			
	Overall N=449 n (%)	**CP-CML N=270 n (%)**	**AP-CML N=85 n (%)**	**BP-CML/ Ph+ ALL N=94 n (%)**
Any dose reduced				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No				
Dose interruptions of at least 3 days				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No				
Dose modifications: patients with at least one of the following				
Interruption*	[redacted]	[redacted]	[redacted]	[redacted]
Resumed				
Reduction				
Re-escalation†				
Last non-missing dose for ongoing patients				
N ongoing	[redacted]	[redacted]	[redacted]	[redacted]
15 mg				
30 mg				
45 mg				
[redacted]				

In the total population (N=449), 67.7% of patients had a dose reduction, and 70.8% of patients had a dose interruption.

Khoury et al. 2012[3] reported that in the bosutinib study dose interruptions were required for 70% of patients. During the study, 20/118 (17%) patients had their dose of bosutinib escalated to 600 mg/day for lack of efficacy.

A17. *Please provide brief details on the terminology criteria used to assess adverse events in the PACE study (e.g. Grade 1, 2, 3 etc.).*

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v. 4.0).

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Definitions of Grades: 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, and 5=Death.

A18. *For completeness of Table 4-14, Table 4-15, Table 4-16 (p84-85) and Table 4-19 (p94), please provide further details of n/N (%) for any grade, grade 3/4 adverse events (treatment related non-haematological adverse events, haematological treatment related adverse events and vascular occlusive events) in the PACE study (all lines and ≥3L separately) for CP-CML, AP-CML, BP-CML and Ph+ CML. Please provide similar data for the bosutinib study.*

Ponatinib

In the tables below, we provide further details on AEs (any Grade/Grade 3+) occurring in patients with CP-CML, AP-CML, BP-CML, and Ph+ ALL from the PACE study. The majority of patients in the study received ponatinib in the third line or later (CP-CML: 251/270 [93%], AP-CML: 80/84 [94%], BP-CML: 59/62 [95%], and Ph+ ALL: 26/32 [81%]) and results are in general presented for "any line" of treatment. For CP-CML, however, we provide additional safety data reported by line of therapy (3L, 4L, and 5L). For completeness, we provide treatment-emergent arterial occlusive AEs (any Grade, Grade 3/4, Grade 5) for CP-CML, AP-CML, BP-CML, and Ph+ ALL in the PACE study. These results are from the updated PACE study results (PACE data cut-off, 3 August 2015).

TRAEs/TEAEs in ≥10% of patients across study populations for CP-CML, AP-CML, and BP-CML/Ph+ ALL (PACE data cut-off, 3 August 2015)

	Ponatinib					
	CP-CML n (%)		AP-CML n (%)		BP-CML/Ph+ ALL n (%)	
	Any Grade	Grade 3+	Any Grade	Grade 3+	Any Grade	Grade 3+
Number of patients	270		85		94	
Any TRAE/TEAE	[redacted]		[redacted]		[redacted]	
Haematologic						
Thrombocytopaenia	[redacted]		[redacted]		[redacted]	
Neutropaenia	[redacted]		[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]		[redacted]	
Gastrointestinal						
Abdominal pain	[redacted]		[redacted]		[redacted]	
Constipation	[redacted]		[redacted]		[redacted]	
Nausea	[redacted]		[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]		[redacted]	
Investigations						
Lipase increase	[redacted]		[redacted]		[redacted]	
ALT increased	[redacted]		[redacted]		[redacted]	
AST increased	[redacted]		[redacted]		[redacted]	
Blood alkaline phosphatase increased	[redacted]		[redacted]		[redacted]	
Other						

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Rash						
Dry skin						
Headache						
Fatigue						
Arthralgia						
Myalgia						
Pain in extremity						
Muscle spams						
Asthenia						
Rash pruritic						
Vascular disorders						
Hypertension						
Cardiac disorders occurring in ≥1% of patients						
Angina pectoris						
Atrial fibrillation						
Coronary artery disease						
Cardiac failure congestive						
Pericardial effusion						
Acute myocardial infarction/myocardial infarction						
Acute coronary syndrome						
Palpitations						
Tachycardia						
Cardiac failure						
Coronary artery occlusion						
Bradycardia						
Cardiac failure chronic						
Ischaemic cardiomyopathy						
Left ventricular dysfunction						
Cardiac arrest						

TEAEs in ≥10% (any Grade) of patients by line of therapy (CP-CML) (PACE data cut-off, 3 August 2015)

	Ponatinib			
	All lines	**3L**	**4L**	**5L**
Number of patients	270	97	142	12
Any TEAE				
Rash				
Abdominal pain				
Thrombocytopaenia				
Headache				
Dry skin				

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Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropaenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spams	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Weighted decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]

TEAEs (Grade +3) in ≥5% of patients overall by line of therapy (CP-CML) (PACE data cut-off, 3 August 2015)

	Ponatinib			
	All lines	**3L**	**4L**	**5L**
Number of patients	270	97	142	12
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropaenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]

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Treatment-emergent arterial occlusive AEs in ≥1% of patients

CP-CML: Treatment-emergent arterial occlusive AEs in ≥1% of patients with CP-CML (PACE data cut-off, 3 August 2015)

	Ponatinib		
	CP-CML N=270 n (%)		
	Grade		
	Any	3/4	5
Any arterial occlusive AE	[redacted]	[redacted]	[redacted]
Angina pectoris			
Peripheral arterial occlusive disease			
Acute myocardial infarction/myocardial infarction			
Coronary artery disease			
Intermittent claudication			
Cerebrovascular accident			
Peripheral artery stenosis			
Cerebral infarction			
Carotid artery stenosis			
Transient ischaemic attack			
Peripheral ischaemia			
Acute coronary syndrome			
Coronary artery occlusion			
Extremity necrosis			
[redacted]			

AP-CML: Treatment-emergent arterial occlusive AEs in ≥1% of patients with AP-CML (PACE data cut-off, 3 August 2015)

	Ponatinib		
	AP-CML N=85 n (%)		
	Grade		
	Any	3/4	5
Any arterial occlusive AE	[redacted]	[redacted]	[redacted]
Acute myocardial infarction/myocardial infarction			
Angina pectoris			
Coronary artery disease			
Cerebrovascular accident			
Peripheral arterial occlusive disease			
Acute coronary syndrome			
Aphasia			
Cerebral infarction			
Cerebral ischaemia			
Coronary artery occlusion			
Extremity necrosis			
Ischaemic cardiomyopathy			

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Peripheral ischaemia	[redacted]		[redacted]		[redacted]	
Stress cardiomyopathy						
Subclavian artery stenosis						
Vertebral artery stenosis						
[redacted]						

BP-CML: Treatment-emergent arterial occlusive AEs in ≥1% of patients with BP-CML (PACE data cut-off, 3 August 2015)

	Ponatinib					
	BP-CML N=62 n (%)					
	Grade					
	Any		3/4		5	
Any arterial occlusive AE	[redacted]		[redacted]		[redacted]	
Acute myocardial infarction/myocardial infarction						
Angina pectoris	[redacted]		[redacted]		[redacted]	
Coronary artery disease						
Embolism arterial						
Peripheral arterial occlusive disease						
Renal artery stenosis						
Splenic infarction						
[redacted]						

Ph+ ALL: Treatment-emergent arterial occlusive AEs in ≥1% of patients with Ph+ ALL (PACE data cut-off, 3 August 2015)

	Ponatinib					
	Ph+ ALL N=32 n (%)					
	Grade					
	Any		3/4		5	
Any arterial occlusive AE	[redacted]		[redacted]		[redacted]	
Cerebral ischaemia						
Coeliac artery stenosis						
Coronary artery stenosis						
Mesenteric arterial occlusion						
Peripheral arterial occlusive disease						
Peripheral ischaemia						
[redacted]						

Bosutinib

In the following tables we present long-term follow-up (≥48 months) safety data from the bosutinib study. For CP-CML, published data are available for ≥3L bosutinib (Cortes et al. 2016).[10] For advanced CML, published data are available only for any line (2L and ≥3L) bosutinib (Gambacorti-Passerini et al. 2015[5]). Results for ≥3L were not reported separately in the publication.

TEAEs in ≥10% of patients with CP-CML overall (source: Cortes et al. 2016[10])

	Bosutinib ≥3L CP-CML

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	Any grade n (%)	Grade 3/4 n (%)
Number of patients	119	119
Any TEAE	119 (100)	81 (68.1)
Haematologic		
Thrombocytopaenia	46 (38.7)	31 (26.1)
Anaemia	24 (20.2)	8 (6.7)
Neutropaenia	25 (21.0)	19 (16.0)
Gastrointestinal		
Diarrhoea	99 (83.2)	11 (9.2)
Nausea	57 (47.9)	1 (0.8)
Vomiting	45 (37.8)	1 (0.8)
Abdominal pain	29 (24.4)	1 (0.8)
Upper abdominal pain	21 (17.6)	0 (0)
Constipation	15 (12.6)	0 (0)
Dyspepsia	12 (10.1)	0 (0)
Investigations		
ALT increased	18 (15.1)	7 (5.9)
Increased blood creatinine	15 (12.6)	0 (0)
Other		
Rash	33 (27.7)	3 (2.5)
Headache	32 (26.9)	4 (3.4)
Fatigue	28 (23.5)	2 (1.7)
Cough	26 (21.8)	0 (0)
Arthralgia	21 (17.6)	1 (0.8)
Pleural effusion	20 (16.8)	6 (5.0)
Pruritus	20 (16.8)	1 (0.8)
Pyrexia	18 (15.1)	0 (0)
Dizziness	18 (15.1)	0 (0)
Decreased appetite	15 (12.6)	1 (0.8)
Nasopharyngitis	14 (11.8)	0 (0)
Back pain	14 (11.8)	3 (2.5)
Dyspnoea	14 (11.8)	2 (1.7)
Influenza	12 (10.1)	0 (0)
Cardiac AEs*	18 (15.1)	9 (7.6)
Vascular AEs†	7 (5.9)	5 (4.2)‡
Hypertension- related AEs	9 (7.6)	2 (1.7)

*Two patients had Grade 5 events.

TEAEs in ≥10% of patients with advanced CML (source: Gambacorti-Passerini et al. 2015[5])

	Bosutinib (2L and ≥3L)			
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
	AP-CML		BP-CML	
Number of patients	79		64	
Haematologic				
Thrombocytopaenia	42 (53)	35 (44)	24 (38)	23 (36
Anaemia	36 (46)	26 (33)	19 (30)	13 (20)
Neutropaenia	15 (19)	14 (18)	17 (27)	16 (25)
Leukopaenia	10 (13)	5 (6)	12 (19)	12 (19)
Gastrointestinal				
Diarrhoea	67 (85)	3 (4)	41 (64)	3 (5)
Nausea	36 (46)	2 (3)	32 (50)	1 (2)
Vomiting	35 (44)	3 (4)	27 (42)	2 (3)

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Abdominal pain	21 (27)	3 (4)	12 (19)	2 (3)
Upper abdominal pain	10 (13)	1 (1)	7 (11)	2 (3)
Constipation	14 (18)	0	9 (14)	1 (2)
Dyspepsia	9 (11)	0	1 (2)	0
Investigations				
ALT increased	12 (15)	6 (8)	4 (6)	1 (2)
Increased blood creatinine	–	–	–	–
AST increased	12 (15)	4 (5)	4 (6)	0
Other				
Rash	27 (34)	3 (4)	20 (31)	2 (3)
Headache	12 (15)	2 (3)	13 (20)	4 (6)
Fatigue	17 (22)	4 (5)	12 (19)	3 (5)
Cough	24 (30)	0	8 (13)	0
Arthralgia	12 (15)	0	8 (13)	0
Pleural effusion	10 (13)	4 (5)	3 (5)	2 (3)
Pruritus				
Pyrexia	28 (35)	1 (1)	25 (39)	2 (3)
Dizziness	11 (14)	1 (1)	8 (13)	0
Decreased appetite	7 (9)	0	12 (19)	0
Nasopharyngitis	–	–	–	–
Back pain	8 (10)	1 (1)	4 (6)	1 (2)
Dyspnoea	15 (19)	7 (9)	12 (19)	2 (3)
Influenza	–	–	–	–
Pneumonia	10 (13)	9 (11)	9 (14)	5 (8)
Pain in extremity	9 (11)	1 (1)	6 (9)	0
Insomnia	8 (10)	0	5 (8)	0
Chest pain	8 (10)	2 (3)	4 (6)	0
Oropharyngeal pain	8 (10)	0	3 (5)	0
Anxiety	8 (10)	0	3 (5)	0
Bone pain	1 (1)	0	7 (11)	2 (3)
Upper respiratory tract infection	8 (11)	0	2 (3)	0
Vascular TEAEs occurring in ≥1 patient				
Hypertension	7 (9)	4 (5)	2 (3)	1 (2)
Cerebral haemorrhage	0	0	1 (2)	0
Subarachnoid haemorrhage	1 (1)	1 (1)	1 (2)	0
Blood pressure increased	1 (1)	0	0	0
Cerebral artery occlusion	1 (1)	1 (1)	0	0
Cerebrovascular accident	0	0	1 (2)	0
Intraventricular haemorrhage	0	0	1 (2)	1 (2)
Ischemic stroke	1 (1)	1 (1)	0	0
Raynaud's phenomenon	0	0	1 (2)	0
Thrombosis	0	0	1 (2)	0

A19. *Please clarify whether the decision to classify the 14 patients with AP-CML with major haematologic response at baseline as non-responders is likely to be favourable or unfavourable to ponatinib.*

The decision to classify the 14 patients with AP-CML who had major haematologic response (MaHR) at baseline as non-responders was taken to align with the PACE study protocol. The per-protocol cytogenetic and haematologic populations in the PACE study excluded patients with baseline CCyR and MaHR, a rigorous approach chosen to demonstrate the efficacy of ponatinib in inducing only newly achieved responses in patients without baseline disease control. In the health economic evaluation, we aligned with the PACE study protocol. This approach was not favourable to ponatinib; on the contrary, patients who maintained MaHR while on ponatinib were not

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recognised using this approach, and classifying these patients as non-responders was unfavourable to ponatinib. Notably, the bosutinib study did not take a similar approach with regard to patients already in response at baseline. Patients deemed responders in the bosutinib study included those who were already in response at baseline. Therefore, we recalculated the bosutinib response rates for the model in order to align with the approach taken in the ponatinib trial, but we could not do the same for the curve for bosutinib response maintenance. This curve for bosutinib includes patients who had haematologic response at baseline, and is therefore favourable to bosutinib.

A20. *Please clarify why the PACE data could not be re-analysed in order that the major haematologic response data was more comparable with that of bosutinib in AP-CML and CP-CML (see p97, CS).*

The endpoints in the two studies were different, with major haematologic response (MaHR) being used in PACE and overall haematologic response (OHR), a broader definition, in the bosutinib study. Of the two, MaHR is the more stringent (please see our response to question C1). From published data it is not possible to use only MaHR in the bosutinib study. Naturally, we do not have access to bosutinib PLD. We note that to use OHR for ponatinib would increase the response rates for ponatinib above the MaHR rates that were observed with 3L ponatinib of 61% in AP-CML and 31% in BP-CML; thus, the approach we have used is conservative with respect to ponatinib. Using OHR for ponatinib to match the bosutinib study would have increased the efficacy measure and thus reduced the incremental cost-effectiveness ratios.

Matching adjusted indirect comparison (MAIC)

A21. *Please comment on the relevance to the NICE decision problem of matching the sample of patients in the PACE study to the sample of patients in the bosutinib study.*

Compared to the bosutinib study population as reported in Khoury et al. 2012[3] and included in the main company evidence submission, the ponatinib patient population included a higher percentage of patients with an age older than the median in the bosutinib trial of 56 years, with the T315I mutation, and with a shorter duration of CML. The ponatinib patient population also consisted of a higher percentage of males, patients who were Caucasian, and patients with an ECOG performance status of 1. Matching patient populations between the studies is relevant to the decision problem as it attempts to provide an adjusted comparison vs bosutinib while minimising potential bias of naïve comparisons. This approach was considered the best and most conservative method to compare response rates between the two drugs, as the matched response rates for ponatinib were lower than those actually observed in the prospective PACE trial of ponatinib.

In addition, to further address any potential uncertainty relating to the ponatinib effectiveness applied in the base case scenario, a cost-effectiveness scenario analysis testing an arbitrary 25% reduction in the number of ponatinib patients achieving a best response of CCyR was provided in the main company

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submission (Table 5-39 and Table 5-45, CS). Although the ICER vs bosutinib is higher in this scenario analysis compared to the base case, the ICER remained under the threshold. A reduction in the effectiveness of ponatinib had minimal impact on the ICERs vs allo-SCT, hydroxycarbamide, and interferon alpha.

In conclusion, matching the sample of patients in the PACE study to the sample of patients in the bosutinib study is a conservative approach to evaluate the cost-effectiveness of ponatinib for treatment in CP-CML.

A22. Please provide the weights used for each patient within the MAIC analysis and comment on the impact on the results of any extreme weights.

Due to the size of the table, we have provided the weights used for each patient within the MAIC analysis in Appendix 26: MAIC–individual weights in the ponatinib cohort .

We analysed the distribution of propensity score weights by response rates as shown in the table below. It appears balanced and not in favour of ponatinib as the CCyR subgroup has the lowest mean weight. Moreover the extreme values (min-max) are uniform in the response categories, meaning that extreme weights are not enhancing one category over the other, causing an imbalance in favour of one comparator over the other.

Distribution of propensity score weights by response rates in the MAIC analysis

	Obs	Mean	Std. Dev.	Min	Max
Entire cohort	97	0.0006718	0.0004262	0.0000907	0.0015911
CCyR patients	63	0.0006344	0.0004364	0.0000907	0.0015911
PCyR patients	6	0.0009189	0.0003423	0.0006954	0.0015843
CHR patients	17	0.0006973	0.0004642	0.0000977	0.0015911
NR patients	11	0.0007118	0.0003335	0.0000964	0.0011918

CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, no response; PCyR, partial haematologic response.

A23. *Please comment on why adjustments for differences in patient characteristics was not accounted for when analysing AP-CML, BP-CML and adverse events.*

Due to the limited data available for AP- and BP-CML, reflecting the small sample sizes and poor prognosis in these disease states, it was not possible to adjust for differences in patient characteristics. In the PACE study, 85 patients with AP-CML and 62 patients with BP-CML were treated with ponatinib,[7] while in the bosutinib study, the number of patients with advanced disease was even lower (n=30 and n=28 ≥3L AP-CML and BP-CML, respectively).[5] For AEs, we evaluated the relevance of the impact generated by AEs in the economic

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analysis. We estimated that the impact of the matching adjustment would have been negligible as the cost of AEs compared with the total cost of treatment was small.

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Section B: Clarification on cost-effectiveness data

Clinical parameters used in the model

B1. ***Priority Question:*** *Please clarify why the Guyot approach to reconstructing the individual patient data was not used to estimate survivor functions for published data? (Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012; 1:9). The ERG considers that the method employed of minimising the sum of squares does not estimate parameters and their uncertainty correctly. Please re-estimate all survivor functions and provide updated results.*

At present there seems to be no clear guidance on the best methodological approach to follow to determine parametric functions from published summary statistics. The Technical Support Document (TSD) TSD14 from the NICE Decision Support Unit (DSU) suggests that "analysts should consider the use of methods introduced by Guyot et al (2012) in order to re-create patient level data"; however, at the same time, the NICE DSU anticipates "that a TSD addressing survival modelling using summary statistics and evidence synthesis will be produced in the future."

We note that two methods have been used in previous NICE appraisals of TKIs for CML: 1) Least-squares estimation (LSE) based on minimisation of the sum of squared errors and 2) PLD reconstruction (although no specific method is mentioned for this approach). In general, an important shortcoming of the traditional LSE method is the equal influence of all the parts of the KM curve on the fitting. PLD reconstruction methods can help to address this issue.

However PLD reconstruction methods, and in particular the Guyot method, rely on further information beyond the KM curve to accurately simulate PLD. More specifically, the number of patients at risk in each time interval and the total number of events is required. In the absence of this information, strong assumptions are needed, and, as reported by Guyot et al., under these assumed conditions the algorithm may produce poor results.

In our company submission, we used 15 curves across the three economic models, as listed in the table below. The available evidence that was presented in the published sources for these 15 curves is indicated by an X in the table. For most cases, the information on the number of patients at risk and the total number of events is not available. Moreover, the small number of patients implied in the curves may further affect the precision of reconstruction methods. For these reasons, we preferred the LSE method.

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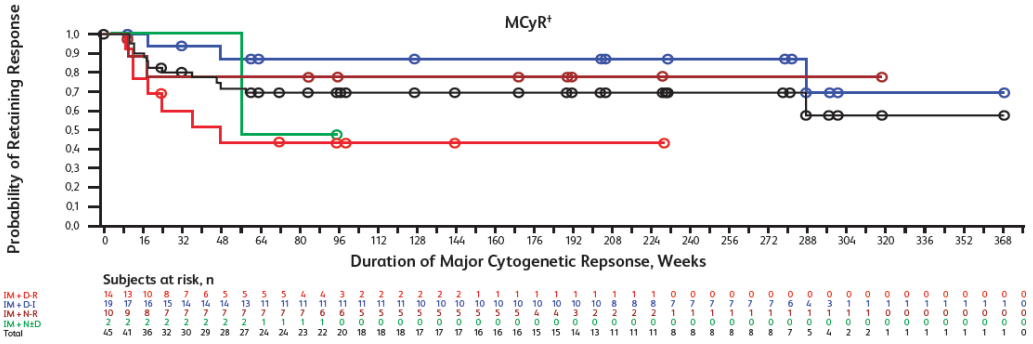
Evidence available within published sources to inform the curves applied in the ponatinib economic analyses

Curve	Number at risk	Total number of events	Source
CP-CML model			
Duration of response bosutinib	x		Gambacorti-Passerini ASH 2014
PFS CCyR			Loveman, 2012
PFS PCyR			Loveman, 2012
PFS CHR			Loveman, 2012
PFS NR			Loveman, 2012
OS SCT in CP		x	Jabbour, 2011
OS SCT in AP		x	Jabbour, 2011
Relapse-free survival after SCT			Craddock, 2000
OS in AP with BSC(*)		x	Kantarjian, 2007
OS in BP with BSC(*)		x	Kantarjian, 2007
AP/BP-CML model			
OS SCT in AP with remission			Radich, 2010
OS SCT in AP w/o remission			Radich, 2010
OS SCT in BP with remission			Radich, 2010
OS SCT in BP w/o remission			Radich, 2010
Ph+ ALL model			
OS with SCT			Tavernier, 2007

(*) curves used also in the AP/BP-CML model.

To further support our point, we analysed the possible impact of the reconstruction method. We worked on the only curve for which the number of patients at risk at different time intervals was available; ie, the duration of response curve for bosutinib, as shown in the figure below.

Probability of maintenance of response with bosutinib among patients who achieve MCyR (Gambacorti-Passerini et al. 2014)[11]



We then reconstructed the PLD of 45 patients using the Guyot method. The following figure compares the original KM curve with the KM function derived from the reconstructed PLD, showing a high degree of overlap.

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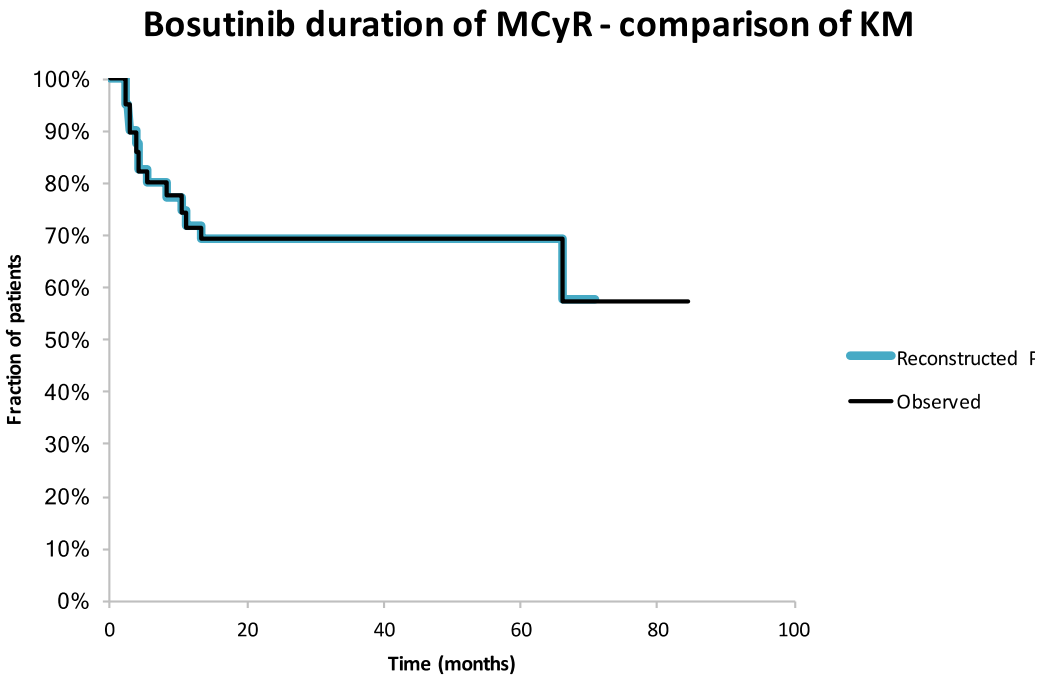
Original KM curve (LSE method) and KM function derived from the reconstructed PLD (Guyot method).



With the reconstructed PLD, we developed a parametric survival analysis to estimate five parametric functions. The Gompertz function was the best fit based on the AIC and BIC criteria, as shown in the table below.

AIC and BIC fit statistics for reconstructed PLD

Fit Statistics	AIC	BIC
EXP	99.29337	101.1
WEIB	95.77548	99.3888
GOMP	91.8642	95.47753
LNRM	92.65719	96.27051
LLOG	94.63274	98.24607

The following figure compares the five parametric functions obtained with the traditional method (LSE) as compared with those obtained from reconstructed PLD.

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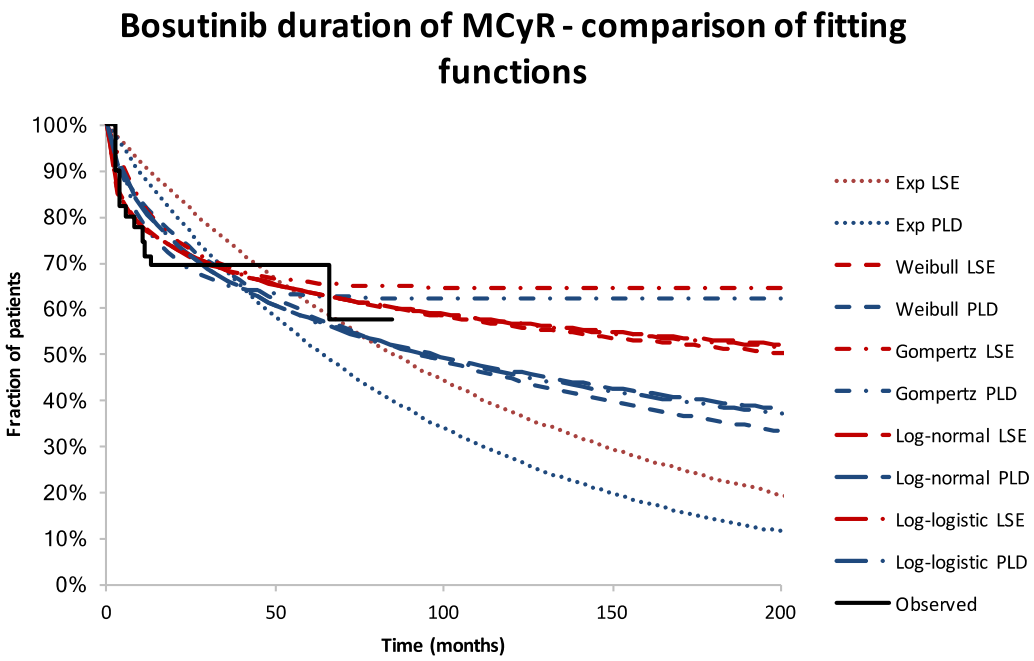
Parametric functions for duration of MCyR with bosutinib—LSE method vs reconstructed PLD (Guyot method)



The functions were somewhat different, especially in their extrapolated portion (200 months corresponds approximately to undiscounted survival of patients treated with ponatinib). However, with both methods the Gompertz function was the best fit, and the two Gompertz functions (LSE and reconstructed PLD) have only a small difference. When using the Gompertz function from reconstructed PLD in the model, the results had only a small variation with respect to our base-case analysis and this difference favoured ponatinib. The table below compares the cost-effectiveness of ponatinib in the base-case (LSE method) and when using reconstructed PLD (Guyot method) to estimate duration of MCyR for bosutinib.

Cost-effectiveness of ponatinib: results with LSE vs Guyot method for estimating duration of MCyR for bosutinib.

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
Base-case results (CP-CML)						
IFN	4.02	2.30	188.917	5.84	[redacted]	9,294
Hydroxy-carbamide	3.95	2.24	136,666	5.90	[redacted]	18,073
Bosutinib	6.09	4.00	150,811	4.14	[redacted]	**22,302**

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SCT	6.74	3.93	209,258	4.22	[redacted]	8,062
Ponatinib	11.12	8.14	[redacted]	–	–	–
Guyot results (CP-CML)						
IFN	4.72	2.30	188,917	5.84	[redacted]	9,294
Hydroxy-carbamide	4.64	2.24	136,666	5.90	[redacted]	18,073
Bosutinib	8.28	3.95	151,342	4.19	[redacted]	**21,947**
SCT	8.77	3.93	209,258	4.22	[redacted]	8,062
Ponatinib	17.37	8.14	[redacted]	–	–	–

In conclusion, in the only case where the use of PLD reconstruction methods would have been made possible by availability of the necessary data, the approach used in the company submission yielded similar results with somewhat higher ICERs, and thus can be regarded as conservative.

B2. ***Priority Question****: Please provide full incremental analyses for the base case results and for relevant sensitivity or scenario analyses.*

Full incremental results for the base case were already provided in the company submission. We had not included full incremental results for all scenario analyses in the original submission as doing so would have exceeded the page limit. During the pre-submission meeting with NICE, we were advised not to exceed this limit.

The tables below present the full incremental analysis results for the base-case and scenario analyses in CP-CML.

Base-case results: CP-CML (Table 5-28, CS)

	Disc. LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.02	2.30	188.917	5.84	[redacted]	9,294
Hydroxy-carbamide	3.95	2.24	136,666	5.90	[redacted]	18,073
Bosutinib	6.09	4.00	150,811	4.14	[redacted]	22,302
SCT	6.74	3.93	209,258	4.22	[redacted]	8,062
Ponatinib	11.12	8.14	[redacted]	–	–	–

Scenario: -25% CCyR

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.72	2.30	188,917	4.44	[redacted]	9,082
Hydroxy-carbamide	4.64	2.24	136,666	4.49	[redacted]	20,610
Bosutinib	8.38	4.00	150,811	2.74	[redacted]	28,630
SCT	8.77	3.93	209,258	2.81	[redacted]	7,110
Ponatinib	14.33	6.74	[redacted]	–	–	–

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Scenario: 4L CP-CML

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.71	2.45	188,095	2.67	[redacted]	14,407
Hydroxy-carbamide	4.62	2.40	135,878	2.72	[redacted]	33,306
Bosutinib	–	–	–	–	–	–
SCT	8.70	4.18	208,946	0.94	[redacted]	18,773
Ponatinib	9.87	5.12	[redacted]	–	–	–

Scenario: HRQoL utility data—Bosutinib STA[12] and Whiteley et al.[13]

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
Bosutinib STA						
IFN	4.72	2.74	188,917	5.60	[redacted]	9,695
Hydroxy-carbamide	4.64	2.68	136,666	5.66		18,818
Bosutinib	8.38	4.37	150,811	3.98	[redacted]	23,217
SCT	8.77	3.98	209,258	4.37		7,778
Ponatinib	17.37	8.35	[redacted]	–	–	–
Whiteley et al.						
IFN	4.72	2.61	188,917	5.68	[redacted]	9,566
Hydroxy-carbamide	4.64	2.56	136,666	5.73		18,602
Bosutinib	8.38	4.27	150,811	4.03	[redacted]	22,956
SCT	8.77	3.93	209,258	4.37		7,782
Ponatinib	17.37	8.29	[redacted]	–	–	–

Scenario: Bosutinib price

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.72	2.30	182,292	5.84	[redacted]	9,887
Hydroxy-carbamide	4.64	2.24	130,018	5.90		18,665
Bosutinib	8.38	4.00	129,300	4.14	[redacted]	26,729
SCT	8.77	3.93	193,473	4.22		11,057
Ponatinib	17.37	8.14	[redacted]	–	–	–

Scenario: Trial-based mortality

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.72	2.30	188,917	3.56	[redacted]	14,547

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Hydroxy-carbamide	4.64	2.24	136,666	3.61	[redacted]	28,811
Bosutinib	5.77	2.96	149,396	2.90	[redacted]	31,500
SCT	8.77	3.93	209,258	1.93	[redacted]	16,293
Ponatinib	11.12	5.86	[redacted]	–	–	–

Scenario: 1.5% discount rate

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.72	2.47	188,917	7.87	[redacted]	6,900
Hydroxy-carbamide	4.64	2.41	136,666	7.93	[redacted]	13,442
Bosutinib	8.38	4.75	150,811	5.59	[redacted]	16,532
SCT	8.77	4.50	209,258	5.84	[redacted]	5,821
Ponatinib	17.37	10.34	[redacted]	–	–	–

Scenario: Background mortality increased 1.5 times

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
IFN	4.71	2.29	188,292	5.38	[redacted]	9,571
Hydroxy-carbamide	4.62	2.24	136,067	5.44	[redacted]	19,088
Bosutinib	7.90	3.86	149,884	3.82	[redacted]	23,573
SCT	8.72	3.92	209,044	3.76	[redacted]	8,195
Ponatinib	15.70	7.68	[redacted]	–	–	–

Scenario: Fitting functions

	LY	Disc. QALY	Disc costs (£)	Incremental QALY (ponatinib vs)	Incremental costs (£) (ponatinib vs)	ICER (£/QALY)
Duration of response, ponatinib (Log-logistic)						
IFN	4.72	2.30	188,917	4.74	[redacted]	13,031
Hydroxy-carbamide	4.64	2.24	136,666	4.79	[redacted]	23,804
Bosutinib	8.38	4.00	150,811	3.04	[redacted]	32,886
SCT	8.77	3.93	209,258	3.11	[redacted]	13,320
Ponatinib	14.41	7.03	[redacted]	–	–	–
Duration of response, bosutinib (Log-logistic)						
IFN	4.72	2.30	188,917	5.84	[redacted]	9,294
Hydroxy-carbamide	4.64	2.24	136,666	5.90	[redacted]	18,073
Bosutinib	7.83	3.79	153,913	4.35	[redacted]	20,532
SCT	8.77	3.93	209,258	4.22	[redacted]	8,062
Ponatinib	17.37	8.14	[redacted]	–	–	–
PFS with CCyR (Log-normal)						
IFN	4.72	2.30	188,917	5.74	[redacted]	9,462
Hydroxy-carbamide	4.64	2.24	136,666	5.79	[redacted]	18,398
Bosutinib	8.31	3.97	151,172	4.07	[redacted]	22,622

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SCT	8.77	3.93	209,258	4.11	[redacted]	8,265
Ponatinib	17.12	8.04	[redacted]	–	–	–
PFS with PCyR (Weibull)						
IFN	4.72	2.30	188,917	5.85	[redacted]	9,297
Hydroxy-carbamide	4.64	2.24	136,666	5.90		18,076
Bosutinib	8.38	4.00	150,823	4.14	[redacted]	22,304
SCT	8.77	3.93	209,258	4.22		8,067
Ponatinib	17.37	8.14	[redacted]	–	–	–
PFS with CHR (Gompertz)						
IFN	4.65	2.26	187,488	5.87	[redacted]	9,479
Hydroxy-carbamide	4.58	2.21	136,859	5.91		17,966
Bosutinib	8.33	3.97	150,695	4.16	[redacted]	22,239
SCT	8.77	3.93	209,258	4.20		8,062
Ponatinib	17.34	8.12	[redacted]	–	–	–
OS for allo-SCT in CP-CML (Gompertz)						
IFN	4.72	2.30	188,917	5.84	[redacted]	9,294
Hydroxy-carbamide	4.64	2.24	136,666	5.90		18,073
Bosutinib	8.38	4.00	150,811	4.14	[redacted]	22,302
SCT	21.09	7.26	317,753	0.88		Dominant
Ponatinib	17.37	8.14	[redacted]	–	–	–
OS for allo-SCT in AP-CML (Gompertz)						
IFN	7.70	3.08	222,792	5.43	[redacted]	6,694
Hydroxy-carbamide	7.62	3.03	170,657	5.48		16,149
Bosutinib	10.89	4.65	179,325	3.85	[redacted]	20,711
SCT	8.77	3.93	209,258	4.58		10,889
Ponatinib	18.78	8.51	[redacted]	–	–	–

B3. ***Priority Question****: Please provide full incremental analyses for the PSA results. Show that sufficient samples have been undertaken so that Monte Carlo sampling error is not a problem if pairwise values are compared, or allow simultaneous comparison of all strategies. Such data would be required, if in certain scenarios or when patient access schemes are taken into account, ponatinib becomes less cost-effective than bosutinib.*

The tables below present the costs and QALYs for ponatinib and bosutinib in the PSA. Note that, due to the stochastic nature of the approach, PSA results may differ from one run of the model to the next. Thus, there may be slight variations from the PSA results in the original submission, though these are too minor to affect the overall conclusions.

We ensured that Monte Carlo sampling error is not a problem with an iterative approach. From a practical point of view we repeated the PSA with a growing number of iterations (100, 200, 300 etc…) since the CEAC appeared to be stable (ie, the curve visually overlapped with the curve obtained at the previous step). This requirement was satisfactorily met at a number of iterations smaller than 1,000. We however adopted 1,000 iterations because this measure is in line with the majority of the models in the published literature.

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CP-CML: Full incremental analysis for the PSA results

	Costs (£)			QALY			ICER (£/QALY)
	Ponatinib	Bosutinib	Incre-mental cost	Ponatinib	Bosutinib	Incre-mental QALY	
Base case	[redacted]	150,811	[redacted]	8.14	4.00	4.14	22,302
PSA mean	[redacted]	152,733	[redacted]	7.62	4.01	3.61	25,208
PSA 95% CI lower	[redacted]	118,253	[redacted]	4.29	2.66	0.21	8,881
PSA 95% CI upper	[redacted]	195,878	[redacted]	9.44	5.48	5.59	165,642

AP-CML: Full incremental analysis for the PSA results

	Costs (£)			QALY			ICER (£/QALY)
	Ponatinib	Bosutinib	Incre-mental cost	Ponatinib	Bosutinib	Incre-mental QALY	
Base case	[redacted]	150,957	[redacted]	3.52	2.62	0.90	-21,050
PSA mean	[redacted]	147,767	[redacted]	3.59	2.66	0.93	-19,369
PSA 95% CI lower	[redacted]	98,521	[redacted]	2.07	1.69	0.09	-179,409
PSA 95% CI upper	[redacted]	208,361	[redacted]	5.63	4.11	2.39	4,209

Ph+ ALL: Full incremental analysis for the PSA results

	Costs(£)			QALY			ICER (£/QALY)
	Ponatinib	Induction chemo-therapy	Incre-mental cost	Ponatinib	Induction chemo-therapy	Incre-mental QALY	
Base case	[redacted]	69,181	[redacted]	2.36	1.84	0.53	11,496
PSA mean	[redacted]	69,251	[redacted]	2.35	1.83	0.52	11,688
PSA 95% CI lower	[redacted]	57,045	[redacted]	1.36	1.13	-0.45	-89,290
PSA 95% CI upper	[redacted]	83,661	[redacted]	3.58	2.79	1.54	125,787

B4. ***Priority Question****: In previous appraisals it has been assumed that it is the level of response that is important for predicting prognoses and that this was*

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independent of the intervention that generated the response. This appears appropriate for CML-, or ALL- related mortality. However, in the submission it is commented that five deaths were assessed as being possibly or probably related to ponatinib treatment (p86). Clarify how this has been taken into account in the modelling.

These in-trial deaths were not explicitly incorporated in the model since survival on ponatinib was modelled from the same survival functions that were applied to bosutinib. We considered this appropriate, given the assumptions that (a) response is the main driver of prognosis and (b) the relationship between response and survival should not depend on which TKI was given. Using in-trial mortality rates instead for drug comparators would have increased the risk of bias, given the relatively small sample sizes and the rarity of death. This point is raised again in Question B6.

B5. ***Priority Question:*** *Please comment on whether all patients are expected to lose their response in the future or whether there is a proportion of patients who will maintain their response over their lifetimes.*

Since the model incorporates age-specific mortality for the general population, there will indeed be a proportion of patients in the model who die not because of loss of response and subsequent disease progression, but rather due to background mortality unrelated to treatment.

B6. ***Priority Question****: In general, particularly for ponatinib, there is insufficient sample data alone with which to estimate parameters in survivor functions. Please provide the following information for each survivor function that is fitted:*

The functions involved for ponatinib are:
CP-CML model

1. Duration of response ponatinib
2. Time on treatment ponatinib

AP/BP-CML model

3. Overall survival in AP
4. Overall survival in BP
5. PFS in AP
6. Time on treatment ponatinib in AP
7. Time on treatment ponatinib in BP

Ph+ ALL model

8. Overall survival
9. Time on treatment

We have addressed this question by updating Appendix 25 of the company submission, as described below (see Appendix 25: Revised Appendix 25—Parametric survival analysis and curve fitting).

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- *A plot of each fitted survivor function extrapolated over the lifetime of the patients.*

The charts for the CP-CML functions were updated from a maximum time of 100 months to 200 months to reflect the lifetime of the patients (with ponatinib the mean undiscounted LYs is approximately 17 years). For the AP/BP and ALL models, the charts presented in Appendix 25 of the main company submission were already presented with the appropriate time scale (100 months), as the mean survival with ponatinib in both models is a maximum of approximately 8 years.

- *Include the number of patients at risk when plotting the observed data.*

For each function, a KM curve with the number of patients at risk was added to new, updated Appendix 25.

- *Comment on the expected hazard of an event over time (e.g. whether it is expected that the hazard of an event will increase, decrease or follow some other relationship over time).*

Given the complexity of the analysis and the number of functions derived from PACE PLD (many of them articulated by level of response) for the three models, it was not feasible to explore the trend of the associated hazard over time for each curve and analyse the effects of their mutual interactions on the economic analysis.

- *Comment on whether it is clinically plausible that there are groups of patients with different baseline characteristics who are likely to be at higher or lower risk of an event.*

In most of the cases we investigated survival-to-event curves by subgroup of patients reaching different levels of response because response to treatment is the main driver of benefit for patients who are indicated for treatment with ponatinib. While it is certainly possible that patients with different baseline characteristics might be at a higher or lower risk of an event, we did not have the stratified data to evaluate this possibility.

- *Comment on the proportion (and associated uncertainty) of patients who are expected to be event-free at some fixed point in the future for each survivor function.*

For each of the three models there are a number of event functions that interact to produce the outcome of the simulation. Giving the number of those functions and the page constraint for the company submission it was not possible to provide detailed information on the proportion of patients that can be event-free

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at different time points. However this information can be now be obtained from the extrapolation charts in Appendix 25: Revised Appendix 25—Parametric survival analysis and curve fitting.

B7. ***Priority Question****: Please clarify why sensitivity analyses were not presented to assess the change of the ICER using different parametric fits to the data. For example, a Gompertz distribution has been fitted to the duration of response for ponatinib, but the log-normal and the log-logistic fits have indistinguishable AIC and BIC values but different extrapolations of the data. Please provide a model that allows selection of the candidate parametric distributions.*

In the main company submission, we presented a scenario analysis changing the parametric fits for duration of response with ponatinib/bosutinib, PFS with CCyR/PCyR/CHR, and OS for allo-SCT in CP-CML and in AP-CML. For example, a log-logistic distribution was fitted to the duration of response for ponatinib and bosutinib. The full incremental analysis results for the base case and for the fitting function scenario are presented in our answer to B2.

New versions of the three economic models (CP-CML, AP-/BP-CML, and Ph+ ALL) have been submitted with our responses to the ERG request for clarification. The revised versions of the models allow users to select alternative parametric functions.

B8. **Priority Question**: Please amend the model to ensure that PFS is not greater than OS, as occurs in the SCT_AP spreadsheets.

In our view the discrepancy as noted by the ERG does not impact model results. In the “SCT_AP” sheet the Markov sub-model simulates the outcomes of patients receiving SCT after progression from CP-CML. In this simulation the patients can either die or relapse. PFS was not simulated here. The probabilities of death and relapse are derived at each Markov cycle from the extrapolation of OS and relapse-free survival as competing events. After a number of cycles the relapse-free survival is stable at around 0.3 (meaning that a fraction of patients will never relapse) and the corresponding probability is zero, while the OS curve keeps on decreasing, determining a constant death probability (the function is exponential). Moreover in this component of the model we verified that the death probability derived from the OS curve is never lower than the corresponding probability of mortality of the general population. Thus, in our view the model does not need to be amended.

B9. **Priority Question**: For PSA, please clarify why Dirichlet distributions were not used to represent uncertainty about the responses in each category, but instead an arbitrary +/-10% was used. Please amend. Furthermore, please clarify why +/-10% was used for costs when the standard error could be derived from HRG costs.

Sampling from a Dirichlet distribution is not readily available from Excel and

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needs specific routines (ie, VBA functions) to be installed. For this reason a simplified approach was used sampling from a Beta distribution for each response level independently and then normalising to ensure that the sum of response rates was 100%. This approach is very close to the use of a Dirichlet distribution as this can be regarded as a multinomial generalisation of a Beta distribution.

We acknowledge, however, that the assumption of a SE of 10% may not be ideal, as the true SE was obtainable from the statistical analysis. This is amended in the updated version of the three models submitted alongside our responses. We would like to highlight the fact that the result of the PSA analysis does not change substantially with respect to what was previously submitted.

Moreover we tested a version of the CP-CML model in which the PSA for response rates is obtained through a routine for Dirichlet sampling derived from Excel functions developed from the CHEBs at the University of Sheffield. The outcome of this PSA analysis largely overlaps with that obtained from the previous version of the model. However the function for Dirichlet sampling causes programming issues with other VBA functions in the model and more specifically with the function that allows the calculation of results for all comparators at the same time (sheet "Results Overall"). For this reason, the Dirichlet sampling is not included in the updated version of the CP-CML model.

In response to the comment "Furthermore, please clarify why +/-10% was used for costs when the standard error could be derived from HRG costs", we did investigate the feasibility of doing so but concluded that we were unable to implement this approach because it is not clear how to derive SE from HRG, which is a list of tariffs lacking multiple values needed to generate a measure of dispersion.

B10. ***Priority Question****: Please clarify how similar the populations are between the ALL patients in PACE and those observed in Pagano 2000. Please clarify the clinical reasons as to why those with no major cytogenetic response with ponatinib treatment are estimated to have a median survival in the region of twice that observed for patients on BSC.*

Overall, among patients with Ph+ ALL in the PACE study, the median age was 62 (20–80) years, with 13/32 (41%) of patients aged ≥65 years. Patients in the PACE study had received at least one prior TKI; most 26/32 (81%) had received ≥2 prior TKIs.[7] In comparison, the population in Pagano 2000[14] consisted of newly diagnosed elderly patients with ALL, with a median age of 77 (65–90) years among patients treated with palliative intent; only 2/12 (17% had the Ph+ chromosome. We acknowledge that the patient population with Ph+ ALL in the PACE study does not precisely correspond to the patient population in Pagano 2000—patients treated with best supportive care were older yet previously untreated—but we were constrained by the fact that no better (ie,

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more relevant) data were available in the literature. The older median age of the patient population in Pagano 2000 may explain why patients with no response with ponatinib are estimated to have a longer median survival than those on best supportive care.

B11. ***Priority Question****: Please clarify why it is assumed in the AP-CML and BP-CML that all patients who get a major haematologic response are eligible for SCT. This contradicts the methodology used in the CP-CML and Ph+ ALL models where a proportion of patients are not assumed to be suitable for allo-SCT.*

This difference in model assumptions was driven by the different health states in which patients entered the respective models, as well as considerations about the most likely treatment pathways. In the CP-CML model, SCT is not offered to patients receiving drug treatment who do not progress (ie, those who remain in the CP health state), but rather is an emergency intervention applied only post-progression, which is adopted in a minority of patients even if a second response is not achieved.

In contrast, in the AP-CML and BP-CML model, all patients have already progressed, and SCT is electively offered to patients achieving response, assuming all responders are suitable to SCT. While we acknowledge that in real-world practice not all responders are eligible for transplant and even among those eligible, not all are able to receive transplant promptly, we note that in the case of BP-CML the proportion of responders is 32%, very similar to the proportion of patients to whom SCT is offered as an option in progressed CP-CML.

In Ph+ ALL, patients who have failed imatinib and dasatinib and are in second relapse are more often in very poor condition and may not be able to withstand or benefit from transplant. Therefore, a scenario where SCT is not a clinical option was considered more plausible in the Ph+ ALL model than in the AP/BP-CML model. Patients with ALL have a very poor prognosis and limited treatment options; in particular, a high unmet medical need exists for patients with Ph+ ALL who are resistant to or intolerant of prior TKI therapies. In the absence of reliable data, we did not hypothesise what proportion of Ph+ ALL patients might be transplant-eligible, but rather ran the model separately for two patient cohorts: SCT suitable and SCT unsuitable.

B12. ***Priority Question****: Please clarify why the results for those with Ph+ ALL are divided into those who can and cannot receive allo-SCT whereas the results for CP-CML are combined. Please clarify for CP-CML whether the ICER for*

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ponatinib differs dependent on whether a patient is suitable for allo-SCT in CP-CML (and in AP-CML and BP-CML if it is assumed that not all patients can receive an allo-SCT).

In the CP-CML model, SCT post-progression is a follow-on therapy, which is adopted in a minority of patients even if a second response is not achieved. The panel of expert clinicians informed our selection of the use of SCT in 27.5% of patients post-progression.

In Ph+ ALL, SCT is the main recommended intervention and ponatinib (or chemotherapy) is used as induction therapy to optimise transplant outcomes; the same is true in AP-CML and BP-CML. In these disease states, SCT is performed solely in patients who respond to an induction therapy.

While data were lacking to rigorously evaluate the impact of suitability for SCT on the ICERs in CML, we expect that patients unsuitable for SCT would have markedly poorer outcomes and thus higher (ie, less favourable) ICERs compared with those suitable for SCT.

B13. *The ERG believes the mortality probability has been calculated incorrectly. The values in columns B and C are believed to be probabilities. As such the first step would be to calculate x '=-(LN(1-D11))/1' and then calculate '=1-exp(-x*.25)'. Thus we believe the mortality probability in G11 to be 0.0010630 rather than 0.0010608. It is acknowledged the change will not affect the ICERs greatly, but it would be useful to ascertain whether the method in the submitted model is incorrect.*

The issue is related to an ambiguous definition in the original source (ONS England Life Tables). To calculate the mortality probability, we used data from column qx, which is defined as "the mortality rate between age x and (x+1); that is, the probability that a person aged x (exact) will die before reaching age (x+1)." In the original source, it is not clear whether qx is a rate or a probability. We interpreted qx as a rate and modelled accordingly. We agree, however, that this aspect will not affect the ICERs substantially.

B14. *Please clarify the clinical plausibility of the different adverse events assumed in the CP-CML and the AP/BP-CML models. For instance, is it reasonable to assume that abdominal pain only occurs in patients with CP-CML but not in patients with AP or BP-CML?*

The methodology used to include AEs is consistent across the three models. AEs included in the model were restricted to Grade 3/4 events occurring in ≥5% of the study population for any given treatment option. The threshold of ≥5% is commonly used. Rates for ponatinib were obtained from the PACE CSR (data cut-off, 3 August 2015), and rates for bosutinib were based on data for patients in a phase 1/2 trial reported by Kantarjian et al. 2014[6] (CP-ML) and Gambacorti-

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Passerini et al. 2015 (AP-/BP-CML).[5] Differences in the AEs incorporated in the different models for ponatinib and bosutinib are, therefore, attributable to differences in the incidence of AEs available in the trials, rather than to a difference in modelling approach.

B15. *Please clarify why all adverse events were believed to have the same HRQoL impact rather than sourcing disutilities for each event separately as has been undertaken for the costs of each adverse event.*

The available literature on utilities for most of the AEs considered in the model is scarce, and even more in the setting of CML. Szabo et al. 2010[15] was selected because the study reports an analysis of preference weights from the general population in four developed countries for standardised health states experienced by persons with CML. Standardised descriptions of seven CML-related health states, characterising CP, AP, and BP, each with responding and nonresponding states, and AEs of treatment were used. Notably, we selected the UK-specific utilities reported by Szabo et al. 2010 to inform the model.

This data source did not report separate disutilities for different AEs, but rather one single health state for treatment cessation due to serious adverse events (SAEs). Accordingly, in the model we incorporated a single AE health state to capture several of the considered AEs, such as thrombocytopaenia, neutropaenia, and diarrhoea. The resulting utility is 0.52, representing a significant decrease in health state. Nevertheless, in the economic analyses, the impact of AEs is always modest, both in terms of QoL and cost.

B16. *Please clarify which distribution was intended to be used for the duration of response to bosutinib. The company submission states that it is the lognormal distribution, based on the sum of squared errors, but the model appears to use the Gompertz distribution.*

We apologise for this typo in the main company submission. The distribution for the duration of response to bosutinib is Gompertz as applied in the model.

B17. *Please clarify whether it is clinically plausible that the probability of death following allo-SCT is independent of whether a patient has relapsed.*

Although we would expect that relapse would increase the risk of death following SCT, we adopted a conservative approach when modelling SCT without incorporating a higher mortality probability. Incorporating a higher mortality for relapse patients would negatively impact the OS with SCT and therefore favour ponatinib.

B18. *Please clarify whether the assumptions made to calculate the time to progression in the AP-CML phase (in 5.4.2.1.1.3.2) include that everyone moves to BP-CML before dying. If so, clarify whether this contradicts the model assumption that patients can die in AP-CML.*

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The assumption to estimate the mean PFS in AP-CML (calculated as the difference from the mean OS in AP and the mean OS in BP) does not imply that everyone progresses to BP-CML before dying. This is because death and progression are considered as non-competing events (ie, death events in AP are also calculated as progression events). The assumption (done in absence of any data from the literature) does not contradict the design of the model.

B19. *Please clarify how the 26.64 days in hospital per cycle in blast phase were calculated and the 2.13 days in hospital in AP were calculated. The ERG's initial calculations gave fairly similar but different values when using data in 4.3.4.1 in Appendix 14.*

These values were calculated by multiplying the average general ward and ICU hospital days per month identified in the UK clinical expert survey times 3 months per cycle:

AP-CML: 3×(0.7+0.01)=2.13
BP-CML: 3×(8.57+0.31)=26.64

Differences in calculations may result if carrying through calculations to full precision in Excel vs using rounded values (to 2 decimal places) as we have done.

B20. *Please clarify why the probability of response loss is independent of whether a patient is on or off treatment.*

In the CP-CML model, the probability of response loss is derived directly from the clinical studies (PACE study for ponatinib and Gambacorti-Passerini for bosutinib).[11] The probability of response loss is independent of whether a patient is on or off treatment only for patients who achieved CCyR. Upon treatment discontinuation, patients in the CCyR category have the probability of response loss that is observed in the clinical study, independent of treatment discontinuation. Upon treatment discontinuation patients in PCyR are considered to lose PCyR and accrue the same response profile of hydroxycarbamide (PFS curve of hydroxycarbamide, 47% CHR and 53% NR).
The reason for the different approach across response categories is explained by the different disease status. By definition, CCyR indicates that there are no detectable Ph+ metaphases, thus reflecting a level of disease control considered optimal in ELN guidelines. When in CCyR, leukaemic clones can still be present, but at a level below the detection of modern cytogenetic analysis. CCyR doesn't necessarily mean the disease is cured, but it reflects a greatly reduced burden of cancer. This notion aligns with the ELN recommendations defining Ph+ 0% as a targeted 12-month optimal response to 2L TKI therapy after imatinib failure. Once CCyR is achieved, disease control will be easier to maintain even in the absence of treatment than it was to achieve. This may be possible, for example, because a patient's immune system might contribute to CML control when in this state.

B21. *For ALL patients, please clarify why the starting age of the patients is*

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independent of whether the patients are deemed suitable for allo-SCT. Clinical advice to the ERG suggests that the probability of being suitable decreases as a patient ages.

PACE study data were used to inform the starting age of patients with Ph+ ALL in the model, and we were thus limited by the small sample size of this group in the trial. No ALL patients in the PACE study underwent allo-SCT following treatment with ponatinib. The median age of the 3L ponatinib Ph+ ALL population in the trial was thus used to inform the starting age for both the SCT suitable and unsuitable populations in the economic analysis.

B22. *Please clarify whether the negative value associated with the major haematological response covariate in PFS is clinically plausible: this results in the estimated PFS being longer for those without a response than for those with a response. It is acknowledged that the PFS Kaplan-Meier estimates are higher for no-response although these are based on small numbers.*

As noted, the negative value associated with the MaHR for PFS in the AP-/BP-CML model is due to the small numbers from the PACE study providing the PFS KM data. We acknowledge that this outcome is counterintuitive. We note, however, that this aspect has practically no impact on the results of the model. The model simulates that patients achieving MaHR receive allo-SCT, so in practice the probability of progressing is not applied in the simulation.

B23. *Please amend the calculations derived from the PSA results. The PSA mean should not be the mean of the ICERs. Additionally, the 95% CI on the ICER should be able to distinguish between dominated and dominant negative values and calculated accordingly*.

The three models were amended as requested to calculate the mean PSA as the ratio between mean incremental costs and mean incremental QALY. The models were also amended to distinguish between dominated and dominant negative (each model now analyses the PSA outcomes by quadrant). New versions of the models have been submitted to NICE to accompany our responses to the ERG's comments.

B24. *Please clarify why in the Ph+ ALL model it is assumed that patients cannot die in cycle 0 if they respond to treatment and SCT is an option. Amend the model if this was not intended.*

In the Ph+ ALL model, patients can die during the first cycle. For instance, in the "Markov comp A" sheet, when ponatinib is selected as the first comparator, the number of deaths is initially zero (cell L6). At the end of the first cycle, the number of deaths is 0.1655 (cell L7). Applying the half cycle correction, the average number of deaths for the first cycle is 0.0827 deaths (cell U7).

B25. *Please clarify the drivers of the models which result in estimated negative QALYs for ponatinib in the PSA analyses run for each of the three models*

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submitted.

In the PSA presented for the CP-CML model (ponatinib vs bosutinib), approximately 1.5% of the iterations had a negative incremental QALY. All these cases were determined by a combination of low CCyR and PCyR rates for ponatinib (with simultaneous high response rates for bosutinib), high progression probabilities for cytogenetic response categories and high probabilities of loss of response for ponatinib. This rather implausible combination determined a lower mean survival for ponatinib patients than for bosutinib patients, translating into a negative incremental QALY.

In the AP/BP-CML model, the PSA was about the comparison ponatinib vs bosutinib in AP (ponatinib was dominant in the base case). The iterations with a negative incremental QALY were very rare (about 0.2%). We analysed these exceptional cases and found that they were determined by the combination of a high response rate for ponatinib (and a simultaneous low response rate for bosutinib) associated with an extremely high mortality after SCT (in some cases 3–4 times higher than the base-case value).

In the Ph+ ALL model, the PSA comparing ponatinib vs induction chemotherapy in SCT suitable patients presented negative incremental QALYs in about 3% of the cases. The combinations analysed were either similar to those identified for the AP/BP model or were determined by a combination of low response rates for ponatinib (as compared to high response rates for the comparator) associated with a very high mortality rate for patients not responding to treatment (and thus not receiving SCT).

B26. *Please clarify whether the ICER for ponatinib may change dependent on whether a person had a T315I mutation. Whilst it has been stated that ponatinib does not have differential efficacy based on this mutation, if comparator interventions do then it would be expected that the ICER would be more favourable for ponatinib in the T315I subgroup and less favourable in the non-T315I mutation group.*

The analysis that was presented in the base case used the main effectiveness indices (ie, response rates and maintenance of response) derived from the MAIC analysis. This analysis adjusted the comparison between ponatinib and bosutinib in order to account for imbalances in baseline characteristics between the two cohorts, including the presence of the T315i mutation. In the bosutinib study only about 6% of patients had the T315I mutation, whereas in the PACE study, the T315I mutation was present in 31% of the patients in 3L. The MAIC adjusted the analysis to compensate for this imbalance, assigning more weight to patients without T315I and less weight to those with the mutation. As a result, the response rates after the adjustment were very similar to those calculated in the non-T315I subgroup of the PACE study. In conclusion, given the fact that response to ponatinib is independent of T315I mutation status, whereas T315I-positive patients are not expected to respond to bosutinib, the analysis we present as a base case is conservative and does not favour ponatinib. We also

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note that in clinical practice only a small fraction of patients present with the T315I mutation.

B27. *Please clarify whether there is a possibility for inaccuracy by fitting curves to the data in Table 5-9, and then additionally using the complete haematologic response rates for patients who lose response. If such patients are included in Table 5-9 this would lead to double counting. If double counting is possible, clarify whether this is likely to be favourable or unfavourable to ponatinib.*

We acknowledge that there could be the possibility for a double counting. However we believe this is a conservative approach; ie, unfavourable to ponatinib. If patients losing response did not switch to progression probabilities derived from the CHR curve, they would have retained the progression probabilities derived from CCyR or PCyR curves and the model would have calculated a longer survival and a smaller economic burden due to progression for each of the TKI comparators. Since ponatinib yields higher cytogenetic response rates, it would have obtained a higher benefit in terms of cost-effectiveness.

B28. *Please clarify why alternative parametric distributions other than those from the Generalised F family of distributions or the Gompertz distribution have not been used, including fractional polynomials.*

We considered the distributions that have been used in previous NICE submissions and that are illustrated in the NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data.

We recognise that many other different models are usable, which gives several more degrees of flexibility, such as the mentioned fractional polynomials or other. However, considering the complexity of the current HE analysis (including that three different models with multiple scenario analyses were necessary to cover all indications for ponatinib) and the number of inputs involved, as well as the page-number restrictions of the submission, we consciously chose to apply a simplified approach limited to the use of standard techniques most commonly adopted in NICE submissions.

B29. *Please clarify how the utility decrement of 0.260 for the post-relapse state (p143) was calculated. The ERG could not replicate this value.*

We apologise for the unclear explanation of this calculation in the company submission. The decrement of 0.260 for the post-relapse state was calculated (like all decrements) as the difference from the reference utility of the general population (0.846) to the utility specific of the health state (0.5852). The second figure was obtained weighting the utilities in CP-CML, AP-CML, and BP-CML states by the % of states in relapse as reported by Kantarjian et al. 2002[16] and Olavarria et al. 2003.[17]

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B30. *Please clarify whether in the CP-CML model it was intended that people with a partial cytogenetic response or MHR who discontinue TKI treatment would be assumed to immediately lose their response, albeit having the possibility of a MHR through subsequent hydroxycarbamide use. This contrasts with those in complete cytogenetic response who are assumed to maintain the response post-TKI discontinuation.*

In the CP-CML model, we assume a benefit beyond treatment discontinuation for patients who achieve CCyR. For all other response categories (PCyR, CHR, and no response) patients who discontinue a TKI adopt the response rates of the BSC comparator, hydroxycarbamide. The response rate of hydroxycarbamide includes 47% possibility of CHR (not MaHR; CHR is more difficult to achieve-maintain than MaHR).

B31. *The base case results presented in the submission assumes that ponatinib is not continued if there is no major haematologic response response at 3 months in AP/BP-CML, or are non-responders at 3 months in the CP-CML. Please clarify the impact on the ICER compared to bosutinib if such stopping criteria are applied to bosutinib.*

As bosutinib does not have a corresponding recommendation in its label, we considered it would have been inappropriate for us to have proactively added this option. However, the ERG group can easily assess the effect of this option because the CP and AP/BP models that were submitted provide the option of excluding the stopping rule from ponatinib arm (use the specific dropdown list option in the general setting section of the setting sheet). The impact on ICERs is minimal.

B32. *Please clarify whether the separation of duration of ponatinib response data into those with a complete cytogenetic response and those with a partial cytogenetic response, in contrast to duration of bosutinib responses (which is major cytogenetic response), is likely to be favourable or unfavourable to ponatinib.*

We were limited by the absence of separate KM curves for CCyR and PCyR for bosutinib, and thus had to model the duration of response to bosutinib for MCyR only. This is unfavourable to ponatinib because the curve for duration of CCyR declines more rapidly than that for the less stringent response category of MCyR.

Resource use & costs

B33. ***Priority Question**: Please clarify why it is the half-cycle corrected state values that are used in calculating the main drug costs. It is more likely that all people in the state at the beginning of the cycle would receive treatment. Similar logic applies for treatments post continuation, post-SCT relapse and in AP/BP. Please amend the model if this was not intended.*

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In our simulation, the half-cycle correction is equally applied to benefits and costs as suggested by methodological guidelines when the duration of the cycle is long compared to the timing of events. The use of the half-cycle correction implies that if we have a population of 0.6134 at the beginning of the first cycle in CCyR on-treatment state (Comp A sheet, cell U6, when ponatinib is selected as first comparator) and a population of 0.5800 at the end of it, we have on the average a population of 0.5967 that is accumulating costs and benefits. Assigning the cost of the drug for the entire 3-month period to all subjects at the beginning of any cycle would result in:

- An overestimate of the cost because not all patients remain on treatment for the entire cycle as a combined result of events such as death, progression and discontinuation, that may occur during the cycle;
- An inconsistency in the method because the costs would be accounted on the entire population at the beginning of the cycle, while benefits, namely life-years and QALYs, would be assigned to the average population resident in the health state

B34. ***Priority Question****: Please clarify why it is assumed that treatments used post-SCT failure or in progressed CML (p122) are split equally amongst imatinib, hydroxycarbamide, dasatinib, nilotinib, bosutinib, when this is contrary to evidence provided by the company in Table 27 of Appendix 14. More importantly, the time spent in PFS in AP-CML has been taken from Kantarjian (2007). In this paper 64/84 patients in AP-CML receive 'other treatment' with the remaining 20/84 patients receiving dasatinib or nilotinib. Please amend the model so that the costs represent the treatments used in generating the efficacy data.*

We applied simplifying assumptions for the distribution of treatments post-SCT failure/progression (use of different plausible distributions would have had little impact on the results). We were unable to assign costs for "other treatment" since we don't know which agents were included or what was the distribution of agents within the "other" category.

B35. ***Priority Question****: Please clarify when the SKU price for ponatinib will be confirmed as the list price.*

The SKU price has already been confirmed by the Department of Health.

B36. *Please tabulate and summarise the HRG costs used within the model so that these can be viewed by the appraisal committee. For example: - Nurse led visit NHS Reference Costs 2014 to 2015 - N10AF (Specialist Nursing, Cancer Related, Adult, Face to face). Presently these only appear in the model which is not typically viewed by the appraisal committee who may want to check the values.*

Monitoring and follow-up unit costs used to inform the CML and Ph+ ALL economic analyses

Resource	Unit	Source

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	cost, £	
Outpatient visits		
Nurse-led	66.42	NHS Reference Costs 2014 to 2015 - N10AF (Specialist Nursing, Cancer Related, Adult, Face to face)
Haematologist-led	150.38	NHS Reference Costs 2014 to 2015 - WF01A service code 303 (Non-Admitted Face to Face Attendance, Follow-up; Clinical Haematology)
Tests		
Full blood count	3.01	NHS Reference Costs 2014 to 2015 - DAPS05 (Haematology)
Cytogenetic analysis	6.99	NHS Reference Costs 2014 to 2015 - DAPS01 (Cytology)
Bone marrow aspiration (with biopsy)	517.50	NHS Reference Costs 2014 to 2015 - (SA33Z - DC - Diagnostic Bone Marrow Extraction)
FISH	6.99	NHS Reference Costs 2014 to 2015 - DAPS01 (Cytology)
PCR	25.00	Szczepura et al. Health Technology Assessment 2006; Vol. 10: No. 10
Flow cytometry	6.99	NHS Reference Costs 2014 to 2015 - DAPS01 (Cytology)
Cytochemistry analysis	6.99	NHS Reference Costs 2014 to 2015 - DAPS01 (Cytology)
Blood film exam	3.01	NHS Reference Costs 2014 to 2015 - DAPS05 (Haematology)
Blood chemistry	1.19	NHS Reference Costs 2014 to 2015 - DAPS04 (Clinical Biochemistry)
Kinase domain mutation*	6.99	NHS Reference Costs 2014 to 2015 - DAPS01 (Cytology)
Therapies/interventions		
Blood transfusion	121.85	NHS Blood and Transplant Price List 2014/15 (BC001 - Standard Red Cells)
Donor lymphocyte transfusion	193.15	Assumed same as platelet transfusion
Platelet transfusion	193.15	NHS Blood and Transplant Price List 2014/15 (BC041 - Platelets (1.0 ATD))
Days in hospital	721.00	Finished consultant episode based average costs for a hospital day case (DH NHS Reference Costs 2014-15).

B37. *Clinical advice provided to the ERG suggests that, while it is unlikely for ALL, the savings associated with reduced dose intensity could be recouped in CML. Please provide versions of the model that allow the impact on the ICER of being unable to recoup savings based on reduced dose intensity*.

The ponatinib dosing intensity used in the economic analyses reflects clinical trial dosing from the PACE study. The distribution of the time on treatment in different doses observed in PACE study was validated by a clinical expert (Dr. Clark of the Haematology Department at the Royal Liverpool University Hospital), who confirmed ponatinib dosing intensity in the PACE study reflects ponatinib use in clinical practice.

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Modelling ponatinib at its full-dose intensity would provide an improbable cost-effectiveness analysis. Per SmPC guidance, dose reductions are recommended to manage AEs.[18] In addition, among all CP-CML patients who underwent dose reduction for any reason in the PACE study, preliminary efficacy data show maintenance of response in the majority of these patients (Table 4-23, CS). The current SmPC makes clear that dose reductions should be considered for patients with CP-CML who have achieved a MCyR [redacted]. In line with these recommendations, clinical practice data show that dose reductions are common among patients with CML (Mauro et al. 2015).[19]

[redacted]

All evidence therefore supports ponatinib dose reductions for CML, and it would thus be unrealistic to exclude from the model dose reductions.

B38. *Please clarify how sensitive the ICER is to assumptions regarding the split of induction chemotherapies used in ALL, accounting for 1) full packs being used rather than assuming a cost per mg approach and 2) using a distribution of weight rather than a fixed value. Analysis 2 would need to be run in conjunction with Analysis 1 to have an impact.*

We calculated the scenario as requested and provide the results below.

When applying the full pack approach (vs the cost per mg approach) the components of induction chemotherapy changed as follows (costs for a 6-week course):

- LALA-94: £4,807 → £5,541
- Hyper-CVAD: £1,296 → £1,385
- Flag-IDA: £3,164 → £3,476

The following outcome results are calculated when the full pack approach is applied (leaving unchanged the uniform split between the three chemotherapeutic regimens)

Ph+ ALL: Full pack approach (chemotherapeutic regimen split unchanged)

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	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Induction chemotherapy	69,564.65	1.84	[redacted]	0.53	10,796
Ponatinib	[redacted]	2.36	–	–	–

To analyse the sensitivity of the ICER to the drug mix composing induction chemotherapy, we explored the outcomes related to an arbitrary mix assigning more weight to less costly therapies (50% Hyper-CVAD, 30% Flag-IDA and 20% LALA-94). The results are reported in the following table

Ph+ ALL: Impact on ICER using a distribution of weight rather than a fixed value for the split of induction chemotherapies

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Induction therapy (base case)	69,180.82	1.84	[redacted]	0.53	11,496
Induction chemotherapy (full pack)	68,945.26	1.84	[redacted]	0.53	11,941
Induction chemotherapy (cost per mg)	68,654.94	1.84	[redacted]	0.53	12,491
Ponatinib	[redacted]	2.36	–	–	–

Compared to the base case (£11,496), the impact on the ICERs was small (3.9%). The ICER is therefore relatively insensitive to changes in the split of induction chemotherapies.

B39. *Please indicate how the costs of the initial SCT and the follow-up costs have been calculated. The numbers reported in the submission do not seem to appear in the provided reference.*

The initial cost of transplantation (£60,092) is calculated as the sum of the transplant unit personnel cost (original value £20,720 inflated to 2014/2015 at £21,138) and the transplantation cost (including UK sourced cord blood donation; original value £38,183 inflated to £38,954).

Health utility

B40. ***Priority Question**: Please clarify why in the CP-CML model the CCyR value*

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was capped at population norm, but the values for other states were left unchanged. This artificially reduces the utility loss of moving from CCyR. Clarify how the results change if the absolute decrements were applied to the population norm values, or if the ratios between the health states were kept constant.

In order to take into account the effect of the ageing of the population when assessing quality of life, the age-specific norms of the general UK population are included in the simulation. This means that rather than using the absolute utilities for the health states in the model, we compared them with the reference norm utility for a sample of the general UK population with the same average age and composition of sexes as the simulated population (reference value 0.846). With this approach all the utilities are implicitly capped at the norm of the general population. In the specific case of the CP-CML model, this happens only for the health state "CP-CML with CCyR" (utility of 0.91), as this is the only health state in which the absolute utility exceeds the population reference value. To avoid calculating negative decrements of utility (ie, an additional utility) we assumed a zero decrement for the CP-CML with CCyR health state. This is equivalent to considering that subjects in that condition have the same quality of life as the average person in the UK with the same age and sex, without any specific impairment due to the disease. This assumption is in line with other assumptions, such as that CP-CML patients do not experience extra mortality due to the disease.

However, to more fully answer this question we performed a scenario analysis to remove this capping. In this case, a negative decrement of utility is calculated for the CP-CML with CCyR state (-0.064). In this scenario the results become slightly more favourable to ponatinib (the ICER is £20,322/QALY vs bosutinib, £7,098/QALY vs. SCT, £16,474/QALY vs. hydroxycarbamide and £8,465/QALY vs IFN) as compared to the base case (£22,302/QALY vs bosutinib, £8,062/QALY vs SCT, £18,073/QALY vs. hydroxycarbamide and £9,294/QALY vs. IFN).

Section C: Textual clarifications and additional points

General

C1. *Please clarify whether major haematologic response (MHA) is more stringent than overall haematologic response (OHR). Multiple times in the text it is said that MHA is more stringent, yet the text (see page 97) also suggests that OHR has to meet the criteria for MHA and additional criteria.*

Compared to MaHR, OHR has a broader definition. The definition for MaHR, as defined in the PACE study, included complete haematologic response (CHR) and no evidence of leukaemia. The definition for OHR, as defined in Gambacorti-Passerini et al. 2015,[5] included CHR and no evidence of leukaemia plus minor haematologic response (MiHR) (for Ph+ ALL) and return to CP if applicable. The table below lists the response criteria. The definitions generally

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overlap, but for patients treated with bosutinib, OHR can include those who return to CP. The outcome of the broader definition is shown in the phase 1/2 bosutinib study: among patients with AP-/BP-CML who improved from or maintained their baseline response, a higher percentage of patients achieved OHR than MaHR.

Definitions of response criteria for AP-CML, BP-CML, and Ph+ ALL

	Ponatinib	Bosutinib
	MaHR: CHR+NEL	**OHR: CHR + NEL + MiHR + return to CP (if applicable)**
CHR	• White blood count ≤institutional ULN • ANC ≥1000/mm³ • Platelets ≥100,000/mm³ • No blasts or promyelocytes in peripheral blood • Bone marrow blasts ≤5% • <5% myelocytes + metamyelocytes in peripheral blood • Basophils <5% in peripheral blood • No extramedullary involvement (including no hepatomegaly or splenomegaly)	• White blood count ≤institutional ULN • ANC ≥1.0×10^9/L • Platelet count ≥100×10^9/L but <450×10^9/L • No blasts or promyelocytes in blood • Blasts ≤5% in bone marrow • Myelocytes + metamyelocytes <5% in blood • Basophils <20% in blood • No extramedullary involvement (including hepato- or splenomegaly)
NEL	• White blood count ≤institutional ULN • No blasts or promyelocytes in peripheral blood • Bone marrow blasts ≤5% • <5% myelocytes + metamyelocytes in peripheral blood • Basophils <5% in peripheral blood • No extramedullary involvement (including no hepatomegaly or splenomegaly) • At least one of the following: (i) 20,000/mm³≤platelets <100,000/mm³ (ii) 500/mm³≤ANC< 1000/mm³	• No blasts or promyelocytes in blood • Blasts ≤5% in bone marrow • Myelocytes + metamyelocytes <5% in blood • Basophils <20% in blood • No extramedullary involvement (including hepato- or splenomegaly) • ANC ≥0.5×10^9 • Platelet count ≥20×10^9 but <450×10^9/L
Return to CP	—	Disappearance of features defining AP and BP, but still in CP, as noted by: • Blasts <15% in both blood and bone marrow • Blasts + promyelocytes <30% in both blood and bone marrow • Basophils <20% in both blood and bone marrow • No extramedullary disease other than spleen and liver
MiHR*	—	• Blasts <15% in bone marrow and blood • Blasts + promyelocytes <30% in bone marrow and same in blood • Basophils <20% in peripheral blood • No extramedullary disease other than spleen and liver

ALL, acute lymphoblastic leukaemia; ANC, absolute neutrophil count; AP, accelerated phase; BP, blast phase; CHR, complete haematologic response; MaHR, major haematologic response; MiHR, minor

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haematologic response; NEL, no evidence of leukaemia; OHR, overall haematologic response; Ph+, Philadelphia positive–chromosome; ULN, upper limit of normal.
*Criteria applicable only for patients with Ph+ ALL.

C2. *Please clarify whether there is a typo in Table 5-9. The values are likely to be the probability of remaining in the progression free state rather than the probability of progression.*

Correct, this is a typographic error. The values in Table 5-9 represent the probability of remaining in the progression-free state (ie, PFS rate) and not the probability of progression. We apologise for any inconvenience.

C3. *Please clarify that the 0.91 utility value for people in CP-CML with response is not used in the submission, as suggested in Table 5.17. The ERG believes that this value is capped to a population norm value.*

Correct, the 0.91 utility value applied in the model was capped to the population norm value.

C4. *Please clarify that it was intended that hyperglycaemia is not included as an adverse event within the model.*

Correct, hyperglycaemia is not included as an adverse event within the model. Although a unit cost for hyperglycaemia was listed in the model, only treatment-related Grade 3/4 adverse events occurring in ≥5% of patients were incorporated in the analysis; Grade 3/4 hyperglycaemia occurred in <5% of patients in the PACE trial and was thus not included as an adverse event in the model.

C5. *Please clarify whether there is a typo in Table 5-62: it is believed that these are the results for BP-CML rather than AP-CML.*

Table 5-62 of the company submission incorrectly reported the PSA results for BP-CML and not AP-CML. The revised table below presents the results for the comparison of ponatinib vs bosutinib in AP-CML, the disease state that accounts for the majority of patients starting treatment with these TKIs in advanced CML. For the full incremental analysis for the PSA results, please see the table presented in B3. We apologise for this typo and any inconvenience caused.

Table 5-62. 95% CI for costs, QALYs, and ICERs

	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Base case	[redacted]	0.90	-21,050
PSA mean	[redacted]	0.91	-25,261
PSA 95% CI lower	[redacted]	0.15	-117,424
PSA 95% CI upper	[redacted]	2.00	3,886

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C6. *Please clarify whether there is a typo in Table 5-68 and that the cost for a day in hospital should be £721 as used in the model and also reported for CML.*

The cost for a day in the hospital presented in Table 5-68 (£714.64) is correct. This value is found in the Ph+ ALL model Direct costs tab, cell H74 and is from a source providing the cost per day for a hospital stay and the number of inpatient days during induction chemotherapy (NICE TA399 [azacitidine]). There is also the possibility of days in the hospital as part of the general healthcare resource usage (HCRU) for the disease. Due to the paucity of relevant data available in the literature, this HCRU component is assumed similar to BP-CML. For this reason the model includes the same cost as considered in the BP-CML model (£721 value; Direct costs sheet, cell H172). However this has no practical impact in the health economic assessment because the tariff is multiplied by 0 days in hospital per cycle during the follow-up.

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Appendices (Redacted)

Appendix 25: Revised Appendix 25—Parametric survival analysis and curve fitting

Appendix 26: MAIC–individual weights in the ponatinib cohort

Appendix 27: CHMP Rapporteur Assessment Report

Appendix 28: Suggested updates to Ponatinib SmPC

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

* The template without any addition by respondents is 6 pages in length, we assume the reference above to 10 pages is in addition to the 6 pages.

* As noted in the next section, our organisation's sole focus is on chronic myeloid leukaemia. We will therefore not be providing any comment on the treatment of acute lymphoblastic leukaemia with ponatinib.

1. About you and your organisation

Your name: David Ryner

Name of your organisation: The Chronic Myelod Leukaemia Support Group (CMLSg)

Your position in the organisation: Chair

Brief description of the organisation: The CMLSg is the only UK registered charity (Reg No 1114037) with a sole focus on Chronic Myeloid Leukaemia (CML). It is patient lead with its Director and three of our Trustees being CML patients. Because of the rarity of CML, CMLSg operates primarily, but not exclusively, online. Our objective is to offer support, information and advocacy to patients and those that care for them so that they can, after treatment, resume a life as close as possible to that lived before diagnosis.

Our website analytics currently shows the average number of unique visitors/month for the last quarter (July to September 2016) to number just under 7,000 although it should of course be remembered that the website's reach is global.

In addition to obtaining funding from the public and to avoid any inference of bias, we are careful to seek funding from all companies that have licensed drug based treatments (Tyrosine Kinase Inhibitors or TKIs) for CML. Our annual audited accounts are available via the Charity Commission website.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

1. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

1.1 CML is a progressive three phase malignancy. It is a rare cancer (incidence around 1:100,000 with 624 new diagnoses reported in England in 2013) and a less well known member of the leukaemia family.

1.2 The wider public perception of leukaemia is gross, with little or no differentiation by type, and tends to be highly negative with a common assumption that life will be much shortened following diagnosis .

1.3 Over 90% of patients are diagnosed in the initial chronic phase (CP) of the disease with some 40% of this group asymptomatic at diagnosis.

1.4 However the patient population for whom ponatinib might be considered an appropriate treatment option in the NHS would be much smaller than the figure cited in 1.1 and would cover the entire patient population not just those newly diagnosed over a calendar year. The manufacturer's estimate is *'...that 84 patients would be eligible for ponatinib in England each year in line with the marketing authorisation'* (NICE Batch 33: Block Scoping Report, Item 5.4), with the Institute describing this population as *'very small'* in the same Report. NHS England also recognises there are '...*relatively small numbers eligible for treatment'* ('Response to the consultee and commentator comments on the draft remit and draft scope' : August 2016 page 6.)

1.5 Although small in number, this minority group of patients has the greatest clinical need since their experience of their post diagnosis treatment is not just one of failure but of successive failure.

1.6 These patients are well aware from their visits to specialist clinics of their increasingly compromised clinical situation as they are of the contrast of their situation with that of the majority of CP patients most of whom will have secured an optimal response to treatment. As such they view themselves a minority within a minority, since CML is a minority (rare) disease.

1.7 Feelings of panic, fear, anxiety and stress dominate their emotional life with the same applying for those who care for them.

1.8 Whilst some of this small CP group have a dwindling number of potentially effective treatment options available to them, some do not and have a clear unmet need.

1.9 For the very small number of patients who have either progressed to, or have been diagnosed in, the accelerated phase (AP) or are in the final blast phase (BP), their outlook, as they will be aware, is and remains poor. Life for patients in AP or BP tends to be radically transformed and will often, unlike for those in CP, be hospital based with all that entails.

2. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

2.1 All patients would like a treatment that would allow them to achieve:

(a) A post treatment outcome that would initially arrest disease progression.

(b) A treatment outcome that would go on to reduce the 'load' of their leukaemia to a point where they are considered 'functionally cured' with that outcome enduring for their expected lifetime had they not been diagnosed.

(c) That the outcome secured following treatment would not be at a punitive side effects 'cost'. Rather treatment would allow them to secure a quality of life (QoL) similar or identical to that enjoyed before disease onset.

(d) With a functional cure and optimal QoL 'banked', a resumption of public life, including working life if applicable, would be a next welcomed outcome.

For carers, the greater the distance travelled along this four stage continuum the better, since this brings successive decreases in the caring burden.

2.1.1 For the group for whom ponatinib treatment is indicated an additional outcome achieved were this treatment to be effective would be that they could rejoin the majority, already effectively treated, CML patient population.

2.1.2 All patients have an overarching ambition that at some future date a zero risk therapy with a curative intent and positive outcome will be developed rendering a CML diagnosis a historical event rather an ongoing everyday reality.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition?

2.2 Our experience of current NHS care is that policy driven decision making has, over time, resulted in a lack of coherence in the TKI treatment options available to specialist clinicians with this sometimes resulting in perverse clinical consequences for patients. This situation is exacerbated by the discounting of accumulated clinical experience in managing adverse events arising from TKI treatments that might have once posed a significant barrier to treatment but no longer do so now.

2.2.1 The situation described in 2.2 has been set out in detail by a leading UK clinician in an article published online in November last year (*'Cancer Drugs Fund and CML: an unhappy alliance'* http://www.oncology-central.com/2015/11/05/cancer-drugs-fund-and-cml-an-unhappy-alliance) and was also the subject of a recent BBC radio programme (*'The Cancer Drugs Fund'* BBC Radio 4 'File on Four' broadcast on 7th June 2016 available as a download at http://www.bbc.co.uk/programmes/b006th08/episodes/downloads).

2.2.2 We welcome the current NICE conducted Cancer Drugs Fund (CDF) Rapid Reconsideration process within which this appraisal falls (ponatinib is a Transition Group 3 member) and which, overall, includes the reconsideration of three of the five TKIs for CML (Transition Group 2 members include bosutinib and dasatinib). This evaluation process has the potential to resolve the issues described in the publication and broadcast noted in 2.2.1 above.

2.2.3 We are encouraged by the July 2016 publication of a positive recommendation for bosutinib treatment for all its licensed indications.

2.2.4 We remain optimistic for a similar outcome for dasatinib as both a first and subsequent treatment (following imatinib failure) for CML. This viewpoint is supported by the contents of an NHS England (NHSE) document published in March of this year entitled *'Clinical Commissioning Policy Statement: Dasatinib for the 1st line treatment, and the 2nd line treatment of imatinib-resistant, chronic myeloid leukaemia'*. Section 2 of the document contains this sentence: *'This policy statement has been developed because dasatinib is a recognized clinically-effective treatment for CML which is now also cost-effective to the NHS'* following an NHSE assessment of, and assumption about, the likely '*price of care'* of dasatinib treatment (see Section 3).

2.2.5 Setting aside the outcome of this appraisal and should our optimism about dasatinib become a reality; the end of the current NHSE financial year should see all TKIs for the treatment of CML (ponatinib excepted) in routine use in the NHS in England.

How acceptable are these treatments and which are preferred and why?

2.3 Should the outcome described in 2.2.5 be realised (setting aside this appraisal), our view is that the current and future patient population will be reassured that effective TKI treatments are now routinely available.

This is in contrast to the situation less than a year ago when three TKIs where accessible only via an application to the CDF and only with more restrictive eligibility criteria operative than their licensed indications. Criteria which were trending to an increase, rather than decrease, in their restrictiveness.

2.3.1 Treatments that are less acceptable to patients are amongst those listed in the comparators section of this appraisal's Final Scope. These are:

(a) Best Supportive Care : This would in practice in the NHS amount to Hydroxycarbamide (HU). We understand the TA derived rationale for its inclusion as a comparator in this appraisal even though there is agreement that its use is unable to secure either a cytogenetic or molecular response.

Unsurprisingly patients are astonished at it being accorded the status of a ‘treatment’ and do not view its use as such. We hope that this appraisal will not be dominated by a futile discussion of survival times on HU either a sole or subsequent ‘treatment’ following TKI treatment(s).

(b) Interferon alpha (IFN): Although IFN is in routine use in some EU member states (notably France and Germany) we would argue IFN would not fall in the category ‘...*currently available NHS care*‘ since its use would now be highly exceptional rather than routine.

Given the punishing side effects that more often than not accompany its use and the success of treatments that fall in the TKI class, any patient would be surprised and disheartened if IFN were a treatment option offered when all available TKIs had not been considered even if their access to TKIs was via a non routine NHS route be that the CDF, an Individual Funding Request (IFR or prior to that an ICDFR) or even a Clinical Trial.

(c) Allogeneic Stem Cell Transplantation (SCT): We agree that SCT remains an option for CP patients experiencing failure with TKI treatment, especially those experiencing multiple TKI failure, and whose disease status indicates progression to the more advanced disease phases is likely.

Although SCT currently remains the only treatment option described as ‘curative’, the high risk that accompanies its deployment renders it as a ‘treatment of last resort‘ to patients to be considered only after all TKI treatments have been either optioned, yet then been found to fail, or had been dismissed as inappropriate.

(d) Bosutinib: Patients acknowledge bosutinib to be a potentially effective treatment for CML. As with all TKI treatments, ‘one size does not fit all’ but we of course accept its status as an effective treatment (see 2.2.3 above).

However in our opinion bosutinib’s most likely line of treatment (at 3rd line) would precede that most likely for ponatinib (at 4th line) although not exclusively so. Reinforcing that view would be the absence of ponatinib in the list of comparators for the recent CDF Rapid Reconsideration of bosutinib.

As an organisation our view would therefore be its reasonable to expect challenge on the comparator status afforded bosutinib in this appraisal.

2.3.2 For patients in the two advanced disease phases, any effective treatment would assign priority to securing a reversal of disease progression back to CP. One option to achieve this objective would be the use of an aggressive chemotherapy regimen (eg FLAG-id). This would be followed by an SCT if a patient was fit enough following chemotherapy and a suitable donor has been located. TKIs have had a place in SCT treatment design for some time although their use is occasioned rather than mandatory.

There is an ongoing clinical trial (MATCHPOINT) involving the use of ponatinib alongside FLAG-id and an SCT for BP patients.

What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers can expect to gain from using the treatment being appraised.

2.4 The benefit of a once a day, home based, tablet TKI treatment that is both clinically effective and well tolerated hardly needs listing especially when

compared to, and contrasted with, agents that fall within traditional chemotherapy treatment regimes.

Ponatinib treatment tallies with that description for TKIs although the entirety of the detail does not extend to all TKIs with, for example, twice a day administration, after fasting, of nilotinib and twice a day administration of dasatinib (although we acknowledge the emerging preference for a once a day rather than twice daily administration of dasatinib treatment).

2.4.1 Ponatinib is the first third generation (3G) TKI treatment for CML and is the most potent of the five TKIs that are licensed for the treatment of CML.

2.4.2 The T315i mutation is an indication for which ponatinib is a licensed treatment since it is the only TKI capable of significant activity against it.

2.4.3 However this 'headline' feature in 2.4.2 masks the clinical effectiveness of ponatinib across the entirety of its licensed indication population. Of note also is that 75% of the pivotal (PACE) clinical trial population did not have the T315i mutation.

The data set out in the poster presentation *'Long term efficacy and safety of ponatinib in heavily pretreated leukaemia patients: 4 year results from the pivotal Phase II PACE trail*'' at this year's annual European Haematology Association conference showed that a substantial number of patients *'...continue to show deep and lasting responses on ponatinib, and approximately 2 years post recommended dose reductions, maintenance of response is high, and the incidence of newly occurring AOEs has decreased.'* http://learningcenter.ehaweb.org/eha/2016/21st/133215/jorge.cortes.long-term.efficacy.and.safety.of.ponatinib.in.heavily.pretreated.html

2.4.4 There is also evidence that ponatinib exerts a suppressive effect on the emergence of mutations resistant to first (1G) and second (2G) generation TKIs.

2.4.5 The selection of 3G ponatinib rather than a 1 or 2G TKI as the TKI of choice for the MATCPOINT clinical trial (see 2.3.2 above) attests to its utility in treating patients in advanced phase disease.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

2.5 See 2.4.1 to 2.4.5 above for evidence of the advantage ponatinib has for patients previously treated with other TKIs including bosutinib.

2.5.1 The advantage enjoyed by ponatinib over the other non TKI comparator treatments is:

(a) Our comments in 2.3.1 (c) above make it clear that TKI treatment, including ponatinib, is favoured by patients over SCT unless successive TKI failure or lack of suitability exhausts all licensed TKIs as treatment options.

However for those patients for whom an SCT is not a feasible treatment option following either bosutinib treatment failure or where bosutinib is not considered appropriate, ponatinib remains the only treatment option that has the potential to be clinically effective.

(b) Patients experience of IFN aligns with the Royal College of Pathologists (RCP) comment that: *' Interferon alfa is no longer used in the management of CML CP and was never used in advanced phase disease'* (p.22 in the NICE '*Response to the consultee and commentator comments on the draft remit and draft scope'* : August 2016), 'Advantage' is therefore an inappropriate term.

(c) Similarly patients would agree with the RCP that: *'Hydroxycarbamide is not an appropriate comparator because it does not affect survival but is simply used as symptom relief. It has absolutely no efficacy in CML acceleration or blast crisis.'* see same page same reference as (b) above.

2.5.2 For some patients these *'other treatments in England'* , including the other TKIs, either lack effectiveness in circumstances where their use might be considered appropriate or their use is simply not a feasible option.

Otherwise why would NHSE note - see page 6 same reference as (b) above - there is *'... a clear clinical demand for this product in its non CDF approved indication*'

2.5.3 Adding to 2,5.2 above is the indication (T315i) currently reimbursed via the CDF which the CDF Panel has acknowledged met its 'unmet need' criteria (NHS England CDF Decision Summary July 2013. Additional Notes section)

2.5.4 As the RCP (joined by the NCRI) also note - see p.2 same reference as (b) above - this group of patients described in 2.5.2 and 2.5.3 *'...are those with greatest clinical need'*. For them ponatinib would offer both a next, and final, TKI treatment.

2.5.5 More broadly, and given our comments on patients understanding of their treatment options, the availability of another TKI, in this case ponatinib, that has proved to be clinically effective is viewed positively not only by patients experiencing challenges with their existing TKI treatment but much more generally by patients who forever remain concerned about a loss of response at some future date and wish for the availablity of a 'reserve' TKI option.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

2.6 Opinion varies amongst patients between those who favour an approach to TKI treatment which delivers, as with 2 & 3 G TKIs, high response rates very quickly and who are willing to tolerate the likely side effects that are often more intense than would be the case were response rates achieved over a longer time span with 1G imaitib.

The latter approach often finds favour amongst other more risk averse, generally older, patients. Ponatinib would be an example of the former.

3. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

3.1 As noted in 2.3.1 (d) individual responses to a particular TKI treatment vary with current clinical management seeking speedy resolution in locating a TKI that is both clinically effective and well tolerated by a particular patient.

3.1.1 At present there are a small number of patients unable to achieve that state who understandably wish to do so and who are well aware of the restrictions currently in place in the NHS that prevent a full exploration of all the licensed treatment options available.

3.1.2 It is not that they do not recognise that current NHS treatments are ineffective per se rather its the case that these treatments are not effective for them whereas they might be for others.

3.1.3 In addition to its clinical basis, the concern is also with the inequity present.

Please list any concerns patients or carers have about the treatment being appraised.

3.2 There are known cardiovascular issues associated with ponatinib treatment. The concern is amplified by the irreversible characteritic that is a feature of the occurence of cardiovascular side effects associated with ponatinib treatment in particular (and for which ponatinib has an FDA Black

Box warning). In response, current clinical management involves establishing a patient's cardiovascular status (often via QRISK methodology), active management where risk factors are identified and ongoing monitoring of all patients treated with ponatinib for these identified risks.

3.2.1 Patients are of course made aware of these risks but they are also aware of their compromised status following earlier treatment failure with other TKIs and, in some cases, their exhibiting the T315i mutation.

3.2.2 Their decision making with their clinician seeks to balance these risks against the potential benefit to be derived from ponatinib treatment whilst also taking into account the mitigating activity taken to address the occurrence of a cardiovascular event.

3.2.3 We would stress that this small group of patients are generally willing to accept much higher levels of risk given their highly compromised clinical status.

3.2.4 We accept there is an impact in terms of day to day clinical practice since management of these risks becomes more onerous for both clinicians and patients than can be the case with other TKI treatments.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

3.3 As stated previously, patients are well aware of differences in individual responses to TKIs as they are of their effectiveness in treating CML.

4. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

5. *Research evidence on patient or carer views of the treatment*

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ✓ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

A CMLSg nominee is a 'consumer representative' member on the CML Subgroup of the NCRI Haematological Oncology Clinical Studies Group. We are therefore familiar with recent published literature but since subgroup clinicians are submitting evidence and will attend the committee meeting we will not comment.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

6. *Equality*

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;

- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

7. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

7.1 Whilst we accept that ponatinib, unlike imatinib, does not represent a 'step change' in treatment for CML, we would argue that its status as being the first member in the 3G class warrants a 'first in class' designation. If that meets the criteria for innovation, ponatinib would qualify as an innovative treatment .

7.1.1 As the only TKI capable of significant effective activity against the T315i mutation and if action against a mutation is not considered too discrete a benefit to qualify as an innovation, then ponatinib is an innovative treatment.

Are there any other issues that you would like the Appraisal Committee to consider?

7.2 Save for a lack of a defined response or the occurrence of a serious adverse event, the EMA Summary of Product Characteristics (SPC) recommends that the starting dose of 45mg/day be continued indefinitely.

7.2.1 However current established clinical practice in England is for a starting dose of 30mg/day. Dose reduction also extends to patients, generally those recruited to the PACE clinical trial, who were started on the recommended dose of 45 mg/day some time ago making departure from the EMA recommended dose an established feature of treatment.

7.2.2 Although we acknowledge that our evidence is anecdotal, we know of no patient who is administering the recommended starting dose and we are aware of patients whose dose is as low as 7.5mg/day (a 15mg tablet halved) or its equivalent (15mg every other day).

7.2.3 In our opinion the economic assessment of the cost effectiveness of ponatinib should reflect real world dosing rather than assume all patients are being treated with a dose none now seem to take.

7.2.4 Should this not occur, fantasy rather than fact will be modelled with potential disadvantaging consequences for real rather than fictitious patients.

8. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

1. Ponatinib is an appropriate treatment for patients with an unmet need. These are:

(a) Patients with a T315i mutation who are not clinically fit for an SCT, or who lack a matched and/or willing SCT donor

(b) Patients who are not clinically fit for an SCT, or who lack a matched and/or willing SCT donor and for whom bosutinib is either not considered an appropriate treatment or who have experienced treatment failure following bosutinib treatment.

2. Ponatinib is an appropriate treatment for patients with significant clinical need who are: These are patients for whom ponatinib is potentially the most effective of the TKI treatments that are available. Unlike the unmet need sub group, it is not that other TKIs are not effective but for them ponatinib is the most effective TKI of those that are licensed although this may not be the case for all patients.

3. The European Leukaemia Net (ELN) http://www.cmladvocates.net/education/eln-recommendations/391 recommendations represent current clinical consensus for the whole pathway of CML treatment. The recommendations provide specialist clinicians with a flexible range of treatment options for their patients. A positive NICE recommendation for ponatinib that aligns, or increases alignment, with those

for ponatinib incorporated in the ELN would ensure the achievement of clinical coherence across the treatment pathway whilst maximising the possibility for a successful outcome for any patient.

4. Dose reduction from that set out in the SPC as the starting dose for ponatinib in its licence is for a very significant number of, if not all, patients both a viable, clinically effective treatment option and representative of current, established, real world clinical practice in England.

5. To exclude the economic impact of dose reduction in an assessment of the cost effectiveness of ponatinib would be perverse and illogical. If pursued as a policy it would add to the existing lack of clarity about the impact of drug based treatments, relative to other treatments, on NHS resources.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. We support people affected by leukaemia, lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndromes, myeloproliferative disorders and aplastic anaemia.

Our current membership database stands at approximately 18,500. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers throughout the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes emotional effects of a

blood cancer and help for those caring for a patient. Our focus is providing information and support for everyone affected by a diagnosis of blood cancer. See http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia CARE receives funding from a range of pharmaceutical companies, but in total those funds do not exceed 15% of our total income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

- http://www.leukaemiacare.org.uk/resources/code-of-practice

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

ALL

Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia, with over 730 people diagnosed in England and Wales each year. Thirty percent of all adults diagnosed with ALL will be Philadelphia chromosome positive (Ph+). Like most blood cancers ALL is strongly correlated to age, although unusually the peak incidence is in children. There

is a second peak incidence in patients over the age of 65. Five-year survival outcomes vary greatly by age, from over 90% in the under 14s, 66% in those aged 15-24, less than 40% in those aged 25-64 and less than 15% in those aged 64 or older. As such, the prognosis for adult patients with the condition is extremely poor.

The most common signs and symptoms are caused by the bone marrow being unable to produce enough normal blood cells. These include anaemia (due to lack of red blood cells), weakness, tiredness, shortness of breath, light-headedness, palpitations, frequent and persistent infections (due to lack of normal white blood cells), purpura (small bruises in skin), nosebleeds, bleeding gums, bleeding and bruising (due to lack of platelets), fever and sweating. Some patients may also have an enlarged liver, spleen or enlarged lymph nodes. Being diagnosed with ALL can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. Many of these feelings can have a profound impact on both their physical and psychological wellbeing. With many patients facing a poor prognosis, this does not affect a patient in isolation but instead creates a “ripple effect”. This can place huge emotional strain on families and friends, many of whom may be affected by the diagnosis.

Due to its relative rarity and non-specific symptoms, patients are usually diagnosed with ALL following the onset of symptoms, when it has often progressed significantly. NCIN conducted a report of patients ‘Routes to Diagnosis’ which showed that 64% of ALL patients are diagnosed following an emergency presentation (emergency GP referral or A&E). This figure was the highest of any cancer type in the report. Diagnosis at an advanced stage, along with a lack of effective treatment options, has a large impact on their prognosis.

CML

Chronic myeloid leukaemia (CML) is a rare, chronic form of leukaemia. There are over 650 people diagnosed in England and Wales each year. It is slightly more common in men than women and, as with most blood cancers it is more prevalent in people over the age of 60. CML is a fatal disease. If left untreated, patients will progress through symptoms, which gradually increase in severity.

Common symptoms include “fatigue”, “pain”, frequent infections (for example a “persistent cough”), “bruises”, abdominal discomfort, fever, aching joints and bones, feeling weak and breathless, “night sweats”, unusual bleeding and unexplained “weight loss”. Many patients with CML have few or even no symptoms at the time they are diagnosed, as CML is often discovered following a routine check-up or a blood test for another condition. There are three types of staging for CML; chronic, accelerated and blast. For those patients who respond to treatment with these options patients will achieve normal life expectancy with high quality of life. Symptom burden varies, often depending on the stage of the disease but most patients will experience some or all of these symptoms as the disease progresses.

“I finally realised something was wrong when I started bruising; huge bruises on my legs that just didn’t make sense.”

Being diagnosed with CML can be “scary” and often leaves patients feeling “numb” or “helpless” - this is sometimes magnified because patients often haven’t heard of the rare condition. Patients will often experience a range of emotional thoughts following a diagnosis and will require support. Patients have to contend with the psychological and emotional side effects of a cancer diagnosis as well as an often profound symptom burden.

“**When I was diagnosed, it was like I had been hit by a truck.”**

Such feelings do not remain with the patient alone but can also be felt by their carers and families. Any improvement in access to treatment for CML will

therefore have a wider beneficial impact than just the patient group in question.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The following outcomes would be important to both ALL and CML patients:

- Duration of response
- Tolerability
- Efficacy
- Quality of Life
- Symptom Control
- Convenience of administration
- Choice of treatment

Patients and their families often struggle dealing with “uncertainty” about their future. Because CML never goes away, having the reassurance of being able to access effective follow-up treatment options should they need it in the future reduces “stress”, “anxiety” and “worry” for patients and their families. Similarly, patients with ALL who have a poor prognosis should initial treatment fail, would benefit from the knowledge that there are follow up treatments available should they require them.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

ALL

There is currently no standard treatment pathway for patients with acute lymphoblastic leukaemia. Their best treatment option will therefore depend on each individual patient's situation.

Philadelphia –positive ALL is the most common genetic abnormality associated with ALL and usually demonstrates a worse prognosis than those with Ph-negative ALL. Due to the aggressive nature of Ph+ ALL, chance of relapse is high and disease reoccurrence is considered the most frequent cause of treatment failure. Typically, a Ph+ ALL patient would be treated with induction phase chemotherapy, often including cyclophosphamide, vincristine, adriamycin and dexamethasone (hyper-CVAD) in combination with a TKI (imatinib). Although remission can be achieved using this rigorous induction phase, patients may eventually relapse and the only "curative" treatment option would be considered a stem cell transplant. Unfortunately, this may not always be a viable option for ALL patients, as many are older or experience co-morbidities and would be unable to withstand such an invasive therapy. There are also a number of added complications associated with stem cell transplants, such as locating a donor, variable patient outcomes and the associated risks.

Imatinib as a standalone therapy for Ph+ ALL patients can be effective with a lower toxicity profile but when in combination with standard chemotherapy, disease free survival has been increased substantially. Existing TKIs typically bind the BCR-ABL kinase in a distinctive manner and because of this resistance to each TKI is possible. Unfortunately, resistance to imatinib can lead to relapse. Bosutinib and nilotinib (second generation TKIs) have demonstrated efficacy against some mutations that imatinib is unable to treat, but neither has demonstrated efficacy against the T315i mutation. As such, there is a need for more intense, mutation-specific therapies in order to treat Ph+ ALL patients who become resistant, refractory or intolerant to currently available treatments.

CML

The introduction of tyrosine kinase inhibitors (TKIs) into clinical practice in 2001 transformed the treatment of CML and for those patients who respond to treatment with these options patients will achieve normal life expectancy with high quality of life.

Treatment options currently recommended by NICE for patients with chronic myeloid leukaemia include imatinib, nilotinib and bosutinib. Whilst imatinib was considered a step-change in the treatment of CML and increased the ten-year survival rates to 80-90%, not all patients responded to it. This was often due to development of mutations. Second generation TKI's (bosutinib, nilotinib and dasatinib) were developed to address this. Although nilotinib and bosutinib have shown efficacy against many of the clinically relevant mutations for which imatinib is ineffective, neither has shown the ability to inhibit BCR-ABL with the T315i mutation. Access to dasatinib is uncertain (via the Cancer Drugs Fund), as it is currently in the process of being reviewed by NICE.

A stem cell transplant is an option for fit patients who have exhausted other treatment choices but would be considered a risk as it is associated with high mortality and requires a matching donor.

There is a clear need then for increased access to additional targeted therapies to actively treat CML patients that are resistant or intolerant to imatinib, nilotinib and bosutinib.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

ALL

Until the development of this drug, there were no approved therapies for patients who proved to be resistance or intolerant to currently available TKI's for the treatment of Ph+ ALL, such as imatinib, nilotinib and bosutinib. In this environment, ponatinib has demonstrated to be highly active in a heavily pre-treated patient population where there are currently very limited options available. In fact, it has a unique mechanism of action and binding location on the BCR-ABL kinase that has been shown to overcome observed resistance to other TKIs and offers additional promise to patients who demonstrate the Ph+ chromosome.

For both CML and Ph+ ALL patients, their families and carers, knowing that there is an alternative line of treatment available (ponatinib) should they need it, will have a huge positive impact on their psychological well-being, even though only a few will ever need to access the treatment. The psychological impact this would have on the few patients that will need to be prescribed ponatinib, for whom it could be the difference between survival or not, is clear.

CML

Second generation TKIs have begun to attend to this potential resistance to the first generation TKI but only ponatinib (a third generation) TKI can actively treat certain mutations, indicating that it could represent a fundamental step in overcoming TKI resistance in this disease area - even if patients have previously been unresponsive or intolerant to other TKI's.

As demonstrated by Cortes et al. it has been estimated that 91% of patients with chronic-phase CML who had the T315i mutation who had a major cytogenetic response would remain in response at one year. Of those patients that did not carry the T315i mutation, 93% demonstrated a complete haematological response and those that had no detectable mutations, 100% had a complete haematological response. This is illustrative of the potent efficacy of ponatinib for CML patients in this setting, regardless of mutation type.

For patients with either disease type that respond to the TKI, they will expect to live as near normal a life as possible and patients can maintain independence and self-care. It will enable people to keep going with day to day activities (e.g. work, education, caring for children/ grandchildren etc.) This is key to the psychological health of these patients and their families as their condition no longer dominates their whole life.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Please see above response.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Because first and second generation TKI's each bind to the BCR-ABL kinase in a characteristic manner, resistance profiles specific to each TKI are therefore inevitable. Ponatinib, which has demonstrated efficacy in this instance, is currently available via the CDF for CML and Ph+ ALL patients in England – but only if they present the T315i mutation. If ponatinib is not available for patients in this indication or for those patients who do not demonstrate this particular mutation, then there will be no available treatment options for patients that are refractory, resistant or intolerant to all currently available TKI treatment options (imatinib, nilotinib and bosutinib).

In this situation patients would be left facing a fatal disease without access to an effective treatment option. As such, it is imperative that novel, effective agents are accessible to patients that require them and have no other treatment options available to them.

Please list any concerns patients or carers have about the treatment being appraised.

Although ponatinib shows promising results in an otherwise difficult to treat disease area, the TKI does cause common side effects such as hypertension, abdominal pain, fatigue, dry skin, constipation, rash, headache, fever, joint pain and nausea. Severe adverse events were also identified as a result of treatment with ponatinib, inclusive of tumour lysis syndrome, liver toxicity and gastrointestinal perforation. As such, patients and their physicians may need to weigh the potential benefits with risks before beginning treatment.

For patients where no other TKI has worked or has stopped working, having an alternative option available would be a necessary measure to ensure active treatment is maintained in order to extend patient survival.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Ponatinib would be particularly beneficial to patients who have been treated with first and second generation TKIs but who were resistant, refractory or intolerant to them. Although ponatinib is currently accessible for both CML and Ph+ ALL patients with the T315i mutation via the Cancer Drugs Fund, there is currently no treatment option available for those without this specific mutation and for whom other TKIs were not appropriate. Should the NICE recommendation be negative, this would seriously limit treatment options for CML and Ph+ ALL patients in this setting.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

N/A

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Ponatinib is currently recommended by the following health technology bodies for the following indications:

Scottish Medicines Consortium

- Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to

dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

All Wales Medicines Strategy Group

- Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

As such, if NICE were to not recommend ponatinib within its full licence indication for NHS patients in England then this would create an inequitable situation in terms of access throughout the UK.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

9. Other issues

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Ponatinib is a novel therapy that has demonstrated to be highly effective in a heavily pre-treated CML patient population who have relapsed, become refractory or intolerant to currently available TKIs. The TKI has demonstrated a similar efficacy for Philadelphia-positive ALL patient population who have demonstrated resistance to other TKIs, including patients with the T315i mutation as well as other mutations and no mutations.

Ponatinib is the only EMA approved TKI capable of inhibiting BCR-ABL "with the gatekeeper T315i kinase domain mutation in patients with CML and Ph+ ALL" as well as other mutations. There is currently no NICE recommended treatment option for patients with this specific mutation.

As such, ponatinib should be considered as an innovative treatment option in a setting where patients have exhausted all possible (accessible) options and would otherwise have a very poor prognosis, with best supportive care as their remaining option.

Are there any other issues that you would like the Appraisal Committee to consider?

As previously mentioned, having an alternative treatment option should currently accessible options not be successful would have a huge impact on patients psychological wellbeing, even though only a few will ever need to access the treatment. Although ponatinib may only be needed by a relatively small number of patients, it is a valuable treatment option for those who need it.

As indicated above, being diagnosed with a blood cancer can have a huge emotional impact on the patient but emotional strain can also be placed on the patient's family and friends. As such, improvements in a patients' treatment and quality of life will also have a wider impact on the lives of those close to them.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Chronic myeloid leukaemia is a rare and chronic cancer which has a profound impact on patients, their carer and family. Living with a CML diagnosis is "difficult", affecting patients both physically and emotionally. Untreated, CML is a fatal disease. If left untreated, patients will progress through symptoms, which gradually increase in severity. The development of TKIs transformed the outlook of CML patients. Patients who respond to treatment with TKIs have a close to normal life-expectancy with a good

quality of life. Unfortunately, there are a small number of patients for whom the currently approved options are not appropriate or sufficient.

- Acute lymphoblastic leukaemia (ALL) is a rare, rapidly progressing form of leukaemia with a substantial symptom burden. If left untreated, ALL is a fatal disease. Due to the aggressive nature of Ph+ ALL, chance of relapse is high and disease reoccurrence is considered the most frequent cause of treatment failure. Typically, a Ph+ ALL patient would be treated with induction phase chemotherapy in combination with a TKI (usually imatinib). Although remission can be achieved using this rigorous induction phase, patients may eventually relapse and the only “curative” treatment option would be considered a stem cell transplant. As with CML, some ALL patients are resistant to imatinib.

- The symptom burden for both diseases, if left untreated, is high. Common symptoms include anaemia, feeling weak and breathless, tiredness, frequent and persistent infections, unusual bleeding and bruising (due to lack of platelets), fever and sweating. As such, an increase in clinically effective, tolerable treatments are necessary to improve patient survival.

- Ponatinib is a novel TKI that demonstrates efficacy where other TKIs have failed. More specifically, it has shown to be particularly effective to treat patients who have become resistant or refractory to currently available TKIs, such as imatinib, nilotinib and bosutinib, because of mutations (including the T315i mutation). Clinical trials showed both CML and Ph+ ALL patients responded well to ponatinib, regardless of whether they were resistant to other TKIs, had a mutation or no mutation.
- Overall, ponatinib can be considered an innovative treatment option and its introduction into routine treatment in these heavily pre-treated, difficult to treat patient populations (who have very limited existing available treatment options) would be considered a step forward in haematological clinical practice.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Thank you for agreeing to make a submission 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 submission, 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: [redacted], RCP registrar. Submitting comments on behalf of:

Name of your organisation:
Are you (tick all that apply): NCRI/RCP/RCR/ACP

Submission coordinated by [redacted]

- 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)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

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?

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?

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)?

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?

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.

In order to manage patients with CML in all phases of the disease, it is essential to use ponatinib according to its licence, and not to impose arbitrary non-scientific restrictions to its use.

Ponatinib should be available for chronic phase, accelerated phase, or blast phase CML patients who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

Chronic myeloid leukaemia is currently treated with tyrosine kinase inhibitors (TKIs) in the NHS. All patients are treated in secondary care by consultant haematologists. Until April 2012 Imatinib was the only NICE approved drug available, but Nilotinib (with a PAS) was also approved by NICE for 1st line use in April 2012 and as a second line agent for patients who were intolerant of or resistant to Imatinib. More recently Bosutinib has been NICE approved, and is now available for use within its licence, and can be accessed, in certain circumstances, second line after imatinib failure (NICE TA 401). Dasatinib is to be considered by NICE in September 2016 for 1st and 2nd line use. Ponatinib, the most potent BCR-ABL inhibitor, is only accessible for patients who have failed other TKIs in the presence of a T315I mutation in England.

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There is a geographical variation in the accessibility of ponatinib- it is available without restriction in Wales and Scotland.

FIRST LINE

Approximately 75- 80% of patients respond satisfactorily to Imatinib / Nilotinib 1st line 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. The updated ELN Guidelines 2013 (Baccarani et al 2013) set out criteria for what is considered as an optimal response at different time-points against which a patient's response can be assessed and also states at different time points what is considered as a failure of treatment with that TKI.

SECOND LINE

Patients who have failed (by ELN criteria) or are intolerant of Imatinib 1st line are eligible to receive Nilotinib as a 2nd line treatment for CML (NICE approved in April 2012), or Bosutinib if nilotinib is not appropriate therapy (TA 401).

Nilotinib 2nd line

Clearly Nilotinib is not a suitable 2nd line alternative for patients who have received it as their first line treatment and have demonstrated intolerance or resistance to it. Although intolerant patients who have responded to treatment may be switched to Imatinib, those who have failed Nilotinib are unlikely to respond to Imatinib as it is has less activity than Nilotinib and is inactive in the presence of many of the known bcr-abl mutations.

Bosutinib 2nd line

Bosutinib can be given 2nd line after imatinib or nilotinib failure, within its licence (NICE TA 401: all phases of CML, >1 treatment with a TKI, where nilotinib, dasatinib, and imatinib are not appropriate).

The other licensed 2nd line tyrosine kinase inhibitors, Dasatinib and Ponatinib have not been approved/assessed by NICE for 2nd line use.

After failure of first line imatinib, 50% of patients will obtain a complete cytogenetic response (CCyR) with any of the second generation TKIs (nilotinib, dasatinib or bosutinib) in CP. CCyR is a surrogate marker of survival. Ponatinib given 2nd line after imatinib failure will induce a much higher rate of response, with 70% CCyR rates reported, as it a more potent BCR-ABL inhibitor.

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After failure of 1st line nilotinib Giving ponatinib after failure of a second generation TKI will be more effective than an alternative 2nd generation TKI, and will reduce the need for subsequent allogeneic stem-cell transplant.
After failure of a 1st line second generation TKI, an alternative 2nd generation TKI has a limited chance of achieving a CCyR, in the order of 10%. Ponatinib is able to achieve far greater rates of CCyR, again in the order of 30-50%.

THIRD LINE
After failure of first line imatinib and failure of one of the 2nd line second generation TKIs, an alternative second generation TKI will induce a CCyR in 10-30% of patients in CP. Ponatinib however will induce roughly 50-60% CCyR rates in these clinical circumstances. At present dasatinib is available 3rd line, refractory/intolerant to imatinib, and intolerant to nilotinib. Bosutinib in this setting will have similar efficacy to dasatinib (or nilotinib). In contrast, ponatinib will induce a higher rate of response in this setting.

Mutations
Many patients may be resistant due to the acquisition of bcr-abl mutations which block the binding or function of TKIs. Some of these mutations block the binding or function of one TKI but are sensitive to others. Ponatinib has far superior potency to any of the other TKIs, and is more sensitive to known mutations are that are only partially sensitive to the other drugs. It remains the only oral agent for the treatment of T315I.

Non-mutation driven resistance
Ponatinib is also far more effective in cases of resistance where a mutation is not detected, to a similar order of magnitude as when a mutation is present. The efficacy of ponatinib is not mutation dependent, but is related to the line of therapy. Patients with the T315I mutation have far greater CCyR rates (70%) as these patients are treated with ponatinib earlier.

Ponatinib has an essential place in the management of CML, second line after initial therapy with a second generation TKI, or third line after failure of imatinib and subsequent failure of a 2nd generation TKI. More recently, the outcome of ponatinib has been found to be superior with regard to overall survival in comparison to stem cell transplant.

Non TKI- treatment options
These include 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. Ponatinib would be very helpful in ethnic minority backgrounds in whom it is very difficult to find a matched donor. 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.

Phase of CML
Until recently, only imatinib was available for advanced phase CML, as nilotinib is not licenced for blast phase. It is of great value that recently we also have bosutinib for advanced phase CML, but it is critical for the correct management of the patients that we have access to the most potent bcr-abl inhibitor, which is ponatinib.

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 implement once it becomes available since it is a simple once daily tablet taken as an out-patient and is similar to the other TKIs which are taken once a day, namely imatinib, dasatinib and bosutinib.

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.

The efficacy of Ponatinib treatment would be 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 very deep / complete molecular remissions as a proportion of these appear to remain disease free. This is being explored in the clinical trial setting but is not yet standard practice.

Dose of ponatinib
A critically important factor to consider is that patients will be treated in the main with a dose of 30mg or less. Not many patients are treated with a dose of 45mg daily, and once a major cytogenetic response is reached, it is advisable that the dose is reduced to 30mg daily. Once a CCyR is achieved, the dose is further reduced to 15mg daily, as from the original PACE study

recommendations. Further dose finding studies will be available and the efficacy of the 10mg dose will be evaluated in the OPTIC study. All cost modelling should be performed on a dose of 30mg or less, as this reflects current practice and advice.

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 ponatinib are comparable to those observed in routine clinical practice in the UK. 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 most important side effect is that of arterial thrombotic events and is reported in 20% of patients treated. This also occurs with nilotinib- the arterio-thrombotic rate of nilotinib is roughly 10%.

Clinicians are aware of this possibility and its risk-benefit management as the drug has been in use in the UK for some time. Clinicians have been instituting the same risk-benefit approach for patients being treated with nilotinib. As with all side-effects, the toxicity is related to the dose, and the aim is to reduce the dose of ponatinib according to response. The cardio-vascular risk monitoring is done in primary care, as for nilotinib. The added benefit for ponatinib is that monitoring of blood sugars and HbAIC is not indicated, whereas for nilotinib this is an additional screening factor.

There are no other side effects that have come to light that were not identified within the clinical trials which have long follow up. Otherwise, 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.

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.

Evidence regarding the efficacy of ponatinib as second, third and fourth line use is available from the published clinical trials. Improved patient outcome with ponatinib in comparison to allo-SCT is also available.

Implementation issues

The NHS is required by the Department of Health 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 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)?

The technology will be straightforward to implement once it becomes available since it is a simple once daily tablet taken as an out-patient. These patients are already being managed in secondary care by Consultant Haematologists who are generally familiar with the use of all TKIs as well as ponatinib as it has been available in previous clinical trials and CDF approved for resistance associated with the T315I mutation.

There are no required concomitant medications or other clinical requirements that are different from the previously approved TKIs. No prophylactic measures have been agreed by the CML community, and screening is no different to that performed for patients on nilotinib.

Ponatinib therapy is associated with less toxicity and more efficacy for patients than the alternative treatments of BMT or interferon respectively. Monitoring of treatment response is the same as for the other well established tyrosine kinase inhibitors. No additional facilities or training would be required.

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 to the awareness that is already given for other TKIs, particularly for

nilotinib. 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 more patients and those from ethnic minorities who are currently unable to benefit from allogeneic haemopoietic stem cell transplantation which is currently the only existing alternative treatment for those who fail other TKIs.
Allowing clinicians the option of choosing ponatinib appropriately according to the line of therapy, will allow for a greater number of patients to achieve complete cytogenetic and deeper responses.
The scope of this Appraisal needs to be extended to include the use of ponatinib within its licence, without restriction, for all phases of CML in line with the rest of the modern world.

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

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To help you in making your submission, 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.

Your name: [redacted]

Name of your organisation: The Royal College of Pathologists

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)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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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 (CML) has an annual incidence of approximately 1 per 100,000 population. All patients have a chromosomal translocation that results in the creation of a hybrid gene BCR-ABL1, that encodes the resultant hybrid oncogenic tyrosine kinase protein, also called Bcr-Abl1. It is a tri-phasisc disease that usually (95% of patients) presents is the stable chronic phase (CP), in which patients are symptomatic but not at risk of death. Without treatment the disease will terminate at a median of 5 years, in blast crisis (BC). Some patients exhibit a period of instability between CP and BC that is known as the accelerated phase (accn). Approximately 5% of patients will present in BC, which is incurable unless a temporary remission can be achieved allowing a window in which the patient can be offered allogeneic stem cell transplantation (allo-SCT). The latter can be curative, even in the advanced stages of disease.

The management of chronic myeloid leukaemia (CML) is uniform throughout the UK. All patients are offered first line treatment with a tyrosine kinase inhibitor (TKI), a class of drugs which specifically target the dysregulated tyrosine kinase which is the cause of this disease. Three TKI are licensed for first-line treatment, imatinib, dasatinib and nilotinib, and all three are now approved by NICE. However, all three drugs are expensive and it is highly likely that treatment approaches will change when generic imatinib becomes available in the UK in December 2016, such that physicians will be encouraged to start all newly diagnosed patients on generic imatinib. This is not an unreasonable approach because head to head trials of imatinib vs dasatinib or nilotinib have shown no differences in survival at 5 and 6 year follow-ups respectively. However the same studies have shown a reduction in progression to blast crisis in patients treated with dasatinib or nilotinib compared to imatinib, so it is probable that a small difference in survival will eventually appear. Furthermore the first generation drug (imatinib) is known to be of lower potency that the second generation drugs (bosutinib, dasatinib and nilotinib) which are broadly equivalent in efficacy.

However the TKI are so effective, that the majority of patients now die of other causes. In fact population based surveys in the USA and Scandinavia now show that patients who respond well to TKI have a similar life expectancy to the normal population. This actually renders comparative trials with survival as the endpoint, virtually impossible. Most study groups, academic and commercial, have now had to adapt study design to use early deep responses as endpoints because previous studies have shown that these correlate with survival.

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Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

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?

The best indicator of outcome in terms of survival is the depth of response at various time-points in the first year. This is measured via monitoring the amount of residual disease by a molecular test known as RQ-PCR. Optimal response is defined as RQ-PCR results of <10%, <1% and <0.1% at 3, 6 and 12 months respectively after initiating treatment. Optimal responders have excellent overall survivals, akin to the normal population. Non-optimal responders have less good survival, and failure to achieve these milestones in the presence of good drug compliance, is an indication to consider a change of drug. If the first-line agent is imatinib, then some 25% of patients will fail to achieve these milestones. At 5 years from start of treatment, a further 25%, despite good responses, will have changed drug because of toxicity. If first line treatment is dasatinib or nilotinib then less than 10% fail to achieve the milestones. Toxicity is probably a little higher than for imatinib, maybe 20%.

Ideally we would like to identify patients who will fail imatinib, or have intolerable toxicity, at the time of starting treatment, and instead prescribe the drug likely to provide the highest efficacy with the best tolerability, bearing in mind that patients are expected to take these drugs daily for their entire life-time. This is not currently possible so change of drug is based on lack of milestones and side effects. The outcome of these two groups of patients is not necessarily similar. Whereas those who fail imatinib because of side effects (but by definition are good responders) often find nilotinib, dasatinib or bosutinib more tolerable and go on to achieve very deep molecular responses (RQ-PCR <0.01%), patients who fail because of disease resistance are frequently resistant to subsequent drugs. In the phase 2 studies of dasatinib and niloinib for imatinib failure, 70% of the patients had changed drug at least one further time at 4 years follow-up.

This is the group of patients who are most problematic and currently account for 10-15% of the total population of CML patients. This is the group that contains patients who will benefit from ponatinib. There is no good biomarker to identify these patients at diagnosis, and this is an area of active research investigation. We have clinical risk scores (Sokal, Hasford, EUTOS) that are partially useful. High risk patients, as defined by all these scores, have a higher risk of early progression and a lower chance of obtaining deep molecular responses than low risk groups. This has led to many physicians and patients electing to use dasatinib and nilotinib as first line therapy in these high risk groups, for at least three very good reasons. First, this group is the group most likely to progress and die of disease. Phase III randomised studies have shown a lower incidence of progression in high risk patients treated with nilotinib or dasatinib compared to imatinib. Second in the TKI era, progression occurs early in the disease course (in the UK phase III SPIRIT2 study of imatinib vs dasatinib, there were 13 progressions of which 12 occurred in the first year) so the most potent therapy should be given at diagnosis, Finally some of these patients will fail all of the currently available TKI (imatinib, dasatinib, bosutinib, nilotiinib) but could

benefit from allo-SCT. We have known for many years that the success of allo-SCT is dependent on disease phase (so should be performed in CP) and the time from diagnosis to transplant (ideally within the first year of diagnosis), so failure of potent TKI must be identified early. However, allo-SCT carries a high risk of procedural related mortality and morbidity so is not undertaken lightly. If the patient could respond to an alternative TKI, in this case, ponatinib, then a trial of this drug should be offered before embarking on transplant.

Other groups of patients who are known to have poorer prognosis, are those in accn or BC, either at diagnosis or after progression from CP. There is a strong argument for offering these patients the most potent drugs from diagnosis.

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)?

Chronic myeloid leukaemia should be managed in specialist haematology clinics with access to accredited molecular monitoring.

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?

Ponatinib is licensed for patients chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

In the UK it is only available for those who have the T315I mutation. We estimate that only about one-quarter of patients who might benefit from poantinib actually have he T315I mutation.

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.

CML has been the topic of several sets of guidelines, produced by a consensus group of international experts and updated at 3-4 yearly intervals.

Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, Apperley J, Cervantes F, Cortes J, Deininger M, Gratwohl A, Guilhot F, Horowitz M, Hughes T, Kantarjian H, Larson R, Niederwieser D, Silver R, Hehlmann R. Evolving concepts in the management of chronic myeloid leukemia. Recommendations from an expert panel on behalf of the European Leukemia Net. Blood. 2006 108:1809-20.

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Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saußele S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122:872-84

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 alternative treatment for patients who fail 2nd generation drugs, is allo-SCT. Offering alternative 2nd generation drugs is of limited value. It can be a useful strategy if the first 2nd generation was active but intolerable because of side effects, and a very small proportion of patients will have a mutation in the kinase domain of Bcr-Abl1 that renders their disease more sensitive to certain drugs. But for those who are truly resistant to the 2nd generation drug, the only alternative is transplant. Allo-SCT is an expensive personalised procedure with high morbidity and mortality.

Ponatinib is an extremely potent and effective drug, as shown in the phase II study of its use in CP patients who had failed dasatinib and/or nilotinib. For patients with a T315I mutation, approximately 70% achieved a RQ-PCR <1%, and the response was durable in the majority. For those who had failed dasatinib and/or nilotinib and who did not have the T315! mutation, this response rate was 48% and again, durable in the majority. The drug was less effective in accn and blast crisis in terms of duration of response, but for many patients the window of response permitted consideration of allo-SCT

In a phase III study of imatinib vs ponatinib in newly diagnosed patients, ponatinib was highly effective with remarkable rates of deep molecular response, even with short follow-up. However these two studies revealed an unexpected increase in the incidence of vascular thrombotic events in patients treated with ponatinib. Further analysis suggested that the risk was dose related and higher in patients with pre-existing risk factors for vascular events. Nevertheless these results were sufficient to halt development of ponatinib as a first line therapy. Further studies are under way to investigate the dose effect and to see if the adverse events can be mitigated by improved medical care. The current situation is one of balancing risks. If the risk of CML disease progression outweighs the risk of thrombosis, then ponatinib is indicated for its licensed use.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Patients given ponatinib will require regular follow-up and vigilant monitoring of pre-existing co-morbidities and avoidance of emerging medical problems. These include monitoring of liver function, serum amylase and lipase, thyroid function, blood sugar and HbA1C, cholesterol and lipid profile analysis, and blood pressure.

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.

There are excellent pre-existing guidelines for managing CML with TKI (see above). Guidelines are emerging for safe practice in stopping TKI (Hughes TP, Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. Blood. 2016 128:17-23)

Having said this it is unlikely that patients who require ponatinib will be able to stop treatment in the long-term. Most of the patients who will receive ponatinib will do so because of demonstration of resistance to other TKI, suggesting that their disease is more at risk of progression than optimal responders. There may be a few patients who respond deeply and durably to ponatinib, and who received it because of intolerance to the other TKI. It is possible that some of these may be able to stop in the longer term. A rough estimate might be 10% of those who require ponatinib, so 1-1.5% of the entire population of patients.

The haematology community are well aware of the side effects of these drugs and will stop for appropriate levels of toxicity. Most of these patients will be discussed more widely in the regional MTD meetings.

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 use of the technology under clinical trial conditions should reflect that observed in clinical practice. Ponatinib is indicated for CML patients who fail second generation TKI and/or those with a T315I mutation. Unfortunately it is currently only available for those patients with a T315I mutation. The clinical trials were well conducted, and several UK centres participated in these studies. The milestones of RQ-PCR responses at 3. 6 and 12 months are applicable to the use of any of the TKI at any stage in the course of the disease, and can be used as surrogate markers of survival. The NCI UK CML Study Group would be willing to monitor the use of ponatinib in the UK and provide advice as to the appropriateness of continuing or discontinuing therapy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

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?

See above. The side effects became apparent during longer follow-up of the phase II study and were immediately brought to the attention of the FDA by the manufacturers

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.

The phase II study of imatinib vs ponatinib was published in May 2016 in Lancet Oncology

The 4 year follow-up of the phase II PACE study has recently been submitted for publication and may be available online by the time of the appraisal. This analysis has been presented at several international meetings in the past 12 months and the slide set is readily available

We have conducted an audit of the use of ponatinib in the UK during the time that it was available on compassionate use for its licensed indication, i.e. for patients who failed a 2nd generation drug with or without the T315I mutation. The analysis is on-going and will have been submitted (but not necessarily published) for publication at the time of the appraisal. This manuscript could be made available at the time of submission on request.

Implementation issues

The NHS is required by the Department of Health 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 to vary this direction.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

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)?

No additional resources would be required as care would be provided in specialist clinics

Equality
Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

For patients who fail TKI the only potentially curable alternative is allo-SCT. If the various TKI are not available for use in circumstances of resistance and intolerance, patients will reach the decision point of allo-SCT earlier than necessary. This introduces an element of discrimination in two regards. First, older patients are more likely to experience procedure related mortality as a consequence of allo-SCT and as a result allo-SCT is rarely offered to patients over 60-65. Since the median age of onset of CML is 55-60 years, this means this age group, if resistant to a second generation drug, cannot be offered a potentially curable therapy. Second, only 15% of patients have HLA-matched sibling donors. Patients from ethnic minorities are less likely to find matched unrelated donors, which restricts the possibility of allo-SCT.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Sara Mulvanny
Name of your nominating organisation: The Chronic Myeloid Leukaemia Support Group
Do you know if your nominating organisation has submitted a statement?

Yes

Do you wish to agree with your nominating organisation's statement?

Yes

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

Yes

- a carer of a patient with the condition?

No

- a patient organisation employee or volunteer?

No

Do you have experience of the treatment being appraised?
Yes

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

CML has affected my life in many ways; sometimes I feel as though my life is punctuated with hospital visits and waiting for test results. However, it's also given me a new perspective on life, I feel as though I can deal with so much more than I could before. I've managed to keep my work life and my condition quite separate: I'm self-employed but none of my clients know about my health difficulties. I prefer to keep it this way. I'm able to do this because my treatment allows me to lead an ordinary life, no one who met me would know about my battle with CML.

I'm lucky enough to have a very supportive family and close circle of friends who have helped me through the various ups and downs of the past 6 years since my diagnosis.

They helped me through the initial shock of my diagnosis and the following emotional turmoil. I experienced a great amount of fear when my first treatment didn't work and a sense of unfairness that I would have to deal with this condition for the rest of my life.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

The most important treatment outcome for me is survival. Being diagnosed when I was 22 years old was a massive shock, and I was not prepared to have my life cut short by a fatal condition.

I would also like my treatment to have as few side effects as possible so that I can continue living normally. It's important that any side effects I do have are manageable and barely noticeable so that they don't interfere with my daily life. This means that I can carry on working and enjoying an active social life without interference from my treatment or condition.

A successful treatment allows me to plan my future without worrying about my condition. It allows me to have career goals, go on holidays, have relationships and live life normally as if I am no different from any of my friends.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Unlike some patients, I've only experienced two TKIs, Dasatinib and then Ponatinib. That is because when I was diagnosed on 30th June 2010 at Basingstoke hospital, I was randomised onto Dasatinib in the Spirit II trial. Therefore, I didn't have Imatinib as my first treatment.

I was diagnosed in the Chronic phase of CML without the T315i mutation, and I have not since developed any mutations.

I remained on Dasatinib till 2nd July 2011 but unfortunately I experienced a rollercoaster of side effects including low platelets and low neutrophils that meant a significant amount of time off treatment in an attempt to stabilise my blood levels. This time was particularly stressful for me as I became very worried about the inconsistency of my treatment. In the end, Dasatinib proved unsuccessful and I was referred to Hammersmith hospital for a bone marrow transplant. Whilst waiting for a suitable donor to be located and going through IVF treatment, I was offered a place on the Ponatinib clinical trial (PACE). I started Ponatinib on 11th August 2011 on 45mg/day. I had my end of PACE trial visit on 5th September 2016 and I'm still on Ponatinib with a reduced dose of 15mg every other day.

Athough Dasatinib works for some patients, the side effects and inadequate response meant that it was not the right treatment for me. I also wanted to avoid the bone marrow transplant because of the health risks and the amount of time it would take me to recover, both in hospital and at home. A TKI treatment allows me to continue living a normal life. The bone marrow transplant would have also have implicatons for later in life such as loss of fertility whereas a successful TKI treatment still offers the opportunity to start a family in years to come.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

When I first started Ponatinib I experienced some minor side effects, the most memorable being the bone aching I experienced in my legs. However, this quickly passed within a couple of weeks. I also had a month off treatment at the start due to low platelets. However, this gap in treatment had no effect on my positive response to Ponatinib and since then I've been lucky enough not to have any time off treatment due to side effects. At the beginning of 2014 I

was advised to start taking Aspirin because of the link to thrombosis, however I experienced extensive bruising so I have switched to Dipyridamole which seems to be more suited to me.

One of the benefits of Ponatinib is that it's a tablet that I take every other day at home. This means that it has miminal impact on my daily life and I don't have to go to the hospital to have injections. This is imporant to me because time at the hospital means time away from work and therefore a loss of earnings. In addition, from a patient's point of view, everytime you go to hospital is a reminder of your on-going treament, so less time at the hospital means that you actually think less about your condition.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

From the beginning Ponatinib had a great effect on my CML. My PCR seemed to fall to a very low, manageable level. This was a massive relief for me when I had struggled in vain with Dasatinib. I started on 45mg/day of Ponatinib on 11th August 2011, my dose was reduced to 30mg/day on 28th October 2013 and then reduced to 15mg on 20th April 2015 and subsequently 15mg/every other day on 14th December 2015. I achieved CCyR on 3rd January 2012 and first reached MMR on 8th October 2012, but achieved a consistent MMR response on 21st October 2013. My most recent PCR result was 0.048% on 5th September 2016.

Ponatinib allows me to lead a completely ordinary, healthy life. I'm able to participate in all family and social activities. This is very important to me as I'm in my late 20's and want to have an active lifestyle. In fact, I'm able to forget about CML on a day to day basis, I only need to remember to take my dose every other day and attend my hospital check-ups which at the moment are every 3 months. Even my hospital visits are less stressful as I'm constantly reassured each time that everything is fine. If I tell someone for the first time about my condition and treatment, they are always very surprised because I look completely normal and healthy.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I know a 30-year-old woman in America who has CML and after having negative experiences with Imatinib, Dasatinib and Nilotinib, now takes 15mg of Ponatinib daily. She has responded very well to Ponatinib and is also in MMR, however she experiences some lethargy that I have never experienced. She doesn't let this stop her having a normal life and finds the side effects manageable.

I also know of another 30-year-old who has had a very successful treatment on Dasatinib, and am therefore aware that some CML drugs work better for some people than others, and also that side effects can be quite different in each patient, therefore it's important to have a range of drugs available.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

My concern is that current NHS treatments such as Ponatinib are restricted and that patients without the T315i mutation don't have the opportunity to have this treatment. This means that because I don't have the mutation, I wouldn't be able to have Ponatinib if I hadn't been on the PACE trial. After my unsuccessful treatment on Dasatinib, my only option would be to have the bone marrow transplant. From a patient point of view, it seems like it would have been an unpleasant and unnecessary procedure given that Ponatinib has been so effective for me.

Based on the experiences of the other CML patients I know, I can see that different CML drugs work differently in each patient and the side effects differ for each patient as well. This means that the more drugs there are available, the better the chance of survival for each patient, especially if the patient has a resistance to other TKIs like myself.

Please list any concerns you have about the treatment being appraised.

I'm aware of the risks of Thrombosis and cardiovascular events that some patients experience whilst taking Ponatinib. The risk of a serious side effect is a concern that most CML patients have, however I'm reassured that my young age and lack of any heart conditions reduce my risk, as well as taking Dipyridamole daily.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Patients with the T315i mutation will benefit most of all from Ponatinib since none of the other TKIs are effective if you have that particular mutation. However, other patients like myself who have had unsuccessful experiences on the other TKIs will benefit greatly as well. Patients like myself who don't have the mutation but are able to lead a normal life because of Ponatinib.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Patients who have existing cardiovascular problems might find Ponatinib less beneficial.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Recommendations from this appraisal could have an adverse impact on patients like myself who don't have the specific T315i mutation and therefore don't have access to an effective CML drug.

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Ponatinib could be considered innovative because it's the only TKI that's effective for the T315i mutation. It also offers another option for patients who are resistant or intolerant of Imatinib, Dasatinib and Nilotinib.

Is there anything else that you would like the Appraisal Committee to consider?

Over the last couple of years I've noticed a hair thinning side effect on Ponatinib. I didn't realise at first because it happened slowly over a couple of years, but I had a scalp biopsy on 3rd May 2016 which showed Telogen Effluvium (a condition where the hair follicles are pushed prematurely into the resting phase) as result of Ponatinib. Although only noticeable to myself, I found it quite upsetting as a woman in her 20's to experience hair thinning,

and became a bit self-conscious of it even though it wasn't particularly noticeable to anyone else. As a result, I reduced my dose from 15mg/day to 15mg every other day on 14th December 2015, I have since noticed a massive improvement, and can see the addition of lots of new hairs all over my scalp. I feel positive that this new hair growth will continue and hopefully my hair will regain its thickness in time. The reduction in my dose didn't have any effect on my PCR response and I remain stable in MMR. It's also worth noting that this reduction in my dose has reduced the overall cost of my treatment.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The successful treatment of my CML on Ponatinib allows me to live a completely normal life.
- Ponatinib has enabled me to reach MMR even though I don't have the T315i mutation, therefore it's important to have a range of CML dugs available to all patients.
- Ponatinib remains effective and I have retained my MMR response even though my dose has been reduced from 45mg/day to 15mg/every other day.
- Ponatinib gives me the opportunity to have a family in the future, whereas the bone marrow transplant would have caused an early menopause.
- My side effects on Ponatinib have been manageable and impermanent, a reduction in my dose has improved a side effect and not affected my response.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Details of the patient access scheme

1.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Ponatinib (brand name: Iclusig®). The patient access scheme is proposed for chronic myeloid leukaemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), per the full licensed EMA indication.

Note that a completed PASLU template was sent to the Department of Health on the 8th of August, 2016. This was the same day that Incyte were invited by NICE to participate in an appraisal. We then received feedback and clarifying questions from the Department of Health on the 17th of August. We incorporated that feedback and sent a revised template back to the Department of Health on the 22nd of August. The Department of Health then requested a teleconference with Incyte, which was held on the 24th of August. Later that same day, the Department of Health forwarded our completed and revised template to PASLU. No information from PASLU was received until the 14th of September, at which point PASLU requested Incyte to complete and sign another confidentiality agreement, in addition to the one already completed and signed for NICE as part of Incyte's acceptance to participate in the appraisal. Incyte completed and sent this additional confidentiality agreement back to PASLU the next day, on the 15th of September. On the 19th of September, PASLU requested clarification from Incyte that the proposed PAS would apply to both England and Wales. That same day, on the 19th of September, Incyte confirmed to PASLU that the proposed PAS would indeed apply to both England on Wales. PASLU has notified us that they intend to submit their advice back to the Department of Health on the 4th of November.

Incyte has done everything possible to rapidly respond to the Department of Health and PASLU and wasted no time submitting the PAS template once a confirmation from NICE was received indicating that an appraisal would indeed take place. Incyte kept the NICE project team aware of all steps taken during this process. We regret that the PAS was not approved by the evidence submission deadline, despite our best efforts.

As per the instructions we received from the NICE project team, the main evidence submission includes only the NHS list price and we are submitting this additional PAS template to provide detailed confidential information on the confidential simple discount scheme we have proposed to the Department of Health. This document also includes confidential information relating to the impact of the confidential discount scheme on the economic model results. Commercial in confidence information in this document has been marked as such.

Once Incyte receive further guidance from the Department of Health, we will immediately notify the NICE project team.

1.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme has been developed to ensure that eligible patients in England can access ponatinib based on clinical need, by allowing the NHS to obtain ponatinib at a discounted price that increases confidence that this breakthrough therapy will be well within the acceptable cost-effectiveness threshold. Incyte are offering this patient access scheme to address the impact of uncertainty inherent in the evaluation of drugs such as ponatinib that are licensed for rare, orphan diseases. Enabling the NHS to provide ponatinib to the indicated population will lower financial hurdles to achieving the significant clinical benefit ponatinib can provide to patients who have few alternative options for their incurable cancer.

As background, the SMC, AWMSG, Canadian HTA authorities, and assessment bodies in many other countries have approved ponatinib use and reimbursement based on clinical and cost-effectiveness analysis without any PAS, at full list prices. Incyte have proposed a PAS to NHS England to ensure that, after more than 3 years of delay since marketing authorisation, agreement will be reached on all sides that ponatinib should be made available in England. [redacted].

We would also note that England is one of only two countries in Western Europe where funding for the licensed indication of ponatinib granted by the European Medicines Agency is not already available.

1.3 Please describe the type of patient access scheme, as defined by the PPRS.

The patient access scheme is a Simple Discount scheme. The scheme is designed to produce minimal impact on NHS resources as it is a simple fixed percentage discount from list price automatically applied on every invoiced sale of ponatinib in England and Wales (see section 1.7). The list prices will not change due to our concerns about international referencing of published prices.

1.4 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 applies to the full licensed indications. That is, adult patients with:

- Chronic phase (CP), accelerated phase (AP), or blast phase (BP) CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
- Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

1.5 Please provide details of when the scheme will apply to the population specified in 1.4. 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 patient access scheme is applied as a simple discount on all ponatinib packs within all licensed indications without regard to any other criteria. Please refer to section 1.4.

1.6 What proportion of the patient population (specified in 1.4) is expected to meet the scheme criteria (specified in 1.5)?

100%; the patient access scheme applies to the full licensed indications.

1.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The proposed patient access scheme will offer a [redacted] discount from the UK list price on ponatinib 15-, 30-, and 45-mg tablet packs (the list price vary).

- Ponatinib 45-mg tablets x 30 tablet bottle* (list price, £5050 ex VAT)
  - [redacted]
- Ponatinib 30-mg tablets x 30 tablet bottle* (list price, £5050 ex VAT)
  - [redacted]
- Ponatinib 15-mg tablets x 30 tablet bottle* (list price, £2525 ex VAT)
  - [redacted]

*Please note that these are pack presentations that have been approved by EMA, however currently, only a 45mg x 30 tablet bottle and 15mg x 60 tablet bottle are available in the UK, both with a list price of £5050 ex VAT . The list prices for the 30mg x 30 tablet bottle and 15mg x 30 tablet bottle have been agreed with the Department of Health and will be launched in the UK in early 2017, but no later than the completion of the ponatinib STA. Therefore, the presentations shown above were the ones included in the evidence submission.

1.8 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 shown on the original invoice from the company distributor (Alloga UK) to the purchasing organisation.

1.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See section 1.8.

1.10 Please provide details of the duration of the scheme.

The simple discount scheme will be in effect from the date of guidance publication until re-review of the guidance and publication of the final decision on the NICE website. At this time we do not foresee any circumstances whereby we may change or withdraw the proposed patient access scheme, but agree that any changes would only be implemented following discussion with, and the agreement of, the Department of Health.

1.11 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?

No equity or equalities issues relate to the ponatinib patient access scheme.

1.12 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.

1.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

2 Cost effectiveness

2.1 If the population to whom the scheme applies (as described in sections 1.4 and 1.5) 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; the patient access scheme applies to the full licensed indications as described in the ponatinib NICE STA submission.

2.2 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.

2.3 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 patient access scheme has been incorporated into the three ponatinib economic models (CP-CML, AP-/BP-CML, and Ph+ ALL) by applying the [redacted] to the prices of all packs. No other changes in the model were made.

2.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable. The clinical effectiveness data applied in the model are unaffected by the patient access scheme and are the same as the data presented in the ponatinib STA (see ponatinib evidence submission document).

2.5 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'.

No additional costs will be associated with the implementation and operation of the patient access scheme since the discount will be automatically applied on every invoiced sale of ponatinib.

2.6 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.

No additional treatment-related costs will be incurred by implementing the patient access scheme.

Summary results

Base-case analysis

2.7 Please present in separate tables the cost-effectiveness results as follows.

- 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).

Table 1 Base-case cost-effectiveness results without the patient access scheme

CP-CML economic model (without the PAS)

	Ponatinib	**Bosutinib**	**Allo-SCT**	**Hydroxy-carbamide**	**IFN alpha**
Intervention cost (£)	[redacted]	31,697.92	-	283.32	52,826.43
Other drug cost (£)	19,753.48	33,924.63	93,694.36	39,459.41	39,324.51
Allo-SCT cost (£)	12,039.49	21,414.92	103,904.11	25,317.42	25,230.87
Monitoring and follow-up cost (£)	40,618.38	58,817.78	7,273.24	66,692.30	66,636.44
AEs cost (£)	1,992.59	461.80	-	-	-
End-of-life cost (£)	3,508.53	4,493.56	4,385.98	4,913.57	4,899.14
Total costs (£)	[redacted]	**150,810.61**	**209,257.69**	**136,666.02**	**188,917.38**
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	6.09	6.74	3.95	4.02
LYG difference	N/A	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	4.00	3.93	2.24	2.30
QALY difference	N/A	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	**N/A**	[redacted]	[redacted]	[redacted]	[redacted]

AP-/BP-CML economic model (without the PAS)

AB-CML	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
Intervention cost (£)	[redacted]	25,696.30	-	-
Other drug cost (£)	256.07	335.64	-	244.09
Allo-SCT cost (£)	67,970.08	35,591.75	111,486.14	-
Monitoring and follow-up cost (£)	52,809.05	83,595.21	-	76,886.37
AEs cost (£)	777.90	1,016.91	-	-
End-of-life cost (£)	4,516.36	4,721.43	5,149.30	5,401.08
Total costs (£)	[redacted]	**150,957.24**	**116,635.44**	**82,531.54**
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]
LYG	[redacted]	5.04	2.87	1.60
LYG difference	N/A	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	2.62	1.86	0.58
QALY difference	N/A	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	**N/A**	[redacted]	[redacted]	[redacted]

BP-CML	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
Intervention cost (£)	[redacted]	8,320.16	-	-
Other drug cost (£)	48.29	52.38	-	152.98
Allo-SCT cost (£)	37,024.32	5,082.90	98,282.74	-
Monitoring and follow-up cost (£)	34,062.65	43,611.83	-	81,285.89
AEs cost (£)	707.32	792.90	-	-
End-of-life cost (£)	5,292.98	5,563.64	5,464.89	5,518.79
Total costs (£)	[redacted]	**63,423.80**	**103,747.64**	**86,957.66**

BP-CML	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]
LYG	[redacted]	0.77	1.27	1.00
LYG difference	N/A	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	0.37	0.85	0.28
QALY difference	N/A	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	**N/A**	[redacted]	[redacted]	[redacted]

Ph+ ALL economic model (without the PAS)

Ph+ ALL	Ponatinib	Induction chemotherapy	BSC
Patients suitable for allo-SCT			
Intervention cost (£)	[redacted]	-	0.00
Chemotherapy cost (£)	1,020.81	17,845.59	4,029.07
Allo-SCT cost (£)	53,413.70	42,203.41	0.00
Monitoring and follow-up cost (£)	33,811.30	19,678.35	31,193.18
AEs cost (£)	568.27	-	0.00
End-of-life cost (£)	4,951.22	5,126.17	5,652.40
Total costs (£)	[redacted]	**84,853.53**	**40,874.65**
Difference in total costs (£)	N/A	[redacted]	[redacted]
LYG	[redacted]	2.96	0.32
LYG difference	N/A	[redacted]	[redacted]
QALYs	[redacted]	1.84	0.09
QALY difference	N/A	[redacted]	[redacted]
ICER (£/QALY)	**N/A**	[redacted]	[redacted]

Ph+ ALL	Ponatinib	BSC
Patients unsuitable for allo-SCT		
Intervention cost (£)	[redacted]	-
Other drug cost (£)	2,189.92	4,029.07
Allo-SCT cost	-	-

Ph+ ALL	Ponatinib	BSC
(£)		
Monitoring and follow-up cost (£)	34,515.27	31,193.18
AEs cost (£)	663.92	-
End-of-life cost (£)	5,478.40	5,652.40
Total costs (£)	[redacted]	**40,874.65**
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	0.32
LYG difference	N/A	[redacted]
QALYs	[redacted]	0.09
QALY difference	N/A	[redacted]
ICER (£/QALY)	**N/A**	[redacted]

AEs, adverse events; allo-SCT; allogeneic stem cell transplantation; IFN, interferon; LYG, life-year gained; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Note: totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

Table 2 Base-case cost-effectiveness results with the patient access scheme

CP-CML economic model (with the PAS)

	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide	IFN alpha
Intervention cost (£)	[redacted]	31,697.92	-	283.32	52,826.43
Other drug cost (£)	19,753.48	33,924.63	93,694.36	39,459.41	39,324.51
Allo-SCT cost (£)	12,039.49	21,414.92	103,904.11	25,317.42	25,230.87
Monitoring and follow-up cost (£)	40,618.38	58,817.78	7,273.24	66,692.30	66,636.44
AEs cost (£)	1,992.59	461.80	-	-	-
End-of-life cost (£)	3,508.53	4,493.56	4,385.98	4,913.57	4,899.14
Total costs (£)	[redacted]	**150,810.61**	**209,257.69**	**136,666.02**	**188,917.38**

	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide	IFN alpha
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	6.09	6.74	3.95	4.02
LYG difference	N/A	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	4.00	3.93	2.24	2.30
QALY difference	N/A	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY) with PAS	**N/A**	**18,213**	**4,042**	**15,200**	**6,395**

AP-/BP-CML economic model (with the PAS)

AB-CML	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
Intervention cost (£)	[redacted]	25,696.30	-	-
Other drug cost (£)	256.07	335.64	-	244.09
Allo-SCT cost (£)	67,970.08	35,591.75	111,486.14	-
Monitoring and follow-up cost (£)	52,809.05	83,595.21	-	76,886.37
AEs cost (£)	777.90	1,016.91	-	-
End-of-life cost (£)	4,516.36	4,721.43	5,149.30	5,401.08
Total costs (£)	[redacted]	**150,957.24**	**116,635.44**	**82,531.54**
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]
LYG	[redacted]	5.04	2.87	1.60
LYG difference	N/A	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	2.62	1.86	0.58
QALY difference	N/A	[redacted]	[redacted]	[redacted]
ICER (£/QALY) with PAS	**N/A**	**Dominant**	**8,942**	**16,643**

BP-CML	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
Intervention cost (£)	[redacted]	8,320.16	-	-
Other drug cost	48.29	52.38	-	152.98

BP-CML	Ponatinib	Bosutinib	Allo-SCT	Hydroxy-carbamide
(£)				
Allo-SCT cost (£)	37,024.32	5,082.90	98,282.74	-
Monitoring and follow-up cost (£)	34,062.65	43,611.83	-	81,285.89
AEs cost (£)	707.32	792.90	-	-
End-of-life cost (£)	5,292.98	5,563.64	5,464.89	5,518.79
Total costs (£)	[redacted]	**63,423.80**	**103,747.64**	**86,957.66**
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]
LYG	[redacted]	0.77	1.27	1.00
LYG difference	N/A	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	0.37	0.85	0.28
QALY difference	N/A	[redacted]	[redacted]	[redacted]
ICER (£/QALY) with PAS	**N/A**	**19,449**	**Dominant**	**Dominant**

Ph+ ALL economic model (with the PAS)

Ph+ ALL	Ponatinib	Induction chemotherapy	BSC
Patients suitable for allo-SCT			
Intervention cost (£)	[redacted]	-	0.00
Chemotherapy cost (£)	1,020.81	17,845.59	4,029.07
Allo-SCT cost (£)	53,413.70	42,203.41	0.00
Monitoring and follow-up cost (£)	33,811.30	19,678.35	31,193.18
AEs cost (£)	568.27	-	0.00
End-of-life cost (£)	4,951.22	5,126.17	5,652.40
Total costs (£)	[redacted]	**84,853.53**	**40,874.65**

Ph+ ALL	Ponatinib	Induction chemotherapy	BSC
Difference in total costs (£)	N/A	[redacted]	[redacted]
LYG	[redacted]	2.96	0.32
LYG difference	N/A	[redacted]	[redacted]
QALYs	[redacted]	1.84	0.09
QALY difference	N/A	[redacted]	[redacted]
ICER (£/QALY) with PAS	**N/A**	**31,123**	**26,624**

Ph+ ALL	Ponatinib	BSC
Patients unsuitable for allo-SCT		
Intervention cost (£)	[redacted]	-
Other drug cost (£)	2,189.92	4,029.07
Allo-SCT cost (£)	-	-
Monitoring and follow-up cost (£)	34,515.27	31,193.18
AEs cost (£)	663.92	-
End-of-life cost (£)	5,478.40	5,652.40
Total costs (£)	[redacted]	**40,874.65**
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	0.32
LYG difference	N/A	[redacted]
QALYs	[redacted]	0.09
QALY difference	N/A	[redacted]
ICER (£/QALY) with PAS	**N/A**	**33,954**

AEs, adverse events; allo-SCT; allogeneic stem cell transplantation; IFN, interferon; LYG, life-year gained; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Note: totals reported in this table are as calculated by the model and may differ slightly from the numbers that would be calculated using the intermediate numbers reported in this table to 2 decimal places, due to rounding error.

2.8 Please present in separate tables the incremental results as follows.

- 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 3 Base-case incremental results without the patient access scheme

CP-CML economic model (without the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYs)	ICER (£/QALYs)
Hydroxy-carbamide	136,666.02	3.95	2.24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	150,810.61	6.09	4.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon alpha	188.917.38	4.02	2.30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	209,257.69	6.74	3.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–

AP-/BP-CML economic model (without the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYs)	ICER (£/QALYs)
AP-CML								
Hydroxy-carbamide	82,531.54	1.60	0.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	116,635.44	2.87	1.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Bosutinib	150,957.24	5.04	2.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BP-CML								
Bosutinib	63,423.80	0.77	0.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Hydroxy-carbamide	86,957.66	1.00	0.28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT	103,747.64	1.27	0.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ph+ ALL economic model (without the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYGs)	ICER (£/QALYs)
Patients suitable for allo-SCT								
BSC	40,874.65	0.32	0.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction chemo-therapy	84,853.53	2.96	1.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Patients unsuitable for allo-SCT								
BSC	40,874.65	0.32	0.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; LYG, life-year gained; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Table 4 Base-case incremental results with the patient access scheme

CP-CML economic model (with the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYs)	ICER (£/QALYs)
Hydroxy-carbamide	136,666.02	3.95	2.24	[redacted]	[redacted]	[redacted]	12,492	15,200
Bosutinib	150,810.61	6.09	4.00	[redacted]	[redacted]	[redacted]	15,006	18,213
Interferon alpha	188.917.38	4.02	2.30	[redacted]	[redacted]	[redacted]	5,263	6,395
Allo-SCT	209,257.69	6.74	3.93	[redacted]	[redacted]	[redacted]	3,883	4,042
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–

AP-/BP-CML economic model (with the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYs)	ICER (£/QALYs)
AP-CML								
Hydroxy-carbamide	82,531.54	1.60	0.58	[redacted]	[redacted]	[redacted]	10,914	16,643
Allo-SCT	116,635.44	2.87	1.86	[redacted]	[redacted]	[redacted]	4,613	8,942
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Bosutinib	150,957.24	5.04	2.62	[redacted]	[redacted]	[redacted]	Dominant	Dominant
BP-CML								
Bosutinib	63,423.80	0.77	0.37	[redacted]	[redacted]	[redacted]	13,581	19,449
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Hydroxy-carbamide	86,957.66	1.00	0.28	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Allo-SCT	103,747.64	1.27	0.85	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Ph+ ALL economic model (with the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYGs)	ICER (£/QALYs)
Patients suitable for allo-SCT								
BSC	40,874.65	0.32	0.09	[redacted]	[redacted]	[redacted]	17,202	26,624
Induction chemo-therapy	84,853.53	2.96	1.84	[redacted]	[redacted]	[redacted]	18,735	31,123
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Patients unsuitable for allo-SCT								
BSC	40,874.65	0.32	0.09	[redacted]	[redacted]	[redacted]	18,553	33,954
Ponatinib	[redacted]	[redacted]	[redacted]	–	–	–	–	–

Allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; LYG, life-year gained; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

Sensitivity analyses

2.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

CP-CML Economic Model

Results of the univariate sensitivity analysis are presented as a tornado plot below for the pairwise comparison of ponatinib vs bosutinib. From this plot, it is apparent that the ICERs are most sensitive to changes in the discount rate on outcomes, hospital days for patients in BP-CML, and the cost of ponatinib in patients who achieve complete cytogenetic response (CCyR). Other influential parameters included the discount rate for costs, and the CCyR rate with ponatinib and bosutinib.

AP-/BP-CML Economic Model

Results of the univariate sensitivity analysis are presented as a tornado plot below for the pairwise comparison of ponatinib vs bosutinib. From this plot, it is apparent that the ICERs are most sensitive to changes in the days in hospital, the discount rate on costs, and the MaHR rate with ponatinib.

Ph+ ALL Economic Model

Results of the univariate sensitivity analysis are presented as a tornado plot below for the pairwise comparison of ponatinib vs BSC (patients unsuitable for allo-SCT). From this plot, it is apparent that the ICERs are most sensitive to changes in the response rate with ponatinib and OS with BSC. The third most

influential parameter is the number of hospital days in patients without response.

2.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

CP-CML Economic Model

The figure below shows the incremental costs and QALYs derived from the 1000 simulations of the probabilistic sensitivity analysis (PSA) for ponatinib vs bosutinib. This graph demonstrates that most simulations are generally consistent with the mean result; there are few extreme values.

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

The figure below shows the cost-effectiveness acceptability curve derived from the PSA. As can be seen, at an ICER threshold of approximately £25,000, over [redacted] of simulations are cost-effective. At a willingness-to-pay (WTP) threshold of ≤£20,000, [redacted] of iterations are cost-effective and at a WTP threshold of ≤£30,000, [redacted] of iterations are cost-effective.

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values.

AP-/BP-CML Economic Model

Results are presented for the comparison of ponatinib vs bosutinib in AP-CML (which accounts for the majority of patients starting treatment with these TKIs in advanced CML). The following figure shows that ponatinib yields more QALYs at a lower cost than bosutinib in most iterations.

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

The figure below shows the cost-effectiveness acceptability curve derived from the PSA in AP-CML. Reflecting the dominance of ponatinib over bosutinib in the vast majority of iterations, even at a WTP threshold of £0 ponatinib would be considered cost-effective in more than [redacted] of iterations.

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Ph+ ALL

The figure below shows the incremental costs and QALYs derived from the 1000 simulations of the PSA for ponatinib vs induction chemotherapy in Ph+ ALL. This graph demonstrates that most simulations are generally consistent with the base-case ICER.

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

The cost-effectiveness acceptability curve derived from the PSA is shown below. As can be seen, at an ICER threshold of approximately £34,000, over

[redacted] of simulations are cost-effective. At a WTP threshold of ≤£20,000, [redacted] of iterations are cost-effective and at a WTP threshold of ≤£30,000, [redacted] of iterations are cost-effective.

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

2.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

For a detailed description of the scenario analyses, please see section 5.3.7.8 of the main submission.

CP-CML economic model

Scenario	ICER (£/QALY) for ponatinib vs			
	Bosutinib	Allo-SCT	Hydroxy-carbamide	Interferon alpha
Base case	[redacted]	[redacted]	[redacted]	[redacted]
–25% CCyR	[redacted]	[redacted]	[redacted]	[redacted]
4L CP-CML	[redacted]	[redacted]	[redacted]	[redacted]
Cost of allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]
HRQoL utility	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib STA value	[redacted]	[redacted]	[redacted]	[redacted]
Whiteley et al. paper	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib price	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER (£/QALY) for ponatinib vs			
	Bosutinib	Allo-SCT	Hydroxy-carbamide	Interferon alpha
Trial-based mortality	[redacted]	[redacted]	[redacted]	[redacted]
1.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]
Background mortality +1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Fitting functions				
DoR, ponatinib	[redacted]	[redacted]	[redacted]	[redacted]
DoR, bosutinib	[redacted]	[redacted]	[redacted]	[redacted]
PFS with CCyR	[redacted]	[redacted]	[redacted]	[redacted]
PFS with PCyR	[redacted]	[redacted]	[redacted]	[redacted]
PFS with CHR	[redacted]	[redacted]	[redacted]	[redacted]
OS for allo-SCT in CP-CML	[redacted]	[redacted]	[redacted]	[redacted]
OS for allo-SCT in AP-CML	[redacted]	[redacted]	[redacted]	[redacted]

4L, fourth-line; allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; CML, chronic myeloid leukaemia; CP, chronic phase; CCyR, cytogenetic response; CHR, complete haematologic response; DoR, duration of response; HRQoL, health-related quality-of-life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; OS, overall survival; PCyR, partial cytogenetic response; PFS, progression-free survival.

2.12 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. As a simple discount, the patient access scheme does not depend on clinical variables.

Impact of patient access scheme on ICERs

2.13 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.

The tables below report the results of the base-case and of the scenarios analyses, considering a [redacted] discount on ponatinib 15-mg, 30-mg, and 45-mg packs.

Table 5 Results showing the impact of patient access scheme on ICERs

CP-CML economic model

	ICER (£/QALY) for ponatinib vs							
	Bosutinib		Allo-SCT		Hydroxy-carbamide		Interferon alpha	
Scenario	No PAS	With PAS	No PAS	With PAS	No PAS	With PAS	No PAS	With PAS
Base case	[redacted]	18,213	[redacted]	4,042	[redacted]	15,200	[redacted]	6,395
–25% CCyR	[redacted]	23,514	[redacted]	2,122	[redacted]	17,490	[redacted]	5,925
4L CP-CML	[redacted]	NA	[redacted]	5,953	[redacted]	28,894	[redacted]	9,906
Cost of allo-SCT	[redacted]	18,584	[redacted]	7,881	[redacted]	15,569	[redacted]	6,765
HRQoL utility								
Bosutinib STA	[redacted]	18,960	[redacted]	3,900	[redacted]	15,825	[redacted]	6,671
Whiteley et al.	[redacted]	18,747	[redacted]	3,902	[redacted]	15,644	[redacted]	6,582
Bosutinib price	[redacted]	22,640	[redacted]	7,037	[redacted]	15,791	[redacted]	6,987
Trial-based mortality	[redacted]	25,652	[redacted]	7,507	[redacted]	24,117	[redacted]	9,785
1.5% discount rate	[redacted]	13,501	[redacted]	2,918	[redacted]	11,304	[redacted]	4,748
Background mortality +1.5%	[redacted]	19,179	[redacted]	3,731	[redacted]	16,004	[redacted]	6,457
Fitting functions								
DoR, ponatinib	[redacted]	27,612	[redacted]	8,166	[redacted]	20,460	[redacted]	9,650
DoR, bosutinib	[redacted]	16,637	[redacted]	4,042	[redacted]	15,200	[redacted]	6,395
PFS with CCyR	[redacted]	18,488	[redacted]	4,173	[redacted]	15,494	[redacted]	6,532

Scenario	ICER (£/QALY) for ponatinib vs							
	Bosutinib		Allo-SCT		Hydroxy-carbamide		Interferon alpha	
	No PAS	With PAS	No PAS	With PAS	No PAS	With PAS	No PAS	With PAS
PFS with PCyR	[redacted]	18,215	[redacted]	4,047	[redacted]	15,202	[redacted]	6,398
PFS with CHR	[redacted]	18,166	[redacted]	4,031	[redacted]	15,104	[redacted]	6,595
OS for allo-SCT in CP-CML	[redacted]	18,213	[redacted]	Dominant	[redacted]	15,200	[redacted]	6,395
OS for allo-SCT in AP-CML	[redacted]	16,313	[redacted]	7,189	[redacted]	13,056	[redacted]	3,573

AP-/BP-CML economic model

	ICER (£/QALY) for ponatinib vs					
	Bosutinib		Allo-SCT		Hydroxy-carbamide	
	No PAS	With PAS	No PAS	With PAS	No PAS	With PAS
Base case AP-CML	[redacted]	Dominant	[redacted]	8,942	[redacted]	16,643
Base case BP-CML	[redacted]	19,449	[redacted]	Dominant	[redacted]	Dominant

Ph+ ALL economic model

	ICER (£/QALY) for ponatinib vs			
	Induction chemotherapy		BSC	
	No PAS	With PAS	No PAS	With PAS
Base case patients suitable for allo-SCT	[redacted]	31,123	[redacted]	26,624
Base case patients unsuited for allo-SCT	–	–	[redacted]	33,954

4L, fourth-line; allo-SCT, allogeneic haematopoietic stem cell transplantation; AP, accelerated phase; BSC, best supportive care; CML, chronic myeloid leukaemia; CP, chronic phase; HRQoL, health-related quality-of-life; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year; OS, overall survival.

3 Appendices

3.1 Appendix A: Additional documents

3.1.1 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.

Not applicable

3.2 Appendix B: Details of outcome-based schemes

3.2.1 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.

Not applicable.

3.2.2 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.

Not applicable.

3.2.3 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.

Not applicable.

3.2.4 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).

Not applicable.

3.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

3.2.6 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.

Not applicable.

3.2.7 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.

Not applicable.

3.2.8 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.

Not applicable.

3.2.9 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.

Not applicable.

Ponatinib for treating chronic myeloid leukaemia: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Contributions of authors

Abdullah Pandor and Marrissa Martyn-St James summarised and critiqued the clinical effectiveness data reported within the company's submission. Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. John Stevens critiqued the statistical analyses undertaken by the company. Jean Hamilton produced parametric curves for use in the exploratory analyses. Ruth Wong critiqued the company's search strategy. Jenny Byrne and Claudius Rudin provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AIC	Akaike information criterion
Allo-SCT	Allogeneic stem cell transplant
AP-CML	Accelerated phase chronic myeloid leukaemia
BIC	Bayesian information criterion
BP-CML	Blast phase chronic myeloid leukaemia
BSC	Best supportive care
CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CHR	Complete haemotologic response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CP-CML	Chronic phase chronic myeloid leukaemia
CS	Company's submission
CSR	clinical study report
DoR	Duration of response
ECOG	Eastern Co-operative Oncology Group
EMA	European Medicines Agency
ERG	Evidence Review Group
FDA	US Food and Drug Administration
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
MaHR	Major haematological response
MCyR	Major cytogenetic response
N/A	Not applicable
NMA	network meta-analysis
NICE	National Institute for Health and Care Excellence
NR	No response
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient Access Scheme
PCyR	Partial cytogenetic response

PFS	Progression-free survival
PSA	Probabilistic sensitivity analyses
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
SAE	Serious adverse event
SmPC	Summary of product characteristics
SSE	Sum of squared errors
STA	Single Technology Appraisal
T315I	Threonine-315-Isoleucine
TKI	Tyrosine kinase inhibitor
VOE	Vascular occlusive event

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The decision problem addressed by the company's submission (CS) was generally in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The population considered within the CS, as defined in the scope, is '*adults with chronic phase [CP], accelerated phase [AP], or blast phase [BP] chronic myeloid leukaemia [CML] whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the Threonine-315-Isoleucine [T315I] mutation.*' However, the target population in the CS was in the third-line treatment setting (reflecting the anticipated place in therapy of ponatinib, after treatment failure with imatinib and either nilotinib or dasatinib) and in the fourth-line setting (reflecting its potential use in this setting for some patients). In accordance with the scope, the CS defines the intervention as ponatinib and the comparators as bosutinib, allogenic stem cell transplant (allo-SCT), interferon alfa and best supportive care (BSC). However, interferon alfa was not included as a comparator in AP-CML or BP-CML as it is rarely used to treat CML in the UK. The Evidence Review Group (ERG) clinical advisors concurred with this view. In addition, hydroxycarbamide was used to approximate BSC. Whilst limited justification was provided in the CS, the ERG noted that in a recent Single Technology Appraisal (STA) of bosutinib for previously treated CML, the NICE appraisal committee accepted that hydroxycarbamide was not a disease-modifying treatment and that it was appropriate to consider hydroxycarbamide as a proxy for BSC. Clinical advice received by the ERG also suggested that this was appropriate. The scope specified the following outcome measures: overall survival (OS); progression-free survival (PFS)/event-free survival; response rates; time to response; duration of response (DoR); adverse events/effects (AE) of treatment; and health-related quality of life (HRQoL). All of these outcomes were included in the CS. The health economic outcome employed within the company's health economic model is the incremental cost per quality-adjusted life year (QALY) gained, as set out within the NICE Reference Case. The equity issues highlighted within the CS (p123) was a reference to '*the current inequity in CDF [Cancer Drugs Fund] access to ponatinib between patients with the T315I mutation and those who fall within the indication but do not have this mutation*' and on p30 of the CS where it is stated that allo-SCT '*is associated with equity issues*'. A Patient Access Scheme (PAS) has been approved by the Department of Health for ponatinib. In addition, the CS considers that ponatinib meets the end-of-life criteria for eligible patients with AP-CML or BP-CML.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review of clinical effectiveness evidence. The PACE study, which forms the main supporting evidence for the intervention, was a Phase II, industry-sponsored, single-arm, non-comparative, open-label, multicentre study (including five sites in the UK) designed to evaluate the

efficacy and safety of ponatinib in patients (aged over 18 years) with CML (CP, AP or BP), or Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any tyrosine kinase inhibitor (TKI) therapy. Study participants were heavily pre-treated with prior TKIs and conventional therapy: 37% (167/449) had received two TKIs (imatinib, dasatinib, nilotinib or bosutinib) and 55% (249/449) had received three or more TKIs.

In the PACE study, 449 patients received oral ponatinib at a starting dose of 45mg once daily. Of these, 444 patients were assigned to one of six cohorts (based on disease phase, resistance or intolerance to dasatinib or nilotinib, and the presence of the T315I mutation): (i) CP-CML resistant or intolerant to dasatinib or nilotinib; (ii) CP-CML with the T315I mutation; (iii) AP-CML resistant or intolerant to dasatinib or nilotinib; (iv) AP-CML with the T315I mutation; (v) BP-CML or Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or; (vi) BP-CML or Ph+ ALL with the T315I mutation. The remaining five patients (3 with CP-CML and 2 with AP-CML) that had a history of the T315I mutation were treated with ponatinib but were not assigned to a cohort because the T315I mutation was not confirmed at baseline and the patients had not received nilotinib or dasatinib. The pre-specified efficacy analysis excluded these five patients; however, the safety analysis included all patients who received one or more doses of ponatinib. Therapy was continued until disease progression, unacceptable toxicity, withdrawal of patient consent or following a decision by the investigator. The primary outcome measure for CP-CML patients was major cytogenetic response (MCyR), which included complete cytogenetic responses (CCyR) and partial cytogenetic responses (PCyR) at any time within the first 12 months of the study. Both MCyR and CCyR are widely recognised as valid surrogate endpoints of survival. For patients with AP-CML and BP-CML, the primary outcome measure was major haematological response (MaHR) at 6 months. Although response milestones for patients with AP-CML and BP-CML have not been well-established, treatment strategies involve achieving MaHR, with the aim of proceeding to allo-SCT, if feasible.

Median follow-up among patients in the PACE study was 15 months for CP-CML, 16 months for AP-CML, and 6 months for BP-CML (data cut-off: 9 November 2012). Updated results were reported after a median follow up of 48.2 months (4 years) for CML groups (data cut-off: 3 August 2015).

Among the subgroup of CP-CML patients who received third-line ponatinib (i.e. the main target population in the CS), 67% (95% CI: 57% to 76%) achieved MCyR by 12 months (primary endpoint) and 56% (95% CI: 46% to 66%) reached CCyR. In contrast, among the patients who received fourth-line ponatinib, lower rates of responses were observed (MCyR, 45% [95% CI: 37% to 54%]; CCyR, 39% [95% CI: 31% to 48%]). In an updated analysis (data cut-off: 3 August 2015), 71% of CP-CML patients receiving third-line ponatinib (n=97) achieved a MCyR and 65% reached CCyR (95% CI: not

reported for either outcome). An estimated 88% (95% CI: not reported) of responding patients maintained MCyR for at least 3 years. In contrast, among the patients who received fourth-line ponatinib (n=142), lower rates of responses were observed (MCyr, 49%; CCyR, 45%). At 4 years, the PFS and OS rates in CP-CML patients who received third-line ponatinib were 68% and 79%, respectively (median not reached for either outcome). Similar rates were observed for fourth-line therapy (PFS: 52%; OS: 80%) but both outcomes, PFS and OS, were reduced to 11% with fifth-line therapy. Ponatinib is the only TKI with activity against the T315I mutation. In England (as of December 2016), ponatinib is only available to CML and Ph+ ALL patients with the T315I mutation through the CDF. Although a subgroup analysis by T315I mutation status was not provided in the CS, the ERG notes that among the subgroup of CP-CML patients who had the T315I mutation (n=64, all lines) 70% achieved MCyR by 12 months and 66% reached CCyR (95% CI: not reported for either outcome). All responding patients (100%) maintained MCyR for at least 12 months. In an updated analysis (data cut-off: 3 August 2015), 72% achieved MCyR and 70% reached CCyR (95% CI: not reported for either outcome). At 4 years, PFS and OS were 56% and 72%, respectively for the CP-CML patients who had the T315I mutation.

In the subgroup of AP-CML patients (n=33) who received ponatinib third-line, 61% (95% CI: not reported) had a MaHR within the first 6 months (primary endpoint), 42% achieved a MCyR and 30% reached CCyR (95% CI: not reported for either outcome). In contrast, among the patients who received fourth-line ponatinib (n=44), lower rates of responses were observed (MaHR, 50%; MCyR, 30%; CCyR, 16%).

[redacted] A subgroup analysis by T315I mutation status was not provided in the CS; however, the ERG notes that among the subgroup of AP-CML patients who had the T315I mutation (n=18, all lines), 50% had an MaHR within the first 6 months, 56% achieved MCyR and 33% reached CCyR (95% CI: not reported for any outcome).

[redacted] Due to the small population size and the PACE study design limitations, these findings should be treated with caution.

Among patients with BP-CML (all lines, n=62 [data not reported separately by line of therapy]), 31% (95% CI: 20% to 44%) achieved an MaHR within the first 6 months (primary endpoint), 23% achieved an MCyR and 18% reached CCyR. The rates of PFS and OS at 12 months were estimated to be 19% (median 4 months) and 29% (median 7 months), respectively. [redacted] A subgroup analysis by T315I mutation status was not provided in the CS; however, the ERG notes that among the subgroup of BP-CML patients who had the T315I mutation (n=24, all lines), 29% had an MaHR within the first 6 months, 29% achieved a MCyR and 21% reached a CCyR (95% CI: not reported for any outcome). [redacted] Due to the small population size and the PACE study design limitations, these findings should be treated with caution.

Among CML patients who received at least one dose of the study drug (all lines), 18.5% of CP-CML patients (n=270), 11.8% of AP-CML patients (n=85), and 14.5% of BP-CML patients (n=62) withdrew from treatment due to AEs (PACE data cut-off, 3 August 2015). In CP-CML, 18/97 (19%) of patients withdrew at third-line, 25/142 (18%) withdrew at fourth-line, and 4/12 (33%) withdrew at fifth-line due to AEs (PACE data cut-off, 3 August 2015). [redacted] As noted by the CS (data cut-off 9 November 2012; all lines of therapy: CP-CML n=270, AP-CML n=85; BP-CML n=62), the most common non-haematologic treatment-related AEs (any grade) reported in the PACE study were: skin reactions (rash CP-CML 40%, AP-CML 29%, BP-CML 24%; dry skin CP-CML 39%, AP-CML 25%, BP-CML 116%) and abdominal pain (CP-CML 27%, AP-CML 18%, BP-CML 10%) and the most common haematologic treatment-related AEs (any grade) were thrombocytopenia (CP-CML 41%, AP-CML 42%, BP-CML 27%), neutropenia (CP-CML 16%, AP-CML 23%, BP-CML 26%), and anaemia (CP-CML 10%, AP-CML 16%, BP-CML 23%).

[redacted]

Given the absence of any head-to-head studies comparing ponatinib with other relevant comparators for the treatment of CP-CML, the company undertook a matching-adjusted indirect comparison (MAIC) to facilitate an indirect comparison between treatments and to inform the economic model. The objective of the MAIC was to adjust outcomes to account for imbalances between treatments in (observed) prognostic factors in different studies; prognostic factors were T315I mutation status, sex, median age, race, duration of CML, and Eastern Cooperative Oncology Group (ECOG) performance status. The main effectiveness outcome measures for the MAIC were cytogenetic best response rates, haematologic best response rates and duration of response. The MAIC adjusted responses to ponatinib in the PACE study (Phase II) as if ponatinib had been included in the Phase I/II study that evaluated bosutinib rather than adjusting responses to bosutinib as if it had been included in the PACE study. From the MAIC, the CS concluded that ponatinib provides considerably higher CCyR rates than bosutinib in the third-line (61% vs 24%). The ERG's main critique of the MAIC was that indirect estimates of treatment effect may be biased as a consequence of unmeasured confounders. In addition, no adjustment was made to other outcomes, including overall survival and AEs, or for any AP-CML, and BP-CML outcomes.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the company was reasonably comprehensive. Despite minor limitations in the company's search strategy, the ERG is reasonably confident that all relevant published studies (RCTs and non-randomised/non-controlled evidence) of ponatinib were included in the CS, including data from ongoing studies. The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. The validity assessment tool for non-randomised studies (developed by Chambers *et al*.) was used to appraise the included studies and was considered appropriate by the ERG.

Although the absolute efficacy (measured in terms of surrogate response measures e.g. MCyR, MaHR and CCyR) in the PACE study appears favourable, and the safety appears acceptable, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. In the absence of direct comparative data with other treatments, the main evidence in the CS was derived from a Phase II, industry-sponsored, single-arm, non-comparative, open-label, study. Whilst the study was generally well reported and conducted, single-arm studies are associated with an array of potential biases including a high risk of selection bias (because of the absence of randomisation), performance and detection bias (because of the absence of blinding). In addition, because of the absence of a comparator group in the PACE study, inferences about treatment effects were made indirectly to a Phase I/II study of bosutinib using MAIC as if ponatinib has been included in that study. A further limitation to the robustness of the efficacy and safety data relate to the small subgroups that comprise the target population in the CS, including lack of statistical power for the subgroup assessments. The key uncertainties in the clinical evidence relate to optimal dosing, duration of treatment and magnitude of treatment effect.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted two models (one for CP-CML patients, and one that had the capability to choose either AP-CML or BP-CML patients). The CS separately provided a detailed account of the analyses undertaken although the majority of results presented were based on the list price of ponatinib. Only a small subset of analyses used the PAS (a simple price discount of [redacted]) which had not been formally agreed at the time of submission. The company reported that, with the PAS implemented, in CP-CML the incremental cost-effectiveness ratio (ICER) for ponatinib was: £18,213 per QALY gained compared with bosutinib; £4042 per QALY gained compared with allo-SCT; £15,200 per QALY gained compared with BSC; and £6395 per QALY gained compared with interferon alfa. The corresponding ICERs in AP-CML were: dominant compared with bosutinib; £8942 per QALY gained compared with allo-SCT; and £16,643 per QALY gained compared with BSC. In BP-CML the ICERs were: £19,449 per QALY gained compared with bosutinib; dominant compared with allo-SCT; and dominant compared with BSC.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic evaluation presented in the CS mainly adhered to the decision problem although clinical advice provided to the ERG suggested induction chemotherapy should have been considered as an option in BP-CML. Relatively few programming errors were found within the submitted model, although the ERG did not always agree with the underlying assumptions used in the model, the choice of parameter values or the choice of the distributions used in the company's base case for: OS; PFS; DoR; and relapse-free survival post-allo-SCT. The ERG notes that the uncertainty in the decision was

greatly underestimated by the company. The ERG assessed the potential implications of amending the model by conducting exploratory analyses, the results of which are detailed in Section 1.7.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of ponatinib for the treatment of CML. No major limitations were noted with the review. The PACE study was a well-reported and conducted single-arm study and measured a range of clinically relevant outcomes. Relatively few programming errors were found within the submitted model.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty in the evidence base relates to the lack of direct comparative data with other current treatments such as TKIs. In addition, long-term safety and efficacy data are lacking and it is unclear whether all patients need to continue long-term therapy. The ERG considers that the uncertainty in the decision was greatly underestimated by the company. The results of probabilistic sensitivity analyses were not considered robust by the ERG.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The exploratory analyses undertaken by the ERG are shown in Table 1 (CP-CML), Table 2 (AP-CML) and Table 3 (BP-CML). Full details of the analyses undertaken are provided in Section 5.3. In CP-CML, the choice of the selected curves for OS, PFS, DoR and relapse-free survival affected the ICER, as did assuming drug wastage, and reducing costs post-progression in both CP-CML and post allo-SCT for CP-CML patients. In AP-CML, the largest change in the ICER was caused by the selection of curves. In BP-CML, the largest changes in the ICER were caused by the selection of curves and the introduction of a three-month stopping rule for bosutinib.

In CP-CML the ICER for ponatinib is uncertain, ranging from £22,995 to £42,637 per QALY gained in comparison with bosutinib, from £18,246 to £27,667 per QALY gained in comparison with BSC, and from £18,279 per QALY gained to dominated, but nearer the upper end of this range, in comparison with allo-SCT.

In AP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £20,000 compared with bosutinib, below £18,000 compared with BSC, and from dominating – £63,701, but nearer the upper end of the range, in comparison with allo-SCT.

In BP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £25,000 compared with bosutinib and ponatinib was estimated to dominate BSC. The ICER of allo-SCT compared with ponatinib is estimated to lie between dominating and 63,701, but nearer the lower end of the range.

No formal analyses were conducted for those patients known to have, or not have, the T315I mutation. The ERG believes that if it was known that the T315I mutation was present then bosutinib would not be an appropriate comparator. If the T315I mutation was known not to be present then the ICERs compared with bosutinib are likely to be less favourable to ponatinib, although the extent of the change is unknown.

Table 1: The impact of the ERG's deterministic exploratory analyses in CP-CML: ponatinib compared with bosutinib, BSC and allo-SCT

		Cost per QALY gained (£)		
Ref No	**Exploratory Analyses**	**Pon vs Bos**	**Pon vs BSC**	**Pon vs allo-SCT**
0	N/A (company's base case)	18,213	15,200	4042
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	13,747 – 43,344	12,063 – 22,295	Dominant – 12,091
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	15,319 – 38,710	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	13,747 – 27,616	12,063 – 21,150	Dominant – 12,091
1d	Combining 1b and 1c	15,319 – 25,181	12,063 – 21,150	Dominant – 12,091
2a	Recalculation of the survivor functions (excluding PFS exponentials)	16,297	13,661	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	17,073	14,860	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	18,092	15,424	Dominant
3	Assuming drug wastage	30,754	24,245	16,487
4	Incorporating a three-month stopping rule for bosutinib	21,313	15,200	4042
5	No half-cycle correction of intervention costs	17,785	15,709	5472
6	Including treatment-related deaths	18,099	16,810	6143
7a	Reducing the costs assumed post-progression in CP-CML or post allo-SCT for CP-CML patients to that of BSC.	21,717	18,688	21,712
7b	Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib.	21,584	18,555	21.039
8	Assuming life table data are probabilities not rates	18,226	15,211	4043
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	18,017	15,035	4096
9b	Assuming decrements of HRQoL between CP-CML and other CML states are maintained	17,920	14,954	4125
10	2a, 4,5,6, 7a, 8 and 9a, using the curves believed most credible by the company	23,059	18,308	27,649
11. ERG base case ICERs	As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a) As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,986 – 52,121 22,995 – 42,637	18,246 – 27,667 N/A	18,279 – Dominated N/A

The ERG base case ICERs are likely to be favourable to ponatinib as neither drug wastage nor treatment-related deaths are assumed

All analyses are changes from the company's base case unless stated. ↑ cost per QALY yielded

Table 2: The impact of the ERG's deterministic exploratory analyses in AP-CML: ponatinib compared with BSC and allo-SCT

		Cost per QALY gained (£) – Ponatinib vs	
Ref No	**Exploratory Analyses**	**BSC**	**Allo-SCT**
0	N/A (company's base case)	14,750	13,279
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	7479 – 15,861	Dominating – 95,313
2	Recalculation of the survivor functions	10,358	12,217
3	Assuming drug wastage	15,267	14,199
4	No half-cycle correction of intervention costs	16,580	16,465
5	Including treatment-related deaths	14,747	12,671
6	Assuming life table data are probabilities not rates	14,754	13,285
7	2,3, 4, and 6 using the curves believed most credible by the company	12,975	16,412
8 ERG base case ICER	As 7, but choosing alternative distributions in addition to those selected by the company (range)	7475 – 18,005	Dominating – 63,701

The ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

All analyses are changes from the company's base case unless stated.

Ponatinib typically dominates bosutinib

Table 3: The impact of the ERG's deterministic exploratory analyses in BP-CML: ponatinib compared with bosutinib and allo-SCT

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,601	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	11,184 – 18,808	8,251 - Dominated
2	Recalculation of the survivor functions	15,812	157,193
3	Assuming drug wastage	18,022	Dominated
4	Incorporating a three-month stopping rule for bosutinib	22,910	Dominated
5	No half-cycle correction of intervention costs	18,349	Dominated
6	Including treatment-related deaths	16,665	Dominated
7	Assuming life table data are probabilities not rates	17,601	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	21,214	102,612
9 ERG base case ICER	As 8, but choosing alternative distributions in addition to those selected by the company (range)	17,152 – 22,512	4,035 - Dominated

The ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

All analyses are changes from the company's base case unless stated.

The comparison of ponatinib with allo-SCT is the cost per QALY gained of allo-SCT compared with ponatinib (South-West quadrant).

Ponatinib typically dominates BSC

2 BACKGROUND

This report provides a review of the evidence submitted by the company (Incyte Corporation) in support of ponatinib for treating chronic myeloid leukaemia (CML). It considers both the original company's submission (CS) received on 10th October 2016 and a subsequent response to clarification questions supplied by the company on 11th November 2016. A review of the evidence in support of ponatinib for treating Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) has been considered separately in an accompanying Evidence Review Group (ERG) report.[1]

2.1 Critique of company's description of underlying health problem

The CS (p1, p23-35) provided a reasonable description of the underlying health problem, which is briefly summarised in this section.

CML is a rare type of cancer affecting the blood and is characterised by a proliferation of granulocytes in the bone marrow and blood.[2] Approximately 95% of people with CML have an acquired chromosomal abnormality (known as Philadelphia chromosome positive disease, Ph+) caused by reciprocal translocations between chromosomes 9 and 22.[2, 3] These translocations result in a BCR-ABL fusion gene that encodes an active tyrosine kinase protein which causes uncontrolled cell proliferation.[2]

CML is typically characterised as having three distinct phases: the initial indolent chronic phase (CP-CML) which lasts for several years, an intermediate accelerated phase (AP-CML) which lasts for less than 1 to 1.5 years, and an aggressive blast phase (BP-CML) that is usually fatal within 3 to 6 months.[4] The stage of the disease at diagnosis is an important prognostic factor and may predict the pattern of disease progression.[5] In general, around 90% of CML cases are diagnosed during the chronic phase, with approximately 40% being asymptomatic and diagnosed as a result of a routine blood test.[2] From the chronic phase, people with CML either go through the accelerated phase or move directly into blast crisis in which the disease transforms into a fatal acute leukaemia.[2]

CML occurs in all age groups, but is most common in older adults. In the UK, the median age at diagnosis of CML is 59 years,[6] with an age-standardised incidence rate of 1.2 per 100,000 population.[7] According to the Office for National Statistics (ONS),[8] 631 people in England were newly diagnosed with CML in 2014 (the most recent year for which data are available). However, the CS (p34-35 and p240) estimates that only 113 people per annum with CML will be eligible to receive ponatinib according to its licence indication (i.e. for people with CML in need of third- or later-line tyrosine kinase inhibitor [TKI] therapy or for people who have the Threonine-315-Isoleucine [T315I] mutation). Clinical advisors to the ERG suggest that whilst there is some uncertainty around the proportions used within the calculations, this estimate seems reasonable.

2.2 Critique of company's overview of current service provision

In general, the CS (p1, p36-41) provides a good overview of current service provision for people with CML, which is briefly summarised in this section.

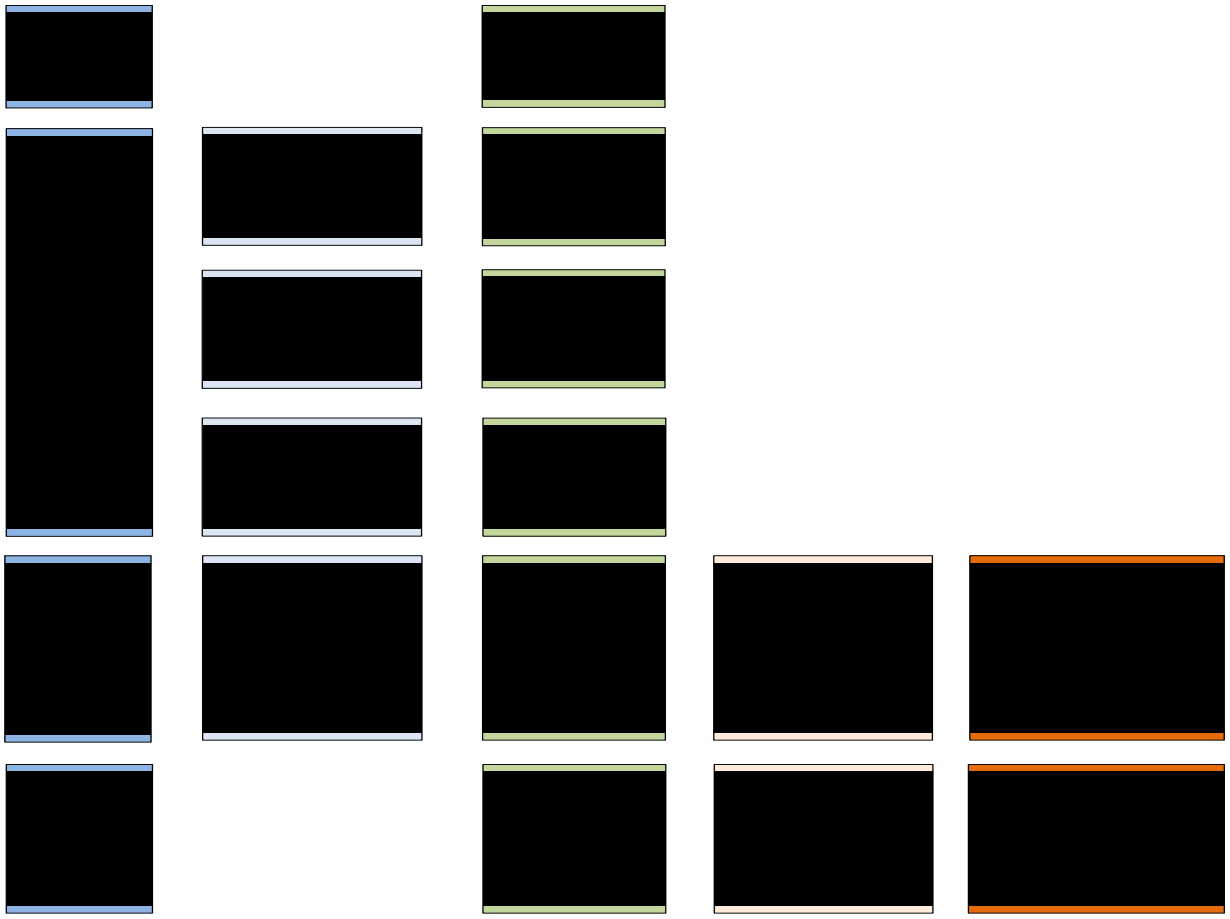
Allogeneic stem cell transplant (allo-SCT) is the only potentially curative treatment for CML. However, it is associated with a substantial rate of morbidity and mortality and is therefore limited by patient suitability as well as the availability of suitable donors.[9] The use of oral TKIs has become the mainstay of treatment in CML (Figure 1). Currently, five TKIs (imatinib,[10] dasatinib,[11] nilotinib,[12] bosutinib[13] and ponatinib)[14] have an EU marketing authorisation for the treatment of CML. Further details of the marketing authorisation of each of these TKIs can be found in CS, Table 3-2, p27.

Guidance issued by National Institute for Health and Care Excellence (NICE) recommends imatinib (standard dose) or nilotinib (with a Patient Access Scheme [PAS]) as first-line treatment options for adults with Ph+ CP-CML, but does not recommend dasatinib.[2] Imatinib is also recommended as an option for the treatment of people with Ph+ CML who initially present in the AP or BP, and for CML that presents in the CP and then progresses to the AP/BP, if imatinib has not been used previously.[15] It is noteworthy that the UK patent protection for imatinib is expected to expire in December 2016, thus substantial cost reductions are expected with generic imatinib[16] which may lead to the potential for increased uptake.

For second- and subsequent-line treatments, NICE recommends nilotinib (with a PAS) for people with Ph+ CP-CML and AP-CML where treatment with imatinib is not tolerated or where there is resistance.[2] Although dasatinib is not recommended by NICE (at the time the ERG report was written dasatinib was undergoing appraisal by NICE through the Cancer Drugs Fund [CDF] reconsideration process[17]), it is available through the CDF[18] and is thus accessible to CP-CML and AP-CML patients in England who are refractory to imatinib, or who have significant intolerance to imatinib or nilotinib (dasatinib was previously available for the treatment of BP-CML through the CDF but it was delisted in March 2015 [CS, p40]). Furthermore, sequential use of second-generation TKIs such as dasatinib after nilotinib is common in UK clinical practice; this view is supported by the ERG's clinical advisors and the company's market research findings from 12 clinical experts actively treating CML in the UK (CS, p40 and Appendix 14). This approach is also recommended in European clinical practice guidelines.[9] However, the CS (p29, p40) notes that there is a lack of clinical evidence to support the benefit of sequential use of second-generation TKIs in people who are resistant/intolerant to prior therapy and sequential use is not an approved indication for these drugs.[10, 11]

Figure 1: Simplified clinical pathway of care for patients with CML in England (adapted from CS, Figure 3-1, p28 and Figure 3-3, p35)

a) Patients who present with CP-CML (for disease progression to AP-CML and BP-CML see Figures 1b and 1c, respectively)



b) Patients who present with AP-CML

c) Patients who present with BP-CML

Allo-SCT, Allogeneic stem cell transplant; BSC, best supportive care; TKI, tyrosine kinase inhibitor

[a] Currently being appraised by NICE as part of this Single Technology Appraisal (assumed position in treatment pathway if recommended by NICE)

Bosutinib (with a PAS) was recently recommended by NICE as an option, within its conditional marketing authorisation, for Ph+ CP, AP- and BP-CML in adults when they have previously had one or more TKI; and imatinib, nilotinib and dasatinib are not appropriate.[19] The ERG notes that although bosutinib may be an option for some patients as a second-line treatment (if other second-generation TKI drugs are not suitable), bosutinib is likely to be predominantly used third-line or later in clinical practice.[20]

Ponatinib is currently only available to patients with the T315I mutation in England through the CDF;[18] however, the company suggests that in clinical practice ponatinib may also be used for adults with CP-, AP-, BP-CML whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate. Other treatment options for people with TKI resistant/intolerant CML include interferon alfa (in rare cases), best supportive/palliative care (including hydroxycarbamide), and allo-SCT.

Further details of relevant clinical guidelines from European LeukemiaNET[9] and the National Comprehensive Cancer Network[21] for the treatment of CML can be found in the CS (see Section 3.6, p37-39).

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

A summary of the decision problem addressed by the CS is reproduced (with minor changes) in Table 4.

Table 4: Decision problem as issued by NICE and addressed by the CS (CML only)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final NICE scope
Population	Adults with CP-CML, AP-CML, or BP-CML, whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation	As per the final scope	N/A
Intervention	Ponatinib	As per the final scope	N/A
Comparator (s)	• Bosutinib • Allo-SCT; with or without chemotherapy • Interferon alfa • BSC (including but not limited to hydroxycarbamide)	• Bosutinib (all phases) • Allo-SCT (all phases) • Interferon alfa (CP-CML) • Hydroxycarbamide as BSC (all phases)	The company stated that interferon alfa was not used as a comparator in AP-CML or BP-CML as it is rarely used to treat CML in the UK (CS, p42) and that there was no evidence of effectiveness in AP-CML or BP-CML (CS, p183)
Outcomes	• Overall survival • Progression-free survival/ event-free survival • Response rates • Time to response • Duration of response (DoR) • Adverse effects of treatment • Health-related quality of life	As per final scope, except that progression-free survival and DoR are applied only to the CP-CML model	DoR is not considered in the AP-CML or BP-CML model as patients who respond to treatment transition to allo-SCT in the first cycle

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final 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 (QALY) • time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective	As per the final scope	N/A

AP-CML, accelerated phase chronic myeloid leukaemia; Allo-SCT, allogeneic stem cell transplant; BP-CML, blast phase chronic myeloid leukaemia; BSC, best supportive care; CS, company submission; CP-CML, chronic phase chronic myeloid leukaemia; N/A, not applicable

3.1 Population

The company's statement of the decision problem defines the population as adults with CP-CML, AP-CML, or BP-CML whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation. This is in line with the final NICE scope.

The key clinical evidence submitted by the company was derived from the PACE (Ponatinib Ph-positive acute lymphoblastic leukaemia [ALL] and CML Evaluation) study.[22] In this single-arm, Phase II study, 34% of people with CML had previously received interferon alfa;[22] however, this is rarely used in the UK.[9, 23, 24] In addition, 96% of patients with CP-CML or AP-CML (data not reported for BP-CML) had previously been treated with first-line imatinib.[25] According to the findings from the company's market research survey (conducted between March and April 2016), of 12 clinical experts actively treating CML in the UK (CS, p40 and Appendix 14), approximately 63% of newly diagnosed patients with CP-CML receive first-line imatinib and over one-third of patients receive nilotinib in the UK. As noted in the expert submission by Professor Jane Apperley, on behalf of the Royal College of Pathologists '…*it*

is highly likely that treatment approaches will change when generic imatinib becomes available in the UK in December 2016, such that physicians will be encouraged to start all newly diagnosed patients on generic imatinib'.[26]

3.2 Intervention

The intervention under consideration in the CS is ponatinib, which matches the intervention described in the final NICE scope. Ponatinib is a third-generation antineoplastic protein kinase inhibitor that was designed to inhibit the kinase activity of the BCR-ABL gene and all mutant variants, including the T315I mutation, in patients failing multiple TKIs.[27]

Ponatinib is currently licensed in the EU (including the UK)[14] for the treatment of adult patients with:

- CP-CML, AP-CML or BP-CML who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation (the population considered within this report).
- Ph+ ALL who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation (the population considered within a separate ERG report).[1]

As noted in the Summary of Product Characteristics (SmPC), prior to the start of therapy with ponatinib, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with ponatinib.[14]

Ponatinib is available as 15mg and 45mg film-coated tablets for oral administration (with or without food). As noted in the CS (p15), a 30mg film-coated tablet has been approved by the European Medicines Agency (EMA) and will be on the market in the UK in early 2017. The recommended starting dose is 45mg once per day with an option for reduced dosing (30mg or 15mg once a day) for the management of haematological and non-haematological toxicities. [redacted].

Treatment with ponatinib should continue as long as the patient does not show evidence of disease progression or unacceptable toxicity. If a complete haematologic response (CHR) has not occurred by 3 months, consideration should be given to discontinuing ponatinib.[14]

Ponatinib is available in 30-tablet packs; the acquisition costs for the 15mg, 30mg (licensed, not yet available) and 45mg tablets are £2525, £5050 and £5050, respectively (CS, Table 2-1, p16). Ponatinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. No other restrictions or contraindications are stated for ponatinib in the CS or the SmPC.[14]

3.3 Comparators

The comparators under consideration in the CS (i.e. bosutinib, allo-SCT, interferon alfa and hydroxycarbamide as best supportive care [BSC]), closely match the comparators described in the final scope.[19] The ERG agrees that these interventions are appropriate relevant comparators; however, some points need further clarification.

Within the CS, the company states that interferon alfa was not used as a comparator in AP-CML or BP-CML as it is rarely used to treat CML in the UK (CS, p42) and that there was no evidence of effectiveness in AP-CML or BP-CML (CS, p183). The ERG's clinical advisors concurred with this view. In addition, only hydroxycarbamide was used to approximate BSC. Whilst limited justification was provided in the CS (p123), the ERG notes that in a recent STA of bosutinib for previously treated CML,[19] the NICE appraisal committee accepted that hydroxycarbamide was not a disease-modifying treatment and that it was appropriate to consider hydroxycarbamide as a proxy for BSC. Clinical advice received by the ERG also suggested that this was appropriate.

The clinical advice provided to the ERG was that induction chemotherapy was a valid comparator in BSC and would be used to induce some form of positive response before considering allo-SCT.

3.4 Outcomes

The final NICE scope[19] outlines seven clinical outcome measures. Most of these are stated to have been addressed in the CS (p2-3). Clinical outcome measures included overall survival (OS), progression-free survival (PFS)/event-free survival, response rates, time to response, duration of response (DoR), adverse events/effects (AE) of treatment and health-related quality of life (HRQoL). These are all considered by the ERG to be appropriate and clinically meaningful outcomes.

The incremental cost per quality-adjusted life year (QALY) gained was used as a measure of cost-effectiveness, which is in accordance with the NICE Reference Case.[23] In the health economic model, the company used a lifetime horizon (up to 100 years) and costs were considered from a NHS and Personal Social Services perspective. The CS (p2-3) states that DoR was not considered in the AP-CML or BP-CML models as patients who respond to treatment transition to allo-SCT in the first cycle. Based on clinical advice, the ERG believes this exclusion to be appropriate. In addition, as HRQoL was not

assessed or reported in the PACE study,[22] the company's *de novo* model used other published evidence to inform health utility parameters.

3.5 Other relevant factors

The equity issues highlighted within the CS (p123) was a reference to '*the current inequity in CDF access to ponatinib between patients with the T315I mutation and those who fall within the indication but do not have this mutation*' and on p30 of the CS where it is stated that allo-SCT '*is associated with equity issues*'.

4 CLINICAL EFFECTIVENESS

This chapter provides a summary and critique of the clinical-effectiveness evidence presented by the company in support of ponatinib for the treatment of CML only.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company performed two broad clinical effectiveness searches to identify all RCTs and non-randomised/non-controlled evidence on the use of ponatinib or its comparators in the treatment of adults with CML (the population considered within this report) and Ph+ ALL (the population considered within a separate ERG report).[1] The original searches were designed to identify studies evaluating all lines of therapy for CML beyond first-line (post-imatinib). However, the updated searches (conducted in July 2016) were amended to reflect the decision problem issued by NICE (post-imatinib and a second-line, second-generation TKI [dasatinib or nilotinib]). Despite a lack of clarity, the ERG assumes the key aims of the CML searches were:

1. To identify all RCTs and non-randomised/non-controlled evidence on the use of ponatinib for the treatment of adults with CP-CML, AP-ML and BP-CML which might potentially be relevant to the decision problem.

2. To identify all RCTs and non-randomised/non-controlled studies for the treatment of adults with CP-CML, AP-ML and BP-CML which might potentially be relevant to the decision problem that would allow indirect comparisons with the comparators specified in the final NICE scope which had not been directly compared with ponatinib.

The ERG further notes that the presentation of these sections in the CS is made somewhat confusing due to extensive cross-referencing between (and within) the main document and appendices.

In brief, for the original searches, several electronic bibliographic databases (including MEDLINE [via Ovid], MEDLINE in Process [via Ovid], EMBASE [via Ovid], Cochrane Central Register of Controlled Trials [via EBM reviews] and the Health Technology Assessment database [via EBM reviews]) and research registers (ClinicalTrials.gov and the WHO International Clinical Trials Platform) were searched covering the period from January 2000 to January/February 2016. Supplementary searches such as scanning of bibliographies of included studies, reviews and various conference proceedings were also undertaken (CS, p42 and company's response to clarification question A2). For the update searches, similar sources appear to have been searched and covered the period to July 2016. However, it is unclear why the Cochrane Database of Systematic reviews and the Database of Abstracts of

Reviews of Effects, which forms part of the EBM Reviews resource were not searched, as additional studies may have been identified from the reviews of primary studies. The ERG also recommends applying forward tracking of citations of key papers and not only references of follow-up for studies. Nevertheless, the ERG considers the chosen electronic databases and internet sources to be appropriate.

The company reported that bibliographic databases were originally searched using predefined search strategies adapted from those used in the STA for bosutinib.[29] Although the company used the same exact terms for the CML populations and search filters (trials, reviews, observational filters), additional terms for the concept of 'resistance' were used to broaden the search strategy and to improve sensitivity (CS, p42). Following further clarification on the additional patient population concept for resistance and line of treatment in both the MEDLINE and EMBASE search strategies, the ERG was satisfied with the company's response (see clarification response,[28] question A2) on the investigation for the impact of including or excluding this concept in the search strategy on the risk of missing key studies.

Despite the noted limitations, the ERG considers all the search strategies to be sufficiently comprehensive to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware. However, as no search details/strategies were provided in the CS, it is unclear whether any relevant AE studies have been missed.

4.1.2 Inclusion criteria

The CS describes appropriate methods of identifying and screening references for inclusion in the systematic reviews of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection were resolved through discussion between reviewers, if required (CS, p42). A summary of the inclusion and exclusion criteria, as reported in the CS (p43), is reproduced (with minor changes) in

Table 5.

Table 5: Inclusion/exclusion criteria used to select CML studies of ponatinib in the CS (adapted Table 4-1 from CS, p43)

	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with CML who are resistant/intolerant to prior treatments • Patients must have received at least one prior treatment for their disease	• Animal studies, *in vitro* studies, and studies in healthy populations
Interventions/ comparators	• Ponatinib, • Dasatinib [a] • Nilotinib [a] • Bosutinib • Stem cell transplantation • Hydroxycarbamide • BSC	• Imatinib, as it is primarily used in the first-line and does not represent a direct comparator for ponatinib
Outcomes	• Response rates • Overall survival • Progression-free survival • Relapse-free survival • Time on treatment • Maintenance of response • Transformation-free survival • Adverse events • Intervention doses • Relative dose intensity	• Mixed-population studies (i.e., those including first-line and later patients) that do not present results in second-line or later patients separately from those in first-line patients
Trial design	• Randomised controlled trials (including crossover studies) • Non-randomised single-arm studies • Observational studies (retrospective and prospective) • Reviews, systematic literature reviews and meta-analyses were initially included to identify relevant articles for manual reference searching	• Letters, comments, editorials, case reports, and pharmacokinetic studies, models (economic or mathematical), surveys, adherence studies, prognostic studies, epidemiological studies, studies of treatment prescribing patterns, and dose-escalation studies • Studies with fewer than 10 patients overall (across all treatment arms) and abstracts without sufficient information
Language restrictions	No limitation by language in searches	Studies in languages other than English excluded during screening

BSC, best supportive care; CML, chronic myeloid leukaemia

[a] In line with the decision problem issued by NICE, the updated CML systematic literature review (conducted in July 2016) did not include studies with dasatinib and/or nilotinib

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. It is noteworthy that the CS (p42-44) initially considered a wider remit to capture the entire evidence base as part of the inclusion criteria (i.e. all lines of therapy for CML beyond first-line: post-imatinib) but then focused the systematic review to those studies directly relevant to the decision problem (i.e. post-imatinib and either dasatinib or nilotinib). As a result, the systematic reviews excluded interventions that were not listed in the decision problem after the study selection stage and thus were not considered further in the CS (see clarification response,[28] question A7). Whilst this approach seems acceptable to the ERG, ideally, systematic reviews should have clearly focused research questions and inclusion/exclusion criteria at the outset.

The company's systematic review excluded studies which were reported only as abstracts; however, limited justification for this exclusion was provided. In order to avoid publication bias, a systematic review should aim to include all relevant studies, regardless of publication status. Although differences often occur between data reported in conference abstracts and their corresponding full reports, differences in results are usually not very large.[30] However, the ERG notes that it can be difficult to appraise study quality from limited details provided in an abstract. As a result, sensitivity analyses may be carried out to examine the effect of including data from conference abstracts.[31]

Finally, the statement of the decision problem proposed that interferon alfa should be considered as a comparator. However, this was excluded as a comparator from the company's systematic review because it is rarely used to treat CML in the UK.[9, 23, 24] The CS (p42) notes that in a recent STA of bosutinib for previously treated CML,[19] the NICE appraisal committee accepted that interferon alfa is rarely used in clinical practice. The ERG's clinical advisors also concurred with this view.

4.1.3 Critique of data extraction

The data extracted and presented in the clinical section of the CS appear appropriate and comprehensive. As noted in the company's clarification response to question A3,[28] data extraction was performed by one reviewer and checked for accuracy by a second reviewer. Whilst this strategy appears acceptable, the ERG notes that the gold standard for data extraction is for multiple individuals to independently perform data extraction, and to compare results and resolve any discrepancies through discussion. Other less robust strategies include single individual data extraction followed by verification (for accuracy and completeness) by a second individual or (the weakest strategy) a single individual conducting data extraction on a single occasion.[30, 32] However, while these methods may result in significantly more errors than two researchers independently performing data extraction, they may also take significantly less time.[30, 32, 33]

4.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in the CS (p73) was based on the quality assessment criteria for non-randomised studies developed by Chambers *et al*.[34] A key strength of this tool is that it addresses both quality of reporting and risk of bias (principally selection and attrition bias). As noted in the company's clarification response to question A8,[28] methodological quality assessment of included studies was performed by two independent reviewers, with disagreements resolved by a third reviewer. The ERG acknowledges that the validity assessment tool used in the CS was acceptable.

4.1.5 Evidence synthesis

The company undertook a narrative synthesis of the evidence for ponatinib; however, no explicit details were provided in the CS on how this approach was undertaken. Ideally, a narrative synthesis approach should be justified, rigorous (i.e. describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[30, 32] Despite the lack of transparency regarding the methods adopted, the ERG acknowledges that the narrative synthesis approach undertaken by the company was acceptable. In the absence of any direct head-to-head studies comparing ponatinib with other relevant therapies for the treatment of CML in patients who were resistant/ intolerant to two prior therapies (i.e. post-imatinib and either dasatinib or nilotinib), the company conducted an MAIC. Further details on the studies included and a critique of the MAIC can be found in Sections 4.3 and 4.4 respectively.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/). Despite this, the diagram represents the identification and selection of all relevant RCTs and non-randomised/non-controlled studies of all lines of therapy for CML beyond first-line (post-imatinib) and appears to be a reasonable record of the literature searching and screening process (see company's clarification response,[28] question A6). However, for clarity, a PRISMA flow diagram that includes details of the final set of studies that were included in the CS (which were directly relevant to the decision problem) would have been beneficial as this would aid the transparency of the identification and selection process.

The company's systematic review of RCTs comparing ponatinib with an appropriate comparator in the population of interest (i.e. patients with CP-CML, AP-CML or BP-CML who are resistant or intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate

or who have T315I mutation) did not identify any relevant studies. In the absence of RCT evidence, the company identified two relevant single-arm, non-comparative studies (a Phase I dose finding study[35, 36] and a Phase II study).[22, 37, 38] However, as noted in the company's clarification response to question A11,[28] the design and context of the Phase I study was '*…not entirely relevant to either the recommended dosing or the licenced indication in the approved product label…*' for ponatinib (further details of this study are briefly provided in the supplementary evidence section). As such, evidence from the Phase II PACE study forms the main pivotal evidence in the CS. Further details of this study are provided in this section.

The company's broader systematic review of RCTs of all treatments for patients with CP-CML, AP-ML and BP-CML in the post-second-generation TKI setting (which was conducted to allow indirect comparisons to be conducted with the comparator interventions listed in the decision problem i.e. bosutinib, allo-SCT and BSC) did not identify any relevant studies. In the absence of RCT evidence, the company identified one relevant non-comparative phase I/II study of bosutinib that provided data on the efficacy and safety of bosutinib after treatment with multiple TKIs (imatinib and dasatinib and/or nilotinib) in patients with Ph+ CP-CML.[39-42] Further details of the Phase I/II bosutinib study are presented in Section 4.3. For allo-SCT, the CS identified one retrospective observational study of allo-SCT in relapsed CML;[43] however, this was not included in the MAIC. The CS (p47) states that '*…the MAIC was done for response categories (CCyR, partial cytogenetic response [PCyR], [CHR, non-responder [NR]), which are not directly applicable in the context of transplantation'* and the ERG concurred with this view. The CS did not identify any relevant studies of BSC in CML.

4.2.1.1 The main pivotal evidence (PACE study)[22, 37, 38]

The CS (p4-6 and p64-99) included one ongoing, phase II, industry-sponsored, single-arm, non-comparative, open-label, multicentre study (including five sites in the UK) designed to evaluate the efficacy of oral ponatinib in 449 people (53% male; 78% Caucasian)[25] with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy (as confirmed by direct sequencing).[22, 25, 27] Study participants in the PACE study were heavily pre-treated with prior TKIs and conventional therapy: 37% (167/449) had received two TKIs (imatinib, dasatinib, nilotinib or bosutinib). This population comprised the target population in the company's decision problem for CP-CML, AP-CML and BP-CML i.e. in the third-line treatment setting, reflecting the anticipated place in therapy of ponatinib, after treatment failure with imatinib and either nilotinib or dasatinib, if used through the CDF (see clarification response,[28] question A1). In the fourth-line setting, 55% (249/449) had received three or more TKIs.[22, 25]

Eligible patients were enrolled between September 2010 and October 2011 and were required to be ≥18 years old (median age, 59 years), have an ECOG performance status ≤2, adequate renal and hepatic function, normal pancreatic status and a normal QT (a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) interval. The key exclusion criteria were: TKI treatment within seven days prior to ponatinib; receipt of certain therapies within a specific time frame prior to receiving ponatinib; lack of recovery from AEs from prior treatments; concomitant medications known to be associated with Torsades de Pointes; stem cell transplant <60 days prior to receiving first dose of ponatinib; ongoing graft-versus-host disease (including requiring immunosuppressive therapy), concurrent treatment with immunosuppressive agents, other than short-course corticosteroids; history of pancreatitis or alcohol abuse; uncontrolled hypertriglyceridemia (triglycerides >450mg/dL).[22] A summary of the study design and population characteristics is provided in Table 6.

Patients (n=444) were assigned to one of the following six cohorts (based on disease phase, resistance or intolerance to dasatinib or nilotinib, and the presence of the T315I mutation): CP-CML resistant or intolerant to dasatinib or nilotinib; CP-CML with the T315I mutation; AP-CML resistant or intolerant to dasatinib or nilotinib; AP-CML with the T315I mutation; BP-CML or Ph+ ALL resistant or intolerant to dasatinib or nilotinib; BP-CML or Ph+ ALL with the T315I mutation. There were five patients (3 with CP-CML and 2 with AP-CML) that had a history of the T315I mutation. These patients were enrolled and treated with ponatinib but were not assigned to a cohort because the T315I mutation was not confirmed at baseline and the patients had not received nilotinib or dasatinib. The pre-specified efficacy analysis excluded these five patients (n=444); however, the safety analysis included all patients who received one or more doses of ponatinib (n=449).[22]

Table 6: Characteristics of the key included study

Study	Location (sites)	Design	Population	Intervention and comparator	Primary outcome measures	Duration
PACE (NCT01207440; AP24534-10-201)[22, 37, 38] Funded by: ARIAD Pharmaceuticals Inc.	66 centres [a] in 12 countries (including 5 sites in the UK, n=30)[b]	Phase II, single arm open-label, non-comparative study (n=449)	Patients (aged ≥ 18 years) with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy No. of prior TKI: 2 (third-line cohort: target population in the company's decision problem) CP-CML, 97[c]/270[d] (36%); AP-CML, 33/85[e] (39%); BP-CML, 22/62 (35%); Ph+ ALL, 14/32 (44%) No. of prior TKI: 3 (fourth-line cohort) CP-CML, 142[c]/270[d] (53%); AP-CML, 44/85[e] (52%); BP-CML, 34/62 (55%); Ph+ ALL, 12/32 (38%)	Ponatinib 45mg tablet taken orally once daily	Major cytogenetic response (MCyR) in patients with CP-CML Major haematologic response (MaHR) patients with in AP-CML, BP-CML and Ph+ ALL	Start date: September 2010 Estimated study completion date: March 2017 (final data collection date for primary outcome measure)[f]

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; TKI, Tyrosine kinase inhibitor

[a] Data discrepancy - reported as 68 sites across 12 countries in European Public Assessment Report[27] and the US Food and Drug Administration medical review[25]

[b] Data from company's response to clarification question A10 (CP-CML, n=28; AP-CML, n=2; BP-CML, n=0; Ph+ ALL, n=0; data not available by line of treatment)[28]

[c] One patient was misclassified at the time of the original (CP-CML, n=98; AP-CML, n=141) analysis

[d] Total population (n=270) includes three patients with CP-CML who were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[e] Total population (n=85) included two patients with AP-CML who were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[f] Data from https://clinicaltrials.gov/ct2/show/record/NCT01207440?view=results (no details provided in CS)

All patients received oral ponatinib at a starting dose of 45mg once daily, with subsequent doses delayed or reduced following AEs.[22] In addition, in October 2013, following a request by the US Food and Drug Administration (FDA), study investigators were instructed to reduce the dose from 45 to 15 mg/day in all CP-CML patients who had achieved a MCyR or better, to 30 mg/day in CP-CML patients who had not already achieved MCyR, and to 30 mg/day for advanced phase patients (CS, p65 and p103).

For CP-CML patients, the primary endpoint was the proportion of patients achieving MCyR at any time within the first 12 months after initiation of treatment (defined as complete cytogenetic response [CCyR] or partial cytogenetic response [PCyR]). For patients with AP-CML, BP-CML or Ph+ ALL at baseline, the primary outcome was the proportion of patients achieving a major haematologic response (MaHR) within the first six months after initiation of treatment. MaHR was defined as complete haematologic response (CHR) or no evidence of leukaemia (confirmed by blood analyses after ≥28 days). Response assessments were performed every 3 months in patients with CP-CML, whereas response assessments in patients with AP-CML, BP-CML or Ph+ ALL were completed at the end of cycle 1 (each cycle was 28 days), cycle 2, and every 2 months thereafter. Secondary endpoints for all diagnoses included a major molecular response, the time to the response, the duration of the response, PFS, OS, and safety. Therapy was continued until disease progression, unacceptable toxicity, withdrawal of patient consent or following a decision by the investigator.[22]

In the PACE study, the planned sample sizes of the cohorts were estimated to rule out pre-specified null response rates with the use of 95% confidence intervals. The rates of a MCyR, MaHR, CHR [complete haematologic response] and major molecular response were calculated using two-sided, exact 95% confidence intervals. The Kaplan–Meier method was used to estimate the DoR, PFS and OS and Fisher's exact test was used for subgroup comparisons. Power was calculated based on effect size in each cohort and ranged from 78% to ≥98%.[22]

4.2.1.2 Ongoing studies of ponatinib

In addition to the PACE study,[22, 37, 38] where follow-up evaluations are ongoing, the CS (p102-103) noted one additional ongoing study, the OPTIC trial[44] (brief details are provided in

Table 7). The CS (p102-103) states that neither of these studies are likely to provide data within the next 12 months. It is noteworthy that the CS did not provide details of the ongoing Management of Transformed Chronic myeloid leukaemia: Ponatinib and Intensive chemotherapy (MATCHPOINT) study,[45] which is due for completion in September 2017 (see

Table 7 for further details).

Table 7: List of key ongoing studies of ponatinib

Criteria	OPTIC study[44]	MATCHPOINT study[45]
Title (official)	A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients With Resistant Chronic Phase Chronic Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses	Management of Transformed Chronic myeloid leukaemia: Ponatinib and Intensive chemotherapy
Study ID number	Clincinaltrials.gov: NCT02467270 AP24534-14-203, 2014-001617-12	ISRCTN98986889
Sponsors and collaborators	Sponsor: ARIAD Pharmaceuticals Collaborators: Not reported	Sponsor: University of Birmingham Funders: Bloodwise, as part of their Trials Acceleration Programme and ARIAD Pharmaceuticals Inc.
Study objective	The purpose of this study is to compare and characterise the efficacy and safety of ponatinib in patients with resistant CP-CML in a range of doses.	The aim of this study is to find a safe and effective dose of ponatinib when used in combination with chemotherapy in patients with BP-CML
Study design	Phase II, randomised, open-label trial	Phase I/II, non-randomised study
Study location	Multinational (approximately 92 sites in 24 countries, including 6 sites in the UK)	UK
Study population	Approximately 450 adult patients (male and female aged ≥ 18 years) with CP-CML and be resistant to at least 2 TKIs. Additional inclusion criteria include Eastern Co-operative Oncology Group performance status ≤2 and adequate renal and hepatic function	Approximately 30 adult patients (male and female aged ≥ 18 years) with Ph+ or BCRABL positive CML in blastic transformation. Additional inclusion criteria include suitability for intensive chemotherapy (FLAG-IDA [fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin]) and adequate renal and liver function
Study interventions	Patients are randomised to one of three treatment groups. • Group A receives oral ponatinib 45mg once daily (starting dose) • Group B receives oral ponatinib 30mg once daily (starting dose) • Group C receives oral ponatinib 30mg once daily (starting dose)	Ponatinib (various doses) in combination with FLAG-IDA
Study outcomes	*Primary outcome*	*Primary outcome* • *CCyR*

Criteria	OPTIC study[44]	MATCHPOINT study[45]
	• MCyR by 12 months, defined as 0%–35% of Ph+ cells in the bone marrow *Secondary outcomes* • Safety, including the rates of VOE, AE, and SAE over a 24-month timeframe.	*Secondary outcomes* • CMV reactivation rate, GVHD, DFS, haematological response, MMR, OS, relapse rate post allogeneic transplant or maintenance therapy, Safety and tolerability.
Start date	June 2015	March 2014
Expected completion date	December 2018	September 2017

AE, adverse events; CCyR, Complete cytogenetic response; CMV, Cytomegalovirus; CP-CML, chronic phase chronic myeloid leukaemia; DFS, disease free survival; Graft Versus Host Disease; MCyR, major cytogenetic response; MMR, major molecular response; OS, overall survival; Ph+, Philadelphia positive; TKI, tyrosine kinase inhibitor; SAE, serious adverse events; VOE, vascular occlusive events

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant published studies (RCTs and non-randomised/non-controlled evidence) were included in the CS and details of ongoing studies that are likely to be reporting additional evidence within 12 months were reported.

4.2.3 Summary and critique of the company's analysis of validity assessment

The company provided a formal appraisal of the validity of the included ponatinib study using the quality assessment criteria for non-randomised studies developed by Chambers *et al*.[34] Although there are numerous tools for assessing the quality of non-randomised intervention studies,[46] the company's justification for choosing this tool seems acceptable (see clarification response,[28] question A8). A key strength of this tool is that it addresses both quality of reporting and risk of bias (principally selection and attrition bias).[34] However, the limitations on the use of this tool were lacking in the CS. The ERG notes that whilst modifying an existing tool is deemed acceptable to meet the requirements of the review question and/or study design,[30, 32] the use of summary scores (as reported in the CS, Table 4-12, p74; and Appendix 8) to distinguish high and low quality studies is questionable and not recommended.[30, 32] Instead, critical assessments should be made and presented separately for each different domain.[30] The completed quality assessment tool for the PACE study, as reported in the CS, is reproduced (with minor changes) in Table 8. It is noteworthy, the ERG remains unclear (despite a response to clarification question A8)[28] as to why the company undertook quality assessments for each publication (citation) of the PACE study separately rather than the PACE study as a whole (as is conventional practice).

Table 8: Quality assessment results for the PACE study as assessed by the company (adapted from CS, Appendix 8)

Criteria used for quality assessment	PACE study[22, 37, 38]	
	Company's assessment	ERG's assessment
1. Were selection/eligibility criteria adequately reported?	Yes	Yes
2. Was the selected population representative of that seen in normal practice?	Yes	Yes
3. Was an appropriate measure of variability reported?	Yes	Yes
4. Was loss to follow-up reported or explained?	Yes	Yes
5. Were at least 90% of those included at baseline followed up?	Yes	Yes
6. Were patients recruited prospectively?	Yes	Yes
7. Were patients recruited consecutively?	Unclear	Unclear
8. Did the study report relevant prognostic factors?	Yes	Yes

In general, based on this quality assessment, the ERG considered the PACE study[22, 37, 38] to be a well-reported and conducted single-arm study; however, some further discussion around specific points is required.

Single-arm studies are associated with an array of potential biases.[47] For example, there is a high risk of selection bias due to the absence of randomisation, and a risk of performance and detection bias due to the absence of blinding.[30, 32] As acknowledged in the CS (p66), a lack of a comparator group in the PACE study limits its ability to compare or demonstrate efficacy with current treatments. In addition, blinded outcome assessment was not undertaken in PACE study (see clarification response,[28] question A9). This would have helped minimise bias,[48] particularly for subjective outcomes.

Although selection/eligibility criteria were adequately described in the prospective PACE study,[22, 37, 38] explicit details on how patients were identified for recruitment into the PACE study were lacking in the CS (including the published paper).[22] Appropriate measures of variability were used, with confidence intervals reported around point estimates to indicate variability for relevant outcomes. Loss to follow-up and reasons for leaving the study early were reported, and more than 90% of patients included at baseline were followed up (see clarification response,[28] question A14). Details on whether patients were recruited consecutively in the PACE study were lacking in the CS (including response to clarification question A8)[28] and the PACE study publications.[22, 37, 38] Nevertheless, clinical advisors to the ERG noted that in terms of age and gender, patients enrolled into the PACE study appeared to be representative of

the CP-CML, AP-CML, BP-CML and Ph+ ALL population in the UK; however, treatment practice in the PACE study[22, 37, 38] was not representative of UK practice (see Section 2.2.) Prognostic factors such disease stage and age were reported and all primary analyses were appropriately analysed: the pre-specified efficacy analysis included all patients [n=444] who were assigned to one of six cohorts, whereas the safety population included all patients [n=449] who received one or more doses of ponatinib.

4.2.4 Summary and critique of results

This section presents the main results from the PACE study, based on information reported in the CS and the company's clarification response, for the target population in the company's decision problem for CP-CML, AP-CML and BP-CML i.e. in the third-line treatment setting (reflecting the anticipated place in therapy of ponatinib, after treatment failure with imatinib and either nilotinib or dasatinib, if used through the CDF) and in the fourth-line setting (reflecting it potential use in this setting for some patients). For completeness, the company also provided results based on the total 'treated' population (all lines of therapy), where applicable.

The primary outcome measure for CP-CML patients was major cytogenetic response (MCyR), which included complete cytogenetic responses (CCyR) and partial cytogenetic responses (PCyR) at any time within the first 12 months of the study. Both MCyR and CCyR are widely recognised as surrogate endpoints of survival[49] and have been used in previous NICE Technology Appraisals (TA241,[2] TA251[2] and TA401)[19] and HTAs by Rogers *et al*.,[24] Pavey *et al*.,[50] and Loveman *et al*.[51] For patients with AP-CML and BP-CML, the primary outcome measure was major haematological response (MaHR) at 6 months. Although response milestones for patients with AP-CML and BP-CML have not been well established, treatment strategies involve achieving MaHR, with the aim of proceeding to allo-SCT, if feasible.[52]

In the original published PACE study, data were reported after a median follow-up of 15 months for CP-CML, 16 months for AP-CML, and 6 months for BP-CML (data cut-off: 9 November 2012).[22] Updated results were reported by Hochhaus *et al*.,[38] after a median follow up of 48.2 months (4 years) for CP-CML patients. Corresponding data for the AP-CML and BP-CML cohorts were derived from the ponatinib clinical study report (CSR)[53] and the company's response to clarification question A13 (data cut off: 3 August 2015).[28] Where appropriate, data have been re-tabulated by the ERG to provide further clarity.

4.2.4.1 Efficacy

4.2.4.1.1. CP-CML

In the PACE study,[22] among the subgroup of CP-CML patients who received third-line ponatinib, 67% (95% CI: 57% to 76%) achieved MCyR by 12 months (primary endpoint) and 56% (95% CI: 46% to 66%) reached CCyR and 36% (95% CI: 26% to 46%) had an MMR. In contrast, among the patients who received fourth-line ponatinib lower rates of responses were observed (MCyr, 45%; CCyR, 39%; MMR, 33%). In an updated analysis (at a median follow up of 48.2 months),[38] 71% (95% CI: not reported) of CP-CML patients receiving third-line ponatinib (n=97) achieved an MCyR and an estimated 88% (95% CI: not reported) of responding patients maintained this response for at least 3 years. A total of 65% of patients with CP-CML reached CCyR and 42% reached MMR (95% CI: not reported for either outcome). In contrast, among the patients who received fourth-line ponatinib (n=142), lower rates of responses were observed (MCyr, 49%; CCyR, 45%; MMR, 37%). At 4 years, the PFS (defined as death, development of AP or BP, loss of CHR in absence of cytogenetic response, loss of MCyR, or increasing white blood cell count without CHR) and OS rates in CP-CML patients who received ponatinib third-line were 68% and 79%, respectively (median not reached for either outcome). Similar rates were observed for fourth-line therapy (PFS: 52%; OS: 80%) but both outcomes, PFS and OS, were reduced to 11% with fifth-line therapy. A summary of the original and updated results, by line of therapy, is presented in Table 9.

Table 9: Study outcomes in the CP-CML cohort of the PACE study (adaption of table in company's response to clarification question A13)[28]

Source	**Cortes *et al.*[22]**				**Hochhaus *et al.*[38]**			
Data cut-off	**Original efficacy results: 9 November 2012**				**Updated efficacy results: 3 August 2015**			
Follow-up	12 months				4 years			
Line of therapy	**All lines**	**3L**	**4L**	**5L**	**All lines**	**3L**	**4L**	**5L**
Number of patients	n=267[a]	n=98[b]	n=141[b]	n=12	n=267[a]	n=97[b]	n=142[b]	n=12
MCyR[c]	56% (95% CI: 50–62)	67% (95% CI: 57–76)	45% (95% CI: 37–54)	58% (95% CI: 28–85)	N/R	71% (95% CI: N/R)	49% (95% CI: N/R)	58% (95% CI: N/R)
CCyR	46% (95% CI: N/R)	56% (95% CI: 46–66)	39% (95% CI: 31–48)	25% (95% CI: 5–57)	N/R	65% (95% CI: N/R)	45% (95% CI: N/R)	33% (95% CI: N/R)
MMR	34% (95% CI: N/R)	36% (95% CI: 26–46)	33% (95% CI: 26–42)	8% (95% CI: 0.2–38)	N/R	42% (95% CI: N/R)	37% (95% CI: N/R)	8% (95% CI: N/R)
Median time to MCyR	2.8 months (range: 1.6–11.13)	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Duration of response (median, 95% CI)	1 day to 19.4 months (not reached, 95% CI: NE)	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Maintained MCyR	91% [d] (95% CI: 85–95)	N/R	N/R	N/R	N/R	88%[e] (95% CI: N/R)	86%[e] (95% CI: N/R)	25%[e] (95% CI: N/R)
PFS (median, 95% CI)	*12 month PFS*: 80% (not reached, 95% CI: NE)	N/R	N/R	N/R	*4 year PFS:* 56% (not reached, 95% CI: NE)	*4 year PFS:* 68% (not reached, 95% CI: NE)	*4 year PFS:* 52% (not reached, 95% CI: NE)	*47 month PFS*: 11% (11.1 months, 95% CI: N/R)
OS (median, 95% CI)	*12 month OS:* 94% (not reached, 95% CI: NE)	N/R	N/R	N/R	*4 year OS:* 77% (not reached, 95% CI: NE)	*4 year OS:* 79% (not reached, 95% CI: NE)	*4 year OS:* 80% (not reached, 95% CI: NE)	*4 year OS:* 11% (38.9 months, 95% CI: N/R)
Transform to AP/BP-CML	1.9%	N/R	N/R	N/R	3.4%	N/R	N/R	N/R

3L, third-line; 4L, fourth-line; 5L, fifth-line; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; NE, not estimable; N/R, not reported; PFS, progression-free survival; OS, overall survival

[a] Three patients with CP-CML were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[b] One patient was misclassified at the time of the original analysis

[c] Primary endpoint for CP-CML cohorts was MCyR, which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

[d] Maintained response at 12 months

[e] Maintained response at 3 years

Ponatinib is the only TKI with activity against the T315I mutation. In England (as of December 2016), ponatinib is only available to CML and Ph+ ALL patients with the T315I mutation through the CDF.[18] Although a subgroup analysis by T315I mutation status was not provided in the CS, the ERG have provided a summary of these results in Table 10. Among the subgroup of CP-CML patients who had the T315I mutation (n=64, all lines)[22] 70% achieved MCyR by 12 months and 66% reached CCyR (95% CI: not reported for either outcome). All responding patients (100%) maintained MCyR for at least 12 months. In an updated analysis (data cut-off: 3 August 2015),[54] 72% of CP-CML patients achieved a MCyR and 70% reached CCyR (95% CI: not reported for either outcome). The estimated PFS and OS at 4 years for the CP-CML patients who had the T315I mutation (n=64, all lines) were 56% and 72%, respectively.

Table 10: Efficacy of ponatinib by T315I mutation status in CP-CML

Source	**Cortes *et al.*[22]**			**Cortes *et al.*[54]**		
Data cut-off	**Original efficacy results: 9 November 2012**			**Updated efficacy results: 3 August 2015**		
Follow-up	12 months			4 years		
Line of therapy	**All lines**			**All lines**		
Number of patients	Overall n=267[a]	Resistant/ Intolerant n=203	T315I mutation n=64	Overall n=267[a]	Resistant/ Intolerant n=203	T315I mutation n=64
MCyR[b]	56%	51%[c]	70%[c]	59%	55%	72%
CCyR	46%	40%	66%	54%	48%	70%
MMR	34%	27%	56%	39%	34%	58%
Median time to MCyR	2.8 months	2.8 months	2.8 months	N/R	N/R	N/R
Maintained MCyR	91%	87%	100%	82%	81%	86%
PFS	*12 month PFS*: 80%	*12 month PFS*[d]: 78%	*12 month PFS*[d]: 83%	*4 year PFS:* 56%	*4 year PFS:* 57%	*4 year PFS:* 56%
OS	*12 month OS:* 94%	*12 month OS*[d]*:* 95%	*12 month OS*[d]*:* 92%	*4 year OS:* 77%	*4 year OS:* 78%	*4 year OS:* 72%

CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; N/R, not reported; OS, overall survival; PFS, progression-free survival

[a] Three patients with CP-CML were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[b] Primary endpoint for CP-CML cohorts was MCyR, which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

[c] CP-CML patients who entered the study in PCyR had to achieve CCyR to meet the criteria for MCyR. In the R/I and T315I cohorts, 39 and 13 patients entered the study in PCyR, respectively. The MCyR rates for these patients were 64% and 92% for R/I and T315I, respectively, and 71% overall.

[d] Data from Cortes *et al*.[54]

4.2.4.1.2. AP-CML

In the subgroup of AP-CML patients (n=33) who received ponatinib third-line, 61% (95% CI: not reported) had an MaHR within the first 6 months (primary endpoint). A total of 42% of patients with AP-CML achieved MCyR, 30% reached CCyR and 24% had an MMR (95% CI: not reported for any outcome). In contrast, among the patients who received fourth-line ponatinib (n=44), lower rates of responses were observed (MaHR, 50%; MCyr, 30%; CCyR, 16%; MMR, 11%).[22]

[redacted] A summary of the original and updated results, by line of therapy, are provided in Table 11.

Table 11: Study outcomes in the AP-CML cohort of the PACE study (adaption of table in company's response to clarification question A13)[28]

Source	Cortes *et al.*[22]				Clinical study report[53a]			
Data cut-off	**Original efficacy results: 9 November 2012**				**Updated efficacy results: 3 August 2015**			
Follow-up	12 months				4 years			
Line of therapy	**All lines**	**3L**	**4L**	**5L**	**All lines**	**3L**	**4L**	**5L**
Number of patients	n=83[b]	n=33	n=44	n=3	n=83[b]	n=33	n=46	N/R
MaHR by 6 months[c]	55% (95% CI: 44–66)	61% (95% CI: N/R)	50% (95% CI: N/R)	67% (95% CI: N/R)	[redacted]	[redacted]	[redacted]	N/R
MCyR	39% (95% CI: N/R)	42% (95% CI: N/R)	30% (95% CI: N/R)	67% (95% CI: N/R)	[redacted]	[redacted]	[redacted]	N/R
CCyR	24% (95% CI: N/R)	30% (95% CI: N/R)	16% (95% CI: N/R)	33% (95% CI: N/R)	[redacted]	[redacted]	[redacted]	N/R
MMR	16% (95% CI: N/R)	24% (95% CI: N/R)	11% (95% CI: N/R)	0 (95% CI: N/R)	[redacted]	[redacted]	[redacted]	N/R
Median time to response	*MaHR:* 3 weeks (range: 2–25) *MCyR:* 3.7 months (range: 0.8–9.7)	N/R	N/R	N/R	[redacted]	N/R	N/R	N/R
Duration of response	*MaHR:* 1 to 21 months or more (median: 12 months, 95% CI: N/R)	N/R	N/R	N/R	[redacted]	N/R	N/R	N/R
Maintained response	*MaHR at 12 months:* 48% (95% CI: N/R) *MCyR at 12 months:* 73% (95% CI: N/R)	N/R	N/R	N/R	[redacted]	N/R	N/R	N/R
PFS	*12 month PFS*: 55% (median: 18 months, 95% CI: N/R)	N/R	N/R	N/R	[redacted]	N/R	N/R	N/R

OS	*12 month OS*: 84% (median not reached, 95% CI: NE)	N/R	N/R	N/R	[redacted]	N/R	N/R	N/R

3L, third-line; 4L, fourth-line; 5L, fifth-line; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; NE, not estimable; N/R, not reported; PFS, progression-free survival; OS, overall survival

[a] Results reported in the clinical study report include patients who had received imatinib, dasatinib, and/or nilotinib, but not bosutinib

[b] Two patients with AP-CML were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[c] Primary endpoint for AP-CML was MaHR defined as complete haematologic responses and no evidence of leukaemia

Although a subgroup analysis by T315I mutation status was not provided in the CS, the ERG have provided a summary of these results in Table 12. Among the subgroup of AP-CML patients who had the T315I mutation (n=18, all lines),[22] 50% (95% CI: not reported) had an MaHR within the first 6 months. A total of 56% of patients with AP-CML achieved MCyR, 33% reached CCyR and 22% had an MMR (95% CI: not reported for any outcome). [redacted]

Despite these findings, the ERG warrant caution in its interpretation due to the small population size and study design limitations.

Table 12: Efficacy of ponatinib by T315I mutation status in AP-CML

Source	**Cortes *et al.*[22]**			**Clinical study report[53]**		
Data cut-off	**Original efficacy results: 9 November 2012**			**Updated efficacy results: 3 August 2015**		
Follow-up	12 months			4 years		
Line of therapy	**All lines**			**All lines**		
Number of patients	Overall n=83[a]	Resistant/ Intolerant n=65	T315I mutation n=18	Overall n=83[a]	Resistant/ Intolerant n=65	T315I mutation n=18
MaHR by 6 months[b]	55%	57%	50%	[redacted]	[redacted]	[redacted]
MCyR	39%	34%	56%	[redacted]	[redacted]	[redacted]
CCyR	24%	22%	33%	[redacted]	[redacted]	[redacted]
MMR	16%	14%	22%	[redacted]	[redacted]	[redacted]
PFS	*12 month PFS*: 55%	N/R	N/R	*4 year PFS*[c]*:* 22%	[redacted]	[redacted]
OS	*12 month OS:* 84%	N/R	N/R	*4 year OS*[c]*:* 51%	[redacted]	[redacted]

CCyR, complete cytogenetic response; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; N/A, not applicable; N/R, not reported; OS, overall survival; PFS, progression-free survival
[a] Two patients with AP-CML were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)
[b] Primary endpoint for AP-CML was MaHR defined as complete haematologic responses and no evidence of leukaemia
[c] Data from Cortes *et al*.[54]

4.2.4.1.3. BP-CML

Among patients with BP-CML (all lines, n=62 [data not reported separately by line of therapy]), 31% (95% CI: 20% to 44%) achieved an MaHR within the first 6 months (primary endpoint). The duration of response ranged from 1 to 20 months or more (median 5 months), and the estimated rate of a sustained response of at least 12 months was 42%. The median time to MaHR for responders was 4.1 weeks (range: 1.7 to 16.1 weeks). Furthermore, MCyR was reached in 23% of patients, and 18% had a CCyR.

The median time to MCyR for responders was 1.9 months (range: 0.9 to 5.5 months), with an estimated 66% of responding patients maintaining this response for at least 12 months. In BP-CML, the rate of PFS and OS at 12 months was estimated to be 19% (median 4 months) and 29% (median 7 months), respectively.[22]

[redacted] A summary of the original and updated results, by line of therapy, are provided in Table 13.

Table 13: Study outcomes in the BP-CML cohort of the PACE study (adaption of table in company's response to clarification question A13)[28]

Source	Cortes *et al.*[22]	Clinical study report[53a]		
Data cut-off	**Original efficacy results: 9 November 2012**	**Updated efficacy results: 3 August 2015**		
Follow-up	12 months	4 years		
Line of therapy	**All lines**	**All lines**	**3L**	**4L**
Number of patients	BP-CML only, n=62	BP-CML/Ph+ ALL combined, n= 94	BP-CML/Ph+ ALL combined, n=38	BP-CML/Ph+ ALL combined, n=48
MaHR by 6 months[b]	31% (95% CI: 20–44)	[redacted]	[redacted]	[redacted]
MCyR	23% (95% CI: N/R)	[redacted]	[redacted]	[redacted]
CCyR	18% (95% CI: N/R)	N/R	[redacted]	[redacted]
Median time to response	*MaHR:* 4.1 weeks (range: 1.7–16.1) *MCyR:* 1.9 months (range: 0.9–5.5)	N/R	N/R	N/R
Duration of response	*MaHR:* 1 to 20 months or more (median: 5 months, 95% CI: N/R)	N/R	N/R	N/R
Maintained response	*MaHR at 12 months :* 42% (95% CI: N/R) *MCyR at 12 months:* 66% (95% CI: N/R)	N/R	N/R	N/R
PFS	*12 month PFS*: 19% (median: 4 months, 95% CI: N/R)	[redacted]	N/R	N/R
OS	*12 month OS*: 29% (median: 7 months; 95% CI: N/R)	[redacted]	N/R	N/R

3L, third-line; 4L, fourth-line; ALL, acute lymphoblastic leukaemia; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; NE, not estimable; N/R, not reported; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive; OS, overall survival.

[a] Data not reported separately for BP-CML cohort and Ph+ ALL cohort

[b] Primary endpoint for BP-CML was MaHR defined as complete haematologic responses and no evidence of leukaemia

[redacted]

Although a subgroup analysis by T315I mutation status was not provided in the CS, the ERG have provided a summary of these results in Table 14. Among the subgroup of BP-CML patients who had

the T315I mutation (n=24, all lines),[22] 29% (95% CI: not reported) had an MaHR within the first 6 months. A total of 29% of patients with BP-CML achieved MCyR and 21% reached CCyR (95% CI: not reported for either outcome). [redacted] Despite these findings, the ERG warrant caution in its interpretation due to the small population size and study design limitations. [redacted]

Table 14: Efficacy of ponatinib by T315I mutation status in BP-CML

Source	**Cortes *et al.*[22]**			**Clinical study report[53a]**		
Data cut-off	**Original efficacy results: 9 November 2012**			**Updated efficacy results: 3 August 2015**		
Follow-up	12 months			4 years		
Line of therapy	**All lines**			**All lines**		
Number of patients	BP-CML only			BP-CML/Ph+ ALL combined		
	Overall n=62	Resistant/ Intolerant n=38	T315I mutation n=24	Overall n=94	Resistant/ Intolerant n=48	T315I mutation n=46
MaHR by 6 months[b]	31%	32%	29%	[redacted]	[redacted]	[redacted]
MCyR	23%	18%	29%	[redacted]	[redacted]	[redacted]
CCyR	18%	16%	21%	[redacted]	[redacted]	[redacted]
PFS	*12 month PFS*: 19%	N/R	N/R	[redacted]	[redacted]	[redacted]
OS	*12 month OS:* 29%	N/R	N/R	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; N/R, not reported; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive;
[a] Data not reported separately for BP-CML cohort and Ph+ ALL cohort
[b] Primary endpoint for BP-CML was MaHR defined as complete haematologic responses and no evidence of leukaemia

4.2.4.2 Safety and tolerability

This section provides the main safety evidence for all patients with CP-CML, AP-CML and BP-CML who received at least one dose of ponatinib within the PACE study (safety population).[22] Where available, results are presented for both the target population in the company's decision problem (i.e., in the third-line treatment setting) and the total population (all lines). Additional safety data was also reported from a Phase I study.[35] Further details of this study are provided in Section 4.6.

4.2.4.2.1. Treatment dose and duration of treatment

The CS does not report the average daily dose of treatment and what proportion of treatment time CP-CML, AP-CML and BP-CML patients were able to maintain the starting ponatinib dose of 45mg per day. Average daily dose and proportion of treatment time at 45mg per day and at any dose to 27 April 2012[55] (all lines) are presented in Table 15. CP-, AP-, and BP-CML patients were only able to maintain 45mg per day for 50%, 60% and 71% respectively, of the entire treatment duration.[25]

Table 15: Average daily dose of ponatinib and percentage of treatment duration at 45mg or any dose for CP-, AP-, and BP-CML patients (all lines) in the PACE study (data derived from the FDA Medical Review Table 33[25])

	CP-CML (n=270)	AP-CML (n=85)	BP-CML (n=62)
Average daily dose, mg	32.1	31.2	39.2
% treatment duration at 45mg per day	50%	60%	71%
% treatment duration at any dose	86%	82%	91%

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia

4.2.4.2.2. Dose reduction and interruption

The CS reports that, in addition to dose reductions following AEs, in October 2013 the FDA instructed dose reductions from 45mg/day to 15mg/day in all CP-CML patients who had achieved a MCyR or better, to 30mg/day in CP-CML patients who had not already achieved MCyR, and to 30mg/day for AP-CML. Prospective dose reductions in all CP-CML patients in the absence of AEs were also introduced in the study (CS, p65) to reduce the risk of vascular occlusive events (VOEs). In response to a request for clarification by the ERG (see clarification response,[28] question A16), the company provided details on dose adjustments to August 2015 in the PACE study (all lines) for CP-CML patients, AP-CML patients, and BP-CML and Ph+ ALL combined, following the recommendations to reduce the dose made in October 2013. The ERG considers the combining of CML and Ph+ ALL patients for this outcome acceptable. A summary of these data, adapted by the ERG, is presented in

Table 16.

[redacted]

Table 16: Summary of dose adjustments by disease group (PACE data cut-off, 3 August 2015[53])

	CP-CML N=270 n (%)	AP-CML N=85 n (%)	BP-CML/ Ph+ ALL N=94 n (%)
Any dose reduced			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Dose interruptions of at least 3 days			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Dose modifications: patients with at least one of the following			
Interruption[a]	[redacted]	[redacted]	[redacted]
Resumed	[redacted]	[redacted]	[redacted]
Reduction	[redacted]	[redacted]	[redacted]
Re-escalation[b]	[redacted]	[redacted]	[redacted]
Last non-missing dose for ongoing patients			
N ongoing	[redacted]	[redacted]	[redacted]
15mg	[redacted]	[redacted]	[redacted]
30mg	[redacted]	[redacted]	[redacted]
45mg	[redacted]	[redacted]	[redacted]

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia

[redacted]

4.2.4.2.3. Discontinuation of treatment

The CS reports that across CML and Ph+ ALL patients combined (all lines), 12% of patients discontinued treatment due to AEs and that treatment was discontinued due to lack of efficacy in 4% of patients and due to progressive disease in 19% of patients (p75). The CS does not report rates of discontinuation for CP-, AP-, and BP-CML patients. A summary of the rates of discontinuation (including reasons for premature termination) for CP-, AP-, and BP-CML patients from the PACE study[22] (all lines) to 9 November 2012 is presented in

Table **17**.

Table 17: Number (%) of CP-, AP-, and BP-CML patients discontinuing treatment in the PACE study: All lines (data derived from Cortes *et al.* [22])

	CP-CML (n=270)	AP-CML (n=85)	BP-CML (n=62)
Had progressive disease	20 (7%)	18 (21%)	31 (50%)
Had adverse event	35 (13%)	9 (11%)	10 (16%)
Died[a]	5 (2%)	2 (2%)	6 (10%)
Withdrew consent	14 (5%)	0 (0%)	3 (5%)
Had other reasons	5 (2%)	6 (7%)	6 (10%)
Lack of efficacy	11 (4%)	3 (4%)	0 (0%)
Physician's decision	8 (3%)	2 (2%)	1 (2%)
Non-compliance	1 (<1%)	0 (0%)	0 (0%)

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia

[a] Four deaths were assessed by the investigators as being possibly or probably related to ponatinib: one patient with CP-CML had pneumonia and one patient with CP-CML had an acute myocardial infarction, one patient with AP-CML had fungal pneumonia, one patient with BP-CML had a gastric haemorrhage

A summary of the rates of discontinuation (including reasons for premature termination) for CP-CML patients from the PACE study (safety population and ≥third-line) at the 4 year follow-up[38] are presented in Table 18. In the total CP-CML population, similar rates of study discontinuation were observed to those in the third-line population at the 4 year follow-up to 3 August 2015.

Table 18: Number (%) of CP-CML patients discontinuing treatment in the PACE study 4-year follow-up to 3 August 2015: All lines (Data derived from Hochhaus *et al*.[38])

Discontinued, n (%)	All CP-CML patients n=270[a]	CP-CML patients who had received 1 prior TKI n=142	CP-CML patients who had received 2 prior TKIs n=97	CP-CML patients who had received 3 prior TKIs n=142	CP-CML patients who had received 4 prior TKIs n=12
Total discontinued	160 (59%)	9 (47%)	53 (55%)	87 (61%)	11 (92%)
AE	50 (19%)	3 (16%)	18 (19%)	25 (18%)	4 (33%)
Withdrawal by patient[b]	30 (11%)	1 (5%)	11 (11%)	15 (11%)	3 (25%)
Disease progression	28 (10%)	3 (16%)	5 (5%)	20 (14%)	0 (0%)
Lack of efficacy	15 (6%)	0 (0%)	2 (2%)	12 (8%)	1 (8%)
Physician decision	11 (4%)	1 (5%)	4 (4%)	5 (4%)	1 (8%)
Death[b]	8 (3%)	0 (0%)	2 (2%)	4 (3%)	2 (17%)
Noncompliance	3 (1%)	0 (0%)	1 (1%)	2 (1%)	0 (0%)
Protocol violation	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Other[c]	14 (5%)	1 (5%)	10 (10%)	3 (2%)	0 (0%)

CP-CML, chronic phase chronic myeloid leukaemia; AE, adverse event; TKI, Tyrosine kinase inhibitor

[a] Includes 3 patients who were non–cohort assigned (post-imatinib, non-T315I) but treated; all 3 remain on study

[b] 2 deaths were assessed by investigators as possibly or probably related to ponatinib (pneumonia, acute myocardial infarction)

[c] Including for transplant (n=11)

In response to a request for clarification by the ERG (see clarification response,[28] question A14), the company provided details on the number of patients who discontinued study treatment permanently due to AEs (including deaths related to study treatment) in the PACE study (all lines and ≥third-line separately) for CP-, AP-, and BP-CML to August 2015 and data by line of therapy derived from patient-level data. A summary of these data, adapted by the ERG, is presented in Table 19 and Table 20. In the total CP-CML population of the PACE study, similar rates of study discontinuation were observed to those in the target populations. [redacted]

Table 19: Number of patients who discontinued study treatment permanently in the PACE study due to AEs including death: company response (sources: Hochhaus *et al.*[38] and ponatinib CSR[53], PACE data cut-off, 3 August 2015)

	CP-CML				AP-CML	BP-CML
Line of therapy	Any line	3L	4L	5L	Any line	Any line
Number of patients, n	270[b]	97	142	12	85[b]	62
Discontinued treatment due to AEs, n (%)	50 (18.5%)	18 (19%)	25 (18%)	4 (33%)	10 (11.8%)	9 (14.5%)
Death related to ponatinib, n (%)	2 (0.7%)	N/R	N/R	N/R	2 (2.4%)	3 [a] (3.2%)[a]

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; N/R, not reported; 3L, third-line; 4L, fourth-line; 5L-fifth-line

[a] Results reported for the combined BP-CML/Ph+ ALL cohort only.

[b] The total numbers of patients in the CP-CML and AP-CML cohorts differ as the first set of data comes from the entire safety cohort, including patients who were treated but not assigned to a cohort. Results derived from patient level data did not include patients who were not assigned to a cohort.

Table 20: Number of patients who discontinued study treatment permanently due to AEs (PACE study Patient Level Data)

	CP-CML				AP-CML				BP-CML			
Line of therapy	Any line	3L	4L	5L	Any line	3L	4L	5L	Any line	3L	4L	5L
Number of patients, n	267[b]	97	142	12	83[b]	32	44	3	62	23	34	3
Discontinued treatment due to AEs, n (%)	[redacted]											
Death related to ponatinib, n (%)	[redacted]											

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; N/R, not reported; 3L, third-line; 4L, fourth-line; 5L-fifth-line

[b] The total numbers of patients in the CP-CML and AP-CML cohorts differ as the first set of data comes from the entire safety cohort, including patients who were treated but not assigned to a cohort. Results derived from patient level data did not include patients who were not assigned to a cohort.

4.2.4.2.4. Treatment-related and treatment-emergent AEs

The CS does not report treatment-related AEs for AP- and BP-CML. A summary of the most common treatment-related AEs for CP-, AP- and BP-CML from the PACE study[22] (all lines) to 9 November 2012 is presented in Table 21. As noted by the CS, the most common non-haematologic treatment-related AEs reported in the PACE study were skin reactions and abdominal pain (p84). The most common haematologic treatment-related AEs reported in the PACE study were thrombocytopenia, neutropenia, and anaemia (p85).

Table 21: Treatment-related AEs from the PACE study for CP-, AP- and BP-CML to November 2012 (revised from Cortes *et al.*[22])

	CP-CML n=270		AP-CML n=85		BP-CML n=62	
	Any grade n (%)	Grade 3 or 4 n (%)	Any grade n (%)	Grade 3 or 4 n (%)	Any grade n (%)	Grade 3 or 4 n (%)
Non-haematologic events						
Rash	107 (40%)	10 (4%)	25 (29%)	3 (4%)	15 (24%)	2 (3%)
Dry skin	104 (39%)	5 (2%)	21 (25%)	1 (1%)	10 (16%)	1 (2%)
Abdominal pain	74 (27%)	20 (7%)	15 (18%)	4 (5%)	6 (10%)	1 (2%)
Headache	63 (23%)	5 (2%)	10 (12%)	0 (0%)	7 (11%)	1 (2%)
Increased lipase	57 (21%)	27 (10%)	12 (14%)	11 (13%)	8 (13%)	7 (11%)
Fatigue	51 (19%)	4 (1%)	17 (20%)	1 (1%)	7 (11%)	2 (3%)
Constipation	53 (20%)	3 (1%)	11 (13%)	1 (1%)	3 (5%)	0 (0%)
Myalgia	46 (17%)	3 (1%)	16 (19%)	0 (0%)	7 (11%)	0 (0%)
Arthralgia	45 (17%)	6 (2%)	16 (19%)	1 (1%)	8 (13%)	0 (0%)
Nausea	38 (14%)	1 (<1%)	9 (11%)	0 (0%)	12 (19%)	0 (0%)
Increased alanine aminotransferase	31 (11%)	9 (3%)	10 (12%)	2 (2%)	5 (8%)	2 (3%)
Pancreatitis	19 (7%)	17 (6%)	7 (8%)	5 (6%)	3 (5%)	2 (3%)
Hypertension	25 (9%)	6 (2%)	6 (7%)	3 (4%)	1 (2%)	1 (2%)
Increased aspartate aminotransferase	24 (9%)	5 (2%)	8 (9%)	3 (4%)	4 (6%)	1 (2%)
Increased blood amylase	16 (6%)	4 (1%)	6 (7%)	3 (4%)	3 (5%)	2 (3%)
Increased gamma-glutamyltransferase	11 (4%)	4 (1%)	7 (8%)	2 (2%)	2 (3%)	1 (2%)
Dyspnea	13 (5%)	4 (1%)	6 (7%)	0 (0%)	4 (6%)	1 (2%)
Cardiac failure	3 (1%)	2 (<1%)	1 (1%)	1 (1%)	2 (3%)	2 (3%)
Haematologic events						
Thrombocytopenia	111 (41%)	86 (32%)	36 (42%)	28 (33%)	17 (27%)	16 (26%)
Neutropenia	44 (16%)	38 (14%)	22 (26%)	22 (26%)	14 (23%)	11 (18%)
Anaemia	27 (10%)	15 (6%)	14 (16%)	8 (9%)	14 (23%)	13 (21%)
Decreased white-cell count	11 (4%)	7 (3%)	7 (8%)	5 (6%)	0 (0%)	0 1 (3%)
Pancytopenia	2 (1%)	2 (1%)	3 (4%)	2 (2%)	3 (5%)	3 (5%)
Febrile neutropenia	1 (<1%)	1 (<1%)	2 (2%)	2 (2%)	2 (3%)	2 (3%)

Treatment-related adverse events were defined as events that the site investigators deemed to have a possible, probable, or definite relationship to ponatinib. Listed are the treatment-related adverse events that were reported in at least 10% of the patients, along with any incidence of grade 3 or 4 events in more than 1% of the total study population
AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia

In response to a request for clarification from the ERG (see clarification response,[28] question A18), the company confirmed that AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v. 4.0;[56] definitions of grades: 1=mild, 2=moderate, 3=severe, 4=life-threatening, and 5=death).

In response to a request for clarification from the ERG (see clarification response,[28] question A18), the company provided details on the treatment-related and treatment-emergent AEs in ≥10% of patients for CP-CML and AP-CML, and for BP-CML and Ph+ ALL combined (all lines) (PACE data cut-off, 3 August 2015). The ERG considers combining BP-CML and Ph+ ALL patients for this outcome to be acceptable. A summary of these data, reproduced by the ERG, is presented in

Table 22.

[redacted]

Table 22: Treatment-related and treatment-emergent AEs in ≥10% of patients CP-CML, AP-CML, and BP-CML/Ph+ ALL in the PACE study (data cut-off, 3 August 2015)

	CP-CML n (%)		AP-CML n (%)		BP-CML/Ph+ ALL n (%)	
	Any Grade	Grade 3+	Any Grade	Grade 3+	Any Grade	Grade 3+
Number of patients	270		85		94	
Any TRAE/TEAE						
Haematologic						
Thrombocytopenia						
Neutropenia						
Anaemia						
Gastrointestinal						
Abdominal pain						
Constipation						
Nausea						
Diarrhoea						
Investigations						
Lipase increase						
ALT increased						
AST increased						
Blood alkaline phosphatase increased						
Other						
Rash						
Dry skin						
Headache						
Fatigue						
Arthralgia						
Myalgia						
Pain in extremity						
Muscle spams						
Asthenia						

Rash pruritic						
Vascular disorders						
Hypertension						
Cardiac disorders occurring in ≥1% of patients						
Angina pectoris						
Atrial fibrillation						
Coronary artery disease						
Cardiac failure congestive						
Pericardial effusion						
Acute myocardial infarction/myocardial infarction						
Acute coronary syndrome						
Palpitations						
Tachycardia						
Cardiac failure						
Coronary artery occlusion						
Bradycardia						
Cardiac failure chronic						
Ischaemic cardiomyopathy						
Left ventricular dysfunction						
Cardiac arrest						

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

A summary of the most common treatment-related grade ≥3 AEs (all lines), as reported by the CS to 3 August 2015 and adapted by the ERG is presented in

Table **23**.

Table 23: Treatment-related AEs from the PACE study for CP-, AP- and BP-CML from the PACE study to August 2015 (revised from CS Table 4-19)

	CP-CML n=97[a]	AP-CML n=85	BP-CML n=62
	Most common ≥Grade 3 AEs, n (%)		
TRAEs/TEAEs reported in >5% of patients			
Abdominal pain	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Leukocytopenia	[redacted]	[redacted]	[redacted]
Increased lipase	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]
Elevated ALT	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
VOEs (number of events per 100 patient-years)			
CV event	[redacted]	[redacted]	[redacted]
Cerebrovascular event	[redacted]	[redacted]	[redacted]
Peripheral arterial occlusive event	[redacted]	[redacted]	[redacted]
Serious venous thrombotic event	[redacted]	[redacted]	[redacted]

Sources: PACE study CSR[53], CP-CML, 14.3.1.3.1.2.6 (p2280–2291); AP-CML, Table 14.3.1.8.1.9 (p3296–3312); BP-CML, Table 14.3.1.8.2.10.1 (p3552); VOEs, Section 14.3.5 Other Safety Measurements, Table 2.2 (p6124–6126).
AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; CV, cardiovascular; TRAE, treatment-related adverse event; TEAE, treatment-emergent adverse event; VOEs, vascular occlusive events
[a] Patients treated with two prior TKIs

In response to a request for clarification from the ERG (see clarification response,[28] question A18), the company provided details on the treatment-emergent AEs, any Grade, in ≥10% of patients and ≥Grade 3 in ≥5% of patients for CP-CML by line of therapy (PACE data cut-off, 3 August 2015). A summary of these data adapted by the ERG is presented in

Table **24**.

[redacted]

Table 24: Treatment-emergent AEs in ≥10% of patients any Grade, and ≥5% of patients Grade ≥3 by line of therapy (CP-CML only) from the PACE study (data cut-off, 3 August 2015)

	All lines	3L	4L	5L
Number of patients	270	97	142	12
TEAEs in ≥10% (any Grade) of patients[a]				
Any TEAE				
Rash				
Abdominal pain				
Thrombocytopenia				
Headache				
Dry skin				
Constipation				
Hypertension				
Arthralgia				
Fatigue				
Nausea				
Lipase increased				
Pyrexia				
Myalgia				
Pain in extremity				
Back pain				
Diarrhoea				
Neutropenia				
Anaemia				
ALT increased				
Vomiting				
Asthenia				
Dyspnoea				
Cough				
Oedema peripheral				
Dizziness				
AST increased				
Muscle spams				
Bone pain				
Upper respiratory tract infection				
Decreased appetite				
Pruritus				
Nasopharyngitis				
Urinary tract infection				
Insomnia				
Musculoskeletal pain				
Erythema				
Weighted decreased				
Pain				
Dry mouth				
TEAEs (Grade +3) in ≥5% of patients[b]				
Any TEAE				
Thrombocytopenia				
Neutropenia				

	All lines	3L	4L	5L
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; TRAE, treatment-related adverse event; TEAE, treatment-emergent adverse event; 3L, third-line; 4L, fourth-line; 5L-fifth-line

a [redacted] b [redacted]

A summary of the treatment-emergent AEs for CP-CML patients from the PACE study (safety population and ≥third-line) at the 4 year follow-up[38] are presented in Table 25. In CP-CML patients, similar rates of AEs were observed in the total population to those in the target (third-line) population at the 4 year follow-up.

Table 25: Number (%) of CP-CML patients discontinuing treatment in the PACE study 4-year follow-up to 3 August 2015: All lines (Data derived from Hochhaus *et al.*[38])

	All CP-CML patients n=270		CP-CML patients who had received: 1 prior TKI n=19		CP-CML patients who had received: 2 prior TKIs n=97		CP-CML patients who had received: 3 prior TKIs n=142		CP-CML patients who had received: 4 prior TKIs n=12	
	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Any Grade n (%)	Grade 3/4 n (%)
At least 1 treatment-emergent AE	270 (100%)	236 (87%)	19 (100%)	15 (79%)	97 (100%)	83 (86%)	142 (100%)	126 (89%)	12 (100%)	12 (100%)
Non-haematologic										
Rash[a]	126 (47%)	10 (4%)	10 (53%)	0 (0%)	42 (43%)	4 (4%)	70 (49%)	5 (4%)	4 (33%)	1 (8%)
Abdominal pain	124 (46%)	27 (10%)	7 (37%)	2 (11%)	47 (48%)	14 (14%)	65 (46%)	10 (7%)	5 (42%)	1 (8%)
Headache	115 (43%)	9 (3%)	8 (42%)	0 (0%)	46 (47%)	3 (3%)	59 (42%)	6 (4%)	2 (17%)	0 (0%)
Dry skin	112 (41%)	9 (3%)	8 (42%)	0 (0%)	37 (38%)	1 (1%)	61 (43%)	7 (5%)	6 (50%)	1 (8%)
Constipation	111 (41%)	7 (3%)	9 (47%)	2 (11%)	45 (46%)	1 (1%)	53 (37%)	4 (3%)	4 (33%)	0 (0%)
Hypertension[b]	92 (34%)	34 (13%)	8 (42%)	2 (11%)	29 (30%)	12 (12%)	54 (38%)	19 (13%)	1 (8%)	1 (8%)
Arthralgia	87 (32%)	8 (3%)	2 (11%)	0 (0%)	32 (33%)	4 (4%)	50 (35%)	3 (2%)	3 (25%)	1 (8%)
Fatigue	80 (30%)	6 (2%)	3 (16%)	0 (0%)	31 (32%)	3 (3%)	44 (31%)	3 (2%)	2 (17%)	0 (0%)
Nausea	75 (28%)	2 (<1%)	4 (21%)	0 (0%)	30 (31%)	1 (1%)	37 (26%)	0 (0%)	4 (33%)	1 (8%)
Increased lipase	72 (27%)	33 (12%)	3 (16%)	1 (5%)	26 (27%)	10 (10%)	38 (27%)	20 (14%)	5 (42%)	2 (17%)
Pyrexia	69 (26%)	3 (1%)	3 (16%)	0 (0%)	22 (23%)	1 (1%)	42 (30%)	2 (1%)	2 (17%)	0 (0%)
Myalgia	65 (24%)	3 (1%)	4 (21%)	0 (0%)	26 (27%)	2 (2%)	32 (23%)	1 (<1%)	3 (25%)	0 (0%)
Pain in extremity	63 (23%)	9 (3%)	2 (11%)	1 (5%)	20 (21%)	3 (3%)	39 (27%)	5 (4%)	2 (17%)	0 (0%)
Back pain	56 (21%)	3 (1%)	2 (11%)	0 (0%)	24 (25%)	1 (1%)	28 (20%)	1 (<1%)	2 (17%)	1 (8%)
Haematologic										
Thrombocytopenia	122 (45%)	95 (35%)	9 (47%)	6 (32%)	40 (41%)	34 (35%)	68 (48%)	50 (35%)	5 (42%)	5 (42%)

[a] Combines the terms erythematous, macular, and papular rash

[b] 241/270 (89%) patients had elevated blood pressure at baseline (148/270 [55%] had ≥140 mm Hg systolic or ≥90 mm Hg diastolic); 187/270 (69%) patients experienced any increase from baseline in blood pressure on study

CP-CML, chronic phase chronic myeloid leukaemia; TKI, Tyrosine kinase inhibitor

4.2.4.2.5. Treatment-related vascular occlusive events

The CS reports that, following a review of updated clinical trial data on ponatinib revealing an accumulation of treatment-emergent VOEs, the EMA issued a set of recommendations regarding the use of ponatinib in November 2013. The EMA recommended that the cardiovascular status of patients be assessed and that cardiovascular risk factors be actively managed prior to, and monitored during, treatment.[57]

In response to a request for clarification from the ERG (see clarification response,[28] question A18), the company provided details on the treatment-emergent arterial occlusive AEs in ≥1% of patients for CP-, AP- and BP-CML (PACE data cut-off, 3 August 2015). A summary of these data, adapted by the ERG, is presented in Table 26.

[redacted]

Table 26: Treatment-emergent arterial occlusive AEs in ≥1% of patients for CP-, AP- and BP-CML in the PACE study (data cut-off, 3 August 2015)

	CP-CML N=270 n (%)[a]			AP-CML N=85 n (%)[b]			BP-CML N=62 n (%)[c]		
	Grade			Grade			Grade		
	Any	3/4	5	Any	3/4	5	Any	3/4	5
Any arterial occlusive AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral arterial occlusive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction/myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermittent claudication	[redacted]	[redacted]	[redacted]						
Cerebrovascular accident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Peripheral artery stenosis	[redacted]	[redacted]	[redacted]						
Cerebral infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Carotid artery stenosis	[redacted]	[redacted]	[redacted]						
Transient ischaemic attack	[redacted]	[redacted]	[redacted]						
Peripheral ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Acute coronary syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

	CP-CML N=270 n (%)[a]			AP-CML N=85 n (%)[b]			BP-CML N=62 n (%)[c]		
	Grade			Grade			Grade		
	Any	3/4	5	Any	3/4	5	Any	3/4	5
Coronary artery occlusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Extremity necrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Aphasia				[redacted]	[redacted]	[redacted]			
Cerebral ischaemia				[redacted]	[redacted]	[redacted]			
Ischaemic cardiomyopathy				[redacted]	[redacted]	[redacted]			
Stress cardiomyopathy				[redacted]	[redacted]	[redacted]			
Subclavian artery stenosis				[redacted]	[redacted]	[redacted]			
Vertebral artery stenosis				[redacted]	[redacted]	[redacted]			
Embolism arterial							[redacted]	[redacted]	[redacted]
Renal artery stenosis							[redacted]	[redacted]	[redacted]
Splenic infarction							[redacted]	[redacted]	[redacted]

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia

[redacted]

4.2.4.2.6. Serious vascular occlusive events

[redacted]

4.2.5 Supplementary evidence

The CS includes supplementary evidence from a Phase I study of ponatinib[35] and from an observational study of ponatinib.[58] Further details are provided in this section.

4.2.5.1 Cortes et al.[35] (Phase I study)

The CS reports that the Phase I ponatinib study was a dose-ranging study. The study population included 81 patients of whom 60 had CP-, AP- or BP-CML (Table 4-10). In response to a request for clarification by the ERG (see clarification response,[28] question A11), the company reported that other populations comprised: Ph+ ALL, acute myeloid leukaemia, myelodysplastic syndrome, multiple myeloma, and myelofibrosis. The CS reported that the median duration of follow-up was 73 weeks (range 7 to 140 weeks) for CP-CML and 13 weeks (range 2 to 121 weeks) for AP-CML, BP-CML and Ph+ ALL combined (Table 4-13).

The CS did not report reasons for withdrawal for CP, AP, or BP-CML. However, these data were reported by Cortes *et al*.[35] and are presented in Table 27.

Table 27: Reasons for treatment discontinuation in the Phase I ponatinib study for CP-, AP-, and BP-CML[35]

	CP CML (N = 43), n (%)	AP- CML (N = 9), n (%)	BP-CML (N = 8), n (%)
Total discontinued treatment	10 (23%)	7 (78%)	8 (100%)
Documented progressive disease	3 (7%)	1 (11%)	5 (62%)
Adverse event	5 (12%)	3 (33%)	0 (0%)
Death[a]	0 (0%)	1 (11%)	1 (12%)
Withdrawal of consent	1 (2%)	1 (11%)	0 (0%)
Administrative decision	1 (2%)	1 (11%)	2 (25%)

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia

[a] All deaths were deemed to be unrelated to ponatinib by the investigators.

A summary of best response rates from the Phase I study as reported within the CS (Table 4-13) and adapted by the ERG is presented in Table 28. The CS reported that median MCyR and MMR duration was not reached for the CP-CML population (MCyR range 8 to 117+ weeks and MMR range 12 to 105+ weeks) and that median MaHR duration in the AP-CML/BP-CML/Ph+ ALL population was 16 weeks (range 0.1 to 64 weeks) (Table 4-13).

Table 28: Best response rates from the Phase I ponatinib study (data derived from the CS Table 4-13)

	CP-CML		**AP- and BP-CML and Ph+ ALL**
Setting	3L setting n/N (%)	4L setting n/N (%)	≥3L setting n/N (%)
CHR	7/7 (100%)	8/9 (89%)	-
MaHR	-	-	8/20 (40%)
MCyR	16/18 (89%)	11/20 (55%)	5/19 (26%)
CCyR	14/18 (78%)	10/20 (50%)	3/19 (16%)
MMR	13/19 (68%)	5/21 (24%)	2/22 (9%)

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CCyR, complete cytogenetic response; CHR, complete haematologic response; CP-CML, chronic phase chronic myeloid leukaemia; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia;

The CS reports that across all populations in the Phase I ponatinib study (n=81), the most common treatment-related ≥Grade 3 AEs were: increased lipase, 6/81 (7%); pancreatitis, 4/81 (5%); increased amylase, 2/81 (2%); prolonged QT interval, 2/81 (2%); thrombocytopenia, 16/81 (20%); neutropenia, 8/81 (10%), and; anaemia, 2/81 (2%) (Table 4-17). Adverse events by population were not reported by the CS and were not reported by Cortes *et al.*[35]

4.2.5.2 Garcia-Gutierrez et al.[58] *(real-world observational data)*

The CS also reports a validation of PACE against real-world observational data (p98). The CS reports a comparison with the Spanish Compassionate Use Program (Garcia-Gutierrez *et al*.[58]). The CS summarises that this study reported on ponatinib treatment among 22 CP-CML patients and one AP-CML patient, who were heavily pre-treated at baseline (37% having received two prior TKIs and 62% having received ≥3 prior TKIs). The median age of diagnosis was 56 years. Overall, 58% of patients achieved a CCyR after a median follow-up of 29 months (range 3–53) and PFS at 3.5 years was 80%. The rates of treatment discontinuation were 25% due to AEs and 25% due to lack of efficacy, while 37% of patients proceeded to allo-SCT and 13% of patients died (CS, p98). The CS observes that, as in the PACE study no differences in response rates were observed between patients with or without

mutations (p98). The CS concludes that, ponatinib use in the real-world appears to be associated with manageable AEs and that the most common non-haematologic AEs were liver toxicity (20%), lipase increase (10%), and hypertension (15%) and no patients on ponatinib had a cardiovascular event (p98).

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of any head-to-head studies comparing ponatinib with other relevant comparators for the treatment of CP-CML, AP-CML or BP-CML, the company undertook an MAIC. The CS reports that the objective of the MAIC was to:

> *'... adjust the main effectiveness outcomes of ponatinib (as included in the cost-effectiveness model) with the baseline characteristics of relevant comparator studies according to the NICE scope (specifically, bosutinib).'(*p46)

The CS (p48) reports that for ponatinib, individual patient data (IPD) from patients in the PACE study who had received 2 prior TKIs (n=97) were used to inform the MAIC[59] The MAIC adjusted responses to ponatinib in the PACE study as if ponatinib had been included in the Phase I/II study that evaluated bosutinib rather than adjusting responses to bosutinib as if it had been included in the PACE study.

4.3.1 Outcomes for the MAIC

The main effectiveness outcome measures that were adjusted for difference in prognostic factors between the PACE study and the Phase I/II bosutinib study in CP-CML were cytogenetic best response rates, haematologic best response rates and DoR. OS, event-free survival and transformation-free survival were not adjusted for differences in prognostic factors between the PACE study and the Phase I/II bosutinib study. In addition, no MAIC was reported in the CS for AP-CML, BP-CML or AEs.

4.3.2 Methods for the MAIC

The methods for the MAIC as detailed in Appendix 18 of the CS are critiqued in Section 4.4

4.3.3 Evidence used in the MAIC

Evidence to inform the MAIC was identified through the company's broad systematic literature review. The inclusion and exclusion criteria in the company's systematic review are reported in Section 4.1.2. In brief, the population of interest for the systematic review was adults aged ≥18 years with CML or Ph+ ALL resistant or intolerant to prior treatments who had received at least one prior treatment for their disease.

The CS reports that the second-generation TKIs dasatinib and nilotinib were not included in the MAIC in accordance with the final NICE scope, in which the only TKI comparator was bosutinib.[20] The CS reports that no studies for BSC were identified in the systematic review and that, although allo-SCT studies were identified in the setting of post–second-generation TKIs, they were not included in the MAIC. The CS provides the rationale that although allo-SCT is considered a relevant comparator, the MAIC was undertaken using response categories (CCyR, partial cytogenetic response [PCyR], [CHR, non-responder [NR]), which are not directly applicable in the context of transplantation (p47).

Although several studies were identified by the systematic review within the CS, only two studies were included in the MAIC. These were the PACE Phase II study that evaluated ponatinib in patients with CP-, BP- and AP-CML and patients with Ph+ ALL, resistant to or intolerant of resistance dasatinib or nilotinib[22] and the study by Khoury *et al*.,[42] a Phase I/II study that evaluated bosutinib in CP-CML patients who had been pre-treated with imatinib followed by dasatinib.

A summary of the study design, and inclusion and exclusion criteria for participants for both studies reported in Appendix 6 Table 6-1 of the CS and adapted by the ERG is presented in Table 29.

Table 29: Study characteristics of the PACE study and the Phase I/II bosutinib study included in the CP-CML MAIC (data derived from the CS Appendix 6 Table 6-1)

Bosutinib **Khoury *et al.*** **(Phase I/II study)[42]**	**Ponatinib** **PACE Cortes *et al.*** **(Phase II)[22]**
Design	
Bosutinib	**Ponatinib**
Non-RCT, single-arm, Phase 1/2, open-label	Non-RCT, single-arm, Phase 2, open-label
Inclusion criteria	
Bosutinib	**Ponatinib**
Adults (≥18 years) with Ph+ CP-CML with prior treatment with imatinib followed by dasatinib and/or nilotinib	Adults (≥18 years) with CP-, AP-, or BP-CML or Ph+ ALL who were resistant to or intolerant of dasatinib or nilotinib or who had developed the T315I mutation after any TKI therapy
ECOG PS 0-1	ECOG PS ≤2
Adequate bone marrow, hepatic, and renal function	Adequate renal and hepatic function
Not pregnant or breastfeeding	Not pregnancy or lactation For females of childbearing potential, a negative pregnancy test prior to enrolment Female and male patients of childbearing potential must agree to use an effective form of contraception with sexual partners throughout participation in study
	Minimum life expectancy of ≥3 months
	Normal pancreatic status No history of pancreatitis
	Normal QTcF interval on screening ECG evaluation
	Ability to comply with study procedures
Exclusion criteria	
Bosutinib	**Ponatinib**
Antiproliferative or antileukaemia treatment within 7 days of bosutinib initiation (except hydroxyurea or anagrelide)	Receipt of TKI therapy within 7 days prior to receiving first dose of ponatinib or lack of recovery from AEs (except alopecia) due to agents previously administered. Previous treatment with ponatinib
GVHD (for part 1, no prior GVHD allowed; for part 2, no treated or untreated GVHD within 60 days of study initiation)	Evidence of ongoing GVHD or GVHD requiring immunosuppressive therapy
Allo-SCT within 3 months	Auto- or allo-SCT <60 days prior to receiving first dose of ponatinib
Documented history of T315I *BCR-ABL* mutation[a]	
Ph– and *BCR-ABL*−negative CML	
Overt leptomeningeal leukaemia (free of CNS involvement for <2	

months)	
Extramedullary disease only	
Prior history of imatinib intolerance or exposure to sarcoma, Abelson, or sarcoma/Abelson kinase inhibitors (part 1 only)	
	Receipt of certain other therapies[b]
	Taking medications known to be associated with Torsades de Pointes
	Requirement for concurrent immunosuppressive agents, other than short-course corticosteroids
	In CCyR (CP-CML patients) or MaHR (AP-/BP-CML or Ph+ ALL patients) Active CNS disease Significant or active CVD Significant bleeding disorder unrelated to CML or Ph+ ALL History of pancreatitis or alcohol abuse Uncontrolled hypertriglyceridemia Malabsorption syndrome or other GI illness that could affect absorption of orally administered ponatinib
	Diagnosed with another primary malignancy within the past 3 years (except NSCLC, cervical cancer in situ, controlled prostate cancer)
	Major surgery within 14 days prior to first dose of ponatinib
	Ongoing or active infection
	Any condition or illness that, in the opinion of the investigator or the medical monitor, would compromise patient safety or interfere with evaluation of the safety of the study drug
Dosing	
Bosutinib	**Ponatinib**
500mg per day orally	45mg per day orally
Included participants	
Bosutinib	**Ponatinib**
All patients	Total patients assigned to a cohort (efficacy); all patients who received ≥1 dose of ponatinib (safety)

Abl, Abelson; AEs, adverse events; allo-SCT, allogeneic stem cell transplantation; AP-CML, accelerated phase chronic myeloid leukaemia; BCR-ABL, breakpoint cluster region-Abelson; BP-CML, blast phase chronic myeloid leukaemia; CCyR, complete cytogenetic response; CNS, central nervous system; CP-CML, chronic phase chronic myeloid leukaemia; CVD, cardiovascular disease; ECG, Electrocardiogram; ECOG PS, Eastern Co-operative Oncology Group performance status; GI, gastrointestinal; GVHD, Graft-versus-host disease; IPD, individual patient data; MaHR, major haematologic response; NA, not applicable; Non-RCT, non-randomised controlled trial; NSCLC, non–small-cell lung cancer; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; QD, once daily; QTcF, QT corrected (Fridericia); R/I, resistant or intolerant; RCT, randomised controlled trial; Src, sarcoma; T315I, Threonine-315-Isoleucine

[a] n=7 patients with T315I mutation were included in the bosutinib study by Khoury *et al*.[42]

[b] Patients were excluded if they had received hydroxyurea or anagrelide ≤24 hours prior to receiving the first dose of ponatinib; interferon, cytarabine, or immunotherapy within 14 days, or any other cytotoxic chemotherapy; radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib. Additionally, patients with BP-CML were excluded if they had received chemotherapy within 14 days prior to the first dose of ponatinib, and patients with Ph+ ALL were excluded if that had received prior to the first dose of ponatinib corticosteroids within 24 hours, or vincristine within 7 days , or other chemotherapy within 14 days. All patients are excluded if they had not recovered from greater than Grade 1 AEs (except alopecia) due to agents previously administered

Both studies were single-arm (non-comparator) open-label intervention studies. Notable differences were: that the PACE study[22] was Phase II only whereas the Bosutinib study by Khoury *et al*.[42] was a Phase I/II study, and that the PACE study[22] included CP-CML, AP-CML, BP-CML and Ph+ ALL patients whereas the bosutinib study by Khoury *et al*.[42] only included CP-CML patients.

The MAIC was undertaken using baseline characteristics and effectiveness data from the CP-CML subgroup from the PACE study[22] (n=97) to predict responses as if ponatinib had been included in the bosutinib study by Khoury *et al*.[42] (n=118). According to the CS (p48) no MAICs were undertaken for AP-CML or BP-CML because of a lack of comprehensive data in the third-line setting.

The CS reports that the PACE study data used in the MAIC analysis were IPD for CP-CML patients who had received 2 prior TKIs (n=97) to 3 August 2015 (CS, p49).[59] The CS reports that the data from the study by Khoury *et al*.[42] used in the MAIC analysis included all Phase I and Phase II patients (n=118), who had failed imatinib as well as either dasatinib or nilotinib (n=114), and patients who had failed imatinib, dasatinib, and nilotinib (n=4) (p49). Baseline characteristics for the MAIC were: T315I mutation status; sex; median age; race; duration of CML; and ECOG performance status. The CS (p49) reports that medians were interpreted in the MAIC as binary characteristics.

The CS reports that formal appraisal of the validity of the studies included in the MAIC was undertaken using the quality assessment criteria reported by Chambers *et al*.,[34] for non-randomised studies. The ERG considers the company's justification for using this assessment method to be acceptable (see clarification response,[28] question A8). However, limitations of the method were not reported in the CS. As reported in section 4.1.4, the ERG notes that the use of summary scores to distinguish overall high and low quality studies is not recommended. The completed assessment tool[34] for the studies included in the MAIC is presented in

Table **30**.

Based on this quality assessment, the ERG considers that both studies that were included in the MAIC[22, 42] to be well-reported single-arm studies. However, consideration of specific points relating to single-arm study designs is required, as follows.

Single-arm studies are associated with potential biases.[47] There is a high risk of selection bias due to the absence of randomisation, and a risk of performance and detection bias due to the absence of blinding.[30, 32] As acknowledged in the CS (p66), a lack of a comparator group limits the ability of a single-arm study to compare or demonstrate effectiveness compared with other treatments. In addition, blinded outcome assessment was not undertaken in PACE study (see clarification response,[28] question A9). This would have helped minimise bias,[48] particularly for subjective outcomes. Blinded outcome assessment was not reported by the study by Khoury *et al*.[42]

Although eligibility criteria for both studies included in the MAIC were reported in the original publications,[22, 42] details on how patients were recruited into either study were not. Appropriate measures of variability were used, with confidence intervals reported around point estimates to indicate variability for relevant outcomes for both studies. Loss to follow-up and reasons for leaving the study early were reported, and more than 90% of patients included at baseline were followed up (for the PACE study, see clarification response,[28] question A14). Consecutive recruitment of patients was not reported for the PACE study.[22] The study by Khoury *et al*.[42] also did not report on consecutive recruitment. However, the quality assessment included in the ERG report for bosutinib reported that participants were recruited consecutively (p58).[60] The ERG report for bosutinib reported that this was derived from the bosutinib CS. Clinical advisors to the ERG noted that in terms of age and gender, patients enrolled into the PACE study appeared to be representative of the CP-CML population. However, the MAIC adjusts responses to ponatinib in the PACE study as if ponatinib had been included in the Phase I/II study that evaluated bosutinib rather than adjusting responses to bosutinib as if it had been included in the PACE study.

On the whole, both studies in the MAIC were considered by the ERG to be well reported and conducted single-arm intervention studies.

Table 30: Quality assessment results of studies included in the MAIC (adapted from CS, Appendix 8)

Criteria used for quality assessment	Cortes *et al.*[22]		Khoury *et al.*[42]	
	Company's assessment	ERG's assessment	Company's assessment	ERG's assessment
1. Were selection/ eligibility criteria adequately reported	Yes	Yes	Yes	Yes
2. Was the selected population representative of that seen in normal practice?	Yes	Yes	Yes	Yes
3. Was an appropriate measure of variability reported?	Yes	Yes	Yes	Yes
4. Was loss to follow-up reported or explained?	Yes	Yes	Yes	Yes
5. Were at least 90% of those included at baseline followed up?	Yes	Yes	Yes	Yes
6. Were patients recruited prospectively?	Yes	Yes	Yes	Yes
7. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Yes[a]
8. Did the study report relevant prognostic factors?	Yes	Yes	Yes	Yes

[a] Information not reported in Khoury *et al.*[42] Data obtained from bosutinib ERG report (p58)[60]

4.3.4 Baseline parameters for the MAIC

Baseline parameters for the MAIC (see clarification response,[28] question A12, Table 4-3), adapted by the ERG, are presented in Table 31.

Table 31: Baseline parameters used in the MAIC for CP-CML (data derived from response to clarification question A12, Table 4-3)[28]

Baseline parameter	Bosutinib Khoury *et al.*[42] (Phase I/II study) N=118	Ponatinib PACE Cortes *et al.*[22] (Phase II) N=97[a]	Ponatinib Matching-adjusted N=69[b]
Median age, n/N (%) >56.0 years	59/118 (50.0)	52/97 (53.6)	– (50.0)
Sex, male, n/N (%)	53/118 (44.9)	52/97 (51.5)	– (44.9)
T315I mutation at study entry, n/N (%)	7/118 (5.9)	30/97 (30.9)	– (5.9)
Race, white, n/N (%)	85/118 (72.0)	77/97 (79.4)	– (72.0)
Median duration of CML, n/N (%) >6.7 years	59/118 (50.0)	41/97 (42.3)	– (50.0)
ECOG PS with 1, n/N (%)	31/117 (26.5)	29/97 (29.9)	– (26.5)

CML, Chronic myeloid leukaemia; ECOG PS, Eastern Co-operative Oncology Group performance status
[a] Patients in the PACE trial who had received 2 prior TKIs (n=97) were used to inform the MAIC
[b] Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights

4.3.5 Results from the MAIC

Strictly, inferences about the relative effect of ponatinib are as if it was evaluated against bosutinib in a population of patients represented by those in the Phase I/II bosutinib study. The CS (p6) states that results from the MAIC indicate that ponatinib provides considerably higher CCyR rates than bosutinib in the third-line (61% vs 24%). The CS (p6) reports that the adjusted ponatinib response rates were used to inform the CP-CML economic analysis.

A summary of the MAIC results reported in Table 4-4 of the CS (see clarification response,[28] question A12) and adapted by the ERG is presented in

Table 32.

Table 32: Best response rates before and after matching with bosutinib in the MAIC (data derived from the CS Table 4-4 and response to clarification question A12)[28]

Best response	Bosutinib Khoury *et al.* [42] (Phase I/II study) N=118	Ponatinib PACE Cortes *et al.*[22] (Phase II) N=97[a]	Ponatinib Matching-adjusted N=69[b]
CCyR, n/N (%)	26/108 (24.07%)	63/97 (64.95%)	61.34%
PCyR, n/N (%)	9/108 (8.33%)	6/97 (6.19%)	8.46%
CHR, n/N (%)	44/116 (37.93%)	17/97 (17.53%)	18.19%
No response, n/N (%)	(29.66%)[c]	11/97 (11.34%)	12.01%

CCyR, complete cytogenetic response; CHR, complete haematologic response; PCyR, partial cytogenetic response
[a] Patients in the PACE trial who had received 2 prior TKIs (n=97) were used to inform the MAIC
[b] Effective sample size was computed as the square of the summed weights divided by the sum of the squared weights
[c] For bosutinib, there is no n/N for the 'no response' rate because the value was calculated as 1 minus the other response rates (see clarification response,[28] question A12)

The CS (p48) reports that an MAIC evaluating effectiveness was not undertaken for AP- or BP-CML because of a lack of comprehensive data in the third-line setting. A MAIC for AE is not reported within the CS.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company's systematic literature review found that there were no RCTs comparing ponatinib with any of the treatments in the comparator decision set for the treatment of CML in the post-second-generation TKI setting in patients resistant/intolerant to prior therapy. Consequently, a conventional network meta-analysis (NMA) allowing a synthesis of evidence and simultaneous comparison of treatments based on within-study estimates of treatments effect was not possible. Furthermore, the

studies that were identified in the systematic literature review were all single-arm studies, which do not provide estimates of within-study treatment effects. A within-study estimate of treatment effect provides an unbiased estimate based on a randomised comparison that ensures that, on average, treatment groups will be balanced for known and unknown confounders. In the absence of within-study estimates of treatment effect it was necessary to use an alternative approach to make indirect comparisons.

The company used an MAIC in patients with CP-CML to facilitate an indirect comparison between treatments to inform the economic model (Signorovitch *et al*.,[61]). The objective of an MAIC is to adjust outcomes to account for imbalances between treatments in (observed) prognostic factors in different studies. Briefly, the method makes use of IPD from a study of one of the treatments in the comparator decision set (referred to as the index study) and weights the outcome for each patient using an approach similar to propensity score weighting so that their average baseline characteristics match those of the comparator treatment. MAIC generates adjusted responses that would be expected if the treatment in the index study had been administered to patients in the comparator study. MAIC was originally developed in the context of RCTs with a common comparator but where there was an imbalance in treatment effect modifiers that would generate biased indirect estimates of treatment effect; however, the method has been advocated in situations when there is no common comparator (Signorovitch *et al*.,[61]). There are several limitations with the method and also with regard to the relevance of it as applied in the CS.

The CS states that, '*the subjects in the PACE study represent patients for whom treatment is indicated, parallel the population described in the NICE scope, and represent the population who will be treated in clinical practice in England. The median age of patients enrolled in the PACE trial was the same as the median age of disease onset for CML in the UK, 59 years'*. Given that the PACE study is said to represent the population of patients who will be treated in clinical practice in England, it is unclear what the relevance is of adjusting responses to a population of patients represented by the sample of patients included in the Khoury *et al*.[62] In clarification question A21,[28] the company was asked to comment on the relevance to the NICE decision problem of matching the sample of patients in the PACE study to the sample of patients in the Khoury *et al.*[62] however, the company only reiterated the need to acount for differences in prognostic factors. In addition, it is unclear what the company considers to be the to be the median age of disease onset for CML in the England given that they suggest it is 59 years based on the PACE study and 50 years based on the matching adjustment.

In general, in single-arm studies, it is not possible to account for an imbalance in unmeasured prognostic factors using sample data alone; thus, indirect estimates of treatment effect may be biased as a consequence of unmeasured confounders. In response to clarification question A21,[28] the company reiterated that, in an attempt to account for unmeasured confounding on the effectiveness of ponatinib, an arbitrary 25% reduction in the number of ponatinib patients achieving a best response of CCyR was applied in a cost-effectiveness scenario analysis. In fact, this was a 25% reduction in the number of ponatinib patients achieving a best response of CCyR and corresponding increase in the number of patients with PCyR rather than a 25% reduction in the effectiveness of ponatinib across response categories which could have been applied to the treatment effect estimated using an ordered categorical data model.

In response to clarification question B26,[28] the company stated that '*response to ponatinib is independent of T315I mutation status, whereas T315I-positive patients are not expected to respond to bosutinib.'* Nevertheless, an adjustment was made for an imbalance in the percentage of patients with the T315I mutation at baseline in each study in spite of the fact that patients with the T315I mutation would be offered ponatinib at the outset. The ERG believes that a fairer comparison that acknowledges the treatment pathway would have been to remove the patients with the T315I mutation from the bosutinib arm.

A further complication arises when there are multiple comparators each providing only summary data because the patient population changes with each comparison depending on the characteristics of the patients in each comparator study; inferences will be conditional on the patient population.

In response to clarification question A23,[28] the company stated that adjustments for differences in patient characteristics was not accounted for when analysing AP-CML, BP-CML and AEs because of the limited data available in AP-CML and BP-CML patients and because the impact of the matching adjustment on AEs would have been negligible owing to the cost of AEs compared with the total cost of treatment being small. AP-CML and BP CML response rates used in the economic model were taken from the cohort of patients in the PACE study. This is an example of an arm-based analysis that ignores the potential impact of any differences in the patient population defined by the sample of patients in the PACE study and the characteristics of the patients in the target patient population. The limited availability of data should be reflected in imprecise estimates of response used in the economic model.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As the company undertook a reasonably comprehensive systematic review (no major limitations were noted) of ponatinib for treating CML, no additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence for ponatinib CML (CP, AP or BP) in the CS is based on a systematic review of the safety and efficacy of current treatments for adult CP-CML, AP-CML or BP-CML patients being treated in the second-line or later. The ERG is confident that all relevant studies (published and unpublished) of ponatinib were included in the CS, including data from ongoing studies. Although the ERG is confident that no other published studies evaluating ponatinib in this population are likely to have been missed, the CS did not report if any attempt was made by the company to contact authors of the included studies to request potential additional unpublished data and it is therefore not entirely clear if all relevant data have been included. However, overall the ERG considers the systematic review reported in the CS to be of an acceptable standard.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

A key limitation of the efficacy and safety data for ponatinib reported in the CS relates to study design. The PACE study was a single-arm intervention study without an internal control group with which to estimate a treatment effect[22] and single-arm studies are associated with several biases.[47] Furthermore, the application of the MAIC means that inferences about the relative effect of ponatinib compared to bosutinib apply to a population of patients characterised by the sample of patients in the bosutinib study.

A further limitation to the robustness of the efficacy and safety data for ponatinib reported in the CS relates to the availability of data for the CML populations (CP-, AP-, or BP-CML). Although the CS reported power calculations for participants for each of the CML populations and that these participant numbers were met (p67), these groups comprised all lines of ponatinib therapy, and the majority of participant numbers by line of therapy did not meet the CS reported power calculation. As such, the PACE[22] study was not powered by line of therapy for the CML populations.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The key uncertainties in the clinical evidence for ponatinib relate to the impact of potential unobserved confounders on the estimate of treatment effect, optimal dosing and duration of treatment. Further details are provided below.

4.6.3.1 Optimal dosing

In the PACE study,[22] patients received an initial dose of 45mg of ponatinib orally once daily. The company provide details on dose adjustments to August 2015 in the PACE study made in October 2013 following recommendations on dose reduction by the FDA. Thereafter, a number of dose adjustments were made to participants in the PACE study during treatment rather than *a priori*. As such, it remains unclear if the adjusted lower dosing regimens would have been clinically effective over the entire PACE study period.

4.6.3.2 Treatment duration

In terms of the PACE study starting dose, CP-CML, AP-CML and BP-CML patients were only able to maintain 45mg per day for 50%, 60% and 71% respectively, of the entire treatment duration (to 27 April 2012).[25] In response to a request for clarification from the ERG (see clarification response,[28] question A16), the company provided details on dose adjustments to August 2015 in the PACE study. The company also reported that no data were available on the alternative treatments given to patients who stopped study treatment in the PACE study (see clarification response,[28] question A8). Clinical advisors to the ERG commented that in practice in the UK, stopping treatment is dependent on patient choice, but clinicians would discourage people if not in complete remission. The SmPC posology recommends considering discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days).[14] The PACE study reported outcomes over a median follow-up of 48.2 months (4 years).[38] As a result, the longer term safety and efficacy of ponatinib is currently unknown.

4.6.3.3 Generalisability to the population of England

The PACE study was a large, well designed, single-arm non-comparator intervention study.[22] Across the CML populations in the study, the median age was 60 years for CP- and AP- CML and 53 years for BP-CML,[22] [redacted]. In the UK, the median age at diagnosis of CML is 59 years.[6] Clinical advisors to the ERG considered the PACE study population to be reflective of the CML population in England. Clinical advisors to the ERG also commented that most UK clinicians would try another second-line drug if patients encountered a rash (or other intolerance) on a second-generation TKI, but in the instance of treatment failure would switch to ponatinib at third-line. As such the ERG considers the population in the PACE study to be representative of CML patients in England. However, the treatment effect is estimated as if ponatinib had been included in the Phase I/II study that evaluated bosutinib rather than adjusting responses to bosutinib as if it had been included in the PACE study.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the cost-effectiveness evidence presented by the company.

5.1 ERG's summary and critique of the company's review of cost-effectiveness evidence

This section focusses on previous estimates of cost-effectiveness studies involving ponatinib in CML. Further searches identifying HRQoL are detailed in Section 5.2.7.

5.1.1 Objective of cost effectiveness review

The company stated that the objective of the review of CML cost-effectiveness studies was to identify relevant evidence published from January 2000 – January 2016. The search was updated in July 2016. The following sources were searched: EMBASE and EMBASE Economic conference abstracts (via Ovid); MEDLINE (via Ovid); MEDLINE In-Process & Other Non-Indexed Citations (via Ovid); Cochrane Central Register of Controlled Trials (via EBM Reviews); and Health Technology Assessment (via EMB Reviews). The company's search strategies comprised the terms for the population concept (CML) combined with a sensitive search filter for retrieving cost-effectiveness studies. The ERG considered that the searches were comprehensive and adequate for the cost-effectiveness review.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria used in the literature review is detailed in Table 5-1 of the CS. The ERG considered it to be satisfactory. Key components included: limiting the population to those with CML aged 18 years or over; excluding costs that were not related to the UK; and excluding at the screening stage, papers published in languages other than English.

5.1.3 Findings of the cost effectiveness review

The company reported that 17 studies were identified in the review: seven were full texts identified by the search strategy; seven were conference abstracts identified by the search strategy; and three were not identified by the search strategy but were added manually. None of these studies considered ponatinib as an intervention.

5.1.4 Conclusions of the cost effectiveness review

As none of the identified studies were relevant to the decision problem the company concluded that *de novo* models were required.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE Reference Case checklist

The extent to which the analyses of CML presented within the CS correspond to the final NICE scope CML is detailed in Table 33.

Table 33: Comparability between the analyses within the CS and the final scope issued by NICE (CML only)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final NICE scope	ERG comment
Population	Adults with CP-CML, AP-CML, or BP-CML, whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.	As per the final scope	N/A	N/A
Intervention	Ponatinib	As per the final scope	N/A	N/A
Comparator (s)	• Bosutinib • Allo-SCT; with or without chemotherapy • Interferon alfa • BSC (including but not limited to hydroxycarbamide)	• Bosutinib (all phases) • Allo-SCT (all phases) • Interferon alfa (CP-CML) • Hydroxycarbamide as BSC (all phases)	The company stated that interferon alfa was not used as a comparator in AP-CML or BP-CML as it is rarely used to treat CML in the UK and that there was no evidence of effectiveness in AP-CML or BP-CML.	Based on clinical advice the ERG believes that the exclusion of interferon alfa in AP-CML and BP-CML is appropriate. Only hydroxycarbamide was used to represent BSC: clinical advice received by the ERG suggested that this was appropriate.
Outcomes	• OS • PFS/ event-free survival • Response rates • Time to response • DoR • Adverse effects (AEs) of treatment	As per final scope, except that PFS and DoR are applied only to the CP-CML model	DoR is not considered in the AP-CML or BP-CML model as patients who respond to treatment transition to allo-SCT in the first cycle.	Based on clinical advice, the ERG believes that the exclusion of DoR within the AP-CML and the BP-CML model is appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final NICE scope	ERG comment
	• Health-related quality of life (HRQoL)			
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 (QALY) • time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective.	As per the final scope	N/A	The CS did not provide full incremental analyses but instead provided pairwise comparisons of each intervention with ponatinib. Whilst a fully incremental analysis can be calculated from the pairwise analyses for the deterministic results, the accuracy cannot be guaranteed for the probabilistic results due to Monte-Carlo sampling error. The CS only reports results from probabilistic sensitivity analyses (PSA) for ponatinib vs bosutinib which could be insufficient.

5.2.2 Model structures

The company submitted two models in relation to the cost-effectiveness of ponatinib in CML. The first model assumes that patients would become eligible for ponatinib treatment whilst in CP-CML. The second model assumes that the patient would become eligible for ponatinib either in AP-CML or BP-CML, with the model allowing the user to select which phase of CML to analyse. The model structures will be presented in turn. Both models evaluate the cost-effectiveness of ponatinib versus its comparators from the perspective of the NHS and Personal Social Services over a lifetime horizon (up to 100 years). Health outcomes and costs were discounted at a rate of 3.5% per annum. Both models employ a state transition approach, with three-month time cycles including a half-cycle correction. The models submitted by the company were amended in the light of the clarification process. In order to avoid confusion, only the revised models are discussed within this report. Following the submission of the CS a PAS, a simple discount of [redacted]%, has been accepted. The ERG has revised the results presented by the company to incorporate the PAS.

5.2.2.1 The CP-CML model

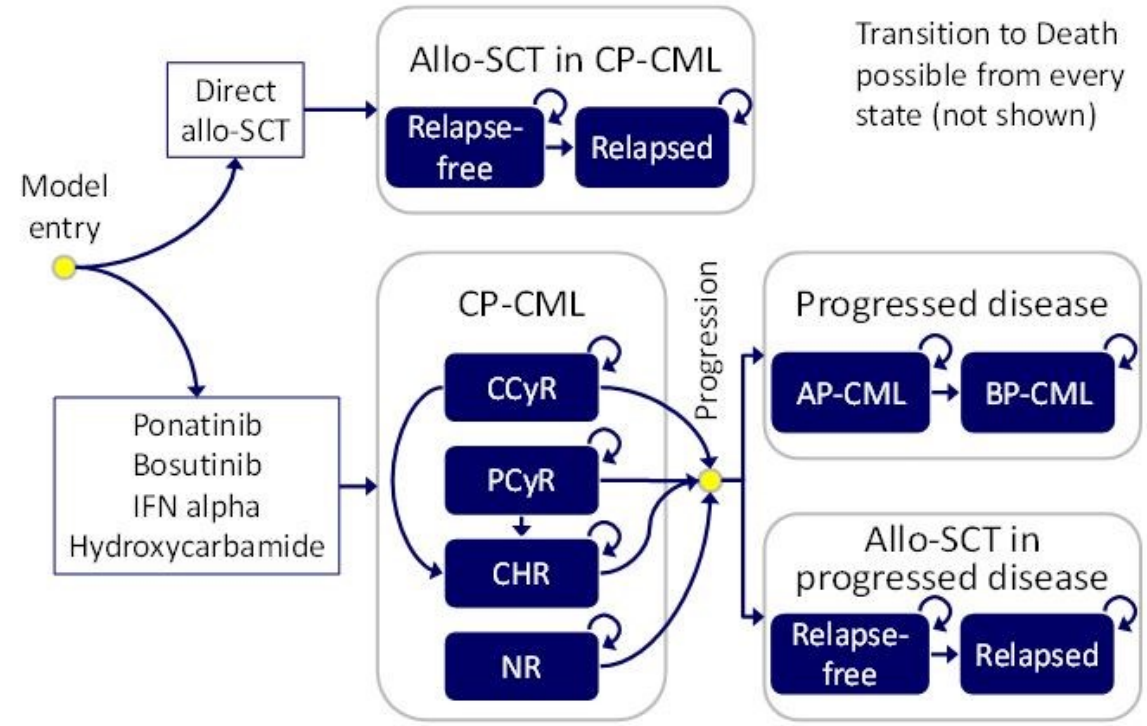
The schematic representation of the CP-CML model provided by the company (Figure 5-3 of the CS, p120) is reproduced in

Detailed descriptions are provided hereafter, however, to aid the reader, in brief, the patients receiving non-allo-SCT treatments experience one of four response levels: CCyR; PCyR; CHR or no response (NR). The rate of progression to AP-CML is dependent on the response level, but not the treatment that generated the response. Post-progression outcomes are assumed to be independent of initial treatment and are associated with increased risk of mortality and of further progression to BP-CML where the risk of mortality is further increased. Progression to AP-CML and BP-CML are additionally associated with increased costs. For patients receiving allo-SCT the patient may relapse which increases the risk of mortality and the costs incurred. It is noted that the risk of mortality is assumed to be markedly higher for those in CP-CML who have an allo-SCT compared with those who remain in CP-CML on treatments other than allo-SCT.

Figure 2.

Detailed descriptions are provided hereafter, however, to aid the reader, in brief, the patients receiving non-allo-SCT treatments experience one of four response levels: CCyR; PCyR; CHR or no response (NR). The rate of progression to AP-CML is dependent on the response level, but not the treatment that generated the response. Post-progression outcomes are assumed to be independent of initial treatment and are associated with increased risk of mortality and of further progression to BP-CML where the risk of mortality is further increased. Progression to AP-CML and BP-CML are additionally associated with increased costs. For patients receiving allo-SCT the patient may relapse which increases the risk of mortality and the costs incurred. It is noted that the risk of mortality is assumed to be markedly higher for those in CP-CML who have an allo-SCT compared with those who remain in CP-CML on treatments other than allo-SCT.

Figure 2: Schematic representation of the CP-CML model provided by the company



Allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukaemia; CP, chronic phase; IFN alpha: interferon alpha; NR, no response; PCyR, partial cytogenetic response.

On entering the model, the hypothetical patient could receive one of five interventions: (i) ponatinib; (ii) bosutinib; (iii) interferon alfa; (iv) hydroxycarbamide (which is assumed to represent BSC); or (v) allo-SCT. For those patients receiving ponatinib, bosutinib, interferon alfa, or hydroxycarbamide, henceforth grouped collectively as non-allo-SCT treatments, the modelling approach is identical; the modelling approach differs, however, for those patients who receive allo-SCT directly upon model entry. For both treatment pathways, death could occur at any time point.

5.2.2.1.1 Patients receiving non-allo-SCT treatments

For patients receiving non-allo-SCT treatments, the model simulates the response of patients to the treatment; this is assumed to occur in the first cycle only. It was assumed that patients would fall into one of four mutually exclusive and exhaustive states: (i) CCyR; (ii) PCyR; (iii) CHR; and (iv) NR. These have been ranked in ascending chance of disease progression with the most favourable being CCyR and the least favourable being NR. The model has the functionality to discontinue ponatinib treatment if the patient experiences NR.

For patients simulated to receive a CHR or NR, the next event in the model (a term which has been used in the ERG report to identify the next event whilst excluding remaining in the same health state) would

be: death; progression of disease; or discontinuation of treatment. Clinical advice to the ERG indicated that there would be a proportion of patients who would initially receive non-allo-SCT treatment but would later have an allo-SCT whilst in CP-CML. The company did not consider providing allo-SCT before the patient had progressed to AP-CML a possibility. The impact of allowing allo-SCT in CP-CML after non-allo-SCT treatment is unknown.

Discontinuation of treatment was not assumed to happen for those receiving interferon alfa or BSC. For those in CCyR or PCyR, in addition to the events possible in CHR or NR, a patient could lose response to the treatment, in which case it was assumed that the response was reduced to CHR. Following discontinuation of treatment in PCyR, CHR or NR, it was assumed that response would immediately be lost and the patient would regress to the NR state, albeit with the possibility of an immediate CHR due to subsequent BSC use. Following discontinuation of treatment for patients in CCyR, it was assumed that patients remained in CCyR.

Following progression, the patient either receives allo-SCT if deemed appropriate or enters AP-CML. For patients in AP-CML, the next event is either death or progression to BP-CML, from which the next event is death. For patients receiving allo-SCT, following progression, the next event is either death or relapse; once a patient has relapsed the only event possible is death.

To guide the reader, a simplified aide memoire has been developed which indicates the path of the hypothetical patients following an event. This is shown in

Table 34.

Table 34: Aide memoire for patient pathway following an event in the CP-CML model for patients on non-allo-SCT treatments

Event	Patient moves to……	Comments
Disease progression	the allo-SCT post-progression model if allo-SCT is appropriate otherwise the AP-CML sub-model	N/A
Loss of response	the patient moves to the CHR health state within the CP-CML model	Only applicable for those in CCyR or PCyR
Discontinuation of treatment	if in CCyR the patient remains in CCyR, if in PCyR, CHR or NR the patient is assumed to have either a CHR or NR based on the efficacy of BSC	Only applicable for those on ponatinib and bosutinib.
Death	the dead state	N/A

5.2.2.1.2 Patients receiving allo-SCT treatment directly after entering the model

For patients receiving allo-SCT directly after entering the model, the next event is either relapse or death; once a patient has relapsed the only event possible is death. Clinical advice to the ERG suggests that patients who relapse after transplant are likely to receive induction chemotherapy with, or without, donor lymphocyte infusion, but this was not allowed within the model.

5.2.2.2 The AP-CML / BP-CML model

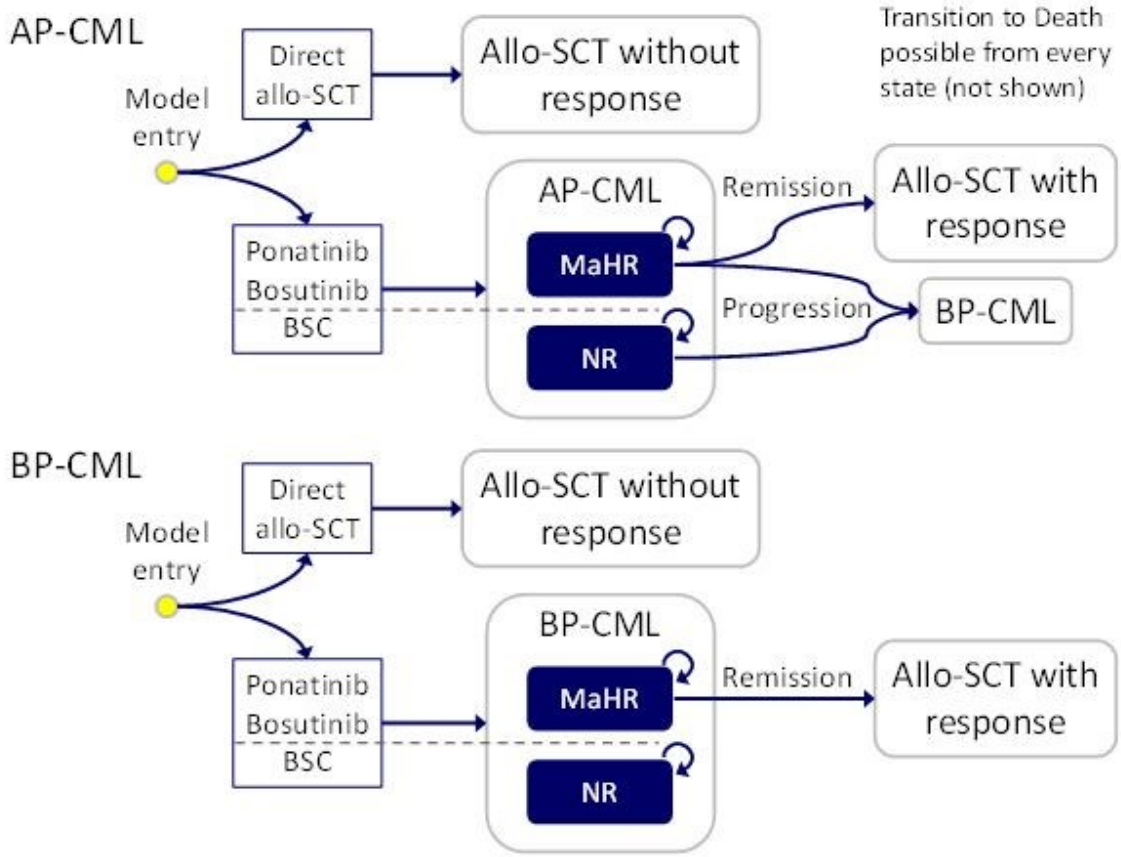
The schematic representation of the AP-CML / BP-CML model provided by the company (Figure 5-17 of the CS, p184) has been reproduced in Figure 3. This model allows the user to select either the AP-CML population or the BP-CML population: the structure is similar for both populations with the key difference being that patients with AP-CML could further progress to BP-CML, which was not possible for those patients presenting with BP-CML.

To aid interpretation, the text in Figure 3 which states 'allo-SCT without response' and 'allo-SCT with response' do not refer to the outcome of allo-SCT but are used to differentiate whether a patient has an MaHR prior to the allo-SCT, in which case the survival prognosis is assumed better than in patients without an MaHR. The ERG notes that the company did not explore an option whereby SCT could be used rather than BSC in patients who did not achieve an MaHR after a non-allo-SCT treatment.

Fuller details are provided hereafter, but in brief patients with AP-CML or BP-CML can receive non-allo-SCT treatments or allo-SCT. The goal of non-allo-SCT treatments is that the disease status of the patients may be improved, which can result in improved prognoses once allo-SCT is performed. This

has been termed as a 'bridge to allo-SCT'. If an MaHR response is generated through a non-allo-SCT treatment, then the patient would receive an allo-SCT. Patients without an MaHR do not receive an allo-SCT and either the next event is death, or progression to BP-CML for those who present in AP-CML.

Figure 3: Schematic representations of the AP-CML and BP-CML models provided by the company



Allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast phase; BSC, best supportive care; CML, chronic myeloid leukaemia; MaHR, major haematologic response; NR, no response.

Note: dashed line indicates that patients receiving BSC cannot achieve MaHR, and thus remain nonresponders; patients receiving ponatinib or bosutinib can either achieve MaHR or be nonresponders.

5.2.2.2.1 Patients receiving non-allo-SCT treatments

For patients receiving non-allo-SCT treatments in both AP-CML and BP-CML, the model simulates the response of patients to the treatment which is assumed to be either MaHR or NR. The model has the functionality to explore the discontinuation of ponatinib treatment in those patients who do not experience an MaHR. Figure 3 does not correctly represent the mathematical model as the figure indicates that it is possible to stay in the MaHR state; within the model it is assumed that all patients with an MaHR would have an allo-SCT. The assumption of all patients being suitable for allo-SCT is

contradictory to the assumption used in CP-CML where only a proportion of patients are assumed suitable for allo-SCT.

For those patients starting in AP-CML who have an MaHR and therefore have an allo-SCT, the next event is death; for the remainder of patients who experience NR, the next event is death or disease progression to BP-CML, from which the next event will be death. For those patients starting in BP-CML who have an MaHR and therefore have an allo-SCT, the next event is death: for the remainder of patients with NR the next event is death.

To guide the reader a simplified aide memoire has been developed which indicates the path of the hypothetical patients following an event (see Table 35).

Table 35: Aide memoire for patient pathway following an event in the AP-CML / BP CML model for patients on non-allo-SCT treatments

Event	Patient moves to……	Comments
Disease progression	the BP-CML sub-model	Only applicable for those in AP-CML
MaHR response	the Allo-SCT post-response model	All patients are assumed suitable for allo-SCT
Death	the dead state	N/A

5.2.2.2.2 Patients receiving allo-SCT treatment directly after entering the model

For patients receiving allo-SCT directly after entering the model, the next event is death.

5.2.3 Population

The populations modelled for each of the three CML types are provided in Table 33.

Table 36: Characteristics of the hypothetical patients used in the CP-CML, the AP-CML, and the BP-CML models

Type of CML	Initial Age (years)	Proportion male (%)	Source
CP-CML	54.5	44.9	The MAIC in the CS
AP-CML	54.6	41.8	PACE[22]
BP-CML	50.4	60.0	PACE[22]

5.2.4 Intervention and comparators

5.2.4.1 The intervention

The intervention being appraised is ponatinib which is a third-generation antineoplastic protein kinase inhibitor. Further details are provided in Section 3.2

5.2.4.2 The comparators in CP-CML

Within the CP-CML model, five strategies are compared. These strategies are described in Section 5.2.2.1. The comparators to the ponatinib strategy in CP-CML are strategies starting with: bosutinib; interferon alfa; BSC; and allo-SCT.

5.2.4.3 The comparators in both AP-CML and BP-CML

Within both AP-CML and BP-CML, four strategies are compared. The comparators to the ponatinib strategy in AP-CML are strategies starting with: bosutinib; interferon alfa; BSC; and allo-SCT. Clinical advice provided to the ERG suggests that induction chemotherapy should also be a comparator to ponatinib.

5.2.5 Treatment effectiveness

A key driver of patients' long-term prognoses, both in terms of life expectancy and utility, is the assumed response rates for non-allo-SCT treatments. These are divided into CCyR; PCyR; CHR; and NR for those in CP-CML and MaHR or NR for those in AP-CML or BP-CML. For those who receive allo-SCT the submitted model does not differentiate life expectancy between those who relapse and those who do not, although a utility difference is assumed.

5.2.5.1 Treatment effectiveness in CP-CML

The response rates assumed in the model for each treatment in CP-CML are detailed in

Table 37. Whilst data were available from the PACE study for ponatinib this could not be linked with data from bosutinib. As such a MAIC was conducted to attempt to produce more reliable comparative statistics: this resulted in a reduction in the proportion of patients with CCyR due to ponatinib and an increase in the remaining response categories. The MAIC-adjusted values are used in the analyses, although the values from the PACE study[22] are provided in

Table 37 for comparative purposes. Response rate data for bosutinib were taken directly from Khoury *et al.*[42] The literature review undertaken by the company did not identify data for either interferon alfa or hydroxycarbamide (assumed to represent BSC). As such, previously reported estimates of median CHR rates reported by Dalziel *et al.*[63] were used.

Table 37: Assumed response rates for each treatment in CP-CML

Treatment	CCyR (%)	PCyR (%)	CHR (%)	NR (%)	Source
Ponatinib	64.95	6.19	17.53	11.34	PACE*[22]
Ponatinib	61.34	8.46	18.19	12.01	Company's MAIC
Bosutinib	24.07	8.33	37.93	29.66	Khoury *et al.*[42]
Interferon alfa	0.00	0.00	47.00	53.00	Dalziel *et al.*[63]
BSC	0.00	0.00	41.00	59.00	Dalziel *et al.*[63]

*Not used in the company's analyses

5.2.5.2 Treatment effectiveness in AP-CML

The response rates assumed in the model for each treatment in AP-CML are detailed in Table 38. No adjustment was made to account for the absence of a link between data for ponatinib and data for bosutinib. Instead, a naïve unadjusted indirect comparison was conducted based on the data from the relevant arms of two independent studies. The company assumed that BSC would not provide an MaHR.

Table 38: Assumed response rates for each treatment in AP-CML

Treatment	MaHR (%)	Non-MaHR (%)	Source
Ponatinib	55.7	44.3	PACE[22]
Bosutinib	29.2	70.8	Gambacorti-Passerini *et al*[39]
BSC	0.0	100.0	Company assumption

5.2.5.3 Treatment effectiveness in BP-CML

The response rates assumed in the model for each treatment in BP-CML are detailed in Table 39. No adjustment was made to account for the absence of a link between data for ponatinib and data for bosutinib. Instead, a naïve unadjusted indirect comparison was conducted with the data from the relevant arms of two independent studies used. The company assumed that BSC would not provide an MaHR.

Table 39: Assumed response rates for each treatment in BP-CML

Treatment	MaHR (%)	Non-MaHR (%)	Source
Ponatinib	31.7	68.3	PACE[22]
Bosutinib	4.3	95.7	Gambacorti-Passerini *et al*[39]
BSC	0.0	100.0	Company assumption

5.2.5.4 Adverse and serious adverse events associated with treatment

Further details on AEs and SAEs are provided in Section 4.2.4.2. The company's model assumes that AEs occur only in patients treated with ponatinib and bosutinib whilst SAEs, relating to vascular events, only occur for those receiving ponatinib. The probability of a patient experiencing a treatment-related SAE in CP-CML is reproduced from the CS (Table 5-24, p155) in

Table 40, and the corresponding data for patients with AP-CML or BP-CML are reproduced from the CS (Table 5-51, p194) in

Table 41 and Table 42. AEs are assumed to only occur once, and within the first cycle (i.e. within three months of treatment initiation). The company provided no comment on why the rates of AEs can vary markedly between phases of CML. The rates of SAE were calculated from the PACE study[22] and were assumed to be a per-cycle risk. No comment was made by the company regarding the different rates of SAEs between phases of CML.

Table 40: Assumed SAE rates and costs for ponatinib and bosutinib in CP-CML in the company's model

Adverse event	Ponatinib	Bosutinib	Unit cost (£)	Source
Abdominal pain	[redacted]	0.00%	752.10	Ref costs 2014/15
Anaemia	[redacted]	6.78%	1,827.13	NHS ETF 2015/16
Diarrhoea	[redacted]	8.47%	801.95	Ref costs 2014/15
Hyperglycemia	[redacted]	0.00%	1,271.46	Ref costs 2014/15
Hypophosphataemia	[redacted]	0.00%	721.00	Assumed to be one day in hospital
Leukocytopaenia	[redacted]	0.00%	633.26	Assumed equal to neutropenia
Lipase increased	[redacted]	0.00%	721.00	Assumed to be one day in hospital
Neutropenia	[redacted]	15.25%	633.26	Ref costs 2014/15
Pancreatitis	[redacted]	0.00%	1,121.98	Ref costs 2014/15
ALT elevation	[redacted]	5.93%	1,121.98	Ref costs 2014/15
GGT increased	[redacted]	0.00%	1,121.98	Ref costs 2014/15
Thrombocytopenia	[redacted]	26.27%	421.74	Ref costs 2014/15
Serious adverse events				
Cardiovascular events	[redacted]	-	2,357.00	NHS ETF 2015/16
Cerebrovascular events	[redacted]	-	2,962.00	NHS ETF 2015/16
Peripheral vascular event	[redacted]	-	2,872.00	NHS ETF 2015/16
Venous thromboembolism event	[redacted]	-	552.00	NHS ETF 2015/16

ALT: alanine aminotransferase; GGT: Gamma-glutamyltransferase; Ref costs 2014/15: NHS Reference costs 2014 to 2015; NHS ETF 2015/15: NHS Enhanced tariff option 2015 to 2016

Table 41: Assumed SAE rates and costs for ponatinib and bosutinib in AP-CML in the company's model

Adverse event	Ponatinib	Bosutinib	Unit cost, £	Source
Anaemia	[redacted]	21.00%	1,827.13	NHS ETF 2015/16
Leukocytopaenia	[redacted]	-	633.26	Assumed equal to neutropenia
Lipase increased	[redacted]	11.30%	721.00	Assumed to be one day in hospital
Neutropenia	[redacted]	17.70%	633.26	Ref costs 2014/15
Pancreatitis	[redacted]	-	1,121.98	Ref costs 2014/15
Thrombocytopenia	[redacted]	25.80%	421.74	Ref costs 2014/15
Serious adverse events				
Cardiovascular events	[redacted]	1.98%	2,357.00	NHS ETF 2015/16
Cerebrovascular events	[redacted]	-	2,962.00	NHS ETF 2015/16
Peripheral vascular event	[redacted]	0.67%	2,872.00	NHS ETF 2015/16
Venous thromboembolism event	[redacted]	-	552.00	NHS ETF 2015/16

Ref costs 2014/15: NHS Reference costs 2014 to 2015; NHS ETF 2015/15: NHS Enhanced tariff option 2015 to 2016

Table 42: Assumed SAE rates and costs for ponatinib and bosutinib in BP-CML in the company's model

Adverse event	Ponatinib	Bosutinib	Unit cost, £	Source
Anaemia	[redacted]	20.31%	1,827.13	NHS ETF 2015/16
Leukocytopaenia	[redacted]	18.75%	633.26	Assumed equal to neutropenia
Neutropenia	[redacted]	25.00%	633.26	Ref costs 2014/15
ALT elevation	[redacted]	-	1,121.98	Ref costs 2014/15
Thrombocytopenia	[redacted]	35.94%	421.74	Ref costs 2014/15

ALT: alanine aminotransferase; Ref costs 2014/15: NHS Reference costs 2014 to 2015; NHS ETF 2015/15: NHS Enhanced tariff option 2015 to 2016

5.2.6 Extrapolation of surrogate outcomes and linkages between health states

Following estimation of the response rates associated with each treatment, many other parameters in the model are determined solely by the response level (CCyR; PCyR; CHR; and NR), and are based on data taken from published literature and are independent of the initial treatment. Such assumptions are necessary where pivotal studies are of relatively short duration, but the reliance on extrapolating from surrogate outcomes increases the uncertainty in the results. The following sections, one set for each phase of CML, detail the extrapolation of surrogate outcomes and attempt to explain how health states

link. For all response levels, the company's model assumes that patients in CP-CML states have the same risk of death as that reported for the age- and gender-matched general population.[64] The company's model assumes that the yearly data are rates of death, whereas the ERG believes these data are probabilities of death.

In cases when the company did not have access to patient-level time-to-event data, the company digitised published Kaplan-Meier survivor functions and used the Solver add-in in Microsoft Excel® to generate parametric survivor functions by minimising the sum of squared errors (SSE) between the predicted survival curve and that of the digitised points. Although this method provides estimates of the parameters for each parametric survivor function, it provides no meaningful estimates of the variances (and covariances) associated with the parameters. In response to a request for clarification (question B1)[28] the company was asked to clarify why the method to reconstruct the patient-level data proposed by Guyot *et al.*[65] was not used. The company stated that 'it has a preference for their approach because there is no clear guidance on which method should be used. Two methods have been used in previous NICE appraisals of TKIs for CML: the method proposed by Guyot *et al.*[65] may produce poor results when neither the total number of events nor the number of patients at risk other than at time zero are provided. The small number of patients included in some studies may affect the precision (by which the ERG assumes is meant the accuracy of the estimates) of the reconstruction method'. It is true that the Guyot *et al.*[65] method makes the strong assumption that there are no censored observations over the follow-up period when neither the total number of events nor the number of patients at risk beyond the start of the study are reported, and this will adversely affect the quality of the results. However, the ERG has a preference for this method, particularly because it allows estimates of uncertainty about parameters in survivor functions to be estimated. The ERG noticed that some of the Solver solutions were local minima, or that Solver had not been run correctly: re-running Solver produced lower SSE than those using the parameters reported by the company and provided different fits to those reported by the company. Additionally, the fitting of the log-logistic appeared to be sometimes misspecified due to linking to an inappropriate cell.

The CS states that a strength of their analysis is the use of the sample data from the PACE study to extrapolate survivor functions. However, the ERG considers it a weakness to extrapolate survivor functions using sample data alone, particularly in cases where there were few events in studies with relatively short duration of follow-up, and should be informed by external clinical data / opinion where possible.

Apart from the Gompertz distribution, all other models fitted by the company to the data are members of the Generalised F distribution. In response to clarification question B28,[28] the company stated that it only considered distributions used in previous submissions described in NICE Decision Support Unit Technical Support Document 14[66] and that while other models may provide flexibility, the complexity of the current analysis, the number of inputs involved and the page-number restrictions of the submission affected their choice of models to fit. The ERG has concerns that this approach does not give sufficient weight to expert clinical knowledge and the expected shape of the hazard function over time in the target population of patients. In addition, the choice of parametric model for inclusion in the base case tended to be based on AIC and BIC when patient-level data were available and the SSE when patient-level data were not available. The ERG recommends caution when using AIC and BIC alone to choose between competing models: AIC and BIC provide a measure of which model from a pre-defined set of models represents the sample data best, not whether it is a good model, or whether it provides clinically plausible estimate of event rates beyond the duration of study; the smallest value alone is not associated with the best model because differences in BIC less than two are considered irrelevant.[67] The ERG does not consider the SSE as a single criterion for guiding model choice to be a good basis for choosing between models in this context if only because it is not possible to say what might be considered a meaningful difference in SSE values between models.

It is not clear from the CS whether the survivor functions are adjusted for the differences in patient populations between the PACE and bosutinib studies.

The ERG does not believe that the choice of survivor functions used in the base case is robust and that it fails to adequately quantify parameter uncertainty required in the economic model when patient-level data are not available.

5.2.6.1 Extrapolation of surrogate outcomes and linkages between health states in CP-CML

5.2.6.1.1 For patients who experience a CCyR

Patients can exit the CCyR state in a number of ways: death; progressed disease; or loss of response. With the exception of death, which is assumed to equal that of the general population, these events are discussed in turn.

5.2.6.1.1.1 Exiting the CCyR state due to progressed disease

The model assumes that the risk of progression to AP-CML in the CCyR state of CP-CML is independent of treatment. Following progression of disease, the costs and QALYs for a patient entering AP-CML is estimated as detailed in Section 5.2.6.1.5.

The relationship between response level and progression was estimated by the company using data presented in Loveman *et al*.[51] which was evidence considered by NICE in an appraisal of dasatinib, high-dose imatinib and nilotinib which were stated to have come from BMS study 034. It is noted that there were few events for those patients with CCyR and that the estimated PFS at 48 months was 94.2%.

The company selected the Gompertz distribution for the risk of progressing from CCyR, although the range in the SSE between the candidate distributions was small (0.00085 – 0.00102) and the extrapolated survivor functions are different (Figure 4). The selection of the Gompertz survivor function, which estimates the fewest progressions, is likely to be favourable to ponatinib because ponatinib is estimated to produce the highest proportion of patients with a CCyR response.

Figure 4: Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with CCyR (CIC data)

5.2.6.1.1.2

Exiting the CCyR state due to loss of response

The company assumed that the risk of progression to AP-CML in the CCyR state of CP-CML was treatment-specific. Following loss of response, patients are assumed to reside in the CHR response state.

5.2.6.1.1.2.1 Loss of CCyR for patients on ponatinib treatment

For ponatinib, the company undertook standard survival analysis fitting exponential, Weibull, Gompertz, log-normal and log-logistic distributions to data from PACE.[22] The analysis included all data from patients with CCyR and PCyR and used response level as a covariate. From the analyses undertaken, the company states that progression could be characterised best by a Gompertz distribution because it had the lowest AIC and BIC. Relative goodness-of-fit measures indicate which survivor function provide the best representation of the observed data out of the set of models fitted, but do not indicate whether it is a good model or how well the survivor function represents clinical experts' estimations of the unobserved data. The ERG was not convinced that sufficient evidence had been presented to justify the selection of the Gompertz curve in the base case because the AIC and BIC statistics were within 2 units (which is typically taken to be indistinguishable, see Table 43) and yet the survivor functions produced significantly different extrapolations (see Figure 5) with the Gompertz survivor function declining only slightly between months 40 and 100 relative to the log-normal and the log-logistic survivor functions. It is commented that a sizeable majority of patients had a maintained response at 48 months.

Table 43: AIC and BIC statistics presented by the company relating to the DoR for CCyR following ponatinib treatment (CIC data)

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Figure 5: Extrapolation of the candidate curves presented by the company relating to the DoR of CCyR following ponatinib treatment (CIC data)

5.2.6.1.1.2.2 Loss of CCyR for patients on bosutinib treatment

For bosutinib, the company digitised data from Gambacorti-Passerini *et al*[40] that reported the DoR after MCyR. The company used the Solver add-in in Microsoft Excel to estimate the parameters of survivor functions: this method has limitations as previously described. The log-normal distribution was selected by the company as the best fit based on the lowest SSE. The extrapolations of the survivor functions are provided in

Figure 6.

The ERG comments that there was ambiguity regarding which curve was used for the DoR for bosutinib, as Table 5-26 in the CS states that the log-normal was used, which has the lowest AIC value, however, Table 5-44 in the CS states that the Gompertz was used. The model supplied by the company following clarification states that the Gompertz was the default and this distribution is used in the results presented by the company. As such, the ERG has assumed the Gompertz was used, which is the same distribution used for the DoR for ponatinib.

Figure 6: Extrapolation of the candidate curves presented by the company relating to the DoR of MCyR following bosutinib treatment (CIC data)

5.2.6.1.1.2.3 Loss of CCyR for patients on interferon alfa treatment and BSC

Neither interferon alfa nor BSC were assumed to produce a CCyR.

5.2.6.1.1.3 Treatment discontinuation in CCyR

Patients in CCyR who discontinue treatment are assumed to remain in CCyR. This contrasts with patients in PCyR, CHR, and NR, whereby those who discontinue treatment are assumed to have either a CHR or NR based on the assumed efficacy of BSC.

5.2.6.1.1.3.1 Ponatinib treatment discontinuation for patients in CCyR

For ponatinib, survivor functions were fitted to data from the PACE study.[22] These are presented in Figure 7. AIC and BIC statistics with covariates for response levels are presented in Table 44.

Figure 7: Time to treatment discontinuation in CCyR whilst on ponatinib (CIC data)

[redacted]

Table 44: AIC and BIC statistics presented by the company relating to the time on ponatinib treatment in CP-CML (CIC data)

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Despite the fact that the exponential distribution did not provide the best fit to the observed data, this distribution was selected by the company '*for consistency with the function used for bosutinib*' (CS, p134). However, the ERG comments that some inconsistency remain as treatment discontinuation for ponatinib was assumed to differ between response states whereas the same distribution representing time to discontinuation was used for bosutinib in all health states.

5.2.6.1.1.3.2 Bosutinib treatment discontinuation for patients in CCyR

The company used the median time on bosutinib treatment of 8.30 months, over a median follow-up 28.5 months reported by Khoury[42] to fit an exponential survivor function. The use of an exponential distribution assumes constant hazards.

5.2.6.1.1.3.3 Interferon alfa treatment or BSC discontinuation for patients in CCyR

This is not considered as neither interferon alfa nor BSC were assumed to produce a CCyR.

5.2.6.1.2 For patients who experience a PCyR

Patients can exit the PCyR state in a number of ways: death; progressed disease; loss of response; or through discontinuation of treatment. These, excluding death, are discussed in turn.

5.2.6.1.2.1 Exiting the PCyR state due to progressed disease

The company assumed that the risk of progression to AP-CML in the PCyR state of CP-CML was independent of treatment. Following progression of disease, the costs and QALYs for a patient entering AP-CML are estimated as detailed in Section 5.2.6.1.5. The methodology used by the company to estimate progression is detailed in 5.2.6.1.1.1.

The company had made an error in the estimation of the log-logistic distribution for PCyR, CHR and NR, by using the gamma value from the CCyR state. This has been amended by the ERG: the subsequent text is based on the results after the ERG's correction was applied.

The company selected the Gompertz distribution for the risk of progressing from PCyR, although the range in the SSE between the Gompertz, Weibull, log-logistic and log-normal distributions was small (0.00086 – 0.00111) and the extrapolated survivor functions are noticeably different (

Figure 8). The selection of the Gompertz curve, which estimates the most progressions, is likely to be favourable to ponatinib compared with bosutinib as ponatinib is estimated to produce a lower proportion of patients with a PCyR response.

Figure 8: Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with PCyR (log-logistic amended by the ERG) (CIC data)

5.2.6.1.2.2 Exiting the PCyR state due to loss of response

The company's model assumes that the risk of progression to AP-CML in the CCyR state of CP-CML was treatment-specific. Following loss of response, a patient was assumed to reside in the CHR response state.

5.2.6.1.2.2.1 Loss of PCyR for patients on ponatinib treatment

The analyses performed by the company, and the ERG's criticism of the selection of the Gompertz distribution are detailed in 5.2.6.1.1.2. The extrapolated survivor functions are presented in

Figure 9. Few patients were observed to have PCyR as shown by the large decrease in patients with DoR following an event.

Figure 9: Extrapolation of the candidate curves presented by the company relating to the DoR of PCyR following ponatinib treatment (CIC data)

5.2.6.1.2.2.2 Loss of PCyR for patients on bosutinib treatment

Since the bosutinib data for response were categorised only for MCyR, the company assumed the DoR for those with PCyR was equal to that of CCyR (Section 5.2.6.1.1.3).

5.2.6.1.2.2.3 Loss of PCyR for patients on interferon alfa treatment or BSC

Neither interferon alfa nor BSC were assumed to produce a PCyR.

5.2.6.1.2.3 Exiting the PCyR state due to discontinuation of treatment

Patients who discontinue treatment are assumed to lose their PCyR and will either have a CHR or NR based on the assumed efficacy of BSC as detailed in

Table 37.

5.2.6.1.2.3.1 Ponatinib treatment discontinuation for patients in PCyR

The methodology used by the company is detailed in 5.2.6.1.1.3. The extrapolations of curves fitted to the survivor function are shown in

Figure 10. The exponential distribution, which assumes constant hazards, was chosen by the company '*for consistency with the function used for bosutinib*.' (CS, p134) The exponential distribution was not shown to be a good fit to the underlying data.

Figure 10: Time to treatment discontinuation in PCyR whilst on ponatinib (CIC data)

5.2.6.1.2.3.2 Bosutinib treatment discontinuation for patients in PCyR

The time on bosutinib treatment in PCyR was the same as that assumed in CCyR. See Section 5.2.6.1.1.3.2 for further details.

5.2.6.1.2.3.3 Interferon alfa treatment and BSC discontinuation for patients in PCyR

Neither interferon alfa nor BSC were assumed to produce a CCyR.

5.2.6.1.3 For patients who experience a CHR

Patients can exit the CHR state in a number of ways: death; progressed disease; or through discontinuation of treatment. These, excluding death, are discussed in turn.

5.2.6.1.3.1 Exiting the CHR state due to progressed disease

The company's model assumes that the risk of progression to AP-CML in the CHR state of CP-CML was independent of treatment. Following progression of disease, the costs and QALYs for a patient entering AP-CML are estimated as detailed in Section 5.2.6.1.5. The methodology used by the company to estimate progression is detailed in 5.2.6.1.1.1.

The company selected the Weibull distribution for the risk of progressing from CHR, although the range in the SSE between the Weibull, Gompertz, log-logistic and log-normal distributions was relatively small (0.00694 – 0.00127) and the extrapolated survivor functions are noticeably different (Figure 11).

Figure 11: Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with CHR (log-logistic amended by the ERG) (CIC data)

5.2.6.1.3.2 Exiting the CHR state due to discontinuation of treatment

Patients who discontinue treatment are assumed to lose their CHR and will either return to CHR or have NR based on the assumed efficacy of BSC as detailed in

Table 37.

5.2.6.1.3.2.1 Ponatinib treatment discontinuation for patients in CHR

The methodology used by the company is detailed in Section 5.2.6.1.1.3. The extrapolation of the survivor functions is shown in

Figure 12. An exponential distribution was assumed for '*consistency with bosutinib*' although was shown to be a poor fit to the observed data.

Figure 12: Time to treatment discontinuation in CHR whilst on ponatinib (CIC data)

5.2.6.1.3.2.2 Bosutinib treatment discontinuation for patients in CHR

The time on bosutinib treatment in CHR was the same as that assumed in CCyR. See Section 5.2.6.1.1.3.2 for further details.

5.2.6.1.3.2.3 Interferon alfa treatment and BSC discontinuation for patients in CHR

The model assumes that neither interferon alfa or BSC would be discontinued.

5.2.6.1.4 For patients who experience NR

Patients can exit the NR state in a number of ways: death; progressed disease; or through discontinuation of treatment. These, excluding death, are discussed in turn.

5.2.6.1.4.1 Exiting the NR state due to progressed disease

The company's model assumes that the risk of progression to AP-CML in the NR state of CP-CML was independent of treatment. Following progression of disease, the costs and QALYs for a patient entering AP-CML are estimated as detailed in Section 5.2.6.1.5. The methodology used by the company to estimate progression is detailed in Section 5.2.6.1.1.1: as previously stated this methodology has limitations.

The company selected the exponential distribution for the risk of progressing from NR, although the SSE for the exponential function (0.3164) was considerably higher than for the remaining distributions (0.0026-0.0924). The company stated that the choice of the exponential distribution was '*based on*

clinical plausibility'. The extrapolated curves are shown in Figure 13: as shown in the figure, the exponential survivor function has a much lower predicted long term PFS than the remaining curves. Clinical advice received by the ERG suggested that the proportion of patients in PFS would lie between the exponential and the log-normal lines.

Figure 13: Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with NR (log-logistic amended by the ERG) (CIC data)

5.2.6.1.4.2 Exiting the NR state due to discontinuation of treatment

Patients who discontinue treatment are assumed to have a CHR or stay with NR based on the assumed efficacy of BSC as detailed in

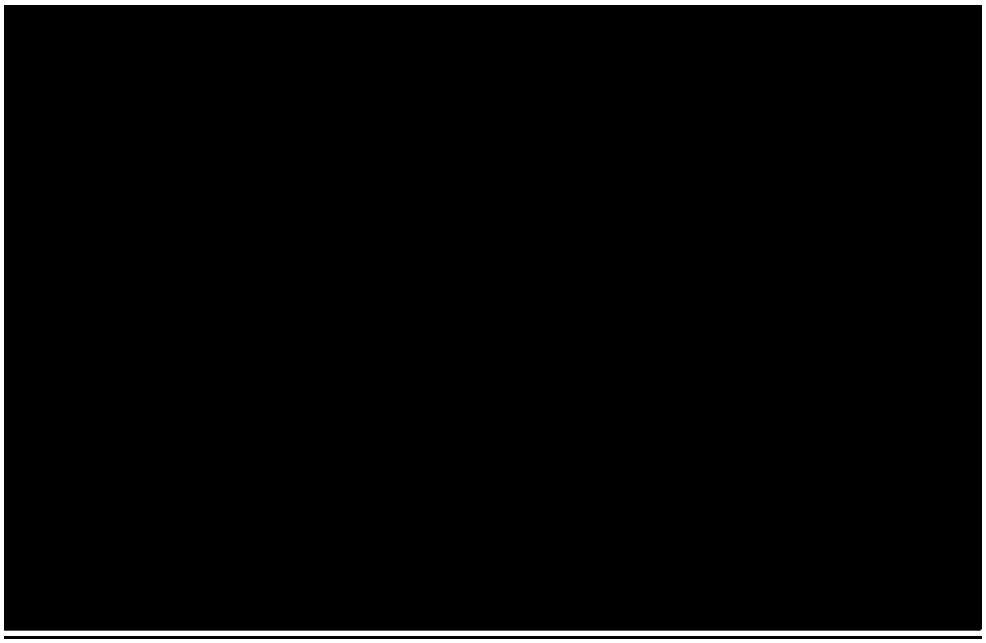
Table 37.

5.2.6.1.4.2.1 Ponatinib treatment discontinuation for patients in NR

The methodology used by the company is detailed in Section 5.2.6.1.1.3. The extrapolations of the survivor functions are shown in

Figure 14. Due to the long plateau due to no observed events between ten and fifty months all parametric curves provided a poor fit to the observed data.

Figure 14: Time to treatment discontinuation in NR whilst on ponatinib (CIC data)



5.2.6.1.4.2.2 Bosutinib treatment discontinuation for patients in NR

The time on bosutinib treatment in NR was assumed to be the same as that in CCyR. See Section 5.2.6.1.1.3.2 for further details.

5.2.6.1.4.2.3 Interferon alfa treatment and BSC discontinuation for patients in NR

The model assumes that patients would not discontinue either interferon alfa treatment or BSC.

5.2.6.1.5 Modelling assumptions for patients who progress to AP-CML from CP-CML

The pathway taken by the patient is dependent on whether the patient is deemed suitable for allo-SCT. Based on a UK survey undertaken by the company (Appendix 14 of the CS), this probability is assumed to be 27.3%. The mean time to progression from CP-CML is estimated separately for each treatment and this value is added to the starting age for a cohort of patients who progress. Following progression, the discounted costs and QALYs are calculated both for patients who are suitable and for patients who are not suitable for allo-SCT assuming that the event occurs at model entry. These values are then discounted again to take the time of progression into consideration and are added when patients progress. This method, which the company refer to as 'double-discounting' is technically not as accurate as more complex methods, such as using multiple tunnel states or using an individual patient model, but the ERG believes that the approach is reasonable as the inaccuracy will be small.

5.2.6.1.5.1 Modelling assumptions for those not suitable for allo-SCT

Patients who are not suitable for allo-SCT enter AP-CML. From AP-CML, the patient can progress to BP-CML or die. It is assumed that following progression, 20% receive dasatinib, 20% receive nilotinib. 20% receive bosutinib, 20% receive imatinib and 20% receive BSC. The ERG comments that these treatments (excluding BSC) were not used when the clinical data used within the model for OS were generated (see Section 5.2.6.1.5.1.2).

5.2.6.1.5.1.1 Probability of progression to BP-CML from AP-CML

The company used data presented in Kantarjian *et al*.[68] to estimate the OS in AP-CML and the OS in BP-CML. The difference between the two OS values was 9.16 months and assumed that this was equivalent to the mean PFS in AP-CML. This value of 9.16 months was used to derive an exponential distribution. The ERG considers that this assumption may be inaccurate because only those patients surviving to BP-CML are included in the BP-CML data, but deems the assumption reasonable for the purposes of decision making.

5.2.6.1.5.1.2 Probability of death when in AP-CML

To estimate the probability of death in AP-CML, the company digitised data from Kantarjian *et al*.[68] and fitted parametric curves to the data minimising the SSE: as previously detailed, this approach has limitations. The company selected the log-normal distribution as the best fit to the data because it had the lowest SSE (0.0079) although all survivor functions had values below 0.027. The fitted survivor functions are shown in

Figure 15. The data are mature resulting in the extrapolations of the survivor functions lying relatively close together. The ERG comments that the non-allo-SCT treatments used in Kantarjian *et al*.[68] were predominantly 'other', which did not include dasatinib, nilotinib or bosutinib: this contradicts the treatment costs assumed by the company whilst in AP-CML.

Figure 15: Probability of death when in AP-CML (CIC data)

5.2.6.1.5.1.3 Probability of death when in BP-CML

For patients who have progressed from AP-CML to BP-CML, the probability of death was estimated using data from Kantarjian *et al*.[68] The data were digitised and parametric curves were fitted to the data by minimising the SSE. The company selected the log-logistic distribution, although the range in the SSE was small (0.007-0.05). As the data were relatively mature, the extrapolations of the survivor functions were fairly similar. The plot of the curve fits is provided in

Figure 16.

Figure 16: Probability of death when in BP-CML (CIC data)

5.2.6.1.5.2 Modelling assumptions for those suitable for allo-SCT

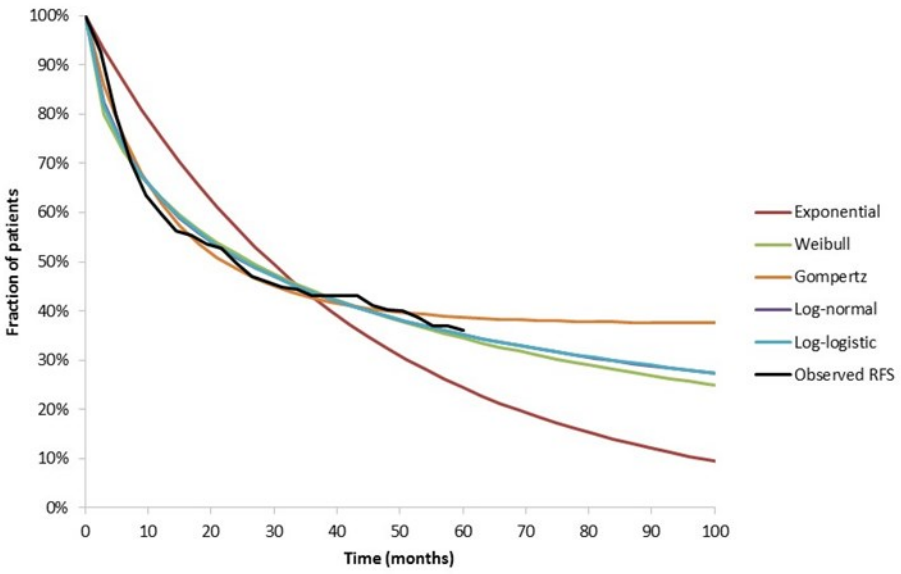
For patients suitable for allo-SCT, the next event can be relapse or death.

5.2.6.1.5.2.1 Probability of relapse following allo-SCT

The probability of relapse used in the model was derived from data presented in Craddock *et al*.[69] The data was digitised and different distributions fitted to these data by minimising the SSE. The range in SSE was relatively small, from 0.03 – 0.11 excluding the exponential distribution. The company selected the Gompertz distribution. (

Figure 17) Relapse was not assumed to alter the risk of death but is assumed to decrease the utility of the patient and increase the assumed CML-related costs. It is assumed that following relapse 20% receive dasatinib, 20% receive nilotinib. 20% receive bosutinib, 20% receive imatinib and 20% receive BSC. As previously stated, the ERG believes that a more appropriate cost would be that of BSC only.

Figure 17: Fitted curves to the risk of relapse following allo-SCT



5.2.6.1.5.2.2 Probability of death following allo-SCT

The probability of death used in the model was estiamted from data presented in Jabbour *et al*.[43] The data for patients in the 'advanced stage' were digitised and different parametric survivor functions were fitted to the data by minimising the SSE. The range in SSE was relatively small, from 0.03 – 0.08, excluding the exponential distribution. The company selected the exponential distribution, which predicts a much lower probability of survival than other curves, in particular the Gompertz distribution (Figure 18). If the probability of death estimated by the curve is lower than that of the age-matched population then the value for the age-matched population is used in preference.

Figure 18: Fitted curves to the risk of death following allo-SCT in AP-CML (CIC data)

The ERG notes that a different data source is used for survival post-allo-SCT in patients with AP-CML or BP-CML: this source also included data on survival for patients with CP-CML (Radich[70]). Clinical advice provided to the ERG supported the company's decision not to use Radich for CP-CML patients as the results relate to patients who have only failed imatinib, as the data collection started prior to the introduction of dasatinib and nilotinib. As such, these patients may be selected group of fit patients and are not similar to those being considered for ponatinib.

Immediately prior to the submission of the report a clinical advisor became aware of data on OS after allo-SCT for patients in CP-CML who had received previous therapy with nilotinib or dasatinib[71] presented at the American Society of Haematology (San Diego; December 2016). These data, which have been collected for up to six years after allo-SCT, appear to be the most appropriate data source and are contained in

Figure 19.

Figure 19: Data relating to OS following allo-SCT in patients who have received prior nilotinib or dasatinib (AIC data)

These data support the flattening of the Kaplan-Meier rather than the company's choice of the exponential distribution.

[redacted]

5.2.6.1.6 Modelling assumptions for patients who have allo-SCT on entering the model

Patients in CP-CML who have allo-SCT on model entry are assumed to enter a relapse-free state. From this state the patient can relapse or die.

5.2.6.1.6.1 Probability of relapse following allo-SCT on model entry

The probability of relapse for those who have an allo-SCT on model entry is assumed to be the same as for patients who have allo-SCT following a non-allo-SCT treatment. See Section 5.2.6.1.5.2.1 for more details.

5.2.6.1.6.2 Probability of death following allo-SCT on model entry

The probability of death following allo-SCT in CP-CML is assumed to be lower than that following allo-SCT after a patient has progressed to AP-CML (Section 5.2.6.1.5.2.2). The data for patients in CP-CML were digitised and different survivor functions were fitted to the data by minimising the SSE:. The range in SSE was relatively small, from 0.04 – 0.08, excluding the exponential distribution. The company selected the exponential distribution, which predicts a much lower probability of survival than other curves, in particular the Gompertz distribution (Figure 20). If the probability of death estimated by the survivor function is lower than that of the age-matched population then the value for the age-matched population is used in preference.

Figure 20: Fitted curves to the risk of death following allo-SCT in CP-CML (CIC data)

5.2.6.2 Extrapolation of surrogate outcomes and linkages between health states in AP-CML

5.2.6.2.1 Transition probabilities for patients in AP-CML who experience an MaHR

Patients exit the MaHR state by undergoing allo-SCT. The company's model assumes that there are no deaths in the initial three-month period if an MaHR was obtained and the patient was eligible for allo-SCT.

5.2.6.2.1.1 Exiting the MaHR state due to death

Whilst the model does not allow death from the MaHR state for those suitable for allo-SCT (see Section 5.2.6.2.1 Transition probabilities for patients in AP-CML who experience an MaHR, the calculated survivor functions are presented as they are required to estimate the probability of death in the non-MaHR state.

5.2.6.2.1.1.1 Probability of death for patients on ponatinib treatment

Although not used in the model, as all patients with an MaHR was assumed to receive allo-SCT, the time of death for those with an MaHR was estimated, jointly with those with NR, by fitting parametric distributions to the data from PACE.[22] For completeness, these survivor functions are reproduced in

Figure 21.

Figure 21: Fitted curves to the OS data for those in AP-CML who get an MaHR on ponatinib treatment (CIC data)

AIC and BIC values were calculated for each curve using whether an MaHR was achieved as a covariate. These values are reproduced in Table 45.

Table 45: AIC and BIC statistics presented by the company relating to OS for patients on ponatinib treatment in AP-CML (CIC data)

The company selected the log-normal distribution as being the best fit to the data as it had the lowest AIC and BIC values. However, the BIC values were fairly similar and the estimated number of survivors at 100 months varied.

5.2.6.2.1.1.2 Probability of death for patients on bosutinib treatment

The company's model assumes that the OS following an MaHR is equal for ponatinib and bosutinib for patients in AP-CML.

5.2.6.2.1.1.3 Probability of death for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section 5.2.6.1.5.1.2.

5.2.6.2.1.2 Exiting the MaHR state due to disease progression

5.2.6.2.1.2.1 Probability of progression for patients on ponatinib treatment

Although not used in the model, as all patients with an MaHR was assumed to receive allo-SCT, the time of death for those with an MaHR was estimated, jointly with those with NR, by fitting parametric distributions to the data from PACE.[22] For completeness, these survivor functions are reproduced in Figure 22.

Figure 22: Fitted curves to the time to progression data for those in AP-CML who get an MaHR on ponatinib treatment (CIC data)

AIC and BIC values were calculated for each curve using whether the patient achieved MaHR as a covariate. These values are reproduced in Table 46.

Table 46: AIC and BIC statistics presented by the company relating to OS for patients on ponatinib treatment in AP-CML (CIC data)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The company selected the log-normal distribution as being the best fit to the data because it had the lowest AIC and BIC values. However, other survivor functions generate similar BIC values but produce different extrapolations.

5.2.6.2.1.2.2 Probability of progression for patients on bosutinib treatment

The company's model assumes that the risks of progression following an MaHR is equal for ponatinib and bosutinib for patients in AP-CML.

5.2.6.2.1.2.3 Probability of progression for patients on BSC

The methodology for estimating PFS for patients on BSC is identical to that described in Section 5.2.6.1.5.1.1.

5.2.6.2.2 Transition probabilities for patients who experience NR

The next event for patients in AP-CML who experience NR is either death or disease progression.

5.2.6.2.2.1 Exiting the NR state due to death

5.2.6.2.2.1.1 Probability of death for patients on ponatinib treatment

The goodness-of-fit statistics for candidate distributions are shown in Table 45. The company selected the log-normal distribution for use in the base case as it had the lowest AIC and BIC values. However, other survivor functions are associated with similar BIC values but produce different extrapolations. The parametric curves are reproduced in Figure 23.

Figure 23: Fitted curves to the OS data for those in BP-CML who get NR on ponatinib treatment (CIC data)

5.2.6.2.2.1.2 Probability of death for patients on bosutinib treatment

The company's model assumes that the OS following an MaHR is equal for ponatinib and bosutinib for patients in AP-CML.

5.2.6.2.2.1.3 Probability of death for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section 5.2.6.1.5.1.2.

5.2.6.2.2.2 Exiting the NR state due to disease progression

5.2.6.2.2.2.1 The probability of progression for patients on ponatinib treatment

The methodology used is detailed in Section 5.2.6.2.1.2.1 Probability of progression for patients on ponatinib treatment. The goodness-of-fit statistics are provided in Table 46. The extrapolated survivor functions are presented in Figure 24. As shown in the figure, the survivor functions produce different extrapolations.

Figure 24: Fitted curves to the time to progression data for those in AP-CML who get NR on ponatinib treatment (CIC data)

[redacted]

5.2.6.2.2.2.1 Probability of progression for patients on bosutinib treatment

The company's model assumes that the risks of progression following an MaHR is equal for ponatinib and bosutinib for patients in AP-CML.

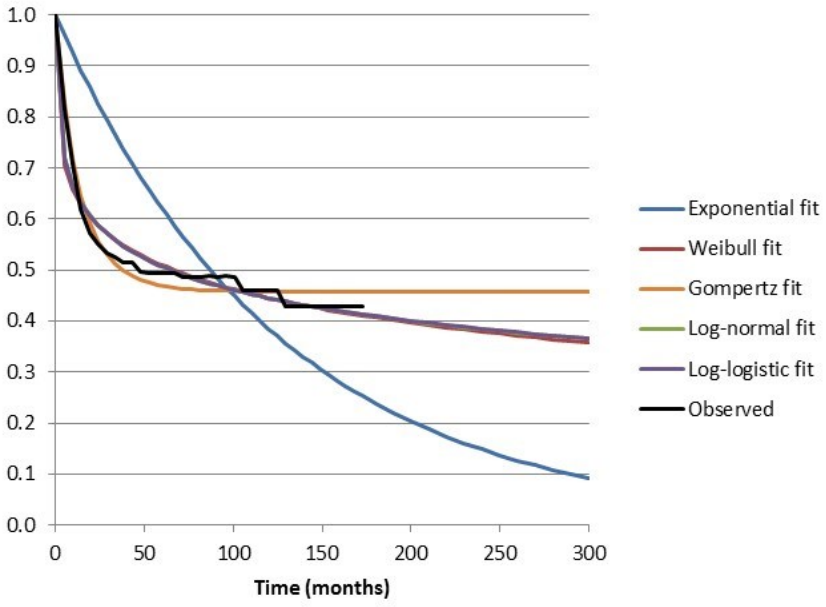
5.2.6.2.2.2.1 Probability of progression for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section 5.2.6.1.5.1.1.

5.2.6.2.3 Modelling assumptions for patients who have allo-SCT after an MaHR in AP-CML

Patients in AP-CML who have allo-SCT after an MaHR are assumed to remain in this state until death. The assumed probability of death was estimated from data in Radich,[70] which provided data on the following three groups of patients: (i) those with AP-CML; (ii) those with BP-CML in remission; and (iii) those with BP-CML without remission. Patients with MaHR in AP-CML were assumed to be equivalent to those reported as in AP-CML by Radich.[70] Parametric curves were fitted to the data by minimising the SSE and are illustrated in Figure 25. In this instance, the company did not select the curve that fitted best (the Gompertz with a value of 0.02) but instead selected the exponential distribution (with a value of 0.82) as this was believed to be more clinically plausible: the use of an exponential distribution assumes constant hazards. Clinical advice provided to the ERG suggest that the Gompertz fit was likely to be more plausible than the exponential as deaths occur relatively early following allo-SCT, but patients who survive for five years have a much lower risk of mortality.

Figure 25: Fitted curves to OS data for those in AP-CML who get allo-SCT after MaHR



Clinical advice provided to the ERG stated that the Radich[70] data were likely to be applicable for AP-CML and BP-CML patients, even though the data presented for CP-CML patients were not considered appropriate.

5.2.6.2.4 Modelling assumptions for patients who have allo-SCT on entering the model in AP-CML

Patients in AP-CML who have allo-SCT on entering the model are assumed to remain in this state until death. The probability of death was derived from Radich[70] assuming that the ratio between the two curves relating to BP-CML (remission and non-remission) would be applicable in AP-CML and that patients who had allo-SCT directly on entering the model were equivalent to AP-CML without remission.

5.2.6.3 Extrapolation of surrogate outcomes and linkages between health states in BP-CML

5.2.6.3.1 Transition probabilities for patients in BP-CML who experience an MaHR

Patients exit the MaHR state by undergoing allo-SCT as it is assumed that all patients are eligible for allo-SCT. The company's model assumes that there are no deaths until after allo-SCT occurs (at three months).

5.2.6.3.1.1 Exiting the MaHR state due to death

Whilst the model does not allow death from the MaHR state, the calculated curves are presented as they are required to estimate the probability of death in the non-MaHR state.

5.2.6.3.1.1.1 The probability of death for patients on ponatinib treatment

The process for people in BP-CML was similar to that for those in AP-CML, with OS estimated simultaneously for those with MaHR and NR through the use of a covariate for response level. The AIC and BIC statistics are presented in Table 47.

Table 47: AIC and BIC statistics presented by the company relating to OS for patients on ponatinib treatment in AP-CML (CIC data)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The fitted survivor functions are presented in

Figure 26. The company selected the log-normal distribution for use in the base case model, the exponential distribution had the lowest BIC value. The BIC values were similar across all functions thus the choice of the best fit is thus subject to considerable uncertainty.

Figure 26: Fitted curves to the OS data for those in BP-CML who get an MaHR on ponatinib treatment (CIC data)

5.2.6.3.1.1.2 Probability of death for patients on bosutinib treatment

The company's model assumes that the OS following an MaHR is equal for ponatinib and bosutinib for patients in BP-CML.

5.2.6.2.1.1.3 Probability of death for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section 5.2.6.1.5.1.2.

5.2.6.3.2 Transition probabilities for patients in BP-CML who experience NR

The next event for patients in BP-CML who have NR is death.

5.2.6.3.2.1 Exiting the MaHR state due to death

5.2.6.3.2.1.1 Probability of death for patients on ponatinib treatment

The curve-fitting process for people in BP-CML was similar to that for AP-CML. Goodness-of-fit statistics for the candidate distributions are shown in Table 47. The company selected the log-normal distribution as being the best fit to the data as it had the lowest AIC. The parametric curves are reproduced in

Figure 27. However, other curves have relatively similar values and produce different extrapolations. The survival rate beyond 20 weeks for the log-normal curve is greater than for the exponential distribution, which is plausibly a better fit to the data: this is likely to be favourable to ponatinib.

Figure 27: Fitted curves to the OS data for those in BP-CML who get NR on ponatinib treatment (CIC data)

5.2.6.3.1.1.2 Probability of death for patients on bosutinib treatment

The company's model assumes that the OS following NR is equal for ponatinib and bosutinib for patients in BP-CML.

5.2.6.3.1.1.3 Probability of death for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section 5.2.6.1.5.1.3.

5.2.6.3.3 Modelling assumptions for patients who have allo-SCT after an MaHR in BP-CML

Patients in BP-CML who have allo-SCT after an MaHR are assumed to remain in this state until death. The assumed probability of death was estimated from data in Radich.[70] Patients with MaHR in BP-CML were assumed to be equivalent to those reported by Radich[70] as being in BP-CML with remission. Parametric curves were fitted to the data by minimising the SSE and are illustrated in Figure 28. The company did not select the distribution that fitted best (the log-logistic function – SSE 0.03) but instead selected the exponential distribution (SSE 0.96) as this was believed to be more clinically plausible. An exponential distribution assumes constant hazards.

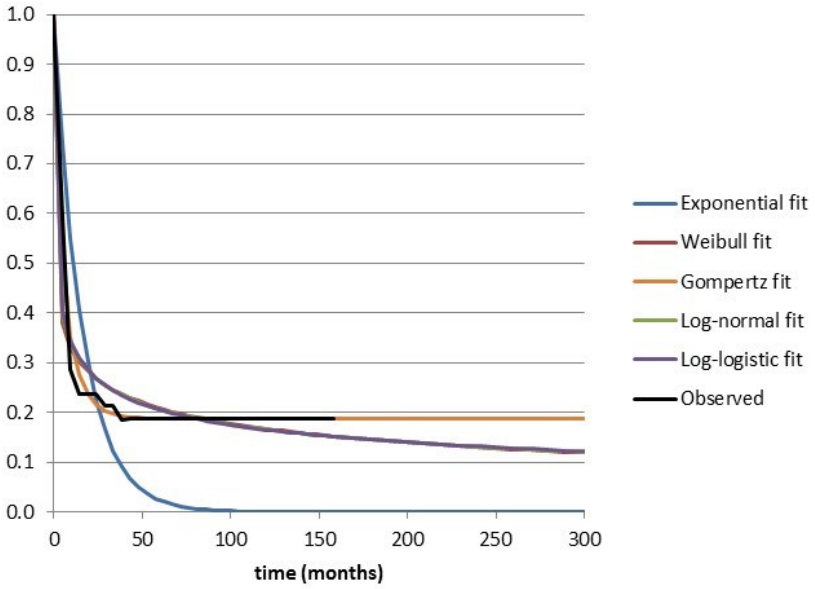
Figure 28: Fitted curves to the time to death for those in BP-CML who get allo-SCT after MaHR (CIC data)

5.2.6.3.4 Modelling assumptions for patients who have allo-SCT on entering the model in BP-CML

The assumed probability of death was estimated from data in Radich.[70] Patients with BP-CML who have allo-SCT directly on entering the model were assumed to be equivalent to those in BP-CML without remission. Parametric curves were fitted to the data by minimising the SSE and are illustrated in

Figure 29. The company did not select the curve that fitted best (the Gompertz – SSE: 0.01) but instead selected the exponential distribution (SSE: 0.93) as this was believed to be more clinically plausible. An exponential distribution assumes constant hazards.

Figure 29: Fitted curves to the time to death for those in BP-CML who get allo-SCT on model entry



5.2.7 Health-related quality of life

5.2.7.1 Selection of HRQoL decrements for patients with CML

The company identified one study[72] in the systematic literature review conducted for clinical efficacy, that provided HRQoL data but deemed that this study was not appropriate for a combination of the following reasons: it was a conference abstract with few details; it focussed on a narrow population; it was a retrospective observational study where clinicians responded; and the results could not be mapped to a utility. The ERG deems these reasons for exclusion to be reasonable. The PACE study did not record HRQoL.[22]

The company therefore performed a systematic review to identify evidence regarding HRQoL. An initial search focussed on published data between January 2000 and January 2016 with the search updated in July 2016. The following sources were searched: EMBASE and EMBASE Economic conference abstracts (via Ovid), MEDLINE (via Ovid), MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), Cochrane Central Register of Controlled Trials (via EBM Reviews), and Health Technology Assessment (via EMB Reviews). The company's search strategies comprised the terms for the population concept (CML) combined with sensitive search filters for retrieving quality of life studies. The ERG considered that the searches were comprehensive and adequate for the identifying evidence relating to HRQoL.

The CS (p138) includes a PRISMA flow diagram which concludes that nine articles were included in the HRQoL results. A summary of the nine studies is presented in Table 5.11 of the CS (p139). The company believed that two studies reported by Guest *et al*.[73, 74] and one study reported by Szabo *et al*.[75] were the most relevant as these concentrated on the disease rather than an intervention. The Szabo *et al*. study included CP-CML, AP-CML and BP-CML, whereas the Guest *et al.* studies were more focussed on the HRQoL of people in CML with different response levels. More details on the Szabo *et al*. study is provided in the CS (p140). Briefly, the study interviewed 357 people (97 from the UK) and employed time trade-off methods for valuing seven health states; these health states and their associated HRQoL are provided in

Table 48. It is assumed that any disutility associated with SAEs would only occur during the first model cycle.

Table 48: Estimated HRQoL reported by Szabo *et al.*[75] and the utility decrement assumed in the model

Health State	Estimated HRQoL (95% CI)	Utility decrement assumed in the model
CP-CML responding to treatment	0.91 (0.89 – 0.94)	0
CP-CML not responding to treatment	0.73 (0.69 – 0.78)	0.116
AP-CML responding to treatment	0.78 (0.74 – 0.82)	0.006
AP-CML not responding to treatment	0.53 (0.48 – 0.58)	0.316
BP-CML responding to treatment	0.56 (0.52 – 0.60)	0.286
BP-CML not responding to treatment	0.29 (0.24 – 0.33)	0.556
Treatment withdrawal due to SAEs	0.52 (0.46 – 0.58)	0.326

The value for patients with CP-CML who are responding to treatment is higher than the company's preferred source for utility estimates for the general public,[76] (See Section 5.2.7.3 Selection of utility values for members of the general public) which report utility values of 0.84 (males) and 0.85 (females) aged between 45 – 54 years. The company addressed this issue by capping the utility of those with CP-CML who are responding to treatment to that of the age- and gender-matched general population. The other utility values were left unchanged: this created a problem in that neither the absolute QALY difference between CP-CML and the remaining health states nor the relative ratio observed in Szabo *et al*.[75] were maintained in the model due to capping the value for people with CP-CML who respond to treatment. For example, assuming that the utility for people in CP-CML who were responding to treatment was capped at 0.84, the absolute difference between this state and those in AP-CML not

responding to treatment, reported to be 0.53 in Szabo *et al*. would be 0.316, rather than the 0.38 reported by Szabo *et al*.[75]

For patients starting the model in CP-CML, the definition of response to treatment was a CCyR; for those starting the model in AP-CML or BP-CML the definition of response to treatment was an MaHR.

5.2.7.2 Selection of HRQoL decrements for patients who have had an allo-SCT

The CS does not report how the utility values for patients who had an allo-SCT had been identified and therefore there is a possibility that the values used may have been chosen selectively. However, the value assumed for patients six months after allo-SCT was used in previous evaluations of CML.[51] The company estimated the utility decrement associated with each time period or relapse (see Table 49). The utility value post-relapse was estimated assuming that 36% of relapses occur in patients with CP-CML; 30% in patients with AP-CML; and 34% in patients with BP-CML and assuming that the utility decrements reported in Table 48 are appropriate. The ERG could not replicate the value reported by the company; however, as the results are relatively insensitive to this value, this issue has not been investigated further.

Table 49: Utility decrements associated with allo-SCT assumed by the company

Period after allo-SCT	Utility decrement assumed in the model	Source.
Up to three months post-allo-SCT	0.296	Van Agthoven *et al*.[77]
Between three and six months post-allo-SCT	0.216	Assumption: midpoint between value up to three months and beyond six months
Six months and longer post-allo-SCT	0.136	Loveman *et al*.[51]
Post-relapse	0.260	Derived from Kantarjian *et al*.[78] and Olaverria *et al*.[79]

5.2.7.3 Selection of utility values for members of the general public

The model used data presented by Kind *et al*.[76] to represent the HRQoL for the general population (see Table 50). The utility decrements reported in Table 48 and Table 49 are applied to the data in Table 50.

Whilst there are potentially more recent general population data[80] that could have been used, the ERG does not believe this would noticeably affect the results and this issue has not been investigated further.

Table 50: General population HRQoL used in the model[76]

Age band (years)	Males	Females
Under 25	0.94	0.94
25-34	0.93	0.93
35-44	0.91	0.91
45-54	0.84	0.85
55-64	0.78	0.81
65-74	0.78	0.78
75 and over	0.71	0.71

5.2.8 Resources and costs

5.2.8.1 Assumed acquisition costs of CML interventions

The company estimated the costs of CML for the following treatments: ponatinib; bosutinib; interferon alfa; BSC; imatinib; dasatinib; and nilotinib. As instructed by NICE, the company used the list prices for all treatments although confidential PAS discounts exist for bosutinib, dasatinib and nilotinib. A confidential appendix which contains results including the PAS discounts for treatments other than ponatinib has also been submitted to NICE as a separate document. Furthermore, during the timelines of this appraisal, imatinib is expected to lose its patent which could result in a large percentage reduction in acquisition cost.

The acquisition prices used by the company are reproduced in Table 51.

Table 51: Acquisition prices used in the company model

Drug	mg per unit	Units per pack	Cost per pack, £	Source
Ponatinib*	15	30	2,525.50	SKU price
	30	30	5,050.00	
	45	30	5,050.00	
Dasatinib	20	60	1,252.48	BNF
	50	60	2,504.96	
	80	30	2,504.96	
	100	30	2,504.96	
	140	30	2,504.96	
Nilotinib	150	112	2,432.85	BNF
	200	112	2,432.85	
Bosutinib	100	28	859.17	BNF
	500	28	3,436.67	
Imatinib	100	60	918.23	BNF
	400	30	1,836.48	
Hydroxycarbamide	500	100	10.47	BNF

BNF: British National Formulary; *International units

5.2.8.1.1 Assumed relative dose intensities of treatments

5.2.8.1.1.1 Assumed dose intensity of ponatinib

The assumed dose intensity of ponatinib was taken from the PACE study.[22] These data for patients in CP-CML are stated to be academic-in-confidence and are shown in Table 52. The data for patients with AP-CML and BP-CML are provided in Table 53. The company assumes that there would be no drug wastage: that is, that any doses missed in previous prescriptions would be stored and eventually one fewer prescription would be needed. The clinical advisors to the ERG considered this to be plausible, although the ERG has performed a scenario analysis to explore the impact of including wastage on the incremental cost-effectiveness ratio (ICER).

Table 52: Relative dose intensity assumed for ponatinib in CML patients

Ponatinib dose (mg per day)	Proportion of days on treatment			
	CCyR	PCyR	CHR	NR
0	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]

30	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]

CCyR: Complete cytogenetic response; PCyR: Partial cytogenetic response; CHR: Complete haematologic response; NR: No response

Table 53: Relative dose intensity assumed for ponatinib in AP-CML and BP-CML patients

Ponatinib dose (mg per day)	Proportion of days on treatment	
	AP-CML	BP-CML
0	[redacted]	[redacted]
15	[redacted]	[redacted]
30	[redacted]	[redacted]
45	[redacted]	[redacted]

AP: Accelerated phase; BP: Blast phase; CML: Chronic Myeloid Leukemia

5.2.8.1.1.2 Assumed dose intensity of bosutinib

The assumed dose intensity of bosutinib is assumed to equal the median dose intensity reported in Khoury *et al*.[42] of 95.6%.

5.2.8.1.1.3 Assumed dose intensity of BSC

The company's model assumes that the relative dose intensity of BSC is 100%.

5.2.8.1.1.4 Assumed dose intensities of dasatinib, nilotinib and imatinib used after progression of CML or allo-SCT relapse

The relative dose intensity of dasatinib was set to 100% from Shah *et al*.,[81] the dose intensity for nilotinib was assumed to be 99.7%,[82] whilst the company assumed that it was 100% for imatinib.

5.2.8.1.2 A summary of treatment acquisition costs

The assumed cost of each treatment per three-month cycle can be obtained by multiplying the acquisition cost by the relative dose intensity. These values are shown in Table 54.

Table 54: Cost of each CML treatment by cycle

Intervention	Cost per cycle (£)
Ponatinib in CP-CML (CCyR)	[redacted]
Ponatinib in CP-CML (PCyR)	[redacted]
Ponatinib in CP-CML (CHR)	[redacted]

Ponatinib in CP-CML (NR)	[redacted]
Ponatinib in AP-CML (CHR)	[redacted]
Ponatinib in BP-CML (NR)	[redacted]
Dasatinib	7624
Imatinib	5590
Nilotinib	7910
Interferon alfa	6833
Bosutinib	10,714
BSC	38

5.2.8.2 Assumed monitoring and hospital costs associated with CML treatments

Monitoring costs were assumed equivalent for all therapies in the same phase of CML, apart from additional cardiovascular monitoring for people receiving ponatinib treatment. The monitoring resources assumed within the model are replicated in Table 55.

In order to monitor potential cardiovascular events associated with ponatinib it was assumed that there would be an appointment every six months. The appointment was assumed to cost the same as a haematologist visit (£150.38).

Table 55: Monitoring and hospital resources required by CML phase and the assumed unit costs

Resource	CP-CML		AP/BP-CML	Unit cost, £	Source
	CCyR	No CCyR			
Outpatient visits					
Nurse-led	0.29	0.38	0.51	66.42	NHS Reference Costs 2014 to 2015
Haematologist-led	0.93	1.72	3.63	150.38	NHS Reference Costs 2014 to 2015
Tests					
Full blood count	1.13	1.97	4.38	3.01	NHS Reference Costs 2014 to 2015
Cytogenetic analysis	0.58	0.74	0.90	6.99	NHS Reference Costs 2014 to 2015
Bone marrow aspiration (with biopsy)	0.03	0.30	0.30	517.50	NHS Reference Costs 2014 to 2015
FISH	0.22	0.56	0.13	6.99	NHS Reference Costs 2014 to 2015
PCR	0.79	1.31	1.68	25.00	Szczepura et al. 2006 [49]
Flow cytometry	0.09	0.13	0.45	6.99	NHS Reference Costs 2014 to 2015
Cytochemistry analysis	–	0.05	0.12	6.99	NHS Reference Costs 2014 to 2015
Blood film exam	0.50	1.09	2.19	3.01	NHS Reference Costs 2014 to 2015
Blood chemistry	1.13	1.88	3.15	1.19	NHS Reference Costs 2014 to 2015
Kinase domain mutation*	–	–	0.13	6.99	NHS Reference Costs 2014 to 2015
Therapies/interventions					
Blood transfusion	0.01	0.01	1.98	121.85	NHS Blood and Transplant Price List 2014/15
Donor lymphocyte transfusion	–	–	–	193.15	Assumption: same as platelet transfusion
Platelet transfusion	–	–	0.30	193.15	NHS Blood and Transplant Price List 2014/15
Days in hospital				721.00	Average costs for a hospital day case based on finished consultant episodes (NHS Reference Costs 2014 to 2015)
CP	–	–			
AP			2.13		
BP			26.64		

AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CP, chronic phase; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction.

*Once only.

Ponatinib is assumed to have an additional cost of £75.19 per cycle to monitor cardiovascular events

A summary of the monitoring and hospital costs is provided in Table 56.

Table 56: Summarised monitoring and hospital costs per cycle

Health State	Monitoring costs (£)
CP- CML with CCyR	208
CP-CML without CCyR	495
AP- CML	2648
BP-CML	20,319

5.2.8.3 Assumed costs associated with allo-SCT

The company assumed that the cost of allo-SCT was £60,092. This estimate was based on data from the UK Stem Cell Strategy Oversight Committee[83] and is assumed to be independent of phase of CML The follow-up costs decreased over time, with a per cycle cost of: £12,215 in year 1; £3518 in year 2, and £420 in year 3. The company ran a scenario analysis where the costs associated with allo-SCT used in a relatively recent STA[29] were used instead (see Table 5-41 of the CS for further details).

5.2.8.4 The assumed costs associated with adverse events and serious adverse events

These costs are provided in

Table 40 (CP-CML), Table 41 (AP-CML) and Table 42 (BP-CML).

5.2.8.5 The assumed costs associated with end of life

The company's model assumes that all patients incur additional costs at death. The ERG notes that this may be inappropriate for patients who die of non-CML causes but is unlikely to markedly affect the ICER. This cost was estimated to be £5,766 per person based on a survey undertaken by the company. The components of this calculation are shown in Table 57 (reproduced from Table 5-25, p 156 of the CS).

Table 57: Estimated cost of end-of-life care

Description	Value	Daily cost, £	Source
In-patient stay, days	21.5	463.77	Marie Curie Cancer Care
Patients treated in hospital, %	51.5	-	Assumption
Hospice stay, days	17.4	158.23	Marie Curie Cancer Care
Patients treated in hospice, %	23.1	-	Assumption
Average end-of-life care cost, £		5,765.76	

5.2.9 Cost-effectiveness results

As stated, the results presented are from the company's revised models re-run by the ERG having applied the approved PAS for ponatinib (a discount of [redacted]). It should be noted that the results presented in this report do not incorporate the PAS for bosutinib, nilotinib, or dasatinib: these results are contained in a confidential appendix. The results have been divided into those for patients with: CP-CML; AP-CML; and BP-CML.

5.2.9.1 The company's results for patients with CP-CML

5.2.9.1.1 The company's base case results for patients with CP-CML

The base case results are presented in Table 58.

Table 58: The company's base case results for patients with CP-CML

Treatment	Life years gained	Discounted costs (£)	Discounted QALYs	ICER (£/QALY gained)	
				Ponatinib versus comparator	Full Incremental analysis
BSC	4.64	136,666	2.24	15,200	

Bosutinib	8.38	150,811	4.00	18,213	8,072
Interferon alfa	4.72	188,917	2.30	6395	Dominated
Allo-SCT	8.77	209,258	3.93	4042	Dominated
Ponatinib	[redacted]	[redacted]	[redacted]	-	18,213

5.2.9.1.2 The company's one-way sensitivity analyses for patients with CP-CML

The function contained within the company's model was used to generate a tornado plot that is replicated in Figure 30. Typically, the standard error of the mean was assumed to be 10% of the central value. As this function allowed only pairwise comparisons, the ERG analysed the ICER compared with the previous intervention on the efficiency frontier (in this case, bosutinib). Based on the company's assumptions, the ICER for ponatinib compared with bosutinib remained consistently below £25,000 per QALY gained.

Figure 30: Tornado diagram assessing the sensitivity of the ICER of ponatinib compared with bosutinib to changes in individual parameters (CIC data)

5.2.9.1.3 The company's probabilistic sensitivity analyses for patients with CP-CML

Similar to the one-way sensitivity analysis, the PSA was set up for pairwise comparisons only. As before, the ERG analysed the ICER compared with the previous intervention on the efficiency frontier (in this case, bosutinib): it was thought unlikely that the efficiency frontier would change. Based on the company's assumptions the ICER for ponatinib compared with bosutinib was approximately £20,000 per QALY gained (Table 59). One thousand PSA iterations were run. The ERG noticed variations in the ICER of £500 across repeat PSA runs. The ERG has numerous concerns regarding the robustness of the PSA undertaken.

Table 59: The company's probabilistic ICER for ponatinib compared with bosutinib for patients with CP-CML

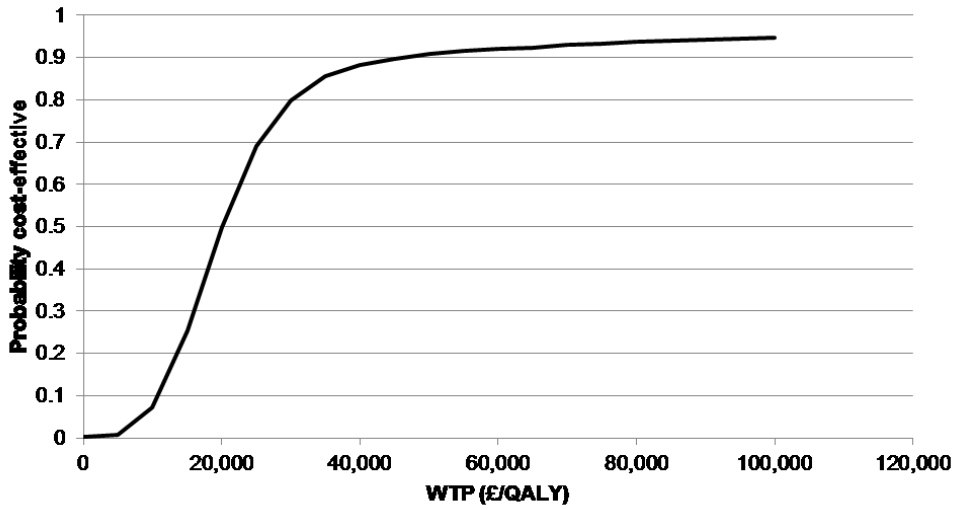
Treatment	Discounted costs (£)	Discounted QALYs	ICER (cost per QALY gained (£))
Bosutinib	152,599	3.98	
Ponatinib	[redacted]	[redacted]	20,657

The results from the PSA are shown in a cost-effectiveness plane (Figure 31) and a cost-effectiveness acceptability curve (Figure 32).

Figure 31: The company's PSA results for ponatinib compared with bosutinib for CP-CML patients shown on a cost-effectiveness plane (CIC data)

[redacted]

Figure 32: The company's PSA results for ponatinib compared with bosutinib for CP-CML patients shown on a cost-effectiveness acceptability curve (CIC data)



The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (51%); £30,000 (81%); and £50,000 (91%).

The company presented scenario analyses within the CS (Table 5-45), although these were at list price. These analyses have not been re-run by the ERG using the PAS discount for ponatinib.

5.2.9.2 The company's results for patients with AP-CML

5.2.9.2.1 The company's base case results for patients with AP-CML

The base case results are presented in Table 60.

Table 60: The company's base case results for patients with AP-CML

Treatment	Life years gained	Discounted costs (£)	Discounted QALYs	ICER (£/(cost per QALY gained)	
				Ponatinib versus comparator	Full Incremental analysis
BSC	1.91	95,263	0.58	14,750	-
Allo SCT	3.20	116,635	1.86	13,279	Extendedly Dominated
Ponatinib	[redacted]	[redacted]	[redacted]	-	14,750
Bosutinib	6.77	162,419	2.62	Dominant	Dominated

5.2.9.2.2 The company's one-way sensitivity analyses for patients with AP-CML

The function contained within the company's model was used to generate a tornado plot that is replicated in

Figure **33**. Typically, the standard error of the mean was assumed to be 10% of the central estimate. Based on the company's assumptions, the ICER for ponatinib compared with BSC remained consistently below £25,000 per QALY gained.

Figure 33: Tornado diagram assessing the sensitivity of the ICER of ponatinib compared with BSC to changes in individual parameters (CIC data)

5.2.9.2.3 The company's probabilistic sensitivity analyses for patients with AP-CML

One thousand PSA iterations were run. Results are presented for the ICER of ponatinib compared with BSC (see Table 61). The results from the PSA are shown in a cost-effectiveness plane (Figure 34) and a cost-effectiveness acceptability curve (see Figure 35). The ERG has numerous concerns regarding the robustness of the PSA undertaken.

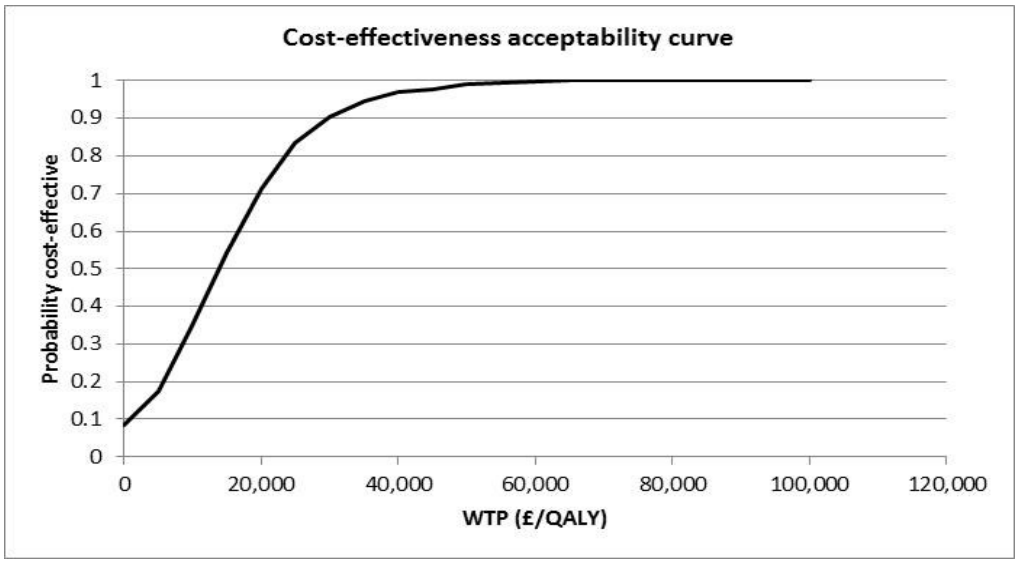
Table 61: The company's probabilistic ICER for ponatinib compared with BSC for patients with AP-CML

Treatment	Discounted Costs (£)	Discounted QALYs	ICER (cost (£) per QALY gained)
BSC	93,364	0.58	-
Ponatinib	[redacted]	[redacted]	13,481

Figure 34: The company's PSA results for ponatinib compared with bosutinib for AP-CML patients shown on a cost-effectiveness plane (CIC data)

[redacted]

Figure 35: The company's PSA results for ponatinib compared with bosutinib for AP-CML patients shown on a cost-effectiveness acceptability curve (CIC data)



The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (71%); £30,000 (90%); and £50,000 (99%).

5.2.9.3 The company's results for patients with BP-CML

5.2.9.3.1 The company's base case results for patients with BP-CML

The base case results are presented in Table 62.

Table 62: The company's base case results for patients with BP-CML

Treatment	Life years gained	Discounted costs (£)	Discounted QALYs	ICER ((cost (£) per QALY gained)	
				Ponatinib versus comparator	Full Incremental analysis
Bosutinib	0.85	71,473	0.37	17,601	-
Ponatinib	[redacted]	[redacted]	[redacted]	-	£17,601
BSC	1.16	101,961	0.28	Dominant	Dominated
Allo-SCT	1.34	103,748	0.85	Dominant	Dominated

5.2.9.3.2 The company's one-way sensitivity analyses for patients with BP-CML

The function contained within the company's model was used to generate a tornado plot that is replicated in Figure 36. Typically, the standard error of the mean was assumed to be 10% of the central value. Based on the company's assumptions, the ICER for ponatinib compared with bosutinib remained consistently below £30,000 per QALY gained.

Figure 36: Tornado diagram assessing the sensitivity of the ICER of ponatinib compared with bosutinib to changes in individual parameters (CIC data)

5.2.9.3.3 The company's probabilistic sensitivity analyses for patients with BP-CML

One thousand PSA iterations were run. Results are presented for the ICER of ponatinib compared with BSC (Table 63). The results from the PSA are shown in a cost-effectiveness plane (Figure 37) and a cost-effectiveness acceptability curve (

Figure **38**). The ERG has numerous concerns regarding the robustness of the PSA undertaken.

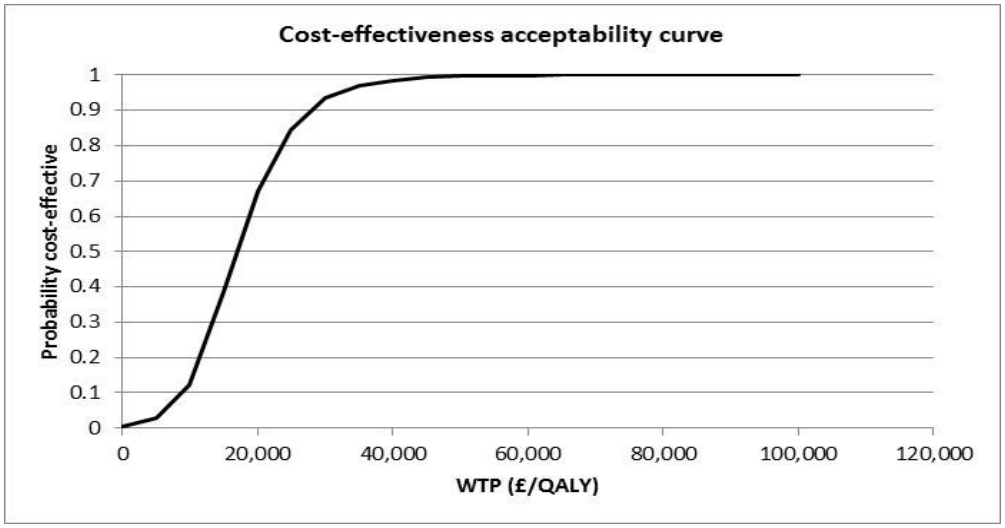
Table 63: The company's probabilistic ICER for ponatinib compared with BSC for patients with BP-CML

Treatment	Discounted costs (£)	Discounted QALYs	ICER (cost (£) per QALY gained)
Bosutinib	73,274	0.39	-
Ponatinib	[redacted]	[redacted]	16,229

Figure 37: The company's PSA results for ponatinib compared with bosutinib for BP-CML patients shown on a cost-effectiveness plane (CIC data)

[redacted]

Figure 38: The company's PSA results for ponatinib compared with bosutinib for BP-CML patients shown on a cost-effectiveness acceptability curve (CIC data)



The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (67%); £30,000 (94%); and £50,000 (100%).

5.2.10 Summary of the ERG's consideration of the model submitted by the company

In general, the ERG is satisfied with the structure of the model having noted that similar reliance on surrogate endpoints, such as level of response, have been accepted in previous NICE appraisals of CML treatments. There is inherent uncertainty introduced by the use of a MAIC, but there was no indication that this had been undertaken with an objective of favouring ponatinib. The data used to estimate the resource use were deemed reasonable and only a minor concern was raised by the ERG regarding the impact of capping utility for those with CP-CML who respond to treatment. The biggest concern of the ERG is that the parametric distributions fitted where individual patient data were not available is inappropriate, and that for all distributions there was insufficient exploration of the impact on the ICER of the selection of alternative curves that were considered plausible. The model also ignored any possibility of treatment-related death. The ERG believes that the PSA undertaken by the company was not robust die to the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters. Further limitations have been identified, although to spare repetition these are only listed in Section 5.3.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of exploratory sensitivity analyses (see Sections 5.3.1 to Section 5.3.9). Analyses that the ERG would like to have conducted but which were not possible are discussed in Section 5.3.10. The results of the exploratory analyses are provided in Section 6.

For CP-CML the analysis was of ponatinib compared to bosutinib. For AP-CML, two comparators were used, BSC and SCT as the efficiency frontier was likely to change based on the chosen assumptions: bosutinib was typically dominated by ponatinib. For BP-CML the comparison was of ponatinib compared to bosutinib.

PSA has not been conducted due to insufficient time, the wide range of ICERs using different assumptions, and the ERG's belief that the PSA undertaken by the company is not robust.

5.3.1 Choosing alternative curves to those selected by the company

The ERG believes insufficient sensitivity analyses were undertaken by the company. Kass *et al*.[67] state that a difference in the BIC of less than two is barely worth a mention, whilst only difference values of six or greater indicate strong evidence that one curve may be preferable to another. In addition, the BIC does not take clinical plausibility of the extrapolation into account. Taking the BIC and clinical plausibility into consideration, the ERG undertook exploratory results using alternative curve fits to those selected by the company. A list of curves considered to be potentially credible by the ERG and the clinical advisors to the ERG are provided in Table 64 for the CP-CML model and Table 65 for the AP-CML / BP-CML model. Exploring all combinations of curves in the CP-CML model would result in 34,560 results: this was not considered feasible within the time scales of the appraisal. Instead, where multiple curves were thought plausible, the company's base case was explored along with the curve that had the most different extrapolation from the company's default curve, to test extreme values, resulting in 1024 scenarios run. The exception was for the DoR for ponatinib where the log-normal function was chosen rather than log-logistic function so that the same functions were used for ponatib and for bosutinib.

For brevity, the ICERs relating to the 1024 CP-CML scenarios have not been included in this report, although the Excel file containing all the answers will be brought to the committee so that the ICERs for specific scenarios can be provided as required. A similar approach to curve fitting has been taken for the AP-CML scenarios and the BP-CML scenarios.

In addition to the multiple scenarios, the ERG does not believe the exponential distribution fitted to the PFS data for NR in CP-CML is robust as the predicted value at month 40 was considerably less than the observed value (see Figure 13). In exploratory analyses, the ERG fitted an exponential to these data assuming that it passed through the final data point. Additional analyses were undertaken assuming that

the same method (that is an exponential curve passing through the final point) was applied for the PFS values related to CCyR, PCyR and NR.

5.3.2 Re-calculation of the survivor functions

As previously stated the ERG has concerns with the estimation of survivor functions provided by the company. The ERG has calculated these where possible, using the approach advocated by Guyot *et al*.[65] with full details provided in Appendix 1.

The ERG comments that the final two columns in both Table 64 and Table 65 use the same data. As such these estimates are identical between the models. The discussion of the ERG's fitted curves to these data are only presented once in Appendix 1.

Table 64: Distributions considered to be credible fits to the data and for clinical plausibility in the extrapolation phase. CP-CML model

Parameters for which the ERG did not routinely undertake alternative curve fitting					Parameters for which the ERG did undertake alternative curve fitting					
DoR - ponatinib	PFS with CCyR	PFS with PCyR	PFS with CHR	PFS with NR	DoR - bosutinib	OS after SCT in CP-CML	OS after SCT in AP-CML	Relapse-free survival after SCT	OS in AP-CML	OS in BP-CML
Gomp (C)	Gomp (C)	Gomp (C)	Gomp	Exp (C)	Gomp (C)	Exp (C)	Exp (C)	Gomp (C)	Log-N (C)	Log-N (A)
Log-N (A)	Log-N	Log-N (A)	Log-N	Log-N (A)	Log-N (A)	Gomp (A)	Gomp (A)	Log-N (A)		Log-L (C)
Log-L	Log-L	Log-L	Log-L (A)			Log-N	Log-N			
	Weib (A)	Weib	Weib (C)				Log-L			
							Weib			

Exp = exponential; Gomp = Gompertz; Log-L = log-logistic; Log-N = Log-normal; Weib = Weibull

(C) denotes that the distribution was used within the company's model; (A) denotes that it was the alternative curve used in the exploratory analyses.
Note that an additional analysis was undertaken using the ERG estimated exponential distributions for all PFS values

Table 65: Distributions considered to be credible fits to the data and for clinical plausibility in the extrapolation phase. AP-CML and BP-CML model

Parameters for which the ERG did not undertake alternative curve fitting								Parameters for which the ERG did undertake alternative curve fitting					
OS in AP-CML	OS in BP-CML	PFS in AP-CML	Time on Treatment in AP-CML ponatinib	Time on Treatment in BP-CML ponatinib	Time on treatment in AP-CML bosutinib	Time on treatment in BP-CML bosutinib	Time to PFS on BSC	OS post-allo-SCT in AP-CML with remission	OS post-allo-SCT in AP-CML without remission	OS post-allo-SCT in BP-CML with remission	OS post-allo-SCT in BP-CML without remission	OS in AP-CML on BSC	OS in BP-CML on BSC
Exp (A)	Exp (A)	Log-N (C)	Exp (C)	Exp (C)	Exp (C)	Exp (C)	Exp (C)	Exp(C)	Exp(C)	Exp(C)	Exp(C)	Log-N (C)	Log-N (A)
Log-N (C)	Log-N (C)	Log-L (A)						Gomp (A)	Gomp (A)	Gomp (A)	Gomp (A)		Log-L (C)

Exp = exponential; Gomp = Gompertz; Log-L = log-logistic; Log-N = Log-normal; Weib = Weibull

(C) denotes that the distribution was used within the company's model; (A) denotes that it was the alternative curve used in the exploratory analyses.
Note that an additional analysis was undertaken using the ERG estimated exponential distributions for all PFS values

5.3.3 Assuming drug wastage

The company's model assumes that missed dosages of treatment will be saved and that ultimately fewer packs of ponatinib or bosutinib would be used, which is equivalent to assuming no drug wastage. The ERG conducted analyses assuming that dosages not taken would not be recouped but would incur the cost but produce no clinical benefit. Clinical advice to the ERG indicated that stock-piling of pills and skipping a pack may be possible in CP-CML, but may be less likely in AP-CML or BP-CML.

5.3.4 Introducing a stopping rule for bosutinib

The company's model assumes that unlike patients receiving ponatinib, patients receiving bosutinib would continue to receive bosutinib despite no response in CP-CML, or despite failing to achieve an MaHR in AP-CML or BP-CML. The ERG has amended the model to allow the same stopping rules for ponatinib to bosutinib to be considered. The clinical experts to the ERG believe that it is likely to be clinician dependent, but that many clinicians would stop if there was no response experienced.

5.3.5 Removing the half-cycle correction for intervention costs

The company's model half-cycle corrects the costs for interventions. In their response to clarification,[28] (question B33) the company states that '*not all patients remain on treatment for the entire cycle as a combined result of events such as death, progression and discontinuation, that may occur during the cycle.*' For precisely this reason, the ERG believes that the intervention costs should not be half-cycle corrected, as should a patient discontinue or die, the intervention provided to the patient would not be re-used and would need to be disposed of. The ERG method will over-estimate the impact as it is unlikely that medicines will be provided at three-monthly periods, except for stable CP-CML patients after the initial few months of treatment. However, as the company's model uses three-month time cycles this was the best approximation that could be explored within the time constraints of the appraisal.

5.3.6 Incorporating the impact of deaths related to an intervention

The company does not incorporate the possibility of treatment-related death despite providing such information within the clarification response process[28] (questions A15 and B4). The values for treatment-related death used in the exploratory model were for ponatinib: [redacted]/267 in CP-CML ([redacted]%); [redacted]/83 in AP-CML ([redacted]%); and [redacted]/62 ([redacted]%) in BP-CML.[38, 53] For bosutinib these values were: 1/118 in CP-CML[41] (0.8%); and 2/167 (1.2%) for patients in AP-CML and BP-CML.[39] In order to explore the impact of treatment-related death, it was assumed that patients affected would gain zero QALYs at a cost of one cycle of treatment.

5.3.7 Amending the costs of treatment post CP-CML progression and post-allo-SCT relapse

The company assumes that following progression of disease in CML and for patients who relapse post allo-SCT that patients would be split equally between, nilotinib, dasatinib, bosutinib, imatinib and BSC. There is a logical error in that bosutinib would not be used after bosutinib failure, however more importantly, the survival estimates are not aligned with the cost-estimates. The PFS for patients in AP-CML and BP-CML were taken from Kantarjian *et al*.[68] using data from patients for whom imatinib had failed who then received treatment other than dasatinib, nilotinib, or allo-SCT. This was represented by an 'other' curve which had a poorer prognosis than either dasatinib, or nilotinib grouped, or allo-SCT, and is thus likely to be close to BSC. As such, the ERG has explored the impact of setting the costs post-CP-CML progression and post-allo-SCT relapse to those of BSC, and has further explored the impact of using the estimated costs of generic imatinib, which was assumed to be 5% of current prices, based on Hill *et al*.[16]

5.3.8 Assuming that the data in the life tables are probabilities rather than rates

The company assumes that the life table data are rates, whereas the ERG believes these data to be probabilities: the terminology used is ambiguous in the source data. The ERG undertook an analysis whereby these data are treated as probabilities.

5.3.9 Using alternative assumptions re HRQoL

The method for modelling HRQoL decrements used by the company artificially decreases the difference in the utility for CML health states reported by Szabo *et al*.[75] The ERG implemented two alternative methods: one in which the relative proportion between other CML states and CP-CML is maintained; and one in which the absolute utility decrements between the CML states is maintained.

5.3.10 Additional work that was not undertaken due to the timelines of the STA

The ERG believes that there are multiple errors with the company's PSA which means that the results produced using the company's method are of limited value. These errors include: inappropriate characterisation of uncertainty and correlation between variables within the results of the survival analyses; and normalisation of values such that the values equalled one rather than this being a fundamental constraint of the sampling, and the arbitrary estimation of the standard error as 10% of the mean when, for example, these could be calculated using the quartile values reported in NHS Reference Costs. Furthermore, an assessment of the impact of continuity corrections, where the count of number of events are low, would have been beneficial. There was insufficient time within the appraisal timescales for the ERG to remedy these problems. The ERG also noted that there was, at times, such

uncertainty in the ICER due to the curve chosen to predict the extrapolation, that the likely change in the ICER due to the PSA, would be less than the changes due to the choice of the distribution.

There was insufficient time for the ERG to revisit previous NICE appraisals of treatments for CML and to compare and contrast the sources used within the modelling for parameter estimates. It was not possible to formally appraise the cost-effectiveness of ponatinib in those who are known to have, or not have, the T315I mutation. The likely impact of the knowledge of the presence, or not, of the T315I mutation has been discussed narratively.

Clinical advice provided to the ERG suggested that many patients receiving an allo-SCT after non-allo-SCT treatments would have this in CP-CML, rather than waiting for the patient to progress to AP-CML, due to better prognosis if the allo-SCT is undertaken in CP-CML. It was not possible in the timelines of the STA for the ERG to produce this analysis.

5.4 Conclusions of the cost-effectiveness section

The CS mainly adhered to the decision problem, however, clinical advice provided to the ERG suggested that induction chemotherapy should have been considered a comparator in BP-CML. The company assumptions result in estimated ICERs, having applied the PAS discount for ponatinib, of: £18,213 per QALY gained compared with bosutinib in CP-CML; £14,750 per QALY gained compared with BSC in AP-CML; and £17,601 per QALY gained compared with bosutinib in CP-CML. However, the ERG does not always agree with the choice of parameter values or distributions used in the company's base case. As such it is believed that the uncertainty in the decision was greatly underestimated by the company. The ERG has assessed the potential implications of changes to the model within Section 6. The results of probabilistic sensitivity analyses were not considered robust by the ERG.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The impacts of the exploratory analyses undertaken are reported in this section. All analyses have been undertaken using the list price of drugs relevant to the decision problem with the exception of ponatinib: the results including the PAS discounts for these drugs are provided in a separate confidential appendix.

The analyses are undertaken in comparison to the previous intervention on the efficiency frontier and against other interventions that could, based on the chosen assumptions, become the previous intervention on the efficiency frontier.

The results presented are subject to further levels of uncertainty, such as the lack of a robust PSA, the lack of continuity corrections for low observed counts, and the inherent uncertainty associated with data produced via an MAIC for the CP-CML analyses.

6.1 Results for CP-CML

The results are presented in Table 66. The ERG's base case does not include drug wastage and thus the ICER is likely to be lower than the ICER if the true level of wastage was incorporated. Treatment-related deaths have not been incorporated in the base case; this is favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large, thereby indicating considerable uncertainty in the ICER.

6.1.1 Results for ponatinib compared with bosutinib for CP-CML patients

For the comparison of ponatinib with bosutinib, the largest drivers of the ICER include: drug wastage; the estimation of costs post-progression and post-allo-SCT relapse; the inclusion of a stopping rule for bosutinib; the use of the log-normal distribution rather than the Gompertz distribution for DoR for both ponatinib and bosutinib; and use of the log-normal distribution rather than the exponential distribution for characterising PFS for those patients who achieve NR from treatment. The fit of the exponential and the log-normal distributions to PFS for those with NR performed by the company can be seen in Figure 13. The company's fit of the Gompertz and log-normal distributions to DoR are shown in Figure 5 and Figure 9 for ponatinib and Figure 6 for bosutinib.

The ERG believes that the ICER is likely to lie in the range £22,995 - £42,097 although any drug wastage would increase these values. The upper bound can be reduced if it is believed that the data for

PFS in NR can be best represented by an exponential curve, although the ERG notes that both the exponential curves fitted by the company and the ERG provide a poor fit to the observed data.

6.1.2 Results for ponatinib compared with BSC for CP-CML patients

For the comparison of ponatinib with BSC, the largest drivers of the ICER include: drug wastage; and the estimation of costs post-progression. For the comparison of ponatinib with BSC, the ERG believes that the ICER is likely to lie in the range £18,246 - £27,667 although any drug wastage or ponatinib-related deaths would increase these values.

6.1.3. Results for ponatinib compared with allo-SCT for CP-CML patients

For the comparison of ponatinib with allo-SCT, the largest drivers of the ICER include: drug wastage; the estimation of costs post-progression and post-allo-SCT relapse; and the assumed distribution for characterising OS following allo-SCT (either Gompertz or exponential) for patients in CP-CML. The company's fits of the Gompertz and exponential distributions to OS data post allo-SCT are provided in Figure 20. The ERG believes that the ICER for the comparison of ponatinib versus allo-SCT is highly uncertain. However, it is likely that the ICER is greater than £18,000 and it possible that ponatinib could be dominated by allo-SCT. When the Gompertz distribution was selected for OS after allo-SCT the ICER was generally greater than £100,000. Clinical advice received by the ERG suggested that the Gompertz distribution was likely to be the more plausible of the two distributions.

6.1.4 Results for ponatinib compared with interferon alfa for AP-CML patients

The ERG believes that probability that interferon alfa would be on the efficiency frontier is low, regardless of the assumptions made. As such, no further analyses were conducted by the ERG.

Table 66: Impact of the ERG's deterministic exploratory analyses in CP-CML

		Cost per QALY gained (£)		
Ref No	**Exploratory Analyses**	**Pon vs Bos**	**Pon vs BSC**	**Pon vs allo-SCT**
0	N/A (company's base case)	18,213	15,200	4042
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	13,747 – 43,344	12,063 – 22,295	Dominant – 12,091
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	15,319 – 38,710	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	13,747 – 27,616	12,063 – 21,150	Dominant – 12,091
1d	Combining 1b and 1c	15,319 – 25,181	12,063 – 21,150	Dominant – 12,091
2a	Recalculation of the survivor functions (excluding PFS exponentials)	16,297	13,661	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	17,073	14,860	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	18,092	15,424	Dominant
3	Assuming drug wastage	30,754	24,245	16,487
4	Incorporating a three-month stopping rule for bosutinib	21,313	15,200	4042
5	No half-cycle correction of intervention costs	17,785	15,709	5472
6	Including treatment-related deaths	18,099	16,810	6143
7a	Reducing the costs assumed post-progression in CP-CML or post allo-SCT for CP-CML patients to that of BSC.	21,717	18,688	21,712
7b	Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib.	21,584	18,555	21.039
8	Assuming life table data are probabilities not rates	18,226	15,211	4043
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	18,017	15,035	4096
9b	Assuming decrements of HRQoL between CP-CML and other CML states are maintained	17,920	14,954	4125
10	2a, 4,5,6, 7a, 8 and 9a, using the curves believed most credible by the company	23,059	18,308	27,649
11. ERG base case ICERs	As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a) As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,986 – 52,121 22,995 – 42,637	18,246 – 27,667 N/A	18,279 – Dominated N/A

The ERG base case ICERs are likely to be favourable to ponatinib as neither drug wastage nor treatment-related deaths are assumed

All analyses are changes from the company's base case unless stated. ↑ cost per QALY yielded

6.2 Results for AP-CML

The results are presented in Table 67.

The ERG's base case includes drug wastage, assuming that prescriptions occur at three-monthly intervals: the ICER would be lower if shorter prescription periods were incorporated, although this was not possible due to the length of time cycles employed in the company's model. Treatment-related deaths have not been incorporated in the base case which is likely to have been favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large in the comparison of ponatinib with allo-SCT indicating considerable uncertainty in the ICER.

6.1.1 Results for ponatinib compared with bosutinib for AP-CML patients

For the comparison of ponatinib with bosutinib, ponatinib typically dominated bosutinib. As such, no further analyses were conducted by the ERG.

6.1.2 Results for ponatinib compared with BSC for AP-CML patients

For the comparison of ponatinib with BSC the ERG believes it unlikely that the ICER is greater than £18,000 per QALY gained.

6.1.3 Results for ponatinib compared with allo-SCT for AP-CML patients

For the comparison of ponatinib with allo-SCT the largest drivers of the ICER is the distribution assumed for OS post allo-SCT. The fits of the Gompertz and exponential distributions to OS data post allo-SCT produced by the company are provided in Figure 25: the distributions estimated by the ERG are shown in Appendix 1 (Figure 46).

The ICER for the comparison of ponatinib with allo-SCT is believed to be uncertain by the ERG: ponatinib could dominate allo-SCT, that is being less expensive and providing more health to the patient, or the ICER could be greater than £63,000 per QALY gained.

Table 67: Impact of the ERG's deterministic exploratory analyses in AP-CML

		Cost per QALY gained (£) – Ponatinib vs	
Ref No	**Exploratory Analyses**	**BSC**	**Allo-SCT**
0	N/A (company's base case)	14,750	13,279
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	7479 – 15,861	Dominating – 95,313
2	Recalculation of the survivor functions	10,358	12,217
3	Assuming drug wastage	15,267	14,199
4	No half-cycle correction of intervention costs	16,580	16,465
5	Including treatment-related deaths	14,747	12,671
6	Assuming life table data are probabilities not rates	14,754	13,285
7	2,3, 4, and 6 using the curves believed most credible by the company	12,975	16,412
8 ERG base case ICER	As 7, but choosing alternative distributions in addition to those selected by the company (range)	7475 – 18,005	Dominating – 63,701

Note: the ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

Ponatinib typically dominates bosutinib

Note: All analyses are changes from the company's base case unless stated.

6.3 Results for BP-CML

The results are presented in

Table 68.

The ERG's base case includes drug wastage, assuming that prescriptions occur at three-monthly intervals: the ICER would be lower if shorter prescription periods were incorporated, although this was not possible due to the length of time cycles employed in the model. Treatment-related deaths have not been incorporated in the base case which is likely to have been favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large in the comparison of ponatinib with allo-SCT indicating considerable uncertainty in the ICER.

6.3.1 Results for ponatinib compared with bosutinib for BP-CML patients

For the comparison of ponatinib with BSC the ERG believes it unlikely that the ICER is greater than £23,000 per QALY gained.

6.3.2 Results for ponatinib compared with BSC for BP-CML patients

For the comparison of ponatinib with BSC, ponatinib typically dominated BSC due to the high costs of monitoring and follow-up of BP-CML patients, which are assumed to be greater than £20,000 per three-month period; these are largely driven by hospitalisation costs. As such, no further analyses were conducted.

6.3.3 Results for ponatinib compared with allo-SCT for BP-CML patients

For the comparison of ponatinib with allo-SCT, the largest drivers of the ICER is the distribution assumed for OS post allo-SCT for those with remission and those without remission (either Gompertz or exponential). The fits of the Gompertz and exponential distributions to OS data post allo-SCT produced by the company are provided in Figure 29: the distributions estimated by the ERG are shown in Appendix 1 (Figure 48).

The ERG considers the ICER for ponatinib versus allo-SCT to be uncertain: allo-SCT could be dominated by ponatinib, that is being more expensive and providing less health to the patient, or the ICER could be lower than £5000 per QALY gained.

Table 68: Impact of the ERG's deterministic exploratory analyses in BP-CML

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,601	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	11,184 – 18,808	8,251 - Dominated
2	Recalculation of the survivor functions	15,812	157,193
3	Assuming drug wastage	18,022	Dominated
4	Incorporating a three-month stopping rule for bosutinib	21,910	Dominated
5	No half-cycle correction of intervention costs	18,396	Dominated
6	Including treatment-related deaths	16,665	Dominated
7	Assuming life table data are probabilities not rates	17,601	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	21,254	102,612
9 ERG base case ICER	As 8, but choosing alternative distributions in addition to those selected by the company (range)	17,066 – 22,512	4,004 - Dominated

Note: the ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

Note: the comparison of ponatinib with allo-SCT is the cost per QALY gained of allo-SCT compared with ponatinib (South-West quadrant).

Ponatinib typically dominates BSC

Note: All analyses are changes from the company's base case unless stated.

6.4 Exploratory analyses for patients known to be with, and without, the T315I mutation

The company did not present results for patients with, and without the T315I mutation.

The ERG believes that for patients known to have the T315I mutation the most appropriate comparison would exclude bosutinib. This results in an estimated ICER in CP-CML in the range £18,246 - £27,667 per QALY gained compared with BSC, and remaining uncertain compared with allo-SCT. In AP-CML, the ICER is estimated to be in the range £7475 - £18,005 per QALY gained compared with BSC, and remaining uncertain compared with allo-SCT. In BP-CML, ponatinib is estimated to dominate BSC, and the ICER is uncertain compared with allo-SCT.

For patients known to not have the T315I mutation it is anticipated that the lower and upper values in the range in the cost per QALY gained compared with bosutinib would increase, that is, become less favourable to ponatinib. However, the precise increase in these values is unknown.

6.5 Exploratory analyses assessing the ICER if induction chemotherapy was considered as a comparator in BP-CML

Clinical advisors to the ERG suggested that induction chemotherapy should have been considered as a comparator in BP-CML. To explore the impacts of allowing this comparator it was assumed that the results for induction chemotherapy in Ph+ ALL were generalisable to patients in BP-CML. The ICER for ponatinib compared with induction chemotherapy has been estimated to be below £12,000 per QALY gained.

7 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

For patients with CP-CML, the company's model predicts that regardless of the intervention that patients would live in excess of four years. As such the ERG does not believe that ponatinib satisfies the end of life criteria in CP-CML

For patients with AP-CML, the company's model estimates that, on average, those patients receiving bosutinib would live in excess of six years; those that receive allo-SCT would live in excess of three years, whilst those who receive BSC would live slightly under two years. It is commented that the average life expectancy for patients on non-allo-SCT treatments is comprised of two groups with different prognoses: those that achieve an MaHR and those that do not. The model predicts a large extension in health for ponatinib compared with BSC, in excess of six years, and thus the ERG believes that ponatinib could satisfy the end of life criteria where BSC is the only comparator in AP-CML, but not when either bosutinib or allo-SCT was an appropriate comparator.

For patients with BP-CML, the company's model estimates that those patients receiving bosutinib, allo-SCT or BSC would not live greater than two years, although this value increases greatly if it is assumed that OS following allo-SCT is characterised by a Gompertz distribution. The model predicts that ponatinib provides greater than three months' of extension of life compared with the comparators. Under these circumstances, the ERG believes that ponatinib is likely to satisfy the end of life criteria for patients with BP-CML, unless it is assumed that the OS following allo-SCT is lengthy. As clinical advice provided to the ERG suggested that some patients can be cured with allo-SCT, the possibility that the OS following allo-SCT being lengthy cannot be discounted.

8 OVERALL CONCLUSIONS

Clinical effectiveness

In the absence of direct comparative data with other treatments, the main evidence in the CS was derived from a phase II, industry-sponsored, single-arm, non-comparative, open-label, study. The efficacy (measured in terms of surrogate response measures e.g. MCyR, MaHR and CCyR) in the PACE study appears favourable, and the safety appears acceptable. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Whilst the study was generally well reported and conducted, single-arm studies are associated with an array of potential biases including a high risk of selection bias (due to the absence of randomisation), performance and detection bias (due to the absence of blinding). In addition, due to the absence of a controlled comparator group in the PACE study, inference of treatment effects (including magnitude) may be confounded and its ability to compare or demonstrate efficacy with other current treatments is limited. A further limitation to the robustness of the efficacy and safety data relate to the small subgroups that comprise the target population in the CS, including lack of statistical power for the subgroup assessments. The key uncertainties in the clinical evidence for CML relate to optimal dosing, duration of treatment and magnitude of treatment effect.

Cost-effectiveness

The ICER of ponatinib compared to the comparators within the scope is typically uncertain, particularly with respect to allo-SCT.

In CP-CML the ERG's estimate of the ICER of ponatinib is uncertain, ranging from £22,863 – £42,097 in comparison with bosutinib, from £18,136 – £27,501 in comparison with BSC and from £18,438 – dominated, but nearer the upper end, of the range, in comparison with allo-SCT.

In AP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £20,000 compared with bosutinib, below £18,000 compared with BSC, and from dominating – £63,701, but nearer the upper end of the range, in comparison with allo-SCT.

In BP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £25,000 compared with bosutinib and ponatinib was estimated to dominate BSC. The ICER of allo-SCT compared with ponatinib is estimated to lie between dominating and 63,701, but nearer the lower end of the range.

8.1 Implications for research

There are no direct comparisons on the clinical and cost effectiveness of third-line ponatinib with other current treatments such as bosutinib in patients with CP-CML, AP-CML and BP-CML. Hence there is

a need for a study that directly compares these treatments, collects sufficient evidence on resource use and costs, and is powered to detect clinically meaningful changes in response outcomes. Studies of ponatinib are also needed to establish the optimal dose and treatment duration and investigate the safety and efficacy for the use in patients who need to restart treatment. In addition, as there are currently no phenotypes (or prognostic factors for relapse) to predict successful stopping further investigations to identify these factors would be beneficial.

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10 APPENDIX

Appendix 1: Fitting parametric survival curves to reconstructed individual patient level data from published Kaplan-Meier data

Exploratory analyses were undertaken by the ERG to explore the impact of using the method proposed by Guyot *et al.*[65] to fit parametric survival curves, as opposed to the method based on minimising the SSE that was adopted by the company. This section summarises the methods and results of these analyses.

1.1 Methods

Published Kaplan-Meier (KM) survival curves were digitised using the Engauge Digitizer.[84] Where the ERG believed that the company's digitisation was of sufficient resolution (capturing each step of the KM curve) the digitised values provided in the company model were used by the ERG. When this was not deemed to be the case the ERG re-digitised the published curves.

IPD was then reconstructed from the digitised curves using the Guyot algorithm.[65] This maps the digitised curves back to KM data by finding numerical solutions to the inverted KM equations. Where available, information on the number of events and the numbers at risk is also incorporated. The following information is used for the IPD reconstruction process:

- Extracted x-axis coordinates, T_k, and y-axis coordinates, S_k, for $k = 1, \ldots, N$ points on the KM curve (**required**).
- Reported number at risk table (**optional**)
- Total number of events (**optional**)

After extracting the T_k and S_k the resulting estimates were checked for any anomalies caused by poor publication quality or human error, when clicking on the published curves, and amended where necessary. The first data point was set to $T_1 = 0$ and the survival estimate at this point was set to $S_1 = 1$. The survival probabilities were constrained to be strictly decreasing over time.

There are four variations on the method depending on the amount of information supplied:

1. Number at risk table and total number of events both supplied
2. No numbers at risk table
3. No total number of events
4. Neither risk table nor total events supplied

For cases 1 and 3 the algorithm assumes censoring at a constant rate within each risk interval (as defined by the reported number at risk table). For case 2 (no number at risk table) there is only one risk interval for the entire study and so censoring is assumed to be at a constant rate over the entire follow-up period. For case 4 it is assumed that there is no censoring during the follow up period (with censoring events at the end of follow-up if the survival curve does not fall to $S_N = 0$). This is a strong assumption and lower quality replication of data is expected in this case due to the lack of information.

Sometimes the published KM survival curves indicated censoring times on the graphs. In this case the censoring times were also digitised, and the IPD produced using the Guyot algorithm was modified to incorporate the more accurate censoring times extracted from the graphs. Whether this was appropriate was considered for each curve on a case by case basis (e.g. when censoring times were clearly indicated in a given risk interval or in the tail of the survival distribution).

Parametric survival fitting was performed in R using the flexsurv package.[85, 86] Comparative model fit over the observed period was evaluated using the AIC and BIC and the fitted curves were plotted to consider the clinical plausibility over an extended time period.

1.2 Results of parametric curve fitting to reconstructed IPD

Model fit statistics for all of the curves for which alternative curve fitting was considered by the ERG are provided in Table 69 for the CP-CML model and in Table 70. The resulting model fits are plotted in Figure 39 to Figure 50.

Table 69: Model fit statistics for ERG alternative curve fitting in the CP-CML model

Graph identifier		Criterion	Parametric model						Info
			Exp	Weib	Gomp	Log-N	Gamm	Log-L	
CP-CML model	**DoR-bosutinib**	**AIC**	146.3	143.2	**138.7**	**139.9**	143.9	141.9	3
		BIC	148.1	146.8	**142.3**	**143.5**	147.5	145.5	
	OS after SCT in CP-CML	**AIC**	**49.2**	50.2	**47.6**	**49.3**	50.3	49.9	2
		BIC	**49.9**	51.7	**49.1**	**50.9**	51.9	51.4	
	OS after SCT in AP-CML	**AIC**	**129.8**	**126.0**	**114.8**	**122.6**	127.0	**124.3**	2
		BIC	**131.2**	**128.8**	**117.6**	**125.4**	129.8	**127.2**	
	Relapse-free survival after SCT	**AIC**	1183.9	1159.9	**1137.6**	**1136.6**	1166.1	1145.2	4
		BIC	1187.1	1166.4	**1144.1**	**1143.1**	1172.6	1151.7	
	OS in AP-CML	**AIC**	427.1	427.1	429.1	**418.0**	425.5	420.2	2
		BIC	429.3	431.4	433.4	**422.4**	429.8	424.5	
	OS in BP-CML	**AIC**	584.0	584.6	582.7	**557.3**	580.3	**557.4**	2
		BIC	586.5	589.7	587.8	**562.5**	585.4	**562.5**	
	OS after SCT in CP-CML	**AIC**	3214.7	3038.6	3084.5	**3009.1**	3047.0	3029.3	4
		BIC	3219.1	3047.3	3093.2	**3017.8**	3055.7	3038.0	
	(alternative from Radich[70])	**BIC**	586.5	589.7	587.8	**562.5**	585.4	**562.5**	

Exp = exponential; Gomp = Gompertz; Log-L = log-logistic; Log-N = log-normal; Weib = Weibull; Gamm-gamma

Info: Information used for reconstruction; 2= no number at risk table; 3= no total number of events; 4= neither risk table nor total number of events supplied.

AIC/BIC values in bold denote distribution that were either used by the company or considered in the ERG's alternative curve fitting

Table 70: Model fit statistics for ERG alternative curve fitting in the AP-CML and BP-CML model

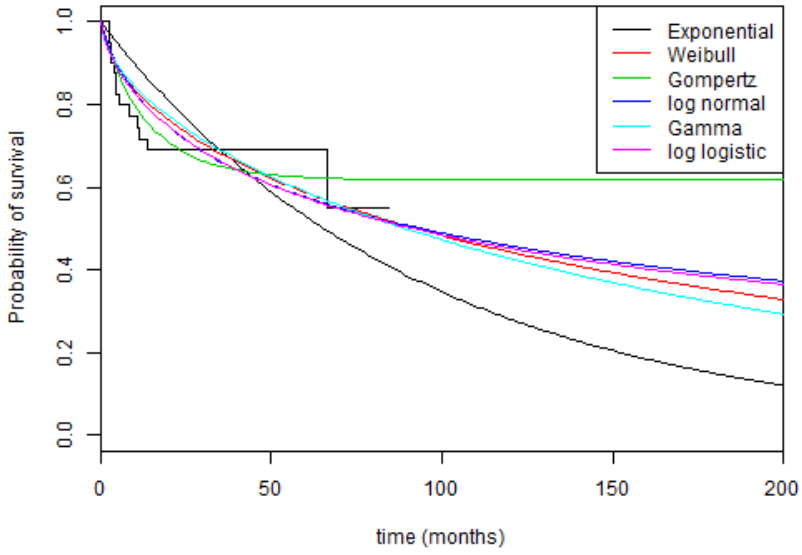
	Graph identifier	Criterion	Parametric model						Info
			Exp	Weib	Gomp	Log-N	Gamm	Log-L	
AP-CML and BP-CML model	OS post-allo-SCT in AP-CML with remission	AIC	**856.2**	795.5	**758.2**	775.8	804.1	783.1	4
		BIC	**859.0**	801.1	**763.8**	781.4	809.7	788.8	
	OS post-allo-SCT in AP-CML without remission	AIC	**963.9**	816.8	**688.6**	778.5	841.5	780.2	derived
		BIC	**966.7**	822.5	**694.3**	784.1	847.2	785.9	
	OS post-allo-SCT in BP-CML with remission	AIC	**478.6**	437.3	**418.7**	424.8	444.0	427.7	4
		BIC	**480.8**	441.6	**423.0**	429.0	448.2	432.0	
	OS post-allo-SCT in BP-CML without remission	AIC	**323.3**	301.3	**265.8**	282.9	309.8	280.1	4
		BIC	**325.1**	304.9	**269.3**	286.5	313.4	283.6	
	OS in AP-CML on BSC	AIC	427.1	427.1	429.1	**418.0**	425.5	420.2	2
		BIC	429.3	431.4	433.4	**422.4**	429.8	424.5	
	OS in BP-CML on BSC	AIC	584.0	584.6	582.7	**557.3**	580.3	**557.4**	2
		BIC	586.5	589.7	587.8	**562.5**	585.4	**562.5**	

Exp = exponential; Gomp = Gompertz; Log-L = log-logistic; Log-N = log-normal; Weib = Weibull; Gamm-gamma

Info: Information used for reconstruction; 2= no number at risk table; 3= no total number of events; 4= neither risk table nor total number of events supplied.

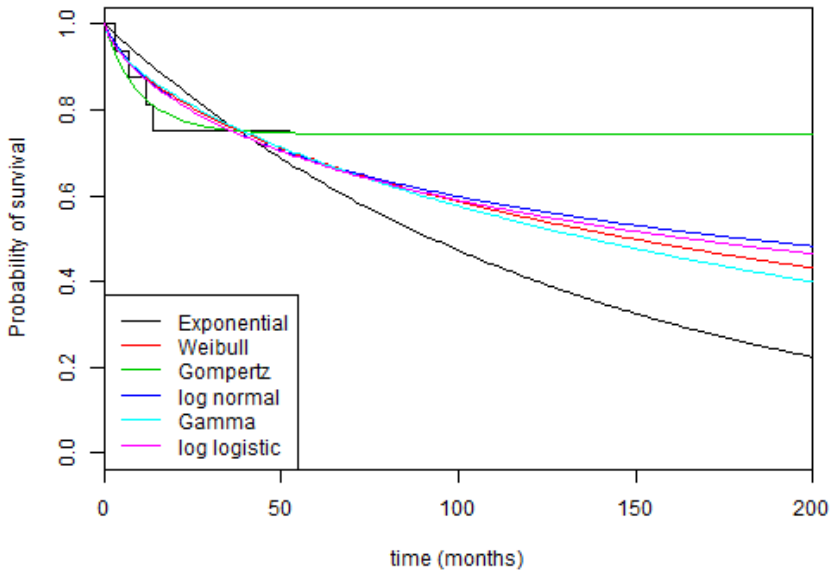
AIC/BIC values in bold denote distribution that were either used by the company or considered in the ERGs alternative curve fitting

Figure 39: Parametric survival functions for DoR for bosutinib, CP-CML model



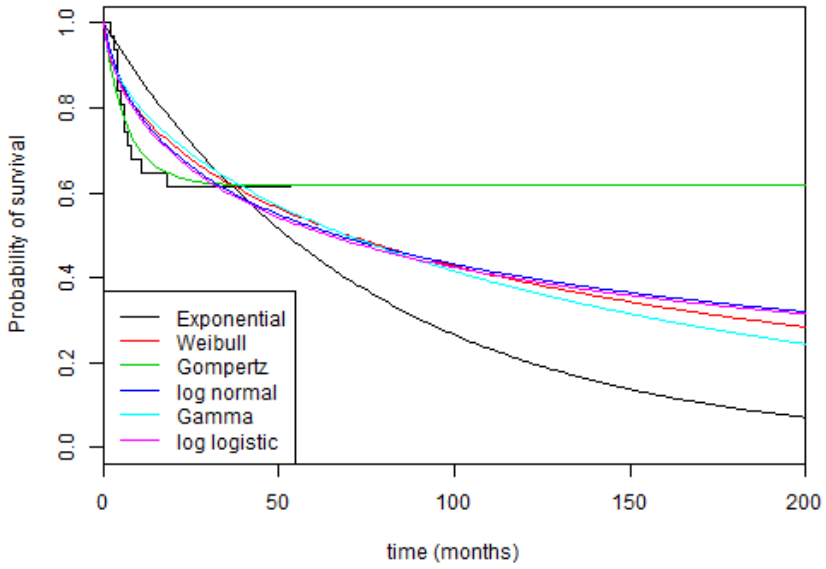
Note that the company's fit to these data are shown in Figure 6.

Figure 40: Parametric survival functions for OS after allo-SCT in CP-CML: CP-CML model



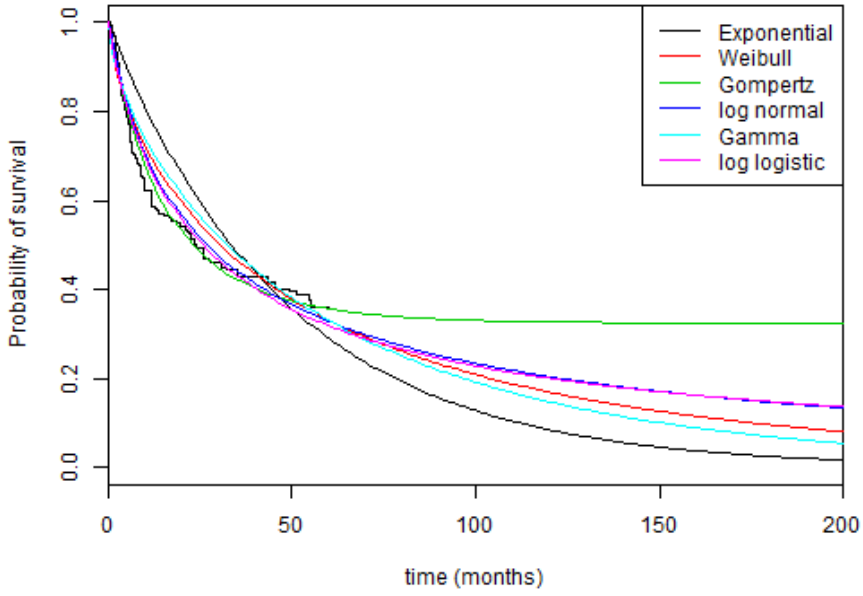
Note that the company's fit to these data are shown in Figure 20.

Figure 41: Parametric survival function OS after allo-SCT in AP-CML: CP-CML model



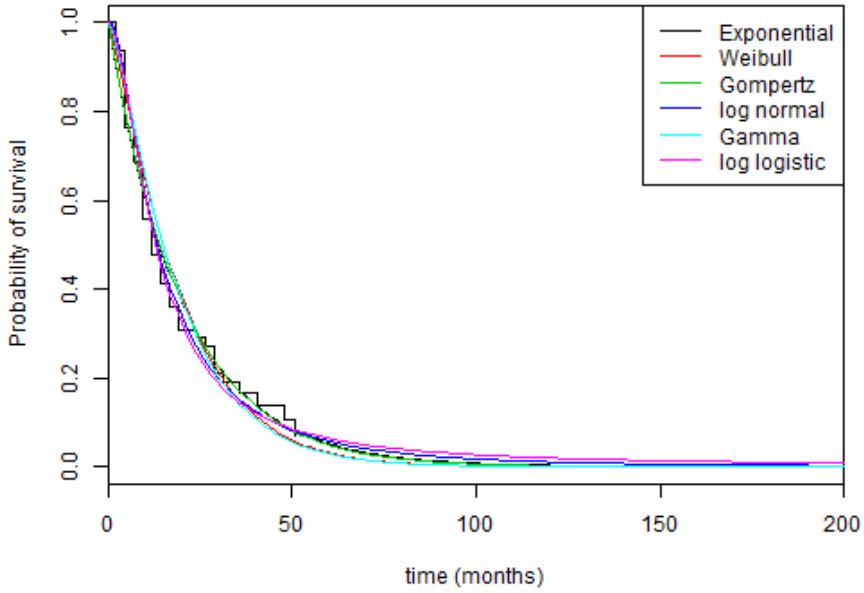
Note that the company's fit to these data are shown in Figure 18.

Figure 42: Parametric survival function for Relapse-free survival after allo-SCT: CP-CML model



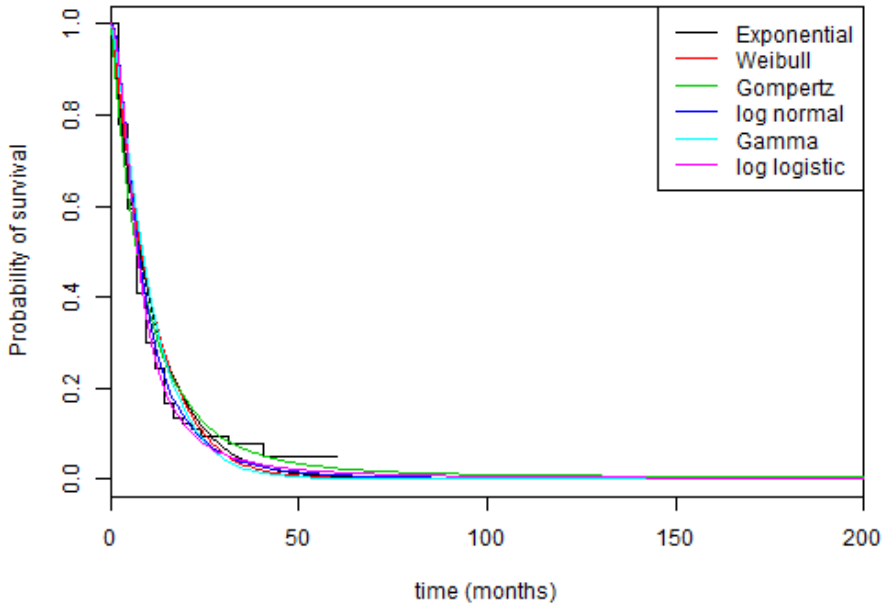
Note that the company's fit to these data are shown in Figure 17.

Figure 43: Parametric survival function OS in AP-CML, CP-CML model



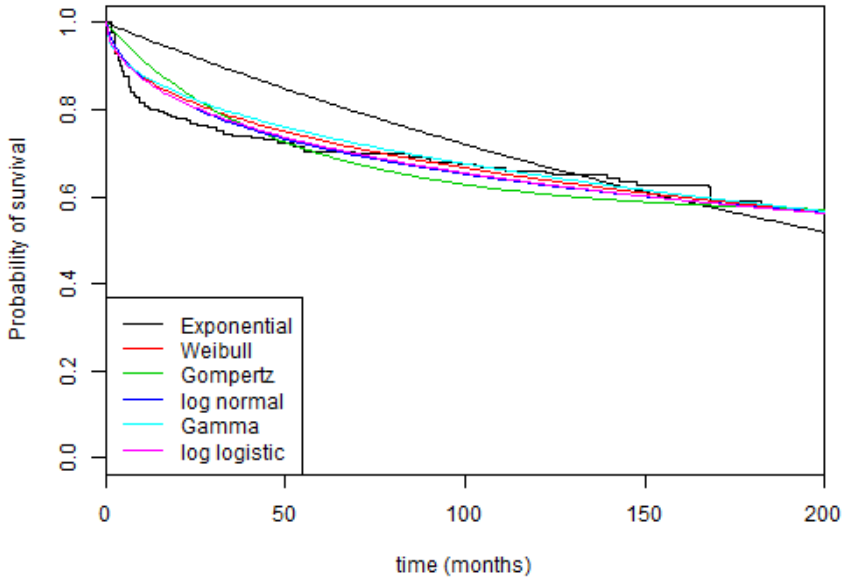
Note that the company's fit to these data are shown in Figure 15.

Figure 44: Parametric survival function for OS in BP-CML, CP-CML model



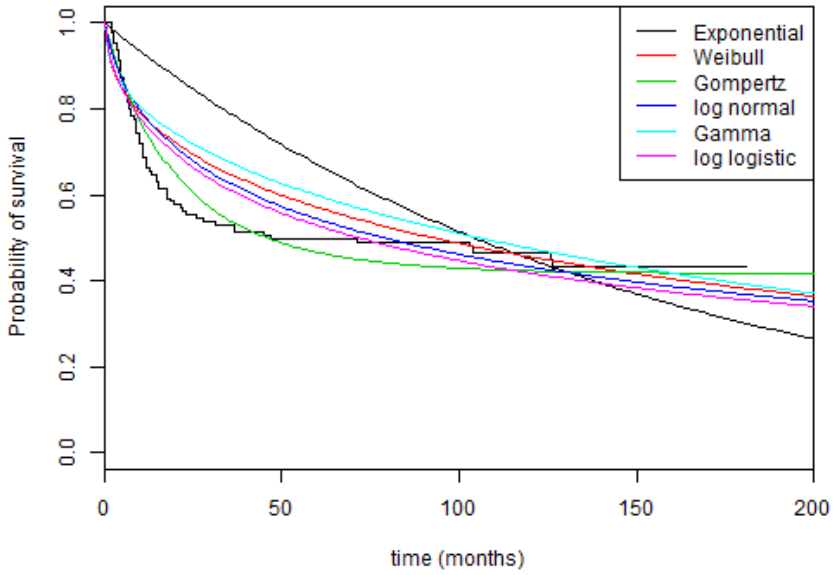
Note that the company's fit to these data are shown in Figure 16.

Figure 45: Parametric survival function for OS after SCT in CP-CML (alternative from Radich[70]): CP-CML model



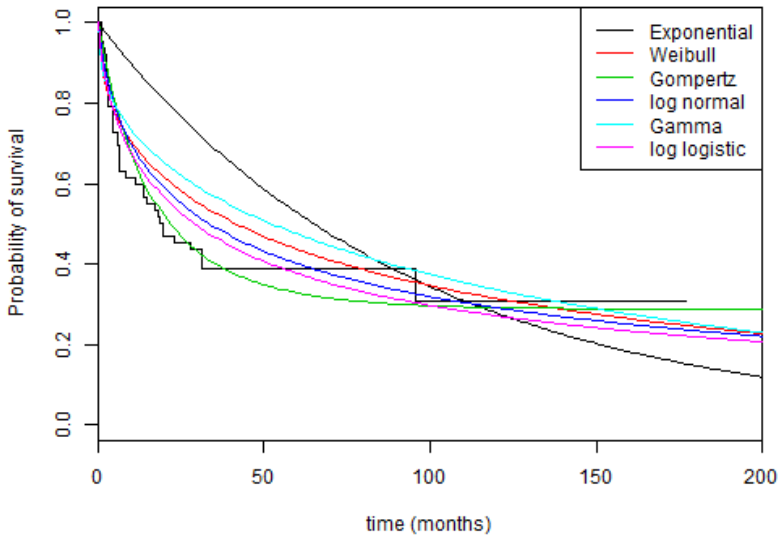
Note that the company did not consider these data within their submitted model.

Figure 46: Parametric survival function for OS post-allo-SCT in AP-CML with remission: AP/BP CML model



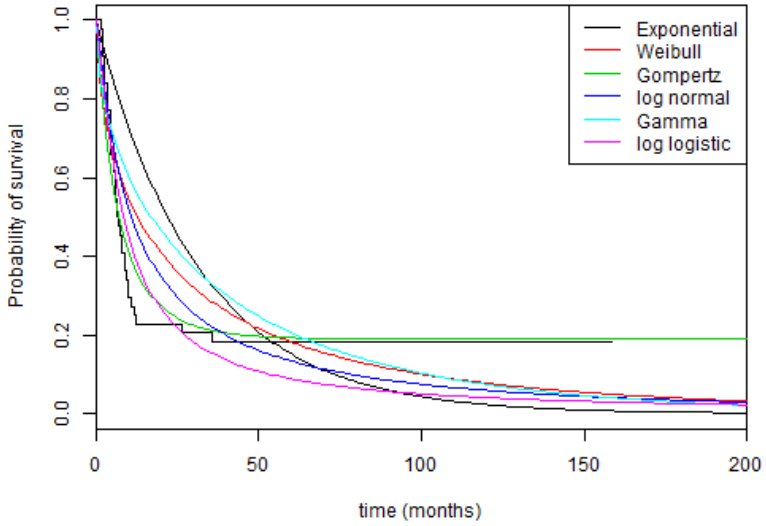
Note the company's fit to these data are shown in Figure 25.

Figure 47: Parametric survival function for OS post-allo-SCT in BP-CML with remission: AP/BP CML model



Note the company's fit to these data are shown in Figure 28.

Figure 48: Parametric survival function for OS post-allo-SCT in BP-CML without remission: AP/BP CML model



Note the company's fit to these data are shown in Figure 29.

1.3 Derived curve for OS post-allo-SCT in AP-CML without remission: AP/BP CML model

Following the approach used by the company, the two OS post-allo-SCT in BP-CML curves (with remission and without remission corresponding to the black lines in Figure 50) were used to provide an approximate relationship between survival in the two response groups at each time point. This relationship was then applied to the KM curve for OS post-allo-SCT in AP-CML with remission (Figure 46) to provide a hypothetical KM curve for OS post-allo-SCT in AP-CML without remission. IPD for this hypothetical group was then recreated using the Guyot algorithm, as with the other curves. The estimated parametric survival curves for this group, shown in Figure 49, are subject to a large degree of uncertainty.

Figure 49: Parametric survival function for OS post-allo-SCT in AP-CML without remission

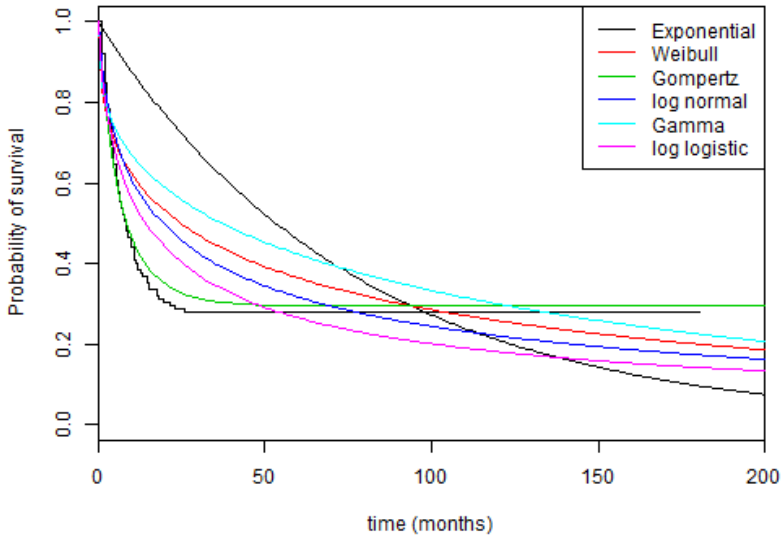
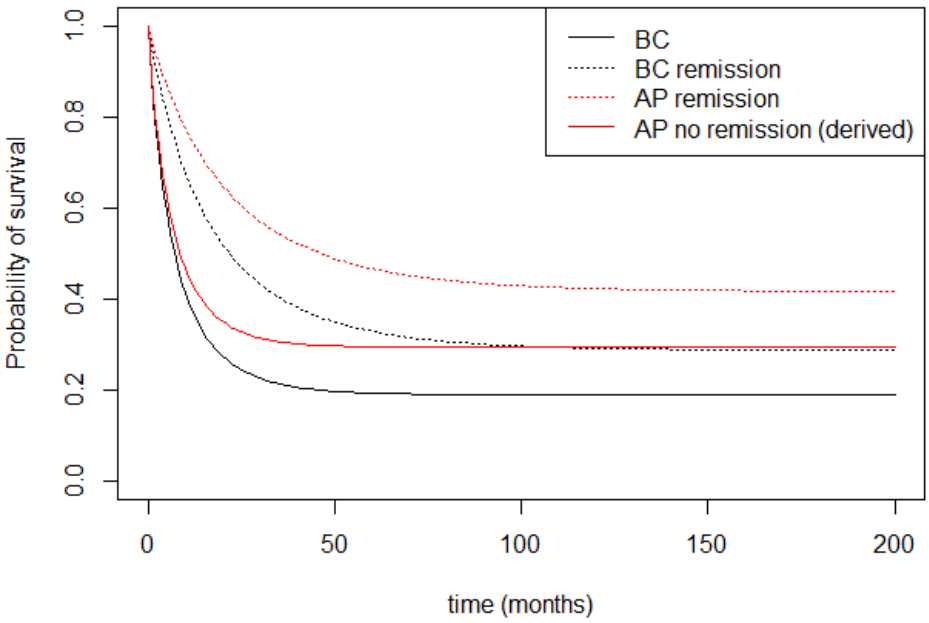


Figure 50: **Gompertz survival function for OS post-allo-SCT in BP-CML with remission and without remission (black) and for OS post-allo-SCT in AP-CML with remission and without remission (red)**



Ponatinib for treating acute lymphoblastic leukaemia: A Single Technology Appraisal

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Declared competing interests of the authors

Dr Clare Rowntree undertook some consulting work in 2015-16 for ARIAD Pharmaceuticals, the manufacturer of ponatinib. This work resulted in an authored published abstract in a health economics journal. None of the other authors have any conflicts of interest to declare.

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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

Abdullah Pandor and Marrissa Martyn-St James summarised and critiqued the clinical effectiveness data reported within the company's submission. Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. John Stevens critiqued the statistical analyses undertaken by the company. Jean Hamilton produced parametric curves for use in the exploratory analyses. Ruth Wong critiqued the company's search strategy. Clare Rowntree provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic stem cell transplant
AP-CML	Accelerated phase chronic myeloid leukaemia
BIC	Bayesian information criterion
BP-CML	Blast phase chronic myeloid leukaemia
BSC	Best supportive care
CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CHR	Complete haematologic response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CP-CML	Chronic phase chronic myeloid leukaemia
CS	Company's submission
CSR	clinical study report
EMA	European Medicines Agency
ERG	Evidence Review Group
FDA	US Food and Drug Administration
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
MAIC	Matching-adjusted indirect comparison
MAHR	Major haematological response
MCyR	Major cytogenetic response
N/A	Not applicable
NICE	National Institute for Health and Care Excellence
NR	No response
OS	Overall survival
PAS	Patient Access Scheme
PCyR	Partial cytogenetic response
PFS	Progression-free survival
Ph+	Philadelphia chromosome-positive
PSA	Probabilistic sensitivity analyses
QALY	Quality-Adjusted Life Year

RCT	Randomised Controlled Trial
RDI	Relative dose intensity
SAE	Serious adverse event
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
SSE	Sum of squared errors
T315I	Threonine-315-Isoleucine
TKI	Tyrosine kinase inhibitor
VOE	Vascular occlusive event

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The decision problem addressed by the company's submission (CS) is generally in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The population considered within the CS, as defined in the scope, is '*adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the Threonine-315-Isoleucine [T315I] mutation'*. However, the target population in the CS was in the third-line treatment setting (reflecting the anticipated place in therapy of ponatinib, after treatment failure with imatinib and dasatinib). In accordance with the final NICE scope, the CS defines the intervention as ponatinib. The CS considers induction chemotherapy plus allogeneic stem cell transplant (allo-SCT) and best supportive care (BSC) as the most relevant comparators; this closely matches the comparators described in the final scope. Clinical advice received by the Evidence Review Group (ERG) suggested that these were appropriate and relevant comparators. The outcome measures identified in the scope: overall survival (OS), progression-free survival (PFS)/event-free survival, response rates, time to response, duration of response, adverse events/effects (AE) of treatment and health-related quality of life (HRQoL) were included. The health economic outcome employed within the company's health economic model is the incremental cost per quality-adjusted life year (QALY) gained, as set out within the NICE Reference Case. The equity issues highlighted within the CS (p123) was a reference to '*the current inequity in CDF [Cancer Drugs Fund] access to ponatinib between patients with the T315I mutation and those who fall within the indication but do not have this mutation*' and on p30 of the CS where it is stated that allo-SCT '*is associated with equity issues*'. A Patient Access Scheme (PAS) has been approved by the Department of Health for ponatinib. In addition, the CS considers that ponatinib meets the end-of-life criteria for eligible patients with Ph+ ALL.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review of clinical effectiveness evidence. The PACE study, which forms the main supporting evidence for the intervention, was a Phase II, industry-sponsored, single-arm, non-comparative, open-label, multicentre study (including five sites in the UK) designed to evaluate the efficacy and safety of ponatinib in patients (aged over 18 years) with CML (CP, AP or BP), or Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any tyrosine kinase inhibitor (TKI) therapy. Study participants were heavily pre-treated with prior TKIs and conventional therapy: 37% (167/449) had received two TKIs (imatinib, dasatinib, nilotinib or bosutinib) and 55% (249/449) had received three or more TKIs.

In the PACE study, 449 patients received oral ponatinib at a starting dose of 45mg once daily. Of these, 444 patients were assigned to one of six cohorts (based on disease phase, resistance or intolerance to dasatinib or nilotinib, and the presence of the T315I mutation): (i) CP-CML resistant or intolerant to dasatinib or nilotinib; (ii) CP-CML with the T315I mutation; (iii) AP-CML resistant or intolerant to dasatinib or nilotinib; (iv) AP-CML with the T315I mutation; (v) BP-CML or Ph+ ALL resistant or intolerant to dasatinib or nilotinib; (vi) BP-CML or Ph+ ALL with the T315I mutation. The remaining five patients (3 with CP-CML and 2 with AP-CML) that had a history of the T315I mutation were treated with ponatinib but were not assigned to a cohort because the T315I mutation was not confirmed at baseline and the patients had not received nilotinib or dasatinib. The pre-specified efficacy analysis excluded these five patients; however, the safety analysis included all patients who received one or more doses of ponatinib. Therapy was continued until disease progression, unacceptable toxicity, withdrawal of patient consent or following a decision by the investigator. The primary outcome measure for Ph+ ALL patients was major haematological response (MaHR), which included complete haematologic response (CHR) and no evidence of leukaemia at 6 months. Although response milestones for patients with Ph+ ALL have not been well established, treatment strategies usually involve achieving a MaHR with the aim of proceeding to allo-SCT, if feasible. However, the ERG's clinical advisor considers MaHR to be a weak surrogate endpoint for patients with Ph+ ALL and considers minimal residual disease levels in the bone marrow (not assessed in the PACE study) to be a better endpoint for bridging to transplant as it is a more stringent criterion.

Median follow-up among patients in the PACE study was 6 months for Ph+ ALL (data cut-off: 9 November 2012). Updated results (data cut-off: 3 August 2015) were reported after a median follow up of 48.2 months (4 years).

The CS does not report data by line of therapy for the main target population of interest i.e. Ph+ ALL patients who are eligible to receive third-line ponatinib. However, among patients with Ph+ ALL (all lines, n=32), 41% (95% CI: 24% to 59%) achieved a MaHR within the first 6 months (primary endpoint) and the estimated rate of a sustained response of at least 12 months was 8%. Furthermore, major cytogenetic response (MCyR) was reached in 47% of patients with an estimated 32% of responding patients maintaining this response for at least 12 months. The rate of PFS and OS at 12 months was estimated to be 7% (median 3 months) and 40% (median 8 months), respectively. In addition, OS at 36 months was estimated to be 16% (median not reported).

[redacted]

[redacted] The ERGs clinical advisor noted that combining survival outcome data for the BP-CML and Ph+ ALL groups is likely to be unfavourable for ponatinib as BP-CML patients are likely to have more mutations and be more resistant to TKIs in general.

Ponatinib is the only TKI with activity against the T315I mutation. In England (as of December 2016), ponatinib is only available to CML and Ph+ ALL patients with the T315I mutation through the CDF. Although a subgroup analysis by T315I mutation status was not provided in the CS, the ERG notes that among the subgroup of Ph+ ALL patients who had the T315I mutation (n=22, all lines), 36% had an MaHR within the first 6 months, 40% achieved a MCyR and 32% reached CCyR (95% CI: not reported for any outcomes). [redacted] Due to the small population size and the PACE study design limitations, these findings should be treated with caution.

Among Ph+ ALL patients who received at least one dose of the study drug in the PACE study (data cut-off: 9 November 2012; all lines of therapy, n=32), 6% withdrew from treatment due to AEs. The most common non-haematologic treatment-related AEs (any grade) were skin reactions (rash, 19% and dry skin, 22%), abdominal pain (19%) and constipation (19%) and the most common haematologic treatment-related AE (grade 3 or 4) were anaemia (12%), neutropenia (12%), thrombocytopenia (6%), febrile neutropenia (6%) and vascular occlusive events (VOE). [redacted]

No indirect comparisons of clinical effectiveness were undertaken within the CS for Ph+ ALL due to the lack of data for comparator interventions.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the company was reasonably comprehensive. Despite minor limitations in the company's search strategy, the ERG is reasonably confident that all relevant published studies (RCTs and non-randomised/non-controlled evidence) of ponatinib were included in the CS, including data from ongoing studies. The specified inclusion and exclusion criteria were mostly appropriate and generally reflect the information given in the decision problem. The validity assessment tool for non-randomised studies (developed by Chambers *et al*.) was used to appraise the included studies and was considered appropriate by the ERG.

Although the efficacy endpoint (measured in terms of surrogate response measures e.g. MaHR, MCyR, and CCyR) in the PACE study appears favourable, and the safety of ponatinib appears acceptable, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. In the absence of direct comparative data with other treatments, the main evidence in the CS was derived from a Phase II, industry-sponsored, single-arm, non-comparative, open-label, study. Whilst the study was generally well reported and conducted, single-arm studies are associated with an array of potential biases including a high risk of selection bias (due to the absence of randomisation), performance and detection bias (due to the absence of blinding). In addition, due to the absence of a controlled comparator group in the PACE study, inference of treatment effects (including magnitude) may be confounded and its ability to compare or demonstrate efficacy with other current treatments is limited. A further limitation to the robustness of the efficacy and safety data relate to the small subgroup that comprises the target population in the CS, including lack of statistical power for the subgroup. The key uncertainties in the clinical evidence relate to optimal dosing, duration of treatment, comparative efficacy and generalisability to the population in England.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a model to assess the incremental cost effectiveness ratio (ICER), in terms of cost per QALY gained for ponatinib in two scenarios: (i) for patients in whom allo-SCT is suitable, and; (ii) for patients in whom allo-SCT is unsuitable. The company estimated that the deterministic ICER was £31,123 per QALY gained compared with induction chemotherapy in patients who could receive allo-SCT, and £33,954 per QALY gained compared with BSC in patients who could not receive allo-SCT. The probabilistic values were £33,064 and £36,156 per QALY gained, respectively.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The CS adhered to the decision problem set out in the final NICE scope. However, the ERG does not always agree with the choice of parameter values or distributions used in the company's base case. As such, the ERG considers that the uncertainty surrounding the decision has been greatly underestimated

by the company. The results of the probabilistic sensitivity analyses were not considered robust by the ERG but were not amended.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of ponatinib for the treatment of CML. No major limitations were noted. The PACE study was well-reported and conducted single-arm study and measured a range of clinically relevant outcomes. Few programming errors were found within the submitted model which was subjected to a cell-by-cell evaluation.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty in the evidence base relates to the lack of direct comparative data with other current treatments such as TKIs. In addition, although the PACE study population appears reflective of the Ph+ ALL population in England, the treatment pathway is not an absolute reflection of UK practice (patients received nilotinib in the PACE study, which is not used in the UK). Long-term safety and efficacy data are also lacking. The ERG believes that the uncertainty in the decision has been greatly underestimated by the company. The results of probabilistic sensitivity analyses were not considered robust by the ERG. The ERG believes that the central estimate produced by the company was considerably unfavourable to ponatinib, due to assumptions regarding OS that were not supported by clinical advice received by the ERG.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The exploratory analyses undertaken by the ERG are shown in Table 1 for those who can receive allo-SCT and Table 2 for those who cannot receive an allo-SCT.

For patients who could receive allo-SCT, recalculation of the OS curve increased the ICER, as did removing the half-cycle correction of intervention costs, and the inclusion of drug wastage. Assuming that the OS for non-response (NR) is independent of whether a patient had received ponatinib, markedly reduced the ICER due to the additional costs of being alive in the NR state. The use of alternative curves to those selected by the company increased the uncertainty and increased the upper range of the ICER. These conclusions also applied to the model where people could not have allo-SCT, with the exclusion of the recalculation of the OS post-allo-SCT which was not relevant in this scenario.

If it is assumed that OS for people in the NR state is independent of whether the patient received ponatinib, as believed by the clinical expert to the ERG, the ICER for ponatinib in people who can receive allo-SCT ranges from dominant to £11,727 per QALY gained when compared with induction chemotherapy, although the ERG notes the naïve indirect comparison used, and from £7892 - £31,696

compared with BSC. For patients who cannot receive allo-SCT the ICER for ponatinib is likely to dominate BSC.

No formal analyses were conducted for those patients known to have, or not have, the T315I mutation. The ERG believes that if it was known that the T315I mutation was present then induction chemotherapy would not be an appropriate comparator. If the T315I mutation was known not to be present then the ICERs compared with induction chemotherapy are likely to be less favourable to ponatinib, although the extent of the change is unknown.

Table 1: The impact of the ERG's deterministic exploratory analyses in patients suitable for allo-SCT

		Cost per QALY (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs induction chemotherapy**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	31,123	26,624
1	Recalculation of the OS post allo-SCT curve	57,140	53,603
2	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	23,838 – 52,559	14,203 – 45,218
3	Assuming drug wastage	32,499	26,944
4	No half-cycle correction of intervention costs	43,766	29,568
5	Including treatment related deaths	28,635	25,864
6	Removal of immortality for a small subset of patients	31,989	26,999
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,983
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,959
8	1, 3,4 and 6 using the curves believed most credible by the company	90,325	62,801
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	11,727	31,696
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant – 11,727	7,892 – 31,696

Allo-SCT, allogeneic stem cell transplant; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders; OS, overall survival; QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

Table 2: The impact of the ERG's deterministic exploratory analyses in patients unsuitable for allo-SCT

		Cost per QALY (£)
Ref No	**Exploratory Analyses**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	33,954
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	25,902 – 36,037
2	Assuming drug wastage	36,835
3	No half-cycle correction of intervention costs	48,073
4	Including treatment related deaths	30,432
5a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant
5b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant
8	2 and 3 using the curves believed most credible by the company	52,317
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	Dominant
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant - Dominant

BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

2 BACKGROUND

This report provides a review of the evidence submitted by Incyte Corporation in support of ponatinib for treating Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL). It considers both the original company submission (CS) received on 10th October 2016 and a subsequent response to clarification questions supplied by Incyte Corporation on 11th November 2016. To avoid repetition, reference has been made to the accompanying Evidence Review Group (ERG) chronic myeloid leukaemia (CML report),[1] where appropriate.

2.1 Critique of company's description of underlying health problem

The CS (p1, p24-36) provided a reasonable description of the underlying health problem, which is briefly summarised in this section.

ALL is a rare and rapidly progressing form of leukaemia characterised by the excess production of immature white blood cells, called lymphoblasts (sometimes referred to as blasts cells). Eventually, this affects the production of normal blood cells which leads to a reduction in the numbers of red cells, white cells and platelets in the blood.[2] ALL represents about 20% of all leukaemias in adults and is the most common form of childhood leukaemia.[3-5] Approximately 25%[4, 6, 7] of adults with ALL have an acquired chromosomal abnormality (known as Ph+ disease) caused by reciprocal translocations between chromosomes 9 and 22. These translocations result in a BCR-ABL fusion gene that encodes an active tyrosine kinase protein which causes uncontrolled cell proliferation. The presence of the Ph chromosome in adults increases with age[3-5] and Ph+ ALL individuals typically have a worse prognosis than those without the abnormality.[8]

Over the past two decades, survival in adult patients with ALL has improved marginally and remains poor, particularly for those patients aged over 50 years.[9, 10] According to data from the National Cancer Intelligence Network, the 5-year relative survival rate for those aged 25-64 years in England was 37.1% for those diagnosed in 2008-10 whereas for individuals over 65 years, the 5-year relative survival was 12.7%.[9] Comparative data for those with Ph+ ALL are not reported in the CS.

In 2014, 654 people in England were newly diagnosed with ALL[11] (the most recent year for which data are available). However, the CS (p34-35 and p240) estimates that only 33 people per annum with Ph+ ALL will be eligible to receive ponatinib according to its licence indication (i.e. for adults with Ph+ ALL in need of third or later-line tyrosine kinase inhibitor [TKI] therapy or for people who have the Threonine-315-Isoleucine [T315I] mutation). Clinical advisors to the ERG suggest that whilst there is some uncertainty around the proportions used within the calculations, this estimate seems reasonable.

2.2 Critique of company's overview of current service provision

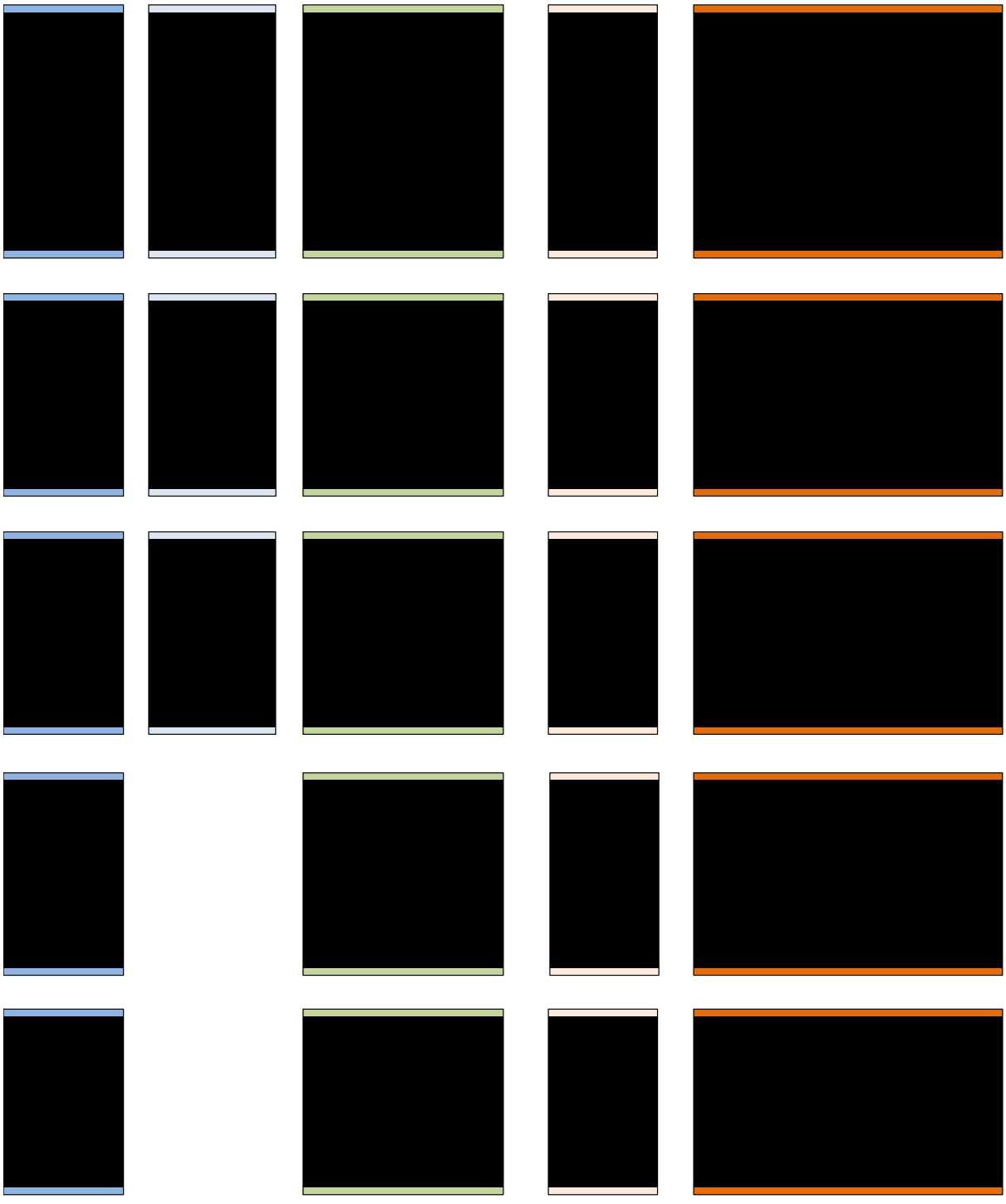
In general, the CS (p1, p37-41) provides a reasonable overview of current service provision for people with Ph+ ALL, which is briefly summarised in this section.

The management of people with Ph+ ALL is complex and there is currently no National Institute for Health and Care Excellence (NICE) guidance or pathways of care for the treatment of adults with Ph+ ALL in England. In general, the treatment of Ph+ ALL varies according to age, general fitness and health at diagnosis and the results of cytogenetic testing.

Allogeneic stem cell transplant (allo-SCT) is the only potentially curative treatment for Ph+ ALL; however, it is limited by patient suitability as well as the availability of suitable donors and is associated with a significant risk of morbidity and mortality.[12] The use of oral TKIs has become an integral component of therapy for people with Ph+ ALL (see Figure 1). Currently, three TKIs (imatinib,[13] dasatinib[14] and ponatinib[15]) have an EU marketing authorisation for the treatment of Ph+ ALL (further details of the marketing authorisation of each of these TKIs can be found in CS, Table 3-3, p31). The CS (p31 and p41) notes that neither imatinib nor dasatinib have been appraised by NICE and the extent to which these TKIs are used in current clinical practice for the treatment of adult Ph+ ALL is unknown. In addition, dasatinib was available for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy including imatinib through the Cancer Drugs Fund until November 2015 when it was removed from the Cancer Drugs Fund list.[16]

In clinical practice, most treatment plans for Ph+ ALL have three phases: (i) induction; (ii) consolidation, and; (iii) maintenance (in adults, later stages of treatment may be replaced by allogeneic transplantation). During these treatment phases, newly diagnosed individuals with Ph+ ALL are treated with chemotherapy combinations including TKI therapy such as imatinib or dasatinib.[2] The aim of using a TKI as induction treatment is to quickly achieve full remission in adult patients with Ph+ ALL. For patients who experience a complete response after induction therapy, allo-SCT offers the best chance of survival.[4, 17] Resistance to TKI may develop and therapeutic options following resistance to TKI are limited.[2] Ponatinib is currently only available to patients with the T315I mutation in England through the Cancer Drugs Fund (CDF);[18] however, the company suggests that in clinical practice ponatinib may also be used for adults with Ph+ ALL whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate. Treatment of relapsed disease generally includes re-induction therapy with combination chemotherapy plus an alternative TKI to that previously used (ideally based on mutation analysis) followed by an allo-SCT in people who are suitable/ eligible. In patients for whom allo-SCT is not suitable, consolidation chemotherapy plus TKI followed by TKI based maintenance therapy may be considered.

Figure 1: Simplified clinical pathway of care for patients with Ph+ ALL in England (adapted from CS, Figure 3-2, p33 and Figure 3-4, p36)



Allo-SCT, Allogeneic stem cell transplant; BSC, best supportive care; TKI, tyrosine kinase inhibitor

[a] Dasatinib was available for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy including imatinib through the Cancer Drugs Fund until November 2015 when it was removed from the Cancer Drugs Fund list.[16]

[b] Currently being appraised by NICE as part of this Single Technology Appraisal (assumed position in treatment pathway if recommended by NICE)

Further details of relevant clinical guidelines from the European Society for Medical Oncology[19] and the National Comprehensive Cancer Network[4] for the treatment of Ph+ ALL in adults can be found in the CS (see Section 3.6, p38-39).

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

A summary of the decision problem addressed by the CS is reproduced (with minor changes) in Table 3.

Table 3: Decision problem as issued by NICE and addressed by the CS (Ph+ ALL only)

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale provided by company if different from the final NICE scope**
Population	Adults with Ph+ ALL whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation	As per the final scope	N/A
Intervention	Ponatinib	As per the final scope	N/A
Comparator (s)	• Established clinical management without ponatinib (including but not limited to best supportive care)	• Induction chemotherapy plus allo-SCT • BSC	N/A
Outcomes	• Overall survival • Progression-free survival/ event-free survival • Response rates • Time to response • Duration of response • Adverse effects of treatment • Health-related quality of life	As per the final scope	Duration of response is not considered in the Ph+ ALL model as patients eligible for allo-SCT who respond to treatment transition to allo-SCT in the first cycle. Duration of response is not explicitly modelled for Ph+ ALL patients who are unsuitable for allo-SCT, but is expected to be reflected in the parametric function for overall survival
Economic analysis	The reference case stipulates that the: • cost effectiveness of treatments should be	As per the final scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final NICE scope
	expressed in terms of incremental cost per quality-adjusted life year (QALY) • time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective		

Allo-SCT, allogeneic stem cell transplant; BSC, best supportive care; N/A, not applicable; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia

3.1 Population

The company's statement of the decision problem defines the population in line with the final NICE scope as adults with whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

The key clinical evidence submitted by the company is derived from the PACE (Ponatinib Ph-positive acute lymphoblastic leukaemia [ALL] and CML Evaluation) study.[20] In this single-arm, Phase II study, 41% (13/32) of people with Ph+ ALL had previously received nilotinib;[20] however, nilotinib is not approved for the treatment of Ph+ ALL in Europe (including the UK).[6, 21] In addition, imatinib is the only TKI to have EU marketing authorisation for first-line treatment of Ph+ ALL in combination with chemotherapy.[13] As a result, all newly diagnosed patients with Ph+ ALL in England are expected to receive first-line imatinib. In the PACE study,[20] only 84% (27/32) of people with Ph+ ALL received imatinib as a prior TKI therapy (any line). Further details on the use of imatinib as a first-line treatment were lacking in the CS and related publications.[6, 20, 22]

3.2 Intervention

The intervention under consideration in the CS is ponatinib, which matches the intervention described in the final NICE scope. Ponatinib is a third generation antineoplastic protein kinase inhibitor that was

designed to inhibit the kinase activity of the BCR-ABL gene and all mutant variants, including the T315I mutation, in patients failing multiple TKIs.[6]

Ponatinib is currently licensed in the EU (including the UK)[15] for the treatment of adult patients with:

- Ph+ ALL who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation (the population considered within this report).
- CP-CML, AP-CML or BP-CML who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation (the population considered within a separate ERG report).[1]

As noted in the Summary of Product Characteristics (SmPC), prior to the start of therapy with ponatinib, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with ponatinib.[15]

Ponatinib is available as 15mg and 45mg film-coated tablets for oral administration (with or without food). A 30mg film-coated tablet has been approved by the European Medicines Agency (EMA) and will be on the market in the UK in early 2017, prior to the conclusion of this STA (CS, p15). The recommended starting dose is 45mg once per day with an option for reduced dosing (30mg or 15mg once a day) for the management of haematological and non-haematological toxicities. [redacted]). Treatment with ponatinib should continue as long as the patient does not show evidence of disease progression or unacceptable toxicity. If a complete haematologic response (CHR) has not occurred by 3 months, consideration should be given to discontinuing ponatinib.[15]

Ponatinib is available in 30-tablet packs; the acquisition costs for the 15mg, 30mg (licensed, not yet available) and 45mg tablets are £2525, £5050 and £5050, respectively (CS, Table 2-1, p16). Ponatinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. No other restrictions or contraindications are stated for ponatinib in the CS or SmPC.[15]

3.3 Comparators

The comparators under consideration in the CS (i.e. induction chemotherapy plus allo-SCT and best supportive care [BSC]), closely match the comparators described in the final NICE scope.[2] Clinical advice received by the ERG suggested that these interventions are appropriate and relevant comparators.

3.4 Outcomes

The NICE scope[2] outlines seven clinical outcome measures. Most of these are stated to have been addressed in the CS (p2-3). Clinical outcome measures included overall survival (OS), progression-free survival (PFS)/event-free survival, response rates, time to response, duration of response, adverse events/effects (AE) of treatment and health-related quality of life (HRQoL). These are all considered by the ERG to be appropriate and clinically meaningful outcomes.

Incremental cost per quality adjusted life years (QALYs) gained was used as a measure of cost-effectiveness, which is in accordance with the NICE Reference Case.[24] In the health economic model, the company used a lifetime horizon (up to 100 years) and costs were considered from an NHS and Personal Social Services perspective. The CS (p2-3) states that duration of response was not considered in the Ph+ ALL model as allo-SCT eligible patients who respond to treatment transition to allo-SCT in the first cycle. However, for Ph+ ALL patients who are unsuitable for allo-SCT, it is expected to be reflected in the parametric function for OS. Based on clinical advice, the ERG believes this exclusion to be appropriate. In addition, as HRQoL was not assessed or reported in the PACE study,[20] hence the company's *de novo* model used other published evidence for HRQoL.

3.5 Other relevant factors

The equity issues highlighted within the CS (p123) was a reference to '*the current inequity in CDF access to ponatinib between patients with the T315I mutation and those who fall within the indication but do not have this mutation*' and on p30 of the CS where it is stated that allo-SCT '*is associated with equity issues*'.

4 CLINICAL EFFECTIVENESS

This chapter provides a summary and critique of the clinical-effectiveness evidence presented by the company in support of ponatinib for the treatment of Ph+ ALL only.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company performed two broad clinical effectiveness searches to identify all RCTs and non-randomised/non-controlled evidence on the use of ponatinib or its comparators in the treatment of adults with Ph+ ALL (the population considered within this report) and CML (the population considered within a separate ERG report).[1] The searches were designed to identify studies evaluating all lines of therapy for Ph+ ALL beyond first-line. Despite a lack of clarity, the ERG assumes the key aims of the Ph+ ALL searches in the CS were:

1. To identify all RCTs and non-randomised/non-controlled evidence on the use of ponatinib for the treatment of adults with Ph+ ALL which might potentially be relevant to the decision problem.

2. To identify all RCTs and non-randomised/non-controlled studies for the treatment of adults with Ph+ ALL which might potentially be relevant to the decision problem that would allow indirect comparisons with the comparators specified in the NICE final scope which had not been directly compared with ponatinib.

The ERG further notes that the presentation of these sections in the CS is somewhat confusing due to extensive cross-referencing between (and within) the main document and appendices.

In brief, for the original searches, several electronic bibliographic databases (including MEDLINE [via Ovid], MEDLINE in Process [via Ovid], EMBASE [via Ovid], Cochrane Central Register of Controlled Trials [via EBM reviews] and the Health Technology Assessment database [via EBM reviews]) and research registers (ClinicalTrials.gov and the WHO International Clinical Trials Platform) were searched covering the period from January 2000 to January/February 2016. Supplementary searches such as scanning of bibliographies of included studies, reviews and various conference proceedings were also undertaken (CS, p42 and company's clarification response to question A2).[23] For the update searches, similar sources appear to have been searched and covered the period to July 2016. However, it is unclear why the Cochrane Database of Systematic reviews and the Database of Abstracts of Reviews of Effects, which forms part of the EMB Reviews resource, were not searched, as additional studies may have been identified from the reviews of primary studies. The ERG also recommends

applying forward tracking of citations of key papers and not only references of follow-up for studies. Nevertheless, the ERG considers the chosen electronic databases and internet sources to be appropriate.

The company's search strategies comprised the terms for the population concept (Ph+ ALL) combined with sensitive search filters (trials, reviews, observational filters). Additional terms for concept 'resistance' were used to broaden the search strategy and improve sensitivity (CS, p42). Following further clarification on the additional patient population concept for resistance and line of treatment in both the MEDLINE and EMBASE search strategies, the ERG was satisfied with the company's response (see clarification response,[23] question A2) on the investigation for the impact of including or excluding this concept in the search strategy on the risk of missing key studies.

Despite the noted limitations, the ERG considers all the search strategies to be sufficiently comprehensive to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware. However, as no search details/strategies for AEs were provided in the CS, it is unclear whether any relevant AE studies have been missed.

4.1.2 Inclusion criteria

The CS describes appropriate methods of identifying and screening references for inclusion in the systematic reviews of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection were resolved through discussion between reviewers, if required (CS, p42). A summary of the inclusion and exclusion criteria, as reported in the CS (p43), is reproduced (with minor changes) in

Table 4.

Table 4: Inclusion/exclusion criteria used to select Ph+ ALL studies of ponatinib in the CS (adaptation of Table 4-1 from CS, p43)

	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with Ph+ ALL who are resistant/intolerant to prior treatments • Patients must have received at least one prior treatment for their disease	• Animal studies, *in vitro* studies, and studies in healthy populations
Interventions/ comparators	• Ponatinib • Stem cell transplantation • BSC	• Imatinib, as it is primarily used in the first-line and does not represent a direct comparator for ponatinib
Outcomes	• Response rates • Overall survival • Progression-free survival • Relapse-free survival • Time on treatment • Maintenance of response • Transformation-free survival • Adverse events • Intervention doses • Relative dose intensity	• Mixed-population studies (i.e., those including first-line and later patients) that do not present results in second-line or later patients separately from those in first-line patients
Trial design	• Randomised controlled trials (including crossover studies) • Non-randomised single-arm studies • Observational studies (retrospective and prospective) • Reviews, systematic literature reviews and meta-analyses were initially included to identify relevant articles for manual reference searching	• Letters, comments, editorials, case reports, and pharmacokinetic studies, models (economic or mathematical), surveys, adherence studies, prognostic studies, epidemiological studies, studies of treatment prescribing patterns, and dose-escalation studies • Studies with fewer than 10 patients overall (across all treatment arms) and abstracts without sufficient information
Language restrictions	No limitation by language in searches	Studies in languages other than English excluded during screening

BSC, best supportive care; Ph+ ALL, Philadelphia chromosome positive acute lymphoblastic leukaemia

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. It is noteworthy that the CS (p42-45) initially considered a wider remit to capture the entire evidence base as part of the inclusion criteria (i.e. all lines of therapy for Ph+ ALL beyond first-line) but then focused the systematic review to those studies directly relevant to the decision problem. As a result, the systematic review excluded interventions that were not listed in the decision problem

after the study selection stage and thus were not considered further in the CS (see clarification response,[23] question A7 and p52 of the CS). Whilst this approach seems acceptable to the ERG, ideally, systematic reviews should have clearly focused research questions and inclusion/exclusion criteria at the outset.

The company's systematic review excluded studies which were reported only as abstracts; however, limited justification for this exclusion was provided. In order to avoid publication bias, a systematic review should aim to include all relevant studies, regardless of publication status. Although differences often occur between data reported in conference abstracts and their corresponding full reports, differences in results are usually not very large.[25] In addition, it can be difficult to appraise study quality from limited details provided in an abstract. As a result, sensitivity analyses may be carried out to examine the effect of including data from conference abstracts.[26]

4.1.3 Critique of data extraction

The data extracted and presented in the clinical section of the CS appear appropriate and comprehensive. As noted in the company's response to clarification question A3,[23] data extraction was performed by one reviewer and checked for accuracy by a second. Whilst this strategy appears acceptable, the ERG notes that the gold standard for data extraction is for multiple individuals to independently perform the data extraction, compare results and resolve any discrepancies through discussion. Other less robust strategies include single individual data extraction followed by verification (for accuracy and completeness) by a second individual or (the weakest strategy) a single individual conducting data extraction on a single occasion.[25, 27] However, while these methods may result in significantly more errors than two researchers independently performing data extraction, they may also take significantly less time.[25, 27, 28]

4.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in the CS (p73) was based on the quality assessment criteria for non-randomised studies developed by Chambers *et al*.[29]. A key strength of this tool is that it addresses both quality of reporting and risk of bias (principally selection and attrition bias). As noted in the company's response to clarification question A8,[23] methodological quality assessment of included studies was performed by two independent reviewers, with disagreements resolved by a third reviewer. The ERG acknowledges that the validity assessment tool used in the CS was acceptable.

4.1.5 Evidence synthesis

The company undertook a narrative synthesis of the evidence for ponatinib; however, no explicit details were provided in the CS on how this approach was undertaken. Ideally, a narrative synthesis approach

should be justified, rigorous (i.e. describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[25, 27] Despite the lack of transparency regarding the methods adopted, the ERG acknowledges that the narrative synthesis approach undertaken by the company was acceptable. In addition, the company provided the following justification for not undertaking indirect comparisons (CS, p48): '*No MAIC [matching-adjusted indirect comparison] was performed to adjust for baseline characteristics in Ph+ ALL due to a lack of applicable data for comparators*'. Further details can be found in Sections 4.3 and 4.4 respectively.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/). Despite this, the diagram (see company's clarification response,[23] question A6) represents the identification and selection of all relevant RCTs and non-randomised/non-controlled studies of all lines of therapy for Ph+ ALL beyond first-line and appears to be a reasonable record of the literature searching and screening process. However, for clarity and to aid the transparency of the identification and selection processes, the PRISMA flow diagram should have ideally included details of the final set of studies that were included in the CS which were directly relevant to the decision problem.

The company's systematic review of RCTs comparing ponatinib with an appropriate comparator in the population of interest (i.e. patients with Ph+ ALL who are resistant or intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate or who have T315I mutation) did not identify any relevant studies. In the absence of RCT evidence, the company identified two relevant single-arm, non-comparative studies (a Phase I dose finding study[30, 31] and a Phase II study).[20, 32, 33] However, as noted in the company's response to clarification question A11,[23] the design and context of the Phase I study was '…*not entirely relevant to either the recommended dosing or the licenced indication in the approved product label*…' for ponatinib (further details of this study are briefly provided in the supplementary evidence section). As such, evidence from the Phase II, PACE study forms the main pivotal evidence in the CS. Further details of this study are provided in this section.

The company's broader systematic review of RCTs of all treatments for patients with Ph+ ALL beyond first-line (which was conducted to allow indirect comparisons to be conducted with the comparator interventions listed in the decision problem i.e. allo-SCT and BSC) did not identify any relevant studies. Similarly, no non-randomised/non-controlled studies evaluating the efficacy of BSC in Ph+ ALL were identified (CS, p52). For allo-SCT, the CS identified one prospective observational study of allo-SCT

in relapsed ALL. However, the ERG was unclear of its relevance in the clinical systematic review as no indirect comparison analyses were undertaken for Ph+ ALL. The CS (p62) states that '*none of the other studies identified in the SLR [systematic literature review] report the rate of remission with salvage treatment by risk groups (i.e. Ph+ ALL), unlike Tavernier et al. 2007, which reports the remission rates with reinduction therapy, by salvage regimen, for patients with Ph+ ALL. Thus, as Tavernier et al. 2007 provides the most comprehensive data that are in line with other published studies, it was selected for inclusion in this submission [i.e. in the economic evaluation].'*

4.2.1.1 The main pivotal evidence (PACE study)[20, 32, 33]

The CS (p4-6 and p64-99) included one ongoing, Phase II, industry-sponsored, single-arm, non-comparative, open-label, multicentre study (including five sites in the UK) designed to evaluate the efficacy of oral ponatinib in 449 people (53% male; 78% Caucasian)[22] with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy (as confirmed by direct sequencing).[6, 20, 22] A summary of the study design and population characteristics is provided in Table 5. Study participants in the PACE study were heavily pre-treated with prior TKIs and conventional therapy: 37% (167/449) had received two TKIs (imatinib, dasatinib, nilotinib or bosutinib). This population comprised the target population in the company's decision problem for Ph+ ALL (CS, p32-33) i.e. in the third-line treatment setting, reflecting the anticipated place in therapy of ponatinib, after treatment failure with prior TKI therapy (e.g. imatinib or dasatinib, if used through the CDF). Further details of the PACE study are provided in Section 4.2.1.1 of the ERG CML report.[1]

Table 5: Characteristics of the key included study

Study	Location (sites)	Design	Population	Intervention and comparator	Primary outcome measures	Duration
PACE (NCT01207440; AP24534-10-201)[20, 32, 33] Funded by: ARIAD Pharmaceuticals Inc.	66 centres [a] in 12 countries (including 5 sites in the UK, n=30)[b]	Phase II, single-arm open-label, non-comparative study (n=449)	Patients (aged ≥ 18 years) with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy No. of prior TKI: 2 (third-line cohort: target population in the company's decision problem) CP-CML, 97[c]/270[d] (36%); AP-CML, 33/85[e] (39%); BP-CML, 22/62 (35%); Ph+ ALL, 14/32 (44%)	Ponatinib 45mg tablet taken orally once daily	Major cytogenetic response (MCyR) in patients with CP-CML Major haematologic response (MaHR) patients with in AP-CML, BP-CML and Ph+ ALL	Start date: September 2010 Estimated study completion date: March 2017 (final data collection date for primary outcome measure)[f]

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CP-CML, chronic phase chronic myeloid leukaemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; TKI, Tyrosine kinase inhibitor

[a] Data discrepancy - reported as 68 sites across 12 countries in European Public Assessment Report[6] and the US Food and Drug Administration medical review[22]

[b] Data from company's clarification response to question A10[23] (CP-CML, n=28; AP-CML, n=2; BP-CML, n=0; Ph+ ALL, n=0; data not available by line of treatment)

[c] One patient was misclassified at the time of the original (CP-CML, n=98; AP-CML, n=141) analysis

[d] Total population (n=270) includes three patients with CP-CML who were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[e] Total population (n=85) included two patients with AP-CML who were excluded from the efficacy population because they were treated but not assigned to a cohort (T315I mutation not confirmed at baseline and patients had not received nilotinib or dasatinib)

[f] Data from https://clinicaltrials.gov/ct2/show/record/NCT01207440?view=results (no details provide in CS)

4.2.1.2 Ongoing studies of ponatinib

In addition to the PACE study,[20, 32, 33] in which follow-up evaluations are ongoing, the CS (p102-103) did not identify any additional ongoing studies of ponatinib in adults with Ph+ ALL. However, further details of two ongoing dose ranging studies (neither of these studies is likely to provide data within the next 12 months) in patients with resistant CP-CML (the OPTIC study)[34] and BP-CML (the MATCHPOINT study)[35] can be found Section 4.2.1.2 of the ERG CML report.[1]

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant published studies (RCTs and non-randomised/non-controlled evidence) were included in the CS and details of ongoing studies that are likely to be reporting additional evidence within 12 months were reported.

4.2.3 Summary and critique of the company's analysis of validity assessment

The company provided a formal appraisal of the validity of the included ponatinib study using the quality assessment criteria for non-randomised studies developed by Chambers *et al*.[29] In general, based on this quality assessment, the ERG considered the PACE study[20, 32, 33] to be a well-reported and conducted single-arm study. However, single-arm studies are associated with an array of potential biases.[36] For example, there is a high risk of selection bias due to the absence of randomisation, and a risk of performance and detection bias due to the absence of blinding.[25, 27] More importantly, as acknowledged in the CS (p66), the lack of a comparator group in the PACE study limits its ability to compare or demonstrate efficacy with current treatments. In addition, blinded outcome assessment was not undertaken in PACE study (see clarification response,[23] question A9). This would have helped minimise bias,[37] particularly for subjective outcomes. Further critique of the company's analysis of validity assessment is provided in Section 4.2.3 of the ERG CML report.[1]

4.2.4 Summary and critique of results

This section presents the main results from the PACE study, based on information reported in the CS and the company's clarification response,[23] for the target population in the company's decision problem for Ph+ ALL i.e. in the third-line treatment setting (reflecting the anticipated place in therapy of ponatinib, after treatment failure with imatinib and dasatinib). For completeness, the company also provided results based on the total 'treated' population (all lines of therapy), where applicable.

The primary outcome measure for Ph+ ALL patients in the PACE study was major haematological response (MaHR), which included complete haematologic responses (CHR) and no evidence of leukaemia at 6 months. Although response milestones for patients with Ph+ ALL have not been well established;[38] treatment strategies usually involve achieving an MaHR with the aim of proceeding to allo-SCT, if feasible. It is noteworthy that the ERG's clinical advisor considers MaHR to be a weak

surrogate endpoint for patients with Ph+ ALL. For example, MaHR maybe a perfectly valid endpoint for patients aged over 60 years who have a good quality of life. However, if used as a bridge to allo-SCT in patients who are resistant/intolerant to prior TKI therapy, this outcome (i.e. achieving normal blood counts) is too weak. Ideally, a better endpoint for bridging to transplant would be minimal residual disease levels in the bone marrow i.e. a more stringent criterion.

In the original published PACE study, data were reported after a median follow-up of 6 months for Ph+ ALL (data cut-off: 9 November 2012).[20] Updated results were derived from the ponatinib clinical study report (CSR)[39] and provided in the company's response to clarification question A13 (data cut off: 3 August 2015).[23] Where appropriate, data have been re-tabulated by the ERG to provide further clarity.

4.2.4.1 Efficacy

4.2.4.1.1. Ph+ ALL

Among patients with Ph+ ALL (all lines, n=32 [data not reported separately by line of therapy]), 41% (95% CI: 24% to 59%) achieved an MaHR within the first 6 months (primary endpoint). The duration of response ranged from 2 to 14 months or more (median 3 months), and the estimated rate of a sustained response of at least 12 months was 8%. The median time to MaHR for responders was 2.9 weeks (range: 1.6 to 24 weeks). Furthermore, MCyR was reached in 47% of patients, and 38% had a CCyR. The median time to MCyR for responders was 1 month (range: 0.9 to 3.7 months), with an estimated 32% of responding patients maintaining this response for at least 12 months. In Ph+ ALL patients, the PFS and OS at 12 months was estimated to be 7% (median 3 months) and 40% (median 8 months), respectively.[20] In addition, OS at 36 months was estimated to be 16% (median not reported).[32]

[redacted] The ERG's clinical advisor noted that combining survival outcome data for the BP-CML and Ph+ ALL groups is likely to be unfavourable for ponatinib as BP-CML patients are likely to have more mutations and be more resistant to TKIs in general. A summary of the original and updated results, by line of therapy, is presented in Table 6.

Table 6: Study outcomes in the Ph+ ALL cohort of the PACE study (adaption of table in company's clarification response to question A13)[23]

Source	Cortes *et al.*[20]	Cortes *et al.*[32]	Clinical study report[39a]		
Data cut-off	**Original efficacy results (cut-off date: 9 November 2012)**	**Updated efficacy results (cut-off date: 2 February 2015)**	**Updated efficacy results (cut-off date: 3 August 2015)**		
Follow-up	12 months	36 months	4 years		
Line of therapy	**All lines**	**All lines**	**All lines**	**3L**	**4L**
Number of patients	Ph+ ALL only, n=32	Ph+ ALL only, n=32	BP-CML/Ph+ ALL combined, n= 94	BP-CML/ Ph+ ALL combined, n=38	BP-CML/ Ph+ ALL combined, n=48
MaHR by 6 months [a]	41% (95% CI: 24–59)	N/R	[redacted]	[redacted]	[redacted]
MCyR	47% (95% CI: NR)	N/R	[redacted]	[redacted]	[redacted]
CCyR	38% (95% CI: NR)	N/R	[redacted]	[redacted]	[redacted]
Median time to response	*MaHR:* 2.9 weeks (range: 1.6–24) *MCyR:* 1 month (range: 0.9–3.7)	N/R	N/R	N/R	N/R
Duration of response	*MaHR:* 2 to 14 months or more (median: 3 months, 95% CI: NR)	N/R	N/R	N/R	N/R
Maintained response	*MaHR at 12 months:* 8% (95% CI: NR) *MCyR at 12 months:* 32% (95% CI: NR)	N/R	N/R	N/R	N/R
PFS	*12 month PFS*: 7% (median: 3 months, 95% CI: NR)	N/R	[redacted]	N/R	N/R
OS	*12 month OS*: 40% (median: 8 months; 95% CI: NR)	*36 month OS*: 16% (median: NR; 95% CI: NR)	[redacted]	N/R	N/R

3L, third-line; 4L, fourth-line; ALL, acute lymphoblastic leukaemia; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; NE, not estimable; N/R, not reported; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive; OS, overall survival.

[a] Data not reported separately for Ph+ ALL cohort only

[b] Primary endpoint for Ph+ ALL was MaHR defined as complete haematologic responses and no evidence of leukaemia

Ponatinib is the only TKI with activity against the T315I mutation. In England (as of December 2016), ponatinib is only available to CML and Ph+ ALL patients with the T315I mutation through the CDF.[18] Although a subgroup analysis by T315I mutation status was not provided in the CS, the ERG have provided a summary of these results in Table 7. Among the subgroup of Ph+ ALL patients who had the T315I mutation (n=22, all lines),[20] 36% (95% CI: not reported) had an MaHR within the first 6 months. A total of 40% of patients with Ph+ ALL achieved MCyR and 32% reached CCyR (95% CI: not reported for either outcome).

[redacted] Despite these findings, the ERG warrant caution in its interpretation due to the small population size and study design limitations.

Table 7: Efficacy of ponatinib by T315I mutation status in Ph+ ALL

Source	**Cortes *et al.*[20]**			**Clinical study report[39a]**		
Data cut-off	**Original efficacy results: 9 November 2012**			**Updated efficacy results: 3 August 2015**		
Follow-up	12 months			4 years		
Line of therapy	**All lines**			**All lines**		
Number of patients	Ph+ ALL only			BP-CML/Ph+ ALL combined		
	Overall n=32	Resistant/ Intolerant n=10	T315I mutation n=22	Overall n=94	Resistant/ Intolerant n=48	T315I mutation n=46
MaHR by 6 months[b]	41%	50%	36%	[redacted]	[redacted]	[redacted]
MCyR	47%	60%	41%	[redacted]	[redacted]	[redacted]
CCyR	38%	50%	32%	[redacted]	[redacted]	[redacted]
PFS	*12 month PFS*: 7%	N/R	N/R	[redacted]	[redacted]	[redacted]
OS	*12 month OS:* 40%	N/R	N/R	[redacted]	[redacted]	[redacted]

ALL, acute lymphoblastic leukaemia; BP, blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; N/R, not reported; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome–positive;
[a] Data not reported separately for Ph+ ALL cohort and BP-CML cohort
[b] Primary endpoint for Ph+ ALL was MaHR defined as complete haematologic responses and no evidence of leukaemia

4.2.4.2 Safety and tolerability

This section provides the main safety evidence for all patients with Ph+ ALL who received at least one dose of ponatinib within the PACE study (safety population).[20] Where available, results are presented for both the target population in the company's decision problem (i.e., in the third-line treatment setting)

and the total population (all lines). Additional safety data were also reported from a Phase I study.[30] Further details of this study are provided in Section 4.6.

4.2.4.2.1. Treatment dose and duration of treatment

The CS does not report the average daily dose of treatment and what proportion of treatment time Ph+ ALL patients were able to maintain the starting ponatinib dose of 45mg per day. Average daily dose and proportion of treatment time at 45mg per day and at any dose to 27 April 2012[22] (all lines) are presented in Table 8. Ph+ ALL patients were able to maintain 45mg per day for 96% of the entire treatment duration.[22]

Table 8: Average daily dose of ponatinib and percentage of treatment duration at 45mg or any dose for Ph+ ALL patients (all lines) in the PACE study (data derived from the FDA Medical Review Table 33[22])

	Ph+ ALL (n=32)
Average daily dose, mg	42.3
% treatment duration at 45mg per day	96%
% treatment duration at any dose	80%

Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia

4.2.4.2.2. Dose reduction and interruption

The CS reports that dose reductions were recommended following AEs. In response to a request for clarification from the ERG (see clarification response,[23] question A16), the company provided details on dose adjustments to August 2015 in the PACE study (all lines) for BP-CML and Ph+ ALL patients combined, following the recommendations to reduce the dose made in October 2013 by the Food and Drug Administration (FDA). The ERG considers the combining of BP-CML and Ph+ ALL patients for this outcome to be acceptable. A summary of these data, adapted by the ERG, is presented in

Table **9**.

[redacted]

Table 9: Summary of dose adjustments in BP-CML/Ph+ ALL patients (PACE data cut-off, 3 August 2015)[39]

	BP-CML/Ph+ ALL N=94 n (%)
Any dose reduced	
Yes	[redacted]
No	[redacted]
Dose interruptions of at least 3 days	
Yes	[redacted]
No	[redacted]
Dose modifications: patients with at least one of the following	
Interruption[a]	[redacted]
Resumed	[redacted]
Reduction	[redacted]
Re-escalation[b]	[redacted]
Last non-missing dose for ongoing patients	
N ongoing	[redacted]
15mg	[redacted]
30mg	[redacted]
45mg	[redacted]

BP-CML, blast phase chronic myeloid leukaemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia

[redacted]

4.2.4.2.3. Discontinuation of treatment

The CS reports that across CML and Ph+ ALL patients combined (all lines), 12% of patients discontinued treatment due to AEs and that treatment was discontinued due to lack of efficacy in 4% of patients and due to progressive disease in 19% of patients (p75 of the CS). The CS does not report rates of discontinuation for Ph+ ALL patients. A summary of the rates of discontinuation (including reasons for premature termination) for Ph+ ALL patients from the PACE study[20] (all lines) to 9 November 2012 is presented in

Table 10. In total, 53% of the Ph+ ALL population discontinued treatment due to progressive disease.

Table 10: Number (%) of Ph+ ALL patients discontinuing treatment in the PACE study: All lines (data derived from Cortes *et al.* [20])

	Ph+ ALL (n=32)
Had progressive disease	17 (53%)
Had adverse event	2 (6%)
Died	5 (16%)
Withdrew consent	1 (3%)
Had other reasons	1 (3%)
Lack of efficacy	4 (12%)
Physician's decision	1 (3%)
Non-compliance	0 (0%)

Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia

4.2.4.2.4. Treatment-related and treatment-emergent AE

The CS does not report treatment-related AEs for Ph+ ALL patients. A summary of the most common treatment-related AEs for Ph+ ALL from the PACE study[20] (all lines) to 9 November 2012 is presented in

Table 11. Amongst Ph+ ALL patients, the most common non-haematologic treatment-related AEs reported in the PACE study were skin reactions, abdominal pain and constipation. The most common haematologic treatment-related AE reported in the PACE study was anaemia.

Table 11: Treatment-related AEs from the PACE study for Ph+ ALL to November 2012 (adapted from Cortes *et al.*[20])

	Ph+ ALL (n=32)	
	Any grade n (%)	Grade 3 or 4 n (%)
Non-haematologic events		
Rash	6 (19%)	1 (3%)
Dry skin	7 (22%)	0 (0%)
Abdominal pain	6 (19%)	2 (6%)
Headache	4 (12%)	0 (0%)
Increased lipase	3 (9%)	2 (6%)
Fatigue	3 (9%)	0 (0%)
Constipation	6 (19%)	1 (3%)
Myalgia	2 (6%)	0 (0%)
Arthralgia	1 (3%)	0 (0%)
Nausea	1 (3%)	0 (0%)
Increased alanine aminotransferase	1 (3%)	1 (3%)
Pancreatitis	0 (0%)	0 (0%)
Hypertension	1 (3%)	1 (3%)
Increased aspartate aminotransferase	1 (3%)	1 (3%)
Increased blood amylase	1 (3%)	0 (0%)
Increased gamma-glutamyl transferase	0 (0%)	0 (0%)
Dyspnea	0 (0%)	0 (0%)
Cardiac failure	0 (0%)	0 (0%)
Haematologic events		
Thrombocytopenia	3 (9%)	2 (6%)
Neutropenia	4 (12%)	4 (12%)
Anaemia	5 (16%)	4 (12%)
Decreased white-cell count	1 (3%)	1 (3%)
Pancytopenia	0 (0%)	0 (0%)
Febrile neutropenia	2 (6%)	2 (6%)

Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia
Treatment-related adverse events were defined as events that the site investigators deemed to have a possible, probable, or definite relationship to ponatinib. Listed are the treatment-related adverse events that were reported in at least 10% of the patients, along with any incidence of grade 3 or 4 events in more than 1% of the total study population.

In response to a request for clarification from the ERG (see clarification response,[23] question A18), the company confirmed that AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v. 4.0[40]; definitions of grades: 1=mild, 2=moderate, 3=severe, 4=life-threatening, and 5=death).

In response to a request for clarification by the ERG (see clarification response,[23] question A18), the company provided details on the treatment-related and treatment-emergent AEs in ≥10% of patients for BP-CML and Ph+ ALL patients combined (all lines) (PACE data cut-off, 3 August 2015). The ERG considers the combining of BP-CML and Ph+ ALL patients for this outcome to be acceptable. A summary of these data, reproduced by the ERG, is presented in Table 12.

[redacted]

Table 12: Treatment-related and treatment-emergent AEs in ≥10% of BP-CML/Ph+ ALL patients (PACE data cut-off, 3 August 2015)

	BP-CML/Ph+ ALL N=94	
	Any Grade, n (%)	Grade 3+, n (%)
Any TRAE/TEAE	[redacted]	[redacted]
Haematologic		
Thrombocytopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Gastrointestinal		
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Investigations		
Lipase increase	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
AST increased	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Other		
Rash	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Muscle spams	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]
Cardiac disorders occurring in ≥1% of patients		
Angina pectoris	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Pericardial effusion	[redacted]	[redacted]
Acute myocardial infarction/myocardial infarction	[redacted]	[redacted]
Acute coronary syndrome	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Tachycardia		
Cardiac failure	[redacted]	[redacted]
Coronary artery occlusion	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]

	BP-CML/Ph+ ALL N=94	
	Any Grade, n (%)	Grade 3+, n (%)
Cardiac failure chronic		
Ischaemic cardiomyopathy		
Left ventricular dysfunction		
Cardiac arrest		

BP-CML, blast phase chronic myeloid leukaemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

A summary of the most common treatment-related Grade ≥3 AEs (all lines), as reported by the CS to 3 August 2015, is presented in Table 13.

Table 13: Treatment-related AEs from the PACE study for Ph+ ALL patients to August 2015 (adapted from CS Table 4-19)

	Ph+ ALL (n=32)
	Most common Grade ≥3 AEs, n (%)
TRAEs/TEAEs reported in >5% of patients	
Abdominal pain	
Anaemia	
Leukocytopenia	
Increased lipase	
Neutropenia	
Febrile neutropenia	
Pancreatitis	
Elevated ALT	
Thrombocytopenia	
VOEs (number of events per 100 patient-years)	
CV event	
Cerebrovascular event	
Peripheral arterial occlusive event	
Serious venous thrombotic event	

BP-CML, blast phase chronic myeloid leukaemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; TRAE, treatment-related adverse event; TEAE, treatment-emergent adverse event; VOE, vascular occlusive event
Sources: PACE study CSR[39], Ph+ ALL, Table 14.3.1.8.2.10.2 (p3569); VOEs, Section 14.3.5 Other Safety Measurements, Table 2.2 (p6124–6126).

4.2.4.2.5. Treatment-related vascular occlusive events (VOEs)

The CS reports that, following a review of updated clinical trial data on ponatinib revealing an accumulation of treatment-emergent VOEs, the EMA issued a set of recommendations regarding the use of ponatinib in November 2013. The EMA recommended that the cardiovascular status of patients be assessed and that cardiovascular risk factors be actively managed prior to, and monitored during, treatment.[41]

In response to a request for clarification by the ERG (see clarification response,[23] question A18), the company provided details on the treatment-emergent arterial occlusive AEs in ≥1% of patients for Ph+

ALL patients (PACE data cut-off, 3 August 2015). A summary of these data adapted by the ERG is presented in Table 14.

Table 14: Treatment-emergent arterial occlusive AEs in ≥1% of Ph+ ALL patients (PACE data cut-off, 3 August 2015)

	Ph+ ALL N=32 n (%)		
	Grade		
	Any	3/4	5
Any arterial occlusive AE	[redacted]	[redacted]	[redacted]
Cerebral ischaemia	[redacted]	[redacted]	[redacted]
Coeliac artery stenosis	[redacted]	[redacted]	[redacted]
Coronary artery stenosis	[redacted]	[redacted]	[redacted]
Mesenteric arterial occlusion	[redacted]	[redacted]	[redacted]
Peripheral arterial occlusive disease	[redacted]	[redacted]	[redacted]
Peripheral ischaemia	[redacted]	[redacted]	[redacted]

AE, adverse event; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia[redacted]

4.2.4.2.6. Serious vascular occlusive events

[redacted]

4.2.5 Supplementary evidence

The CS includes supplementary evidence from a Phase I study of ponatinib.[30] Further details are provided in this section.

4.2.5.1 Cortes et al.[30] (Phase 1 study)

The CS reports that the Phase I ponatinib study was a dose-ranging study. The study population included 81 patients of whom 5 (6.2%) had Ph+ ALL.[30] Median follow-up across all populations (CP-, AP- and BP-CML; Ph+ ALL, acute myeloid leukaemia, myelodysplastic syndrome, multiple myeloma, and myelofibrosis) was 56 weeks (range 2 to 140 weeks).[30] Of the five Ph+ ALL patients, all (100%) withdrew from treatment. Reasons for discontinuation were: documented progressive disease, 1 (20%); AE, 1 (20%); death, 1 (20%), and; administrative decision, 2 (40%). All deaths were deemed to be unrelated to ponatinib by the investigators.[30]

The CS reports that the median duration of follow-up was 13 weeks (range 2 to 121 weeks) for AP-CML, BP-CML and Ph+ ALL patients combined (Table 4-13). A summary of best response rates from the Phase I study for combined AP-CML, BP-CML and Ph+ ALL patients as reported by the CS (Table 4-13) and adapted by the ERG is presented in

Table 15. The ERG considers the combining of CML and Ph+ ALL patients for this outcome in the Phase I study to be acceptable. The CS reports that median MaHR duration in the AP-CML/BP-CML/Ph+ ALL population was 16 weeks (range 0.1 to 64 weeks) (Table 4-13).

Table 15: Best response rates from the Phase I ponatinib study (data derived from the CS Table 4-13)

	AP- and BP-CML and Ph+ ALL ≥3L setting n/N (%)
CHR	-
MaHR	8/20 (40%)
MCyR	5/19 (26%)
CCyR	3/19 (16%)
MMR	2/22 (9%)

AP-CML, accelerated phase chronic myeloid leukaemia; BP-CML, blast phase chronic myeloid leukaemia; CCyR, complete cytogenetic response; CHR, complete haematologic response; CP-CML, chronic phase chronic myeloid leukaemia; MaHR, major haematologic response; MCyR, major cytogenetic response; MMR, major molecular response; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; 3L, third-line

The CS reports that across all populations in the Phase I ponatinib study (n=81), the most common treatment-related ≥Grade 3 AEs were: increased lipase, 6/81 (7%); pancreatitis, 4/81 (5%); increased amylase, 2/81 (2%); prolonged QT (a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) interval, 2/81 (2%); thrombocytopenia, 16/81 (20%); neutropenia, 8/81 (10%); and anaemia, 2/81 (2%) (Table 4-17). Adverse events by population were not reported by the CS and were not reported by Cortes *et al*.[30]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS reports that an MAIC was performed using baseline characteristics and effectiveness data for the CP-CML patient subgroup only. The ERG's critique of this MAIC is reported in the ERG CML report.[1] The CS (p48) reported that an MAIC was not undertaken for Ph+ ALL due to a lack of applicable data for comparators.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS (p48) reports that an MAIC was not undertaken for Ph+ ALL due to a lack of applicable data for comparators.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As the company undertook a reasonably comprehensive systematic review (no major limitations were noted) of ponatinib for treating Ph+ ALL, no additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence for ponatinib Ph+ ALL in the CS is based on a systematic review of the safety and efficacy of current treatments for adult Ph+ ALL patients being treated in the second-line or later. The ERG is confident that all relevant studies (published and unpublished) of ponatinib were included in the CS, including data from ongoing studies. Although the ERG is confident that no other published studies evaluating ponatinib in this population are likely to have been missed, the CS did not report if any attempt was made by the company to contact authors of the included studies to request potential additional unpublished data and it is therefore not entirely clear if all relevant data have been included. However, overall the ERG considers the systematic review reported in the CS to be of an acceptable standard.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

A key limitation to the efficacy and safety data for ponatinib reported in the CS relates to study design. The PACE study was a single-arm intervention study.[20] The CS acknowledges that the lack of a comparator group limits the ability of a single-arm study to compare or demonstrate effectiveness compared with other treatments. Furthermore, single-arm studies are associated with several biases.[36]

A further limitation to the robustness of the efficacy and safety data for ponatinib reported in the CS relates to the availability of data for the Ph+ ALL population. Although the CS (p67) reported power calculations for the Ph+ ALL population, these numbers were not met. Furthermore, the Ph+ ALL population in the PACE study comprised all lines of ponatinib therapy, and participant numbers by line of therapy also did not meet the CS reported power calculation. As such, the PACE[20] study was not powered by line of therapy for the Ph+ ALL population.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The key uncertainties surrounding the clinical evidence for ponatinib relate to optimal dosing, duration of treatment, comparative efficacy and generalisability to the population in England. Further details are provided below.

4.6.3.1 Optimal dosing

In the PACE study,[20] patients received an initial dose of 45mg of ponatinib orally once daily. The company provide details on dose adjustments to August 2015 in the PACE study made in October 2013 following recommendations on dose reduction by the FDA. Thereafter, a number of dose adjustments were made to participants in the PACE study during the course of the study. As such, it remains unclear if the adjusted lower dosing regimens would have been clinically effective over the entire PACE study period.

4.6.3.2 Treatment duration

In terms of the PACE study starting dose, Ph+ ALL patients were able to maintain 45mg per day for 96% of the entire treatment duration (to 27 April 2012).[22] In response to a request for clarification from the ERG (see clarification response,[23] question A16), the company provided details on dose adjustments to August 2015 in the PACE study. The company also reported that no data were available on the alternative treatments given to patients who stopped study treatment in the PACE study (see clarification response,[23] question A8). The SmPC posology recommends considering discontinuation of ponatinib if a complete haematologic response has not occurred by 3 months (90 days).[15] The PACE study reported outcomes over a median follow-up of 48.2 months (4 years).[33] As a result, the longer term safety and efficacy of ponatinib is currently unknown. The ERG also notes that without a comparator group or indirect comparison, the short term efficacy is also uncertain.

4.6.3.3 Generalisability to the population of England

The PACE study was a large, well designed, single-arm non-comparator intervention study.[20] Median age was 62 years for the Ph+ ALL population in the PACE study.[20] [redacted].[39] Survival in adult Ph+ ALL is poor, particularly for patients aged over 50 years.[9, 10] Clinical advisors to the ERG considered the PACE study population to be reflective of the Ph+ ALL population in England in terms of age and gender, but noted that treatment practice in the PACE study for the Ph+ ALL population, was not representative of UK practice (patients received nilotinib, which is not used in the UK). The ERG considers the population characteristics in the PACE study to be representative of Ph+ ALL patients in England, but not the treatment practice.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the cost-effectiveness evidence presented by the company.

5.1 ERG's comment on company's review of cost-effectiveness evidence

This section focusses on previous estimates of cost-effectiveness studies involving ponatinib in ALL. Further searches identifying HRQoL are detailed in Section 5.2.7.1.

5.1.1 Objective of cost-effectiveness review

The company stated that the objective of the review of Ph+ ALL cost-effectiveness studies was to identify relevant evidence published from January 2000 – February 2016. The search was updated in July 2016. The following sources were searched: EMBASE and EMBASE Economic conference abstracts (via Ovid), MEDLINE (via Ovid), MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), Cochrane Central Register of Controlled Trials (via EBM Reviews), and Health Technology Assessment (via EMB Reviews). The company's search strategies comprised the terms for the population concepts (Ph+ ALL) combined with a sensitive search filter for retrieving cost-effectiveness studies. The ERG considered that the searches were comprehensive and adequate for the cost-effectiveness review.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria used in the literature review is detailed in Table 5-1 of the CS. The ERG considered it to be satisfactory. Key components included: limiting the population to those with Ph+ ALL aged 18 years or over; excluding costs that were not related to the UK; and excluding at the screening stage, papers published in languages other than English.

5.1.3 Findings of the cost effectiveness review

The company reported that only one study was included in the review which was a conference abstract.[42]

5.1.4 Conclusions of the cost effectiveness review

The identified abstract assessed the cost-effectiveness of ponatinib compared to BSC in a UK setting for patients who had failed dasatinib treatment. As this study did not include all comparators in the decision problem the company constructed a *de novo* model.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE Reference Case checklist

The comparability between the final scope issued by NICE and the analyses within the CS and the final scope issued by NICE for ALL is detailed in Table 16.

Table 16: Comparability between the analyses within the CS and the final scope issued by NICE (ALL only)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final NICE scope	ERG comment
Population	Adults with Ph+ ALL whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.	As per the final scope	N/A	N/A
Intervention	Ponatinib	As per the final scope	N/A	N/A
Comparator (s)	Established clinical management without ponatinib (including but not limited to best supportive care).	• Induction chemotherapy and allo-SCT • BSC	N/A	N/A
Outcomes	• OS • PFS/ event-free survival • Response rates • Time to response • Duration of response • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	PFS and duration of response are not considered	Duration of response is not considered in the Ph+ ALL model as patients suited for allo-SCT who respond to treatment transition to allo-SCT in the first cycle. Duration of response is not explicitly modelled for Ph+ ALL patients who are unsuitable for allo-SCT, but is expected to be reflected in the parametric function for OS.	Based on clinical advice the ERG believes that the exclusion is appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale provided by company if different from the final NICE scope	ERG comment
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 (QALY) • time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective.	As per the final scope	N/A	The CS did not provide full incremental analyses but instead provided pairwise comparisons of each intervention with ponatinib. Whilst a fully incremental analysis can be calculated from the pairwise analyses for the deterministic results, the accuracy cannot be guaranteed for the probabilistic results due to Monte-Carlo sampling error. The CS only reports results from probabilistic sensitivity analyses (PSA) for ponatinib vs induction chemotherapy which could be insufficient.

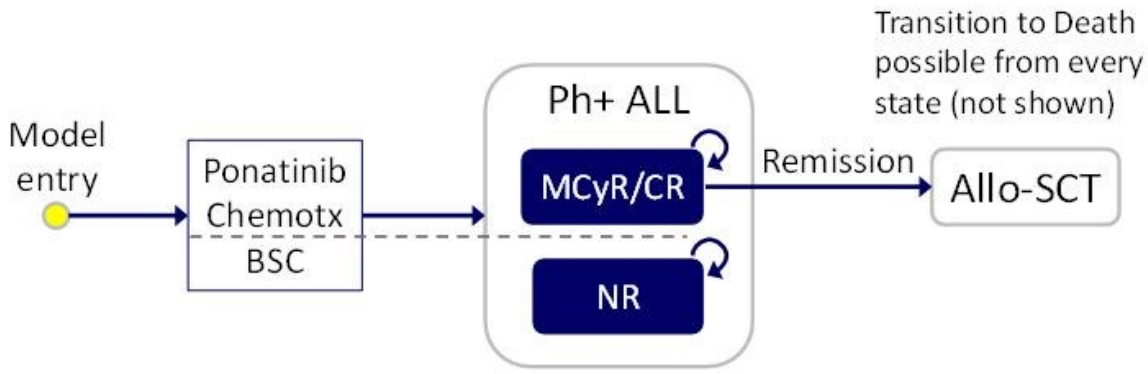
5.2.2 Model structure

The company submitted a model to assess the cost-effectiveness of ponatinib in Ph+ ALL from the perspective of the NHS and Personal Social Services over a lifetime horizon. Both benefits and costs were discounted at a rate of 3.5% per annum. The model employs a state transition approach, with three-monthly time cycles and includes a half-cycle correction. The original submitted model was amended by the company following the clarification process. In order to avoid confusion, only the revised model is discussed within this report. The ERG has calculated results using the company's revised model with the agreed PAS applied (a discount of [redacted]): only results incorporating the PAS are presented within this report.

5.2.2.1 The Ph+ ALL model

The schematic representation of the Ph+ ALL model provided by the company (Figure 5-26 of the CS, p215) is shown in Figure 2. The goal of ponatinib or induction chemotherapy treatment is to generate a response such that the patient can receive allo-SCT. The prognosis for those patients who receive allo-SCT is considerably better than those patients who do not, and thus ponatinib or induction chemotherapy can generate additional life for the patients by being a bridge to allo-SCT.

Figure 2: Schematic representation of the Ph+ ALL model provided by the company



ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; chemotx, chemotherapy; CR, complete remission; MCyR, major cytogenetic response; NR, non-response; Ph+, Philadelphia chromosome–positive.

Note: dashed line indicates that patients receiving BSC cannot achieve MaHR, and thus remain nonresponders; patients receiving ponatinib or chemotherapy can either achieve MCyR or be nonresponders.

On entering the model, a hypothetical patient could receive one of three interventions: (i) ponatinib; (ii) induction chemotherapy; or (iii) BSC. The simulated patient pathway was identical for those patients receiving ponatinib or induction chemotherapy, in that if an MyCR (for ponatinib) or CR (for induction chemotherapy) was achieved, the patient was assumed to receive allo-SCT (if suitable). The different response levels were chosen to align with study data. Clinical advice provided to the ERG suggested that the results following an allo-SCT are better in those patients with minimal residual disease or where

the residual disease burden was less than 1/1000 at the time of transplant. For patients receiving BSC, it was assumed that there would be NR and the patient would remain in this state. For all treatments, death could occur at any time point.

5.2.2.1.1 Patients receiving ponatinib or induction chemotherapy

For patients receiving ponatinib or induction chemotherapy, the model simulates the response of patients to the treatment, which was assumed to occur in the first cycle only. It was assumed that patients would fall into one of two mutually exclusive and exhaustive states: remission (which incorporated either MyCR (ponatinib) or CR (induction chemotherapy) and NR.

For patients simulated to experience remission, the next event in the model (a term which has been used in the ERG report to identify the next event whilst excluding remaining in the same health state) would be allo-SCT, if appropriate. Following allo-SCT, the next event is death. For those who experience NR, and/or who are unsuitable for allo-SCT, the next event is death.

5.2.2.1.2 Patients receiving BSC

For patients receiving BSC, the only event possible is death.

5.2.3 Population

The population modelled is provided in Table 17.

Table 17: Characteristics of the hypothetical patients used in the Ph+ ALL model

	Initial Age (years)	Proportion male (%)	Source
AP-CML	53.0	62.5	PACE[20]

5.2.4 Intervention and comparators

5.2.4.1 The comparators in Ph+ ALL

The intervention being appraised is ponatinib which is a third-generation antineoplastic protein kinase inhibitor administered orally. Further details are provided in Section 3.2.

5.2.4.2 Comparators in Ph+ ALL

Within Ph+ ALL, three strategies are compared: (i) ponatinib; (ii) induction chemotherapy; and (iii) BSC.

5.2.5 Treatment effectiveness

The key driver of patients' long-term prognoses, both in terms of life expectancy and utility, is the assumed remission rates for each treatment option.

5.2.5.1 Treatment effectiveness in Ph+ ALL

The response rates assumed in the model for each treatment in Ph+ ALL are detailed in Table 18. Data for MCyR for ponatinib were taken from the PACE study,[20] whilst data on CR for induction therapy were taken from Tavernier *et al*.[43] The ERG comments that this is a naïve unadjusted indirect comparison and will be uncertain. Advice provided by the clinical advisor to the ERG indicated that MCyR is harder to achieve than CR: if this is correct, the relative effectiveness between ponatinib and induction chemotherapy would be unfavourable to ponatinib.

Table 18: Assumed response rates for each treatment

Treatment	MCyR / CR (%)	NR (%)	Source
Ponatinib	46.88	53.12	PACE[20]
Induction chemotherapy	37.04	62.96	Tavernier *et al*.[43]
BSC	0.00	100.00	Assumption

5.2.5.2 Adverse and serious adverse events associated with treatment

Further details on AEs and SAEs are provided in Section 4.2.4.2. The company assumed that AEs and SAEs were associated only with ponatinib treatment. The probability of a patient experiencing a treatment-related SAE in Ph+ ALL is reproduced from the CS (Table 5-24, p155) in Table 19. AEs are assumed to occur only once, and within the first cycle (three months).

Table 19: Assumed SAE rates and costs for ponatinib in the company's model

Adverse event	Ponatininb	Unit cost, £	Source
Abdominal pain	[redacted]	752.10	Ref costs 2014/15
Anaemia	[redacted]	1,827.13	NHS ETF 2014/15
Lipase increased	[redacted]	721.00	Assumed to require one day in hospital
Neutropenia	[redacted]	633.26	Ref costs 2014/15
Thrombocytopaenia	[redacted]	421.74	Ref costs 2014/15
Serious adverse events			
Peripheral vascular event	[redacted]	2,872.00	Ref costs 2014/15
Venous thromboembolism event	[redacted]	552.00	Ref costs 2014/15

Ref costs 2014/15: NHS Reference costs 2014 to 2015
NHS ETF 2014/15: NHS Enhanced tariff option 2015 to 2016

5.2.6 Extrapolation of surrogate outcomes and linkages between health states

Following estimation of the response rates associated with each treatment many other parameters in the model are assumed independent of initial treatment. This is appropriate where pivotal studies are of relatively short duration, but the reliance on extrapolating from surrogate data increases the uncertainty in the results.

The ERG believes that the method used by the company in fitting curves to digitised survival data is inappropriate. The company used the Solver function in Microsoft Excel® to minimise the sum of squared errors (SSE) between the predicted survival curve and that of the digitised points and, if the extrapolation was believed by the company to be clinically plausible, the curve with the lowest SSE was selected. The ERG has concerns with the approach used as this method weights points equally despite the number of patients contributing data to the curve declining as time progresses. A better approach would be to use the method presented by Guyot *et al.*[44] which would produce superior fits to the underlying data.

5.2.6.1 For patients who experience remission (MCyR or CR)

Patients exit the remission state through either death or by receiving an allo-SCT.

5.2.6.1.1 Exiting the remission state due to allo-SCT

It is assumed that if a patient were suitable for allo-SCT then this would occur.

5.2.6.1.2 Exiting the remission state due to death

If a patient was not suitable for allo-SCT after remission the probability of death was estimated from data collected in the PACE study.[20] The company undertook standard survival analysis using exponential, Weibull, Gompertz, log-normal and log-logistic survivor functions. All distributions pooled data from patients with MCyR and NR and used a covariate for response level. Based on the analyses undertaken, the company stated that the best fit using the AIC and BIC criteria were not in agreement (

Table 20) but that the exponential distribution was selected as it was considered to be more clinically plausible than the Gompertz curve. The extrapolated curves are presented in Figure 3. It was assumed that the risk of death for a patient in remission was independent of the treatment that produced remission, and as such, the same function for ponatinib was also assumed for induction chemotherapy.

Table 20: AIC and BIC statistics presented by the company relating to death in remission (CIC data)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Figure 3: Extrapolation of the candidate curves presented by the company relating to death in remission (CIC data)

[redacted]

5.2.6.2 For patients who experience NR

Patients can only exit the NR state through death.

5.2.6.2.1 Exiting the NR state due to death

Contrary to the assumption employed for people who achieve remission, the risk of death for patients in NR was assumed to be dependent on treatment with different risks assumed for those who initially received ponatinib, induction chemotherapy, or BSC. Clinical opinion provided to the ERG suggested that the life expectancy would be equal for those who experience NR regardless of whether ponatinib or BSC had been provided.

5.2.6.2.1.1 Probability of death in NR for patients who had received ponatinib

The method employed by the company is detailed in Section 5.2.6.1.2 Exiting the remission state due to death with the goodness-of-fit statistics shown in

Table 20. The extrapolation of the curves for patients in NR treated with ponatinib is shown in Figure 4. The exponential curve was selected as this was deemed more clinically plausible than the Gompertz curve.

Figure 4: Extrapolation of the candidate curves presented by the company relating to OS for patients with NR treated with ponatinib (CIC data)

5.2.6.2.1.1.1 Probability of death in NR for patients who had received induction chemotherapy

The company assumed that the probability of death in NR for patients who received induction chemotherapy would be equivalent to those who had received BSC. (Section 5.2.6.2.1.1.2)

5.2.6.2.1.1.2 Probability of death in NR for patients who had received BSC

The company stated that no studies were identified in the systematic review that detailed OS in patients treated with BSC. An estimate was however made based on an Italian single-centre retrospective study in ALL patients.[45] This study reports a median OS of 2.6 months and this value was used to fit an exponential function. The company therefore used a naïve unadjusted indirect comparison between ponatinib and BSC in relation to OS.

5.2.6.3 Assumed duration of treatment

5.2.6.3.1 Assumed duration of ponatinib treatment

The duration of treatment with ponatinib was estimated using individual patient data (IPD) from the PACE study.[20] The CS (p215) implies that the base case assumed that ponatinib treatment would be stopped if remission was not achieved within three months, with an option to continue treatment beyond 3 months. This does not appear to tally with the model whereby there appears to be only one option which is that time on treatment was derived from that observed in the PACE study.

The company undertook standard survival analysis using exponential, Weibull, Gompertz, log-normal and log-logistic survivor functions. All distributions pooled data from patients with MCyR and NR and used a covariate for response level. Based on the analyses undertaken, the company stated that the best fit using the AIC and BIC criteria was the log-logistic curve (Table 21). The extrapolated curves are provided in

Figure 5 for those with an MCyR and in

Figure 6 for those with NR. For patients in whom allo-SCT is unsuitable and/or who have NR, it is assumed that BSC is provided until death once treatment with ponatinib is discontinued.

Table 21: AIC and BIC statistics presented by the company relating to duration of ponatinib treatment (CIC data)

Figure 5: Extrapolation of the candidate curves presented by the company relating to ponatinib treatment for those with a MCyR (CIC data)

Figure 6: Extrapolation of the candidate curves presented by the company relating to ponatinib treatment for those with NR (CIC data)

5.2.6.3.2 Assumed duration of induction chemotherapy treatment

The company's model assumes that a six-week course of induction therapy would be provided; subsequently, patients would receive BSC until death.

5.2.6.3.3 Assumed duration of BSC treatment

The company assumed that BSC treatment would continue until death.

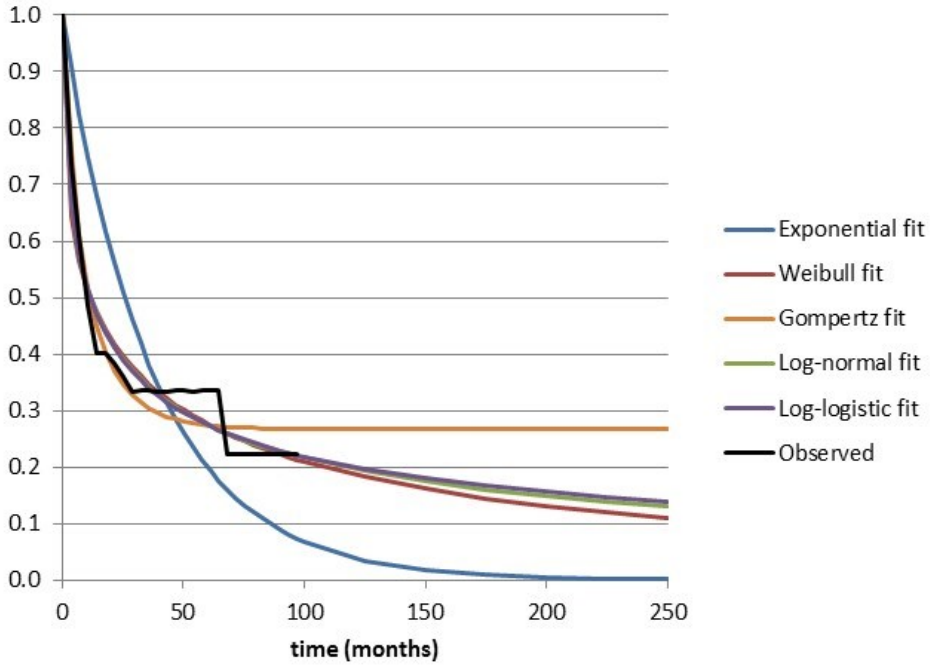
5.2.6.4 Modelling assumptions for patients who progress to allo-SCT

For patients suitable for allo-SCT, the next event is death.

5.2.6.4.1 Probability of death following allo-SCT

The probability of death used in the model was derived from data presented in Tavernier *et al*.[43] The data were digitised and curves were fitted by minimising the SSE between the observed data-points and fitted curves: as previously stated this method has limitations. With the exception of the exponential distribution, the range in SSE was relatively small (0.04 – 0.05). The company selected the log-logistic distribution for use in the base case model. The curves are presented in
Figure 7.

Figure 7: Fitting curves to the risk of death following allo-SCT



5.2.7 Health-related quality of life

5.2.7.1 The selection of HRQoL decrements for patients with ALL

It was not stated whether the company identified any studies reporting HRQoL from the clinical effectiveness review but it is presumed not. The PACE study did not record HRQoL. The company therefore performed a systematic review to identify evidence regarding HRQoL. An initial search focussed on published data between January 2000 and February 2016; the search was updated in July 2016. The following sources were searched: EMBASE and EMBASE Economic conference abstracts (via Ovid); MEDLINE (via Ovid); MEDLINE In-Process & Other Non-Indexed Citations (via Ovid); Cochrane Central Register of Controlled Trials (via EBM Reviews); and Health Technology Assessment (via EMB Reviews). The company's search strategies comprised the terms for the population concepts (Ph+ ALL) combined with a sensitive search filter for retrieving quality of life studies. The ERG considered that the searches were comprehensive and adequate for the review.

The company present a PRISMA flow diagram in the CS (p221) which concludes that no articles were included in the HRQoL results.

In the absence of data, the company assumed that the utilities reported by Szabo *et al*.[46] for BP-CML were applicable for patients with Ph+ ALL. As such, those patients responding to treatment were assumed to have a utility of 0.56 and those patients not responding to treatment had a utility of 0.29. The utilities for all AEs were assumed to be 0.52 based on Szabo *et al*.[46] The utilities decrements associated with allo-SCT are the same as in the CML ERG report[1] (Table 43). The utilities assumed for the general population are the same as those used in the CML report[1] (Table 44).

5.2.8 Resources and costs

5.2.8.1 Assumed acquisition costs of Ph+ ALL interventions

The company has estimated the costs of Ph+ ALL for the following treatments: ponatinib; induction chemotherapy; and BSC. The acquisition prices used by the company are reproduced, following amendments to remove typographical errors, in

Table 22.

Table 22: Acquisition prices used in the company's model

Drug	Daily dose, mg	mg per unit	Units per pack	Cost per pack, £	Daily cost, £
Ponatinib	15	15	30	2525.00	84.17
	30	15	30	5050.00	168.33
	45	45	30	5050.00	168.33
Drug	Daily dose, mg	mg per unit	Units per pack	Cost per pack, £	Cost per mg, £
Induction chemotherapy	500	500	5	100.00	0.04
Cytarabine	20	20	1	121.85	6.09
Mitoxantrone	1,000	1,000	1	85.00	0.09
Methotrexate IV	5	5	5	30.00	1.20
Methotrexate IT	10,000	10,000	5	3065.00	0.06
Asparaginase	2	2	1	26.66	13.33
Vincristine (non-proprietary)	25	25	56	40.00	0.03
Prednisolone (non-proprietary)	500	500	1	9.66	0.02
Cyclophosphamide IV	50	50	1	131.75	2.64
Daunorubicin	10	10	1	165.98	16.60
Idarubicin	50	50	1	103.00	2.06
Doxorubicin	50	50	1	155.00	3.10
Fludarabine	30	30	5	263.52	1.76
Filgrastim (million units)	500	500	5	100.00	0.04
Best supportive care					
Vincristine (non-proprietary)	*	25	56	40.00	0.03
Prednisolone (non-proprietary)	40mg/m^2	500	1	9.66	0.02

Source: BNF *: Vincristine dose is 1.5mg/m^2 weekly

The relative dose intensity of ponatinib was calculated from the PACE study[20] and applied within the model as shown in Table 23. The clinical advisor to the ERG was uncertain whether unused tablets in a prescription would be used elsewhere and thus the ERG undertook a sensitivity analysis assuming that wastage occurred. The cost of induction chemotherapy was assumed to be comprised of equal measures of LALA-94, Hyper CVAD, and Flag IDA which are the protocols reported in Tavernier *et al.*[43] and also to consist of 13.91 days in hospital based on the NICE STA of azacitidine.[47] BSC was assumed to include 12 blood transfusions and 12 platelet transfusions based on expert opinion.

Table 23: Assumed cost per cycle having taken into account relative dose intensity

Treatment	Proportion of time patients in trial spent on each dose	Cost per cycle, £	Source
Ponatinib	[redacted]	[redacted] (List Price)	PACE study[20]; ARIAD Pharmaceuticals
Induction chemotherapy†	-	17.999.73*	BNF
BSC†	-	4,063.87*	Pagano *et al*. 2000[45]

QD: Once per day; †: Six week course; *: Cost applied during first cycle only; BNF: British National Formulary; BSC: Best Supportive care

5.2.8.2 Assumed monitoring and hospitalisation costs associated with Ph+ ALL treatments

Monitoring costs were assumed independent of treatment for the response and non-response states. The company assumed that patients with Ph+ ALL who responded to treatment would require the same monitoring resources as people in CP-CML whilst those with Ph+ ALL who did not respond to treatment were assumed to require the same monitoring resources as people with BP-CML, as shown in Table 49 of the ERG CML report.[1] The company reported monitoring and hospitalisation costs per cycle of £208 for patients with Ph+ ALL who responded and £4862 for Ph+ ALL patients who did not respond. However, there was an error in that the inpatient costs associated with BP-CML were not included which significantly reduced the costs associated with non-response in Ph+ ALL, which rose to £24,070 per cycle when hospitalisation costs were included. This was corrected by the company when it was alerted to this error. No additional costs of monitoring cardiovascular events were considered for ponatinib.

5.2.8.3 Assumed costs associated with allo-SCT

The company assumed that the cost of allo-SCT was £60,092, based on data from the UK Stem Cell Strategy Oversight Committee.[48] The follow-up costs decreased over time, with a per cycle cost of: £12,215 in year 1; £3518 in year 2, and £420 in year 3.

5.2.8.4 Assumed costs associated with adverse events and serious adverse events

These costs are provided in Table 19.

5.2.8.5 Assumed costs associated with end of life

The company assumed that all patients incurred additional costs at death. The cost was assumed to be £5766, as shown in Table 51 of the ERG CML report.[1]

5.2.9 Cost-effectiveness results

The results presented are from the company's revised model and include the PAS for ponatinib (a discount of [redacted]). The results have been divided into those patients for whom allo-SCT is suitable and for those patients where allo-SCT is not suitable. The ERG has numerous concerns regarding the robustness of the probabilistic sensitivity analyses (PSA) undertaken.

5.2.9.1 Company's results for patients who are suitable for allo-SCT

5.2.9.1.1 Company's base case results for patients for whom allo-SCT is suitable

The base case results are presented in Table 24.

Table 24: The company's base case results for patients for whom allo-SCT is suitable

Treatment	Life years gained	Costs (£)	QALYs	ICER (cost per QALY gained) (£)	
				Ponatinib versus comparator	Full Incremental analysis
BSC	0.32	40,875	0.09	26,624	-
Induction chemotherapy	2.96	84,854	1.84	31,123	25,258
Ponatinib	[redacted]	[redacted]	[redacted]	-	31,123

5.2.9.1.2 Company's one-way sensitivity analyses for patients for whom allo-SCT is suitable

The function contained within the company's model was used to generate a tornado plot that is replicated in Figure 8. Typically, the upper and lower values are 95% confidence intervals although the standard error is regularly set to 10% of the central estimate. As this function allowed only a pairwise comparison the ERG analysed the incremental cost effectiveness ratio (ICER) compared with the previous intervention on the efficiency frontier (in this case, induction chemotherapy). As shown in the figure, the ICER is very sensitive to the assumed response rate generated by induction chemotherapy with higher response rates generating an ICER for ponatinib of approximately £250,000 per QALY gained.

Figure 8: Tornado diagram assessing the sensitivity of the ICER of ponatinib compared with induction chemotherapy to changes in individual parameters (CIC data)

5.2.9.1.3 Company's probabilistic sensitivity analyses for patients for whom allo-SCT is suitable

Similar to the one-way sensitivity analysis, the PSA was set up for pairwise comparisons only. As before, the ERG analysed the ICER compared with the previous intervention on the efficiency frontier (in this case, induction chemotherapy). Based on the company's assumptions, the ICER for ponatinib compared with induction chemotherapy was approximately £33,000 per QALY gained. One thousand PSA iterations were run.

Table 25: The company's base case results for patients for whom allo-SCT is suitable

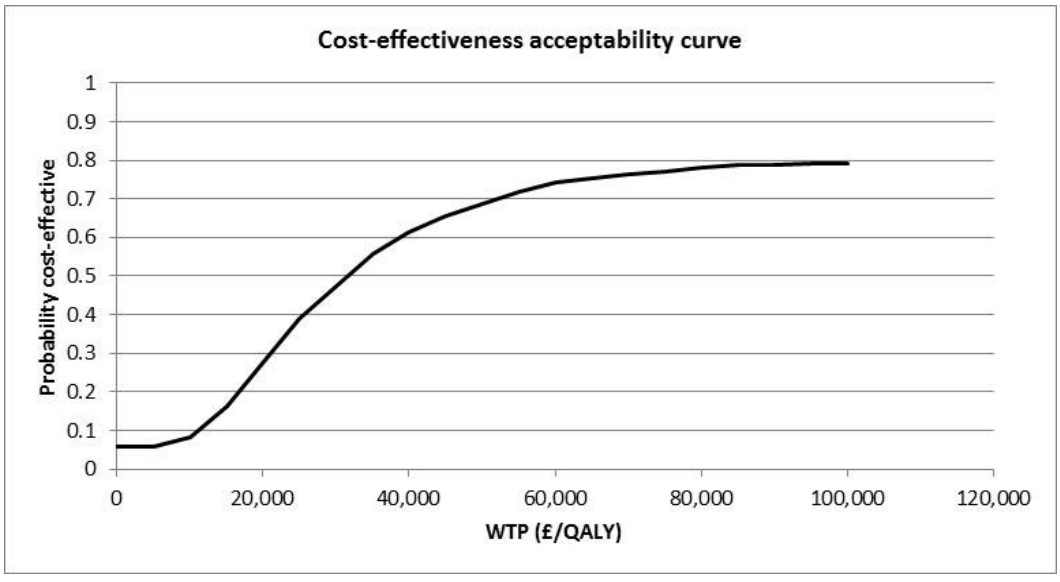
Treatment	Costs (£)	QALYs	ICER (cost per QALY gained) (£)
Induction chemotherapy	85,110	1.84	-
Ponatinib	[redacted]	[redacted]	33,064

The results from the PSA are shown in a cost-effectiveness plane (Figure 9) and a cost-effectiveness acceptability curve (see Figure 10).

Figure 9: The company's PSA results for ponatinib compared with bosutinib for Ph+ ALL patients shown on a cost-effectiveness plane (CIC data)

[redacted]

Figure 10: The company's PSA results for ponatinib compared with bosutinib for Ph+ ALL patients shown on a cost-effectiveness acceptability curve



The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (28%); £30,000 (47%); and £50,000 (69%).

5.2.9.2 Company's results for patients for whom allo-SCT is unsuitable

5.2.9.2.1 Company's base case results for patients for whom allo-SCT is unsuitable

The base case results are presented in

Table **26**.

Table 26: The company's base case results for patients for whom allo-SCT is unsuitable

Treatment	Life years gained	Costs (£)	QALYs	ICER ((cost per QALY gained) (£)
BSC	0.32	40,875	0.09	
Ponatinib	[redacted]	[redacted]	[redacted]	33,954

5.2.9.2.2 The company's one-way sensitivity analyses for patients with Ph+ ALL

The function contained within the company's model was used to generate a tornado plot that is presented in Figure 11**.** As shown in the figure, the ICER was sensitive to the response rate of ponatinib with the value most unfavourable to patients increasing the ICER to approximately £75,000 per QALY gained.

Figure 11: Tornado diagram assessing the sensitivity of the ICER of ponatinib compared with BSC to changes in individual parameters (CIC data)

[redacted]

5.2.9.2.3 Company's probabilistic sensitivity analyses for patients for whom allo-SCT is unsuitable

One thousand PSA iterations were run. Results are presented for the ICER of ponatinib compared with BSC (Table 27). The results from the PSA are shown in a cost-effectiveness plane (Figure 12) and a cost-effectiveness acceptability curve (Figure 13).

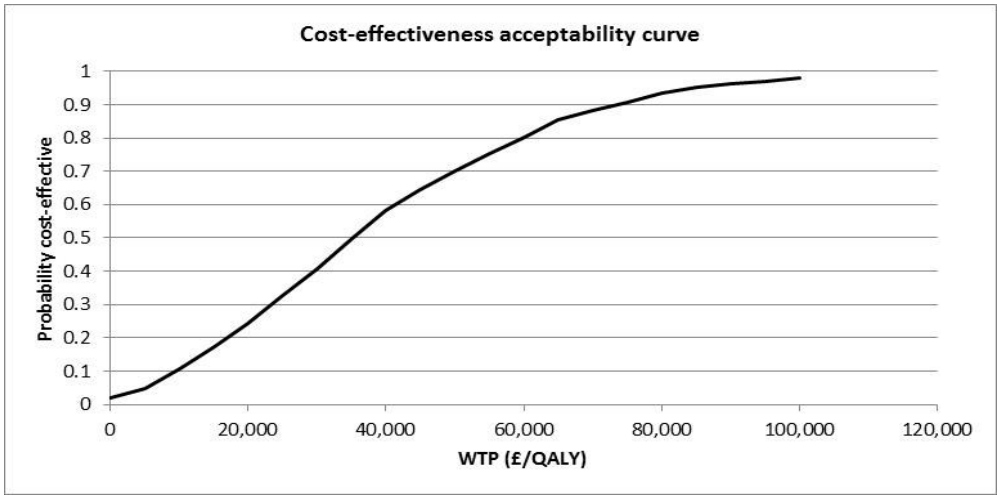
Table 27: The company's probabilistic ICER for ponatinib compared with BSC for patients where allo-SCT was unsuitable

Treatment	Costs (£)	QALYs	ICER (cost per QALY gained)
BSC	40,681	0.09	-
Ponatinib	[redacted]	[redacted]	36,156

Figure 12: The company's PSA results for ponatinib compared with bosutinib for Ph+ ALL patients shown on a cost-effectiveness plane (CIC data)

[redacted]

Figure 13: The company's PSA results for ponatinib compared with bosutinib for Ph+ ALL patients shown on a cost-effectiveness acceptability curve



The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (24%); £30,000 (41%); and £50,000 (70%).

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook exploratory sensitivity analyses, many of which have been detailed in the CML report[1] (Section 5.3). The curves thought to be credible fits to the observed survival data are presented in Table 28, with the curve fitting undertaken by the ERG contained in Appendix 1.

Table 28: Distributions considered to be credible fits to the data and for clinical plausibility in the extrapolation phase. Ph+ ALL model

Parameters for which the ERG did not undertake alternative curve fitting		Parameter for which the ERG did undertake alternative curve fitting
OS - ponatinib	Time on treatment - ponatinib	OS after allo-SCT
Exponential (C)	Log-normal (A)	Gompertz (A)
Gompertz (A)	Log-logistic (C)	Log-normal
		Log-logistic (C)

(C) denotes that the distribution was used within the company's model; (A) denotes that it was the alternative curve used in the exploratory analyses.

Two further exploratory analyses were conducted which are detailed in Section 5.3.1 to Section 5.3.2. Exploratory analyses that the ERG would like to have conducted but which were not possible in the timescales of the appraisal are discussed fully in Section 5.3.9 in the CML report,[1] but are briefly described in Section 5.3.3. The results of the exploratory analyses undertaken for Ph+ ALL are provided in Section 6.

5.3.1 Removal of patient immortality between remission and undergoing allo-SCT in the first cycle for those who are suitable for allo-SCT

Within the company's model, all patients who are suitable for allo-SCT who achieve remission are assumed to survive until the end of cycle 1 when allo-SCT was performed. The ERG has amended the model so that is it possible for patients to die within the three-week period.

5.3.2 Setting the length of survival in non-responders to be equal for those who receive ponatinib treatment and those who receive BSC

The company's model assumes that patients who receive ponatinib and do not respond have a median life expectancy of 5.57 months based on data from PACE.[20] For those patients who do not respond on BSC, the median life expectancy was 2.60 months, as reported by Pagano *et al*.[45] In the clarification response (question B10),[23] the company reported that the median age in Pagano *et al.*[45] was higher (77 years) compared with the median age in PACE (62 years) and that this could have caused the longer mean survival observed in PACE. The ERG has amended the model to explore the impact of setting the survival following non-response equal for those who have ponatinib and those that have BSC which was supported by clinical advice provided to the ERG. The preferred method was by increasing the survival time for those on BSC to that of ponatinib, but an alternative approach was explored which reduced the survival time for patients with no response on ponatinib treatment to that of BSC.

5.3.3 Additional work that was not undertaken due to the timelines of the STA

These analyses were the same as in the CP-CML report[1] and relate to: amending the company's PSA; assessing the impact of continuity corrections; and a formal analysis of the cost-effectiveness of ponatinib in those who are known to have, or not have, the T315I mutation. The likely impact of the knowledge of the presence, or not, of the T315I mutation has been discussed narratively.

5.4 Conclusions of the cost effectiveness section

The CS adhered to the decision problem and the structure of the model appeared appropriate. Few programming errors were found within the submitted model, although the ERG does not always agree with the choice of parameter values or distributions used in the company's base case. As such, the ERG considers that the uncertainty in the decision has been considerably underestimated by the company. Furthermore, there is an inappropriate naïve indirect comparison between OS for those with NR on BSC treatment and those who experience NR on ponatinib treatment, that was not supported by clinical advice to the ERG. Additionally, there was a naïve indirect comparison between ponatinib and induction chemotherapy relating to the proportion of patients that receive MyCR / CR, although the ERG notes that MCyR which was reported in the ponatinib study is harder to achieve than CR, which was reported in the induction chemotherapy study. The ERG has assessed the potential implications of changes to

the model within Section 6. The results of PSA were not considered robust by the ERG but were not amended.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The impact of the exploratory analyses undertaken are reported in this section.

The ERG's base case includes drug wastage, with the assumption, due to the construct of the model that prescriptions are at three-monthly intervals. As such, the ICER is likely to be higher than if the true frequency of prescriptions is included. Treatment-related deaths have also not been incorporated in the base case which is likely to have been favourable to ponatinib compared with both BSC and allo-SCT.

The results presented are subject to further levels of uncertainty, such as the lack of a robust PSA and the lack of continuity corrections for low observed counts.

6.1 Results for people who are suitable for allo-SCT

The results are presented in Table 29.

The ranges in the ICER relating to plausible fits to the survivor function are large indicating considerable uncertainty in the ICER. The fit of the extrapolated curves to the data are shown in Figure 3 and Figure 4 for OS on ponatinib; Figure 5 and

Figure 6 for time on treatment with ponatinib; and Figure 14 (Appendix 1) for OS after allo-SCT.

6.1.1 Results for ponatinib compared with induction chemotherapy

For the comparison of ponatinib with induction chemotherapy, key drivers of the ICER are: the choices of the distribution of the survivor function; the method used to fit the survivor function for survival post allo-SCT; the removal of the half-cycle correction of the intervention costs; and the appropriateness of having differential OS for those who experience NR based on initial treatment. The ERG believes that the ICER for ponatinib compared with induction chemotherapy is likely to be below £12,000 per QALY gained, although notes the uncertainty caused by the naïve indirect comparison.

6.1.2 Results for ponatinib compared with BSC

For the comparison of ponatinib with BSC, the largest drivers of the ICER are the choices of the survivor functions, and the method used to fit the survivor function for survival post allo-SCT. For the comparison of ponatinib with BSC, the ERG believes that the ICER is likely to lie in the range £7,892 to £31,696 per QALY gained.

Table 29: The impact of the ERG's deterministic exploratory analyses in patients suitable for allo-SCT

		Cost per QALY (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs induction chemotherapy**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	31,123	26,624
1	Recalculation of the OS post allo-SCT curve	57,140	53,603
2	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	23,838 – 52,559	14,203 – 45,218
3	Assuming drug wastage	32,499	26,944
4	No half-cycle correction of intervention costs	43,766	29,568
5	Including treatment related deaths	28,635	25,864
6	Removal of immortality for a small subset of patients	31,989	26,999
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,983
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,959
8	1, 3,4 and 6 using the curves believed most credible by the company	90,325	62,801
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	11,727	31,696

10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant – 11,727	7,892 – 31,696

Allo-SCT, allogeneic stem cell transplant; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders; OS, overall survival; QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

6.1.3 Results for patients known to be with, and without, the T315I mutation

The ERG believes that for patients known to have the T315I mutation the most appropriate comparison would exclude induction chemotherapy and would result in an ICER likely to lie in the range £7,892 to £31,696 per QALY gained. For patients known to not have the T315I mutation it is anticipated that the lower and upper values in the range in the cost per QALY gained compared with induction chemotherapy would increase, that is, become less favourable to ponatinib. However, the precise increase in these values is unknown.

6.2 Results for people who are not suitable for allo-SCT

The results are presented in Table 30.

The ranges in the ICER relating to plausible fits to the survivor function are large indicating considerable uncertainty in the ICER. The fit of the extrapolated curves to the data are shown in Figure 3 and Figure 4 for OS on ponatinib; Figure 5 and

Figure 6 for time on treatment with ponatinib; and Figure 7 for OS after allo-SCT.

6.2.1 Results for ponatinib compared with BSC

For the comparison of ponatinib with BSC whether half-cycle correction of intervention costs should be applied, and whether the OS for NR on ponatinib and BSC are equal are key drivers of the ICER. The ERG believes that ponatinib is likely to dominate BSC, although this is dependent on the assumption that OS after NR is independent of whether the patient received ponatinib or BSC.

Table 30: The impact of the ERG's deterministic exploratory analyses in patients unsuitable for allo-SCT

		Cost per QALY (£)
Ref No	**Exploratory Analyses**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	33,954
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	25,902 – 36,037
2	Assuming drug wastage	36,835
3	No half-cycle correction of intervention costs	48,073
4	Including treatment related deaths	30,432
5a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant
5b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant
8	2 and 3 using the curves believed most credible by the company	52,317
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	Dominant
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant - Dominant

BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

7 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

For patients who are suitable for allo-SCT, the company's model estimates that those patients receiving induction chemotherapy would live in excess of six years whilst those who receive BSC would live less than half a year. The model predicts a large extension in life compared with BSC, in excess of seven years, and thus the ERG believes that ponatinib is likely to satisfy the end of life criteria where BSC is the only comparator for patients suitable for allo-SCT.

For patients who are unsuitable for allo-SCT, the company's model estimates that those patients receiving BSC would live less than half a year. The model predicts that ponatinib provides an extension of life of almost one year compared with BSC. Under these circumstances, the ERG believes that ponatinib is likely to satisfy the end of life criteria for patients unsuitable for allo-SCT.

8 OVERALL CONCLUSIONS

Clinical effectiveness

In the absence of direct comparative data with other treatments, the main evidence in the CS was derived from a Phase II, industry-sponsored, single-arm, non-comparative, open-label, study. The efficacy (measured in terms of surrogate response measures e.g. MaHR, MCyR, and CCyR) in the PACE study appears favourable, and the safety appears acceptable. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Whilst the study was generally well reported and conducted, single-arm studies are associated with an array of potential biases including a high risk of selection bias (due to the absence of randomisation), performance and detection bias (due to the absence of blinding). In addition, due to the absence of a controlled comparator group in the PACE study, inference of treatment effects (including magnitude) may be confounded and its ability to compare or demonstrate efficacy with other current treatments is limited. A further limitation to the robustness of the efficacy and safety data relates to the small subgroup that comprises the target population in the CS, including lack of statistical power for the subgroup. The key uncertainties in the clinical evidence for Ph+ ALL relate to optimal dosing, duration of treatment, comparative efficacy and generalisability to the population in England.

Cost-effectiveness

If it is assumed that OS for people in the NR state is independent of whether the patient received ponatinib, as believed by the clinical advisor to the ERG then it is estimated that in people who can receive allo-SCT the ICER for ponatinib lies in the range dominant to £11,727 per QALY gained when compared with induction chemotherapy, and in the range £7892 - £31,696 per QALY gained when compared with BSC. For patients who cannot receive allo-SCT the ICER for ponatinib is likely to be dominant.

8.1 Implications for research

There are no direct comparisons on the clinical and cost effectiveness of third-line ponatinib with other current treatments in patients with Ph+ ALL. Hence there is a need for a study that directly compares these treatments, collects sufficient evidence on resource use and costs, and is powered to detect clinically meaningful changes in response outcomes (including minimal residual disease). Studies of ponatinib are also needed to establish the optimal dose and treatment duration and investigate whether adult patients with Ph+ ALL achieving a molecular remission with ponatinib would still require an allo-SCT and the effect of post-transplant maintenance with ponatinib on the outcomes of allo-SCT.

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10 APPENDIX

Appendix 1: Results of parametric curve fitting to reconstructed IPD

Exploratory analyses were undertaken by the ERG to explore the impact of using the method proposed by Guyot *et al.*[44] to fit parametric survival curves, as opposed to the method based on minimising the SSE that was adopted by the company. Details of the methods used are provided in the CML model appendix.[1]

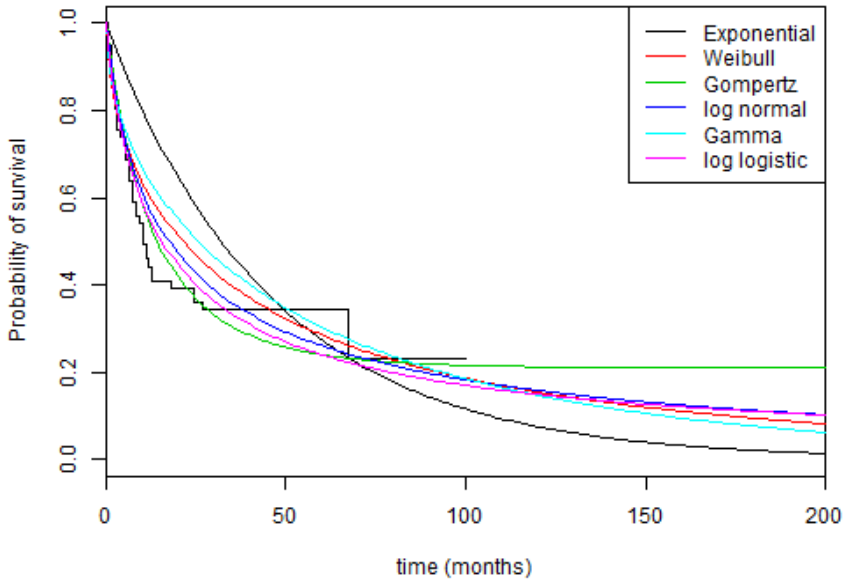
Model fit statistics for the curve for which alternative curve fitting was considered by the ERG are provided in Table 31. The resulting model fits are plotted in Figure 14.

Table 31: Model fit statistics for ERG alternative curve fitting

Graph identifier	Criterion	Parametric model						Info
		Exp	Weib	Gomp	Log-N	Gamm	Log-L	
OS after allo-SCT	AIC	456.7	431.8	**420.5**	**419.6**	437.3	**422.0**	4
	BIC	458.8	436.0	**424.7**	**423.9**	441.5	**426.2**	

Exp = exponential; Gomp = Gompertz; Log-L = log-logistic; Log-N = Log-normal; Weib = Weibull; Gamm=gamma
Info: Information used for reconstruction of IPD; 2= no number at risk table; 3= No total number of events; 4= neither risk table or total number of events supplied.
AIC/BIC values in bold denote distributions that were either used by the company or considered in the ERGs alternative curve fitting

Figure 14: Parametric survival function for OS after allo-SCT



Note the company's fit is reproduced in Figure 7.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

You are asked to check the ERG report from School of Health and Related Research (ScHARR), The University of Sheffield to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 20 December 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Preamble

We sincerely appreciate the time and effort invested by the ERG in its review of our evidence submission, especially as we acknowledge the overall complexity and length of a submission that includes two indications and three models, as ours does in this case.

In general, we highlight some factual inaccuracies in the ERG's report and raise some inconsistencies, including an inverted comparison in the BP model that leads to confusing results. In addition, we have suggested alternatives in some areas where we felt the ERG's selection of certain parameters increased uncertainty or led to clinically implausible results. For example, we suggest below alternative considerations regarding the choice of distribution for the probability of death following allo-SCT because the data source cited by the ERG stems from a very recent abstract and photograph from a conference presentation relating to data from a patient population different from the one indicated for ponatinib, and because the ERG's selected parameter results in modelled survival that appears clinically implausible for acute leukaemia patients (AP & BP CML) that have failed multiple prior treatments. As this one change alone by the ERG appears to have the most impact on the plausible ICER range, we focus our comments on this issue.

Nevertheless, most of the plausible ICERs presented by the ERG, when applying the PAS (approved by the Department of Health on the 23rd November) are well within the range previously accepted by NICE in prior appraisals for rare, orphan cancers. In addition, given the rarity of the disease state for which ponatinib is licensed, the small numbers of patients concerned, we agree with the end-of-life (EoL) designation granted by the ERG for the AP-CML, BP-CML, and Ph+ ALL indications.

The ERG's revised ICERs are mostly below or within NICE's standard £20,000–30,000/QALY range of acceptable cost-effectiveness, even before applying any willingness-to-pay multiplier for this EoL therapy.

Thank you again for the opportunity to comment on the ERG report.

Kind regards,

Anant Murthy, PhD

Incyte

Issue 1 New data supporting the Gompertz function to estimate the probability of death following allo-SCT in CP-CML

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1.5.2.2, pages 116-118, ERG report (CML) The ERG presents new data reported in December 2016 at the American Society of Hematology (ASH) conference in San Diego[1]—after the evidence submission deadline and during the period when we are not permitted to introduce new data—in order to support the selection of the Gompertz distribution to estimate the probability of death following allo-SCT. The ERG presents these data in its report based on a photograph taken at the ASH conference. Naturally, as these data were unavailable to us at the time of submission, and as they have only been presented in abstract form, it is not possible to fully assess their applicability and relevance to the decision problem. At the same time, we understand that we cannot supply new data ourselves at this stage in the appraisal process. In any case, the ERG states "these data, which have been	Incyte requests the addition of the underlined text to add context around the uncertainty of the applicability of the patient population. "These data, which have been collected for up to six years after allo-SCT, provide evidence on OS following allo-SCT in patients who have received prior nilotinib or dasatinib and are in CP1 (first chronic phase) only, and are contained in Figure 19." "These data support the flattening of the Kaplan-Meier rather than the company's choice of the exponential distribution. There is, however, uncertainty with regards to how closely the patient population reflected by these data matches the patient population of relevance to this appraisal as patients in the ERG-cited study may have received allo-SCT without having previously failed a second-generation TKI. In contrast, the manufacturer's model—and indeed the license on which ponatinib is based—includes only patients who have failed dasatinib or nilotinib. The other curves for patients not in CP1 do not flatten. [redacted]	We thank the ERG for bringing this new conference presentation to our attention. We argue, however, that the use of the new data to support the Gompertz function to estimate the probability of death following allo-SCT is inappropriate for the following reasons. **1) Relevance of the new data to the decision problem** We are uncertain of how closely the patient population of the Olavarria et al. 2016 study reflects the patient population in the decision problem. Patients in the Olavarria study were younger (median 45 years), with only median 22 months between diagnosis and allo-SCT, and median 10 months' duration of 2G-TKI treatment. This suggests that patients who had only dasatinib or only nilotinib (57%), received these TKIs in the first- or second-line setting (if patients who received prior imatinib were eligible, which we were unable to ascertain from the abstract). This would place these patients in a better position to achieve positive results with allo-SCT compared with patients who	Neither point is a factual error, and concern points that we expect to be discussed at the Appraisal Committee meeting. The ERG agrees that further details on the Olavarria *et al.* study would be beneficial but as noted by the company the title of the figure does state that patients had been treated with nilotinib or dasatinib. It is unfortunate that the lower curve has not been separated into CP2, AP and BP. Further, the patient numbers are not shown, and the drop at the end of this curve may be caused by a small number of events with few patients (as shown by the sharp drop in the Kaplan-Meier curve). The ERG believes that the rate of death appears to be decreasing across time, which would be aligned with the view of our clinical experts. The ERG comments that the underlying risk of mortality from all

collected for up to six years after allo-SCT, appear to be the most appropriate data source" for OS after allo-SCT for patients in CP-CML. "These data support the flattening of the Kaplan-Meier rather than the company's choice of the exponential distribution. The levels of survival in the data in Figure 19 are greater than those presented by Jabbour et al which would be more favourable to allo-SCT, although the confidence intervals for OS at six years were wide." As a result, the ERG selected a distribution that more closely mirrors the flattening observed in the photograph taken at the ASH conference. We respectfully disagree with this approach. After examining the abstract on which these data and photograph are based, we believe the applicability of this ASH abstract to the models concerned here is highly uncertain because the data stem from a patient population that is younger with less severe disease than the population for which ponatinib is licensed. In addition, the flattened curve shown in the photograph and		have failed at least two prior TKI treatments and are in NR (as in our model). As a result, we cannot agree with the ERG's statement that the ASH abstract reflects the "most appropriate data source" (ERG CP-CML report, page 117). Moreover, we found that the OS curve presented in the abstract is different from the OS curve shown on page 118 of the ERG report. While we have been unable to obtain a copy of the full ASH presentation to investigate potential explanations for this difference, presumably, updated data were presented at the conference, after the abstract had been reviewed and approved by ASH. Nevertheless, the lack of transparent availability of these data makes robust use and interpretation difficult. **2) Gompertz distribution is not appropriate to estimate the probability of death following allo-SCT** According to the OS curve provided by the ERG in the photograph shown in Figure 19, for patients in their first chronic phase (CP1), over time the OS curve becomes flat. Importantly, this is ONLY the case for patients in CP1, whereas for patients in CP2, AP or BP, the	causes has been maintained so that older patients will have a life expectancy that is shorter than younger patients. The ERG also comments that it has presented ranges in the ICER because it cannot select a definitive curve, but highlights that our clinical experts believed that a Gompertz curve was not implausible. Additional text has been added to place the Olavarria *et al.* study in context of the PACER study.

cited by the ERG is from a population less resistant to prior TKI therapy. In fact the curves that are more similar to the patient population of relevance here (CP2, AP, BP) do not flatten out, as can be clearly seen in the photograph obtained by the ERG. In contrast, the data we used from Jabbour et al. were closer to the ponatinib population in the PACE pivotal study. Finally, as we note in our company submission, our approach was validated by clinical opinions obtained from a UK expert, Prof. Richard Clark of the Haematology Department at the Royal Liverpool University Hospital (see section 5.7.1 of our company submission).		curve decreases over time, with a steep decline in the last 2 years. In our model, patients are in a state of no response (NR) at the beginning of the simulation or in progressed disease. Using a curve based on CP1 patients is in conflict with the patient population of relevance to this appraisal. We believe that considering a flat OS over time post-SCT based upon this study is not justifiable. The patient population seems to differ significantly from the patient population in the model, and the choice of the Gompertz function greatly overestimates the survival after allo-SCT in the licensed population addressed by our submission. We would like to point out that the ERG's choice of Gompertz function based on Olavarria is the major technical factor driving the difference from our submission for the entire comparison with allo-SCT across the three phases of the disease (ie, in the CP, AP and BP models). Consequently, we reiterate that the use of data from an abstract, and from conference presentation slides unavailable for review and captured by the ERG in a photograph, in addition to the clear mismatch in patient	

		populations, raise important questions as to the applicability of these data here. In conclusion, the use of the abstract to justify the adoption of the Gompertz distribution is not appropriate and the Gompertz distribution is not the correct function to estimate OS after allo-SCT. In our view, the correct function to estimate OS post–allo-SCT is the exponential distribution. We recalculated the ICER using the amended ERG CP-CML model, selecting the exponential function instead of the Gompertz distribution proposed by the ERG. The ICER for ponatinib vs allo-SCT was calculated to be £24,563*/QALY, higher than our base case with the PAS £4,042/QALY, but still within the range of acceptable cost-effectiveness accepted by NICE in prior appraisals for rare, orphan cancers. *This calculation was made using the amended ERG model. Of note, the calculations done by the ERG are not entirely transparent and in some instances we have not been able to reproduce the results.	

Issue 2 Introducing a stopping rule for bosutinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.3.4, page 152 The ERG report states that "The company's model assumes that unlike patients receiving ponatinib, patients receiving bosutinib would continue to receive bosutinib despite no response in CP-CML, or despite failing to achieve an MaHR in AP-CML or BP-CML. The ERG has amended the model to allow the same stopping rules for ponatinib to bosutinib to be considered. The clinical experts to the ERG believe that it is likely to be clinician dependent, but that many clinicians would stop if there was no response experienced." This paragraph does not accurately capture our rationale for assuming a stopping rule for ponatinib but not bosutinib, nor does it reflect the EMA-approved SmPCs for these products.	Incyte requests that the underlined sentence below be included in the report. "The company's model assumes that unlike patients receiving ponatinib, patients receiving bosutinib would continue to receive bosutinib despite no response in CP-CML, or despite failing to achieve an MaHR in AP-CML or BP-CML. <u>The company adopted this assumption to align with recommended use per the approved product labels; specifically, while the ponatinib SmPC explicitly advises that treatment discontinuation should be considered if a complete haematologic response has not been achieved by three months, the bosutinib SmPC provides no guidance on treatment discontinuation in the absence of response.</u>[2, 3] The ERG has amended the model to allow the same stopping rules for ponatinib to bosutinib to be considered. The clinical experts to the ERG believe that it is likely to be clinician dependent, but that many clinicians would stop if there was no response experienced."	We acknowledge that many of the changes made to the model are clinically plausible, including that clinicians may stop bosutinib in patients who fail to respond to treatment. This being said, we have aimed to use the specific product labels and SmPCs to construct the clinical algorithms in the models. Specifically, to align with the approved use of both agents per their marketing authorisations, we had based our model on SmPC guidance, which supports a stopping rule for ponatinib but does NOT mention a stopping rule for bosutinib. The ponatinib SmPC clearly states: "Consider discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days)."[2] The bosutinib SmPC does not provide any such guidance on treatment discontinuation in the absence of response[3] and implies that patients be treated until progression. In case of ponatinib, the EMA clearly set a time period by which response must be achieved, whereas the lack of such a discontinuation rule in the bosutinib	Text has been added to state the company's rationale for not including a stopping rule for bosutinib.

		SmPC permits continued treatment.	

Issue 3 Exiting the non-response (NR) state due to progressed disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1.4.1, page 111 The ERG selected a function (log-normal) for estimating progression-free survival in the NR state. However, doing so yields a better progression-free survival rate for patients in NR versus those patients in complete haematologic response (CHR) (see justification for amendment). This conflicts with the nature of the disease, treatment goals as stated in published clinical guidelines, and clinical plausibility. As stated in the ERG report: "The company selected the exponential distribution for the risk of progressing from NR, although the SSE for the exponential function (0.3164) was considerably higher than for the remaining distributions (0.0026-0.0924). The company stated that the choice of the exponential distribution was '*based on clinical plausibility*'. The extrapolated curves are shown in	Incyte requests the addition of the suggested underlined text to explain why the log-normal function (or any function other than the exponential function) would overestimate progression-free survival in NR and be favourable to bosutinib. "The extrapolated curves are shown in Figure 13: as shown in the figure, the exponential survivor function has a much lower predicted long term PFS than the remaining curves. <u>All other functions, however, would result in a situation where patients in NR achieve a better outcome than patients in CHR (Figure 13), which would be clinically implausible. This clinical implausibility would bias the comparison in favour of bosutinib.</u> Clinical advice received by the ERG suggested that the proportion of patients in PFS would lie between the exponential and the log-normal lines."	As stated in the ERG report, in our base case, we chose the exponential function "*based on clinical plausibility*". In fact, the exponential function was the only function that guaranteed that PFS for patients who are NOT responding to treatment would be lower than PFS for patients that do achieve CHR with treatment. This can be seen by comparing Figure 11 (PFS for CHR, page 110) and Figure 13 (PFS for NR, page 112) in the ERG report. Comparing the two figures it can be seen that all the functions for NR, except the exponential, are almost flat after about 5–10 months, indicating that the probability of progression for this group of patients is very low after a few model cycles. This is not true for all the curves for CHR, which continuously decrease and in the midterm present a PFS lower than that for NR patients. This presents a major problem related to the low number of events	The ERG acknowledges the criticism made by the company and has amended the text to incorporate: the potential clinical implausibility; possible solutions to constraining the functions; and a caveat on accepting ill-fitting curves as others may not be clinically plausible (p150). The change in the ICER if only the exponential curve was used for PFS for NR have been added in Section 6.1 and in the confidential appendix.

Figure 13: as shown in the figure, the exponential survivor function has a much lower predicted long term PFS than the remaining curves. Clinical advice received by the ERG suggested that the proportion of patients in PFS would lie between the exponential and the log-normal lines." In our submission, we aimed to follow methodological guidelines for selecting the appropriate distribution, yet we always examined the results of each decision to guarantee clinical relevance and plausibility. We therefore disagree with the ERG's selection here. Making the clinically implausible assumption that PFS is longer for non-responders biases the ICERs to favour bosutinib because bosutinib is less effective than ponatinib and is associated with a higher number of patients that do not respond to treatment.		captured in these curves. We want to underline the fact that, regardless of the goodness of the fit of different curves to these data, choosing any function that is not the exponential for NR would require adopting the clinically implausible assumption that patients who have no response to treatment achieve better outcomes than those patients who do successfully respond to treatment. On the contrary, it is an established principle of CML management that treatment response positively predicts outcomes. Notably, the European LeukemiaNet (ELN) 2013 recommendations for CML explicitly state, 'The response to TKI is the most important prognostic factor.'[4] Using a function other than the exponential function drives the ICER higher and explains the dramatically increased ICER in the ERG analysis for the comparison with bosutinib, where about 30% of patients are assumed not to respond (as compared with 12% with ponatinib). Stated another way, making the clinically implausible assumption that PFS is longer for non-responders biases the ICER to favour bosutinib because bosutinib is less effective than ponatinib and is associated with a higher number of patients that do not respond to treatment.	

		Using the ERG's amended models, and changing the function for PFS in NR to exponential (from log-normal), we obtain an ICER vs bosutinib of £29,517/QALY, higher than our base case with the PAS £18,213/QALY, but still within the range accepted by NICE in prior appraisals for rare, orphan cancers. We have recalculated the ICERs vs bosutinib in CP-CML using the amended ERG models after adopting changes to address our concerns with Issues 1–3. That is, the log-normal function in PFS for NR was changed to exponential; the Gompertz function in OS after SCT in AP was changed to exponential; and the stopping rule for bosutinib was removed. When the three aforementioned issues are addressed, we calculate that the ICER per QALY vs bosutinib is £25,073 and within the range of acceptable cost-effectiveness accepted by NICE in prior appraisals for rare, orphan cancers.	

Issue 4 Gompertz function to estimate the probability of death following allo-SCT in AP-CML

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.2.3, page 125 The ERG adopted the Gompertz	Incyte requests addition of text acknowledging that the Gompertz function may overestimate	While we agree with the ERG that the probability of death is higher	This is not a factual error. The clinical advice provided to the

fit for estimating OS in patients with AP-CML after allo-SCT. "In this instance, the company did not select the curve that fitted best (the Gompertz with a value of 0.02) but instead selected the exponential distribution (with a value of 0.82) as this was believed to be more clinically plausible: the use of an exponential distribution assumes constant hazards. Clinical advice provided to the ERG suggest that the Gompertz fit was likely to be more plausible than the exponential as deaths occur relatively early following allo-SCT, but patients who survive for five years have a much lower risk of mortality." We believe the use of the Gompertz function is implausible, as it leads to a probability of death that is almost zero after approximately 30 months.	survival as compared to the clinical opinion obtained by the ERG (lower mortality after 5 years based on ERG clinical opinion, versus after 2.5 years from Gompertz distribution preferred by ERG), and is supported by the acute, late-line state of the AP-CML patients concerned here. Moreover, the Gompertz curve conflicts with the ERG-cited photograph of a recent ASH abstract showing survival after transplant in AP patients to continue to decline well beyond 30 months.	immediately after the procedure and reduced in the midterm, we believe that the choice of the Gompertz function greatly overestimates the survival after allo-SCT. Patients with AP-CML are in an acute disease state, and the population indicated for ponatinib and modeled here includes only patients who have failed multiple prior therapies. Assuming a risk of death nearly similar to the general population is clinically implausible, in our view. As noted in our company submission, this view was also substantiated by a clinical expert, Prof. Richard Clark, during our development of the model. Relatedly, in the ERG conclusion (sentence cited above), clinical expert opinion suggests a much lower mortality for those patients who survive 5 years, which is double the 2.5 years (30 months) that results from the use of Gompertz function. Even when ignoring the clinical opinion we obtained in lieu of the opinions obtained by the ERG, the Gompertz overestimates survival after transplant. Finally, the ERG cites an ASH abstract (see above, or Figure 19 in	ERG suggested that the Gompertz distribution was plausible following allo-SCT in AP-CML. The ERG also comments that ranges of ICERs have been provided and that a definitive choice of curves has not been made. Please see the ERG's response to Issue 1 for further comment re data from the Olavarria *et al.* study As such, the text has not been amended.

		ERG CP-CML report) that itself clearly shows survival in AP after transplant does not flatten out after 30 months. If the ERG relies on that data source for CP-CML, the AP data from that source could also be supportive evidence here, in which case our selection of the exponential function would be the most appropriate, and not the Gompertz function suggested by the ERG. We recalculated the ICER using the amended ERG AP-CML model, selecting the exponential function. In AP-CML, when our base-case selection (exponential) is used instead of the Gompertz distribution, the ICER for ponatinib vs allo-SCT is £13,979/QALY using the ERG's amended model, very similar compared with our base case, with the PAS £13,279/QALY.	

Issue 5 BP-CML: ICER expressed as allo-SCT vs ponatinib instead of ponatinib vs allo-SCT leads to confusion in the ERG report; Inconsistent results reported for ICER of allo-SCT vs ponatinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.7, page 18 The ICER results in BP-CML are inconsistently expressed in the ERG report, leading to confusion.	Incyte requests for consistency in reporting the results in BP-CML that the ICER be expressed in terms of the incremental cost/benefit for <u>ponatinib vs allo-SCT</u>.	We note that the ERG have expressed the ICER in terms of the incremental cost/benefit for allo-SCT vs ponatinib, whereas other comparisons are for ponatinib vs	The rationale for reversing the order for BP-CML is that allo-SCT in Analysis 8 has more QALYs but at a higher cost. It was believed that it was

For the comparisons with bosutinib and best supportive care (BSC), ICERs are expressed in terms of the incremental cost/benefit for ponatinib vs bosutinib/BSC. For allo-SCT, the ICER is expressed in terms of the incremental cost/benefit for allo-SCT vs ponatinib. Results are also presented as allo-SCT vs ponatinib in Table 3 (page 21) and Table 68 (page 161). Moreover, there is an inconsistency in the reporting of results in the ERG report. Table 3, page 21 Table 68, page 161 The ICER range for allo-SCT vs ponatinib in BP-CML is £4,035 – Dominated in Table 3 (page 21) and £4,004 – Dominated in Table 68 (page 161). These results are inconsistent with one another.	Incyte requests the correct results be reported in both Tables 3 and 68, and, as described above in Issue 5, reflect the comparison ponatinib vs allo-SCT.	the comparator. Unless there was a specific reason for this change, we suggest the order of the comparison in BP-CML be reversed to ponatinib vs allo-SCT for consistency with the other ICERs in the report. There appears to be an inconsistency with the ICER results for allo-SCT vs ponatinib in BP-CML reported in the ERG report between Table 3 (page 21) and Table 68 (page 170): ie, £4,035 vs £4,004. In addition, as described above in Issue 5, we suggest reporting the results for the comparison of ponatinib vs allo-SCT.	preferable to present the ICER for allo-SCT compared with ponatinib rather than having ICERs in the South West quadrant and the resultant potential confusion. The Appraisal Committee is experienced enough to note the order of the comparison, although if necessary the company and ERG can clarify this in the meeting. The ERG acknowledges the typo in Table 3 and has changed this to £4,004 to be consistent with Table 68.

Issue 6 BP-CML: Gompertz function to estimate the probability of death following allo-SCT in BP-CML

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.3.3: Results for ponatinib compared with allo-	Incyte requests addition of text acknowledging that the Gompertz function may overestimate	Fitting the Gompertz distribution produces survival in these BP-CML	Not a factual error. The ERG also comments that ranges of

SCT for BP-CML patients (page 160) The ERG adopted the Gompertz fit for estimating OS in patients with BP-CML after allo-SCT. To support the choice of this function for the extrapolation of data taken from the literature, the ERG adds that, "Clinical advice provided to the ERG suggest that the Gompertz fit was likely to be more plausible than the exponential as deaths occur relatively early following allo-SCT, but patients who survive for five years have a much lower risk of mortality." Similarly to Issue 4, we believe the use of the Gompertz function is clinically implausible, as it leads to a probability of death that is almost zero after approximately 30 months.	survival as compared to the clinical opinion obtained by the ERG (lower mortality after 5 years based on ERG clinical opinion, versus after 2.5 years from Gompertz distribution preferred by ERG), and is supported by the acute, late-line state of the BP-CML patients concerned here. Moreover, the Gompertz curve conflicts with the ERG-cited photograph of a recent ASH abstract showing survival after transplant in BP patients to continue to decline well beyond 30 months. We suggest that the exponential function is selected to extrapolate OS after SCT. When changing the Gompertz function with the exponential in the ERG amended model the ICER of the comparison allo-SCT vs. ponatinib (e.g. maintaining the inverted comparison by the ERG, which is identified in Issue 5) is in the range £102,612/QALY – dominated, suggesting that SCT cannot be considered cost-effective when compared with ponatinib in BP-CML.	patients after approximately 30 months that is nearly identical to survival in the general, healthy population. Given that BP patients are in the most acute phase of their disease, have an overall life expectancy of a few months, and have already failed multiple prior TKIs (in accordance with the licensed indication for ponatinib), we believe the survival resulting from the ERG's selection of the Gompertz distribution is implausible. Relatedly, in the ERG justification for selection of the Gompertz distribution, clinical expert opinion collected by the ERG suggests a much lower mortality for those patients who survive 5 years, which is double the 2.5 years (30 months) at which the survival curve flattens out when using the Gompertz function. Finally, the ERG cites an ASH abstract (see above, or Figure 19 in ERG CP-CML report) that itself clearly shows survival in BP after transplant does not flatten out after 30 months. If the ERG relies on that data source for CP-CML, the BP data from that source could also be supportive evidence here, in which case our selection of the exponential function would be the	ICERs have been provided to allow the Appraisal Committee to discuss the plausibility of the curves. The clinical advice provided to the ERG was that the Gompertz function was not implausible. Please see the ERG's response to Issue 1 for further comment re data from the Olavarria *et al.* study

		most appropriate, and not the Gompertz function suggested by the ERG.	

Issue 7 Inconsistent results presented by the ERG, based on the original CS as well as the company responses to clarification questions relating to the AP/BP-CML model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report presents results from two different versions of our AP/BP-CML model. The results in the text of the ERG report appear to refer to the version of the model submitted along with the clarification letter on 11 November 2016, which incorporated updates to the model in our original submission. However, for the scenarios, it appears that the ERG results pertain to the revised version of this model submitted to NICE on 14 November 2016. As a result, what is referred to as "Company submission" for AP and BP is not consistent between the text and the scenario tables.	Incyte recommends adding a footnote to the scenario tables to indicate that the version of the model used for those calculations was the version that was received from the manufacturer on 14 November 2016. This latter version was modified after the ERG clarification process to show the impact on the ICERs when separate resource-use parameters for AP and BP were used to inform the model. Of note, this change had a minimal impact on the ICERs.	During the ERG review period, Incyte submitted two new versions of the AP/BP-CML model: one on 11 November and another on 14 November 2016. Incyte submitted the latter version in response to a request from NICE regarding resource use for AP and BP. In the original submission and the 11 November versions, we made a simplification of resource use and applied parameters for AP to both advanced phases of the disease (AP/BP). The latest version that we submitted on 14 November used separate resource use for AP and BP, based on evidence from the Healthcare Practitioner Survey conducted by Incyte. It appears that results from both November versions of the models are presented in the text and tables of the ERG report. As a result, what the ERG refers to as "Company	Sentences have been added prior to the scenario analyses to indicate that these results have been generated using the models submitted on the 14th December and that this model produces similar results to those of the previous model.

		submission" for AP and BP in fact pertains to two versions of the model. Although we note the impact on the ICER is minor, for transparency reasons, we recommend indicating in the report what version of the model was used to calculate the ICERs that are presented in text and in tables.	

Issue 8 Inconsistency reporting ICER of ponatinib vs bosutinib in AP-CML

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.7, page 18 and Section 8, page 164. The ERG report states "In AP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £20,000 compared with bosutinib, below £18,000 compared with BSC, and from dominating – £63,701, but nearer the upper end of the range, in comparison with allo-SCT." However, in the summary table in the executive summary (Table 2, page 20), and in Section 6.1.1 (page 158), the ERG states that "Ponatinib typically dominates bosutinib".	Incyte requests that the sentences in Section 1.7 (page 18) and Section 8 (page 164) be revised to indicate that in AP-CML, ponatinib typically dominates bosutinib. "In AP-CML the ERG's estimate of the ICER of ponatinib is expected to be dominant compared with bosutinib, below £18,000 compared with BSC, and from dominating – £63,701, but nearer the upper end of the range, in comparison with allo-SCT."	Inconsistent results are reported for the comparison of ponatinib vs bosutinib in AP-CML. Section 1.7 (page 18) and Section 8 (page 164) • ICER of ponatinib is expected to be below £20,000. Table 2 (page 20), Section 6.2 (page 158), and Table 67 (page 159) • Ponatinib typically dominates bosutinib. The correct results indicate that ponatinib typically dominates bosutinib.	The text has been amended to indicate on p18 and on p164 that ponatinib is assumed to dominate bosutinib.

Issue 9 Exclusion of abstracts in clinical systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.2, page 34 (CML report) Section 4.1.2, page 26 (ALL report) The ERG report states that the systematic review "excluded studies which were reported only as abstracts." This is an inaccurate conclusion by the ERG.	Incyte requests the removal of the paragraph: "The company's systematic review excluded studies which were reported only as abstracts...examine the effect of including data from conference abstracts."	This is a factual correction: abstracts from relevant conferences were searched back to 2013. While it is correct that abstracts without sufficient information were excluded, abstracts that met all PICOS criteria were included for consideration. In the end, this did not impact our analyses and does not warrant sensitivity analyses because subsequently published full articles were available before our original submission date for most of the potentially relevant abstracts. Abstracts reporting long-term results from the PACE ponatinib trial were included, but these results reflect the individual patient-level data to which we have access. An abstract reporting long-term third-line results from the pivotal bosutinib trial was included, but these results have subsequently been published in full and do not require revision.	This is not a factual error. The ERG acknowledges that although conference abstracts were searched (CS, p42) the CS stated that (p43 and Table 4-5) abstracts published in abstract form without sufficient information were excluded from the review. In addition, the ERG notes that long-term data from the PACE study, which were published in abstract form by Cortes *et al*., were not included in the CS but were reported by the review group in their ERG report (Table 10, p46; Table 12, p50) As such, the text has not been amended. Cortes J, Pinilla-Ibarz J, Le Coutre P, Paquette R, Chuah C, Nicolini FE*, et al.* 4-year results of the ponatinib phase II PACE trial in patients (pts)

			with heavily pretreated leukemia. *J Clin Oncol (Meeting Abstracts)* 2016;34:(suppl; abstr 7013).

Issue 10 MAIC: Adjustment made for imbalance in the percentage of patients with the T315I mutation at baseline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4, page 82 The ERG report states "The ERG believes that a fairer comparison that acknowledges the treatment pathway would have been to remove the patients with the T315I mutation from the bosutinib arm." The paragraph does not accurately capture that a lack of patient-level bosutinib data prevented a comparison where patients with the T315I mutation were removed from the bosutinib arm.	Incyte requests the addition of the underlined sentence: "The ERG believes that a fairer comparison that acknowledges the treatment pathway would have been to remove the patients with the T315I mutation from the bosutinib arm. Due to a lack of access to patient-level data for bosutinib, the company was unable to conduct an analysis that removed these patients from the bosutinib arm."	For completeness it should be mentioned that the company could not remove patients with the T315I mutation from the bosutinib arm due to lack of data (ie, access to patient-level data), which prevented conducting the analysis using this approach. Nevertheless, it should be noted that even without removing the T315I patients from the bosutinib trial, overall the matching-adjusted indirect comparison (MAIC) was NOT biased in favour of ponatinib. On the contrary, the MAIC was unfavourable to ponatinib as it resulted in a CCyR rate lower than actually observed in the PACE study (61.34% vs 64.95%).	Text has been added to acknowledge the difficulty in performing an MAIC after removing patients with the T315I mutation but that an overall summary could have been produced.

Issue 11 Exiting the CCyR state due to loss of response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1.1.2, page 101 The ERG report states "The company assumed that the risk of progression to AP-CML in the CCyR state of CP-CML was treatment-specific. Following loss of response, patients are assumed to reside in the CHR response state." However, we believe "risk of progression to AP-CML" should in fact say "loss of response."	Incyte requests revising the sentence below for accuracy. "The company assumed that the loss of response in the CCyR state of CP-CML was treatment-specific. Following loss of response, patients are assumed to reside in the CHR response state."	The risk of progression to AP-CML was not treatment-specific, but rather dependent on the response status of the patient. Instead, it was the loss of response in CCyR that was dependent on treatment.	The correction has been made

Issue 12 Exiting the PCyR state due to progressed disease

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1.2.1, page 106 The ERG report states "The selection of the Gompertz curve, which estimates the most progressions, is likely to be favourable to ponatinib compared with bosutinib as ponatinib is estimated to produce a lower proportion of patients with a PCyR response."	Incyte requests revising the sentence as follows: "The selection of the Gompertz curve, which estimates the most progressions, is likely to be slightly unfavourable to ponatinib compared with bosutinib as ponatinib is estimated to produce a marginally higher proportion of patients with a PCyR response."	The rates we use in the model were obtained from the matching-adjusted indirect comparison (Table 32, page 80, ERG report). The PCyR rate for bosutinib was 8.33%, while for ponatinib was 8.46%. Thus, ponatinib has a higher proportion of patients who achieve a PCyR than bosutinib.	The comment re favourable has been deleted to avoid ambiguity. The ERG agrees that clinically the use of the Gompertz is unfavourable to ponatinib, however in terms of cost-effectiveness it is favourable to ponatinib, as the ICER compared with bosutinib increases when the log-normal

The ERG statement is incorrect. The underlined statement should be corrected as ponatinib has a higher proportion of patients who achieve a PCyR.			distribution is used.

Issue 13 Exiting the PCyR state due to loss of response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1.2.2, page 107 The ERG report states "The company's model assumes that the risk of progression to AP-CML in the CCyR state of CP-CML was treatment-specific. Following loss of response, a patient was assumed to reside in the CHR response state." This statement is inaccurate.	Incyte requests revising the sentence below for accuracy. "The company assumed that the loss of response in the PCyR state of CP-CML was treatment-specific. Following loss of response, patients are assumed to reside in the CHR response state."	We believe the ERG is referring to the loss of response in PCyR that depends on treatment, and not the risk of progression to AP-CML in the CCyR state.	The correction has been made

Issue 14 Probability of death for patients on ponatinib treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.3.2.1.1, pages 127-128 The fitted curves to the OS data for those in BP-CML in non-response (NR) on ponatinib treatment show a better survival for patients when the log-normal	Incyte requests the underlined text be changed to say that this is likely unfavourable to ponatinib.	Ponatinib produces higher MaHR rates than comparators, so the number of patients in NR in the ponatinib arm is smaller. Thus, the use of the log-normal curve (which yields better survival for non-responders) would be	The comment re favourable has been deleted to avoid ambiguity. The ERG agrees that clinically the use of the exponential is unfavourable to ponatinib, however in terms of cost-effectiveness it is favourable to ponatinib, as the

distribution is chosen vs the exponential distribution. The ERG reports states that this is favourable to ponatinib. “The survival rate beyond 20 weeks for the log-normal curve is greater than for the exponential distribution, which is plausibly a better fit to the data: this is likely to be favourable to ponatinib.” The statement by the ERG is incorrect.		unfavourable to ponatinib.	ICER compared with bosutinib increases when the exponential distribution is used.

Issue 15 Impact of the ERG’s deterministic exploratory analyses in CP-CML

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 66, page 157 The ICERs presented in the table for Ref No 10 appear to be missing treatment-related deaths.	Incyte believes the ICERs should be £22,936 (ponatinib vs bosutinib), £19,964 (ponatinib vs BSC), and £30,578 (ponatinib vs allo-SCT).	The results presented for Ref 10 in Table 66 (page 157) can be obtained without Ref #6.	The ERG acknowledges a typo, although this is the erroneously addition of #6 to #10. This has been removed. The same change has been made to Table 1.

Issue 16 Typographic errors in the CML report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
CML report: Page 36, paragraph 2, line 2	Add "C"	Typographical error in "AP-CML"	Typographical error corrected to "AP-CML"

Section 5.2.6.3.2.1, page 127 "Exiting the MaHR state due to death"	Incyte believes MaHR should be changed to NR. "Exiting the NR state due to death"	We believe that this heading is intended to refer to the NR group.	Text changed
Section 6.1.1, page 156 and Section 8, page 164 We note a discrepancy in the ICER range against bosutinib for CP-CML patients. "The ERG believes that the ICER is likely to lie in the range £22,995 - £42,097."	Incyte believes the upper value of the range should be £42,637.	In Table 66 (page 157) and in the summary (page 18) this value is £42,637.	Text changed
Pages 18 and 164 "The ICER of allo-SCT compared with ponatinib is estimated to lie between dominating and 63,701, but nearer the lower end of the range." The ICER for BP-CML is incorrect.	Incyte requests the underlined text be replaced with the actual ICER for the comparison of ponatinib vs allo-SCT in BP-CML.	The value 63,701 reported in the executive summary (page 18) and in the overall conclusions (page 164) appears to be a typographic error, as this value applies to AP-CML (per Table 2, page 20, and Table 67, page 159), not to BP-CML.	Text changed

Issue 17 Typographic errors in the ALL report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.6.1, page 12 The ERG report states "The company undertook a reasonably	Incyte requests CML be revised to Ph+ ALL. "The company undertook a reasonably comprehensive systematic review of ponatinib	Incyte conducted separate systematic literature reviews for CML and Ph+ ALL. We believe the ERG's intention in the cited	Typographical error corrected to '…ponatinib for the treatment of Ph+ ALL'

comprehensive systematic review of ponatinib for the treatment of CML."	for the treatment of Ph+ ALL."	passage was to refer to the Ph+ ALL systematic review.	
Table 2, page 14 For the deterministic exploratory analysis Ref No 9, the ERG report states the following scenarios were combined: "1, 3, 4, 6 and 7a using the curves believed most credible by the company". Numbers 1 and 7a, however, do not appear to be considered in Ref No 9.	Incyte believes the exploratory analyses in Ref No 9 should be revised to 2, 3 and 5a for similarity to the case suitable for allo-SCT.	The Ref No 9 exploratory analysis is a combined analysis of several scenarios. However, the referenced scenarios do not align with the data in the table. That is, Ref No 1 is a range and 7a is not listed.	The ERG reviewed the description of Ref No 9 but did not identify an error.
Section 5.2.3, page 47, Table 17 Table 17 in the ERG ALL report lists the patient population as AP-CML.	Incyte requests that in Table 17, row 2, column 1, AP-CML be revised to Ph+ ALL.	The table pertains to the Ph+ ALL population of the PACE study.	Text amended

Issue 18 Induction chemotherapy described as an inappropriate comparator when T315I mutation is present

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.7, page 13 The ERG report states "No formal analyses were conducted for those patients known to have, or not have, the T315I mutation. The ERG believes that if it was known that the T315I mutation was present then induction	Incyte suggests removal of the underlined sentences.	The T315I mutation in the BCR-ABL oncogene confers resistance to TKIs, but is not associated with a differential response to conventional chemotherapy. In our model, induction chemotherapy does not include any TKI because imatinib and dasatinib	Clinical advice provided to the ERG suggested that induction chemotherapy would be less effective in those patients with the T315I mutation. We have added this sentence to the report.

chemotherapy would not be an appropriate comparator. If the T315I mutation was known not to be present then the ICERs compared with induction chemotherapy are likely to be less favourable to ponatinib, although the extent of the change is unknown." The impact of this assumption is also discussed in the ERG report in Section 6.1.3, page 67. Incyte questions the clinical rationale for these assertions.		have already been exhausted. Therefore, we believe that induction therapy should be modelled as being equally effective in T315I-positive or -negative patients, and do not anticipate that excluding T315I-positive patients would yield ICERs that are less favourable to ponatinib. We believe that these two populations should not be evaluated separately.	

References

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Ponatinib for treating chronic myeloid leukaemia: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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conducted single-arm study and measured a range of clinically relevant outcomes. Relatively few programming errors were found within the submitted model.

1.1.1 Weaknesses and areas of uncertainty

The key area of uncertainty in the evidence base relates to the lack of direct comparative data with other current treatments such as TKIs. In addition, long-term safety and efficacy data are lacking and it is unclear whether all patients need to continue long-term therapy. The ERG considers that the uncertainty in the decision was greatly underestimated by the company. The results of probabilistic sensitivity analyses were not considered robust by the ERG.

1.2 Summary of exploratory and sensitivity analyses undertaken by the ERG

The exploratory analyses undertaken by the ERG are shown in Table 1 (CP-CML), Table 2 (AP-CML) and Table 3 (BP-CML). Full details of the analyses undertaken are provided in Section 5.3. The results presented have been generated amending the version of the AP-CML / BP-CML model provided by the company on the 14th December which provided separate resource usages for AP-CML and BP-CML: these results were similar to those generated by the model version submitted on the 11th December which used identical resource usage for AP-CML and BP-CML.

In CP-CML, the choice of the selected curves for OS, PFS, DoR and relapse-free survival affected the ICER, as did assuming drug wastage, and reducing costs post-progression in both CP-CML and post allo-SCT for CP-CML patients. In AP-CML, the largest change in the ICER was caused by the selection of curves. In BP-CML, the largest changes in the ICER were caused by the selection of curves and the introduction of a three-month stopping rule for bosutinib.

In CP-CML the ICER for ponatinib is uncertain, ranging from £22,995 to £42,637 per QALY gained in comparison with bosutinib, from £18,246 to £27,667 per QALY gained in comparison with BSC, and from £18,279 per QALY gained to dominated, but nearer the upper end of this range, in comparison with allo-SCT. If only an exponential function was considered plausible for PFS in non-responders then the ICER compared with bosutinib ranges from £22,995 to £30,741 per QALY gained

In AP-CML the ERG's estimate of the ICER of ponatinib is expected to dominate bosutinib, to be below £18,000 compared with BSC, and from dominating – £63,701, but nearer the upper end of the range, in comparison with allo-SCT.

In BP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £25,000 compared with bosutinib and ponatinib was estimated to dominate BSC. The ICER of allo-SCT compared with ponatinib is estimated to lie between £4004 and dominated, but nearer the lower end of the range.

No formal analyses were conducted for those patients known to have, or not have, the T315I mutation. The ERG believes that if it was known that the T315I mutation was present then bosutinib would not be an appropriate comparator. If the T315I mutation was known not to be present then the ICERs compared with bosutinib are likely to be less favourable to ponatinib, although the extent of the change is unknown.

Table 1: The impact of the ERG's deterministic exploratory analyses in CP-CML: ponatinib compared with bosutinib, BSC and allo-SCT

		Cost per QALY gained (£)		
Ref No	**Exploratory Analyses**	**Pon vs Bos**	**Pon vs BSC**	**Pon vs allo-SCT**
0	N/A (company's base case)	18,213	15,200	4042
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	13,747 – 43,344	12,063 – 22,295	Dominant – 12,091
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	15,319 – 38,710	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	13,747 – 27,616	12,063 – 21,150	Dominant – 12,091
1d	Combining 1b and 1c	15,319 – 25,181	12,063 – 21,150	Dominant – 12,091
2a	Recalculation of the survivor functions (excluding PFS exponentials)	16,297	13,661	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	17,073	14,860	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	18,092	15,424	Dominant
3	Assuming drug wastage	30,754	24,245	16,487
4	Incorporating a three-month stopping rule for bosutinib	21,313	15,200	4042
5	No half-cycle correction of intervention costs	17,785	15,709	5472
6	Including treatment-related deaths	18,099	16,810	6143
7a	Reducing the costs assumed post-progression in CP-CML or post allo-SCT for CP-CML patients to that of BSC.	21,717	18,688	21,712
7b	Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib.	21,584	18,555	21.039
8	Assuming life table data are probabilities not rates	18,226	15,211	4043
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	18,017	15,035	4096
9b	Assuming decrements of HRQoL between CP-CML and other CML states are maintained	17,920	14,954	4125
10	2a, 4,5,[TEXT DELETED]7a, 8 and 9a, using the curves believed most credible by the company	23,059	18,308	27,649
11. ERG base case ICERs	As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a) As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,986 – 52,121 22,995 – 42,637	18,246 – 27,667 N/A	18,279 – Dominated N/A

The ERG base case ICERs are likely to be favourable to ponatinib as neither drug wastage nor treatment-related deaths are assumed

All analyses are changes from the company's base case unless stated. ↑ cost per QALY yielded

Table 2: The impact of the ERG's deterministic exploratory analyses in BP-CML: ponatinib compared with bosutinib and allo-SCT

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,601	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	11,184 – 18,808	8,251 - Dominated
2	Recalculation of the survivor functions	15,812	157,193
3	Assuming drug wastage	18,022	Dominated
4	Incorporating a three-month stopping rule for bosutinib	22,910	Dominated
5	No half-cycle correction of intervention costs	18,349	Dominated
6	Including treatment-related deaths	16,665	Dominated
7	Assuming life table data are probabilities not rates	17,601	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	21,214	102,612
9 ERG base case ICER	As 8, but choosing alternative distributions in addition to those selected by the company (range)	17,066 – 22,545	4,004 - Dominated

The ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

All analyses are changes from the company's base case unless stated.

The comparison of ponatinib with allo-SCT is the cost per QALY gained of allo-SCT compared with ponatinib (South-West quadrant).

Ponatinib typically dominates BSC

appropriate or who have T315I mutation) did not identify any relevant studies. In the absence of RCT evidence, the company identified two relevant single-arm, non-comparative studies (a Phase I dose finding study[35, 36] and a Phase II study).[22, 37, 38] However, as noted in the company's clarification response to question A11,[28] the design and context of the Phase I study was '*…not entirely relevant to either the recommended dosing or the licenced indication in the approved product label…*' for ponatinib (further details of this study are briefly provided in the supplementary evidence section). As such, evidence from the Phase II PACE study forms the main pivotal evidence in the CS. Further details of this study are provided in this section.

The company's broader systematic review of RCTs of all treatments for patients with CP-CML, AP-CML and BP-CML in the post-second-generation TKI setting (which was conducted to allow indirect comparisons to be conducted with the comparator interventions listed in the decision problem i.e. bosutinib, allo-SCT and BSC) did not identify any relevant studies. In the absence of RCT evidence, the company identified one relevant non-comparative phase I/II study of bosutinib that provided data on the efficacy and safety of bosutinib after treatment with multiple TKIs (imatinib and dasatinib and/or nilotinib) in patients with Ph+ CP-CML.[39-42] Further details of the Phase I/II bosutinib study are presented in Section 4.3. For allo-SCT, the CS identified one retrospective observational study of allo-SCT in relapsed CML;[43] however, this was not included in the MAIC. The CS (p47) states that '*...the MAIC was done for response categories (CCyR, partial cytogenetic response [PCyR], [CHR, non-responder [NR]), which are not directly applicable in the context of transplantation'* and the ERG concurred with this view. The CS did not identify any relevant studies of BSC in CML.

1.2.1.1 The main pivotal evidence (PACE study)[22, 37, 38]

The CS (p4-6 and p64-99) included one ongoing, phase II, industry-sponsored, single-arm, non-comparative, open-label, multicentre study (including five sites in the UK) designed to evaluate the efficacy of oral ponatinib in 449 people (53% male; 78% Caucasian)[25] with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy (as confirmed by direct sequencing).[22, 25, 27] Study participants in the PACE study were heavily pre-treated with prior TKIs and conventional therapy: 37% (167/449) had received two TKIs (imatinib, dasatinib, nilotinib or bosutinib). This population comprised the target population in the company's decision problem for CP-CML, AP-CML and BP-CML i.e. in the third-line treatment setting, reflecting the anticipated place in therapy of ponatinib, after treatment failure with imatinib and either nilotinib or dasatinib, if used through the CDF (see clarification response,[28] question A1). In the fourth-line setting, 55% (249/449) had received three or more TKIs.[22, 25]

company reiterated that, in an attempt to account for unmeasured confounding on the effectiveness of ponatinib, an arbitrary 25% reduction in the number of ponatinib patients achieving a best response of CCyR was applied in a cost-effectiveness scenario analysis. In fact, this was a 25% reduction in the number of ponatinib patients achieving a best response of CCyR and corresponding increase in the number of patients with PCyR rather than a 25% reduction in the effectiveness of ponatinib across response categories which could have been applied to the treatment effect estimated using an ordered categorical data model.

In response to clarification question B26,[28] the company stated that '*response to ponatinib is independent of T315I mutation status, whereas T315I-positive patients are not expected to respond to bosutinib.'* Nevertheless, an adjustment was made for an imbalance in the percentage of patients with the T315I mutation at baseline in each study in spite of the fact that patients with the T315I mutation would be offered ponatinib at the outset. The ERG believes that a fairer comparison that acknowledges the treatment pathway would have been to remove the patients with the T315I mutation from the bosutinib arm. However, while ORR could be estimated assuming that such patients were non-responders it would not be possible to perform an MAIC because it would not be known what the characteristics were of the remaining patients.

A further complication arises when there are multiple comparators each providing only summary data because the patient population changes with each comparison depending on the characteristics of the patients in each comparator study; inferences will be conditional on the patient population.

In response to clarification question A23,[28] the company stated that adjustments for differences in patient characteristics was not accounted for when analysing AP-CML, BP-CML and AEs because of the limited data available in AP-CML and BP-CML patients and because the impact of the matching adjustment on AEs would have been negligible owing to the cost of AEs compared with the total cost of treatment being small. AP-CML and BP CML response rates used in the economic model were taken from the cohort of patients in the PACE study. This is an example of an arm-based analysis that ignores the potential impact of any differences in the patient population defined by the sample of patients in the PACE study and the characteristics of the patients in the target patient population. The limited availability of data should be reflected in imprecise estimates of response used in the economic model.

The relationship between response level and progression was estimated by the company using data presented in Loveman *et al*.[51] which was evidence considered by NICE in an appraisal of dasatinib, high-dose imatinib and nilotinib which were stated to have come from BMS study 034. It is noted that there were few events for those patients with CCyR and that the estimated PFS at 48 months was 94.2%.

The company selected the Gompertz distribution for the risk of progressing from CCyR, although the range in the SSE between the candidate distributions was small (0.00085 – 0.00102) and the extrapolated survivor functions are different (Figure 1). The selection of the Gompertz survivor function, which estimates the fewest progressions, is likely to be favourable to ponatinib because ponatinib is estimated to produce the highest proportion of patients with a CCyR response.

Figure 1: Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with CCyR (CIC data)

5.2.6.1.1.1 Exiting the CCyR state due to loss of response

The company assumed that the loss of response in the CCyR state of CP-CML was treatment-specific. Following loss of response, patients are assumed to reside in the CHR response state.

5.2.6.1.1.1.1 Interferon alfa treatment or BSC discontinuation for patients in CCyR

This is not considered as neither interferon alfa nor BSC were assumed to produce a CCyR.

5.2.6.1.2 For patients who experience a PCyR

Patients can exit the PCyR state in a number of ways: death; progressed disease; loss of response; or through discontinuation of treatment. These, excluding death, are discussed in turn.

5.2.6.1.2.1 Exiting the PCyR state due to progressed disease

The company assumed that the risk of progression to AP-CML in the PCyR state of CP-CML was independent of treatment. Following progression of disease, the costs and QALYs for a patient entering AP-CML are estimated as detailed in Section **Error! Reference source not found.**. The methodology used by the company to estimate progression is detailed in **Error! Reference source not found.**.

The company had made an error in the estimation of the log-logistic distribution for PCyR, CHR and NR, by using the gamma value from the CCyR state. This has been amended by the ERG: the subsequent text is based on the results after the ERG's correction was applied.

The company selected the Gompertz distribution for the risk of progressing from PCyR, although the range in the SSE between the Gompertz, Weibull, log-logistic and log-normal distributions was small (0.00086 – 0.00111) and the extrapolated survivor functions are noticeably different (**Error! Reference source not found.**).[TEXT DELETED]

Figure 2: Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with PCyR (log-logistic amended by the ERG) (CIC data)

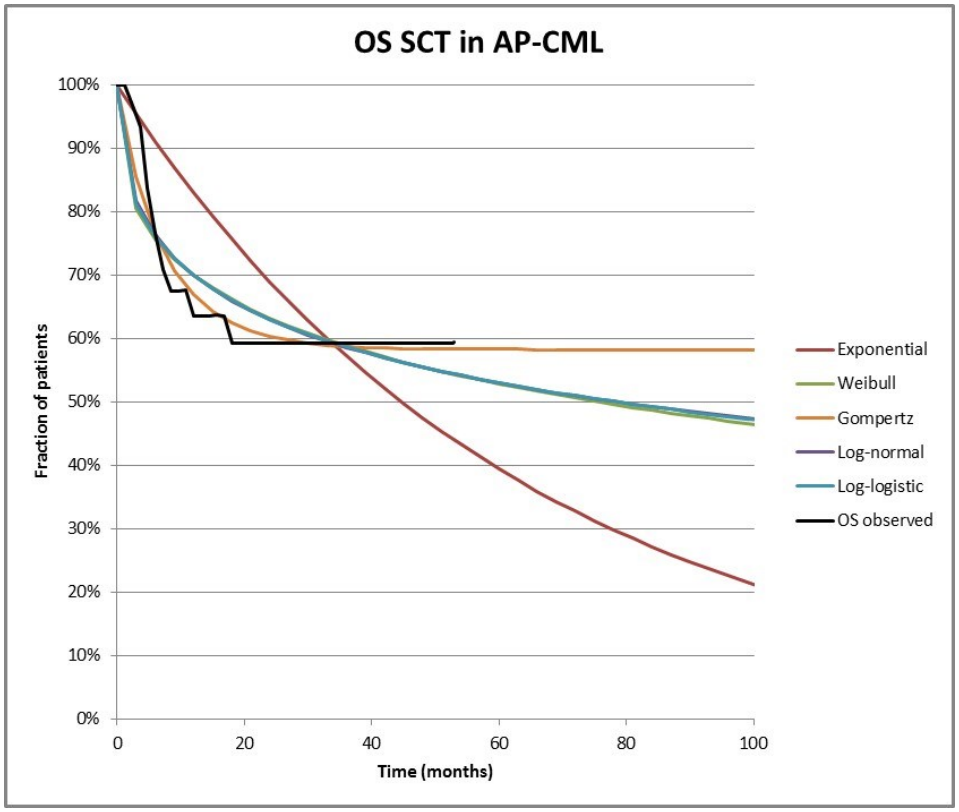
5.2.6.1.2.2 Exiting the PCyR state due to loss of response

The company's model assumes that the loss of response in the PCyR state of CP-CML was treatment-specific. Following loss of response, a patient was assumed to reside in the CHR response state.

5.2.6.1.2.2.1 Loss of PCyR for patients on ponatinib treatment

The analyses performed by the company, and the ERG's criticism of the selection of the Gompertz distribution are detailed in 5.2.6.1.1.1. The extrapolated survivor functions are presented in **Error! Reference source not found.**. Few patients were observed to have PCyR as shown by the large decrease in patients with DoR following an event.

Figure 3: Fitted curves to the risk of death following allo-SCT in AP-CML



The ERG notes that a different data source is used for survival post-allo-SCT in patients with AP-CML or BP-CML: this source also included data on survival for patients with CP-CML (Radich[70]). Clinical advice provided to the ERG supported the company's decision not to use Radich for CP-CML patients as the results relate to patients who have only failed imatinib, as the data collection started prior to the introduction of dasatinib and nilotinib. As such, these patients may be selected group of fit patients and are not similar to those being considered for ponatinib.

Immediately prior to the submission of the report a clinical advisor became aware of data on OS after allo-SCT for patients in CP-CML who had received previous therapy with nilotinib or dasatinib[71] presented at the American Society of Haematology (San Diego; December 2016). These data, which have been collected for up to six years after allo-SCT, provide evidence on OS following allo-SCT in patients who have received prior nilotinib or dasatinib. As such, these data appear to represent a potentially appropriate data source and are contained in **Error! Reference source not found.**. The company state in the fact check process that the patients in the Olavarria *et al.* study were relatively young (median age 45 years), that median time between diagnosis and receiving allo-SCT (22 months) and median duration of treatment with dasatinib or nilotinib (10 months) suggests that these patients would have better prognoses after allo-SCT than those recruited in PACE.[22]

Figure 4: Data relating to OS following allo-SCT in patients who have received prior nilotinib or dasatinib (AIC data)

These data support the flattening of the Kaplan-Meier rather than the company's choice of the exponential distribution. **Error! Reference source not found.** are .

5.2.6.1.3 Modelling assumptions for patients who have allo-SCT on entering the model

Patients in CP-CML who have allo-SCT on model entry are assumed to enter a relapse-free state. From this state the patient can relapse or die.

5.2.6.1.3.1 Probability of relapse following allo-SCT on model entry

The probability of relapse for those who have an allo-SCT on model entry is assumed to be the same as for patients who have allo-SCT following a non-allo-SCT treatment. See Section **Error! Reference source not found.** for more details.

5.2.6.1.3.2 Probability of death following allo-SCT on model entry

The probability of death following allo-SCT in CP-CML is assumed to be lower than that following allo-SCT after a patient has progressed to AP-CML (Section **Error! Reference source not found.**). The data for patients in CP-CML were digitised and different survivor functions were fitted to the data by minimising the SSE:. The range in SSE was relatively small, from 0.04 – 0.08, excluding the

exponential distribution. The company selected the exponential distribution, which predicts a much lower probability of

BIC values were similar across all functions thus the choice of the best fit is thus subject to considerable uncertainty.

Figure 5: Fitted curves to the OS data for those in BP-CML who get an MaHR on ponatinib treatment (CIC data)

5.2.6.3.1.1.2 Probability of death for patients on bosutinib treatment

The company's model assumes that the OS following an MaHR is equal for ponatinib and bosutinib for patients in BP-CML.

5.2.6.2.1.1.3 Probability of death for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section **Error! Reference source not found.**.

5.2.6.3.2 Transition probabilities for patients in BP-CML who experience NR

The next event for patients in BP-CML who have NR is death.

5.2.6.3.2.1 Exiting the NR state due to death

5.2.6.3.2.1.1 Probability of death for patients on ponatinib treatment

The curve-fitting process for people in BP-CML was similar to that for AP-CML. Goodness-of-fit statistics for the candidate distributions are shown in **Error! Reference source not found.**. The company selected the log-normal distribution as being the best fit to the data as it had the lowest AIC. The parametric curves are

reproduced in

Figure 6. However, other curves have relatively similar values and produce different extrapolations. The survival rate beyond 20 weeks for the log-normal curve is greater than for the exponential distribution, which is plausibly a better fit to the data.[TEXT DELETED]

Figure 6: Fitted curves to the OS data for those in BP-CML who get NR on ponatinib treatment (CIC data)

5.2.6.3.1.1.2 Probability of death for patients on bosutinib treatment

The company's model assumes that the OS following NR is equal for ponatinib and bosutinib for patients in BP-CML.

5.2.6.3.1.1.3 Probability of death for patients on BSC

The methodology for estimating OS for patients on BSC is identical to that described in Section **Error! Reference source not found.**.

5.2.6.3.3 Modelling assumptions for patients who have allo-SCT after an MaHR in BP-CML

Patients in BP-CML who have allo-SCT after an MaHR are assumed to remain in this state until death. The assumed probability of death was estimated from data in Radich.[70] Patients with MaHR in BP-CML were assumed to be equivalent to those reported by Radich[70] as being in BP-CML with remission. Parametric curves were fitted to the data by minimising the SSE and are illustrated in **Error! Reference source not found.**. The company did not select the distribution that fitted best (the log-logistic function – SSE

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of exploratory sensitivity analyses (see Sections 5.3.1 to Section 5.3.9). Analyses that the ERG would like to have conducted but which were not possible are discussed in Section 5.3.10. The results of the exploratory analyses are provided in Section 6.

For CP-CML the analysis was of ponatinib compared to bosutinib. For AP-CML, two comparators were used, BSC and SCT as the efficiency frontier was likely to change based on the chosen assumptions: bosutinib was typically dominated by ponatinib. For BP-CML the comparison was of ponatinib compared to bosutinib.

PSA has not been conducted due to insufficient time, the wide range of ICERs using different assumptions, and the ERG's belief that the PSA undertaken by the company is not robust.

5.3.1 Choosing alternative curves to those selected by the company

The ERG believes insufficient sensitivity analyses were undertaken by the company. Kass *et al*.[67] state that a difference in the BIC of less than two is barely worth a mention, whilst only difference values of six or greater indicate strong evidence that one curve may be preferable to another. In addition, the BIC does not take clinical plausibility of the extrapolation into account. Taking the BIC and clinical plausibility into consideration, the ERG undertook exploratory results using alternative curve fits to those selected by the company. A list of curves considered to be potentially credible by the ERG and the clinical advisors to the ERG are provided in **Error! Reference source not found.** for the CP-CML model and **Error! Reference source not found.** for the AP-CML / BP-CML model. Exploring all combinations of curves in the CP-CML model would result in 34,560 results: this was not considered feasible within the time scales of the appraisal. Instead, where multiple curves were thought plausible, the company's base case was explored along with the curve that had the most different extrapolation from the company's default curve, to test extreme values, resulting in 1024 scenarios run. The exception was for the DoR for ponatinib where the log-normal function was chosen rather than log-logistic function so that the same functions were used for ponatib and for bosutinib. The ERG acknowledges that some combinations of curves may produce results that are not clinically plausible, such as the PFS being greater for patients with NR than for patients with CHR. This could be resolved by building a model that considers CHR and NR simultaneously with constraints on parameters to ensure clinical face-validity. This was not something the ERG could do within the timescales and without access to the data. However, the imposition of a function that appears to be a poor fit to the curves solely for clinical plausibility of ranking is not an ideal solution.

5.3.3 *Assuming drug wastage*

The company's model assumes that missed dosages of treatment will be saved and that ultimately fewer packs of ponatinib or bosutinib would be used, which is equivalent to assuming no drug wastage. The ERG conducted analyses assuming that dosages not taken would not be recouped but would incur the cost but produce no clinical benefit. Clinical advice to the ERG indicated that stock-piling of pills and skipping a pack may be possible in CP-CML, but may be less likely in AP-CML or BP-CML.

5.3.4 *Introducing a stopping rule for bosutinib*

The company's model assumes that unlike patients receiving ponatinib, patients receiving bosutinib would continue to receive bosutinib despite no response in CP-CML, or despite failing to achieve an MaHR in AP-CML or BP-CML. The company rationale for this approach was that unlike the SmPC for ponatinib there is no guidance on discontinuation of treatment in the SmPC for bosutinib. However, the clinical experts to the ERG believe that many clinicians would stop bosutinib treatment if there was no response experienced. The ERG has amended the model to allow the same stopping rules for ponatinib to be considered for bosutinib.

5.3.5 *Removing the half-cycle correction for intervention costs*

The company's model half-cycle corrects the costs for interventions. In their response to clarification,[28] (question B33) the company states that '*not all patients remain on treatment for the entire cycle as a combined result of events such as death, progression and discontinuation, that may occur during the cycle.*' For precisely this reason, the ERG believes that the intervention costs should not be half-cycle corrected, as should a patient discontinue or die, the intervention provided to the patient would not be re-used and would need to be disposed of. The ERG method will over-estimate the impact as it is unlikely that medicines will be provided at three-monthly periods, except for stable CP-CML patients after the initial few months of treatment. However, as the company's model uses three-month time cycles this was the best approximation that could be explored within the time constraints of the appraisal.

5.3.6 *Incorporating the impact of deaths related to an intervention*

The company does not incorporate the possibility of treatment-related death despite providing such information within the clarification response process[28] (questions A15 and B4). The values for treatment-related death used in the exploratory model were for ponatinib: [redacted]/267 in CP-CML ([redacted]%); [redacted]/83 in AP-CML ([redacted]%); and [redacted]/62 ([redacted]%) in BP-CML.[38, 53] For bosutinib these values were: 1/118 in CP-CML[41] (0.8%); and 2/167 (1.2%) for patients in AP-CML and BP-CML.[39] In order to explore the

of number of events are low, would have been beneficial. There was insufficient time within the appraisal timescales for the ERG to remedy these problems. The ERG also noted that there was, at times, such uncertainty in the ICER due to the curve chosen to predict the extrapolation, that the likely change in the ICER due to the PSA, would be less than the changes due to the choice of the distribution.

There was insufficient time for the ERG to revisit previous NICE appraisals of treatments for CML and to compare and contrast the sources used within the modelling for parameter estimates. It was not possible to formally appraise the cost-effectiveness of ponatinib in those who are known to have, or not have, the T315I mutation. The likely impact of the knowledge of the presence, or not, of the T315I mutation has been discussed narratively.

Clinical advice provided to the ERG suggested that many patients receiving an allo-SCT after non-allo-SCT treatments would have this in CP-CML, rather than waiting for the patient to progress to AP-CML, due to better prognosis if the allo-SCT is undertaken in CP-CML. It was not possible in the timelines of the STA for the ERG to produce this analysis.

5.4 Conclusions of the cost-effectiveness section

The CS mainly adhered to the decision problem, however, clinical advice provided to the ERG suggested that induction chemotherapy should have been considered a comparator in BP-CML. The company assumptions result in estimated ICERs, having applied the PAS discount for ponatinib, of: £18,213 per QALY gained compared with bosutinib in CP-CML; £14,750 per QALY gained compared with BSC in AP-CML; and £17,601 per QALY gained compared with bosutinib in BP-CML. However, the ERG does not always agree with the choice of parameter values or distributions used in the company's base case. As such it is believed that the uncertainty in the decision was greatly underestimated by the company. The ERG has assessed the potential implications of changes to the model within Section 6. The results of probabilistic sensitivity analyses were not considered robust by the ERG.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The impacts of the exploratory analyses undertaken are reported in this section. All analyses have been undertaken using the list price of drugs relevant to the decision problem with the exception of ponatinib: the results including the PAS discounts for these drugs are provided in a separate confidential appendix. The results presented have been generated amending the version of the AP-CML / BP-CML model provided by the company on the 14th December which provided separate resource usages for AP-CML and BP-CML: these results were similar to those generated by the model version submitted on the 11th December which used identical resource usage for AP-CML and BP-CML.

The analyses are undertaken in comparison to the previous intervention on the efficiency frontier and against other interventions that could, based on the chosen assumptions, become the previous intervention on the efficiency frontier.

The results presented are subject to further levels of uncertainty, such as the lack of a robust PSA, the lack of continuity corrections for low observed counts, and the inherent uncertainty associated with data produced via an MAIC for the CP-CML analyses.

6.2 Results for CP-CML

The results are presented in Table 3. The ERG's base case does not include drug wastage and thus the ICER is likely to be lower than the ICER if the true level of wastage was incorporated. Treatment-related deaths have not been incorporated in the base case; this is favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large, thereby indicating considerable uncertainty in the ICER.

6.1.1 Results for ponatinib compared with bosutinib for CP-CML patients

For the comparison of ponatinib with bosutinib, the largest drivers of the ICER include: drug wastage; the estimation of costs post-progression and post-allo-SCT relapse; the inclusion of a stopping rule for bosutinib; the use of the log-normal distribution rather than the Gompertz distribution for DoR for both ponatinib and bosutinib; and use of the log-normal distribution rather than the exponential distribution for characterising PFS for those patients who achieve NR from treatment. The fit of the exponential and the log-normal distributions to PFS for those with NR performed by the company can

be seen in **Error! Reference source not found.**. The company's fit of the Gompertz and log-normal distributions to DoR are shown in **Error! Reference source not found.** and **Error! Reference source not found.** for ponatinib and **Error! Reference source not found.** for bosutinib.

The ERG believes that the ICER is likely to lie in the range £22,995 - £42,637 although any drug wastage would increase these values. The upper bound can be reduced to £35,859 if it is believed that the data for PFS in NR can be best represented by an exponential curve, although the ERG notes that both the exponential curves fitted by the company and the ERG provide a poor fit to the observed data.

6.1.2 Results for ponatinib compared with BSC for CP-CML patients

For the comparison of ponatinib with BSC, the largest drivers of the ICER include: drug wastage; and the estimation of costs post-progression. For the comparison of ponatinib with BSC, the ERG believes that the ICER is likely to lie in the range £18,246 - £27,667 although any drug wastage or ponatinib-related deaths would increase these values: assuming an exponential curve for PFS in NR would decrease the upper value of the ICER range to £26,591.

6.1.3. Results for ponatinib compared with allo-SCT for CP-CML patients

For the comparison of ponatinib with allo-SCT, the largest drivers of the ICER include: drug wastage; the estimation of costs post-progression and post-allo-SCT relapse; and the assumed distribution for characterising OS following allo-SCT (either Gompertz or exponential) for patients in CP-CML. The company's fits of the Gompertz and exponential distributions to OS data post allo-SCT are provided in **Error! Reference source not found.**. The ERG believes that the ICER for the comparison of ponatinib versus allo-SCT is highly uncertain. However, it is likely that the ICER is greater than £18,000 and it possible that ponatinib could be dominated by allo-SCT. Assuming an exponential distribution for PFS in NR increased the upper estimate of the ICER range to £22,586. When the Gompertz distribution was selected for OS after allo-SCT the ICER was generally greater than £100,000. Clinical advice received by the ERG suggested that the Gompertz distribution was likely to be the more plausible of the two distributions.

6.1.4 Results for ponatinib compared with interferon alfa for AP-CML patients

The ERG believes that probability that interferon alfa would be on the efficiency frontier is low, regardless of the assumptions made. As such, no further analyses were conducted by the ERG.

Table 3: Impact of the ERG's deterministic exploratory analyses in CP-CML

		Cost per QALY gained (£)		
Ref No	**Exploratory Analyses**	**Pon vs Bos**	**Pon vs BSC**	**Pon vs allo-SCT**
0	N/A (company's base case)	18,213	15,200	4042
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	13,747 – 43,344	12,063 – 22,295	Dominant – 12,091
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	15,319 – 38,710	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	13,747 – 27,616	12,063 – 21,150	Dominant – 12,091
1d	Combining 1b and 1c	15,319 – 25,181	12,063 – 21,150	Dominant – 12,091
2a	Recalculation of the survivor functions (excluding PFS exponentials)	16,297	13,661	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	17,073	14,860	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	18,092	15,424	Dominant
3	Assuming drug wastage	30,754	24,245	16,487
4	Incorporating a three-month stopping rule for bosutinib	21,313	15,200	4042
5	No half-cycle correction of intervention costs	17,785	15,709	5472
6	Including treatment-related deaths	18,099	16,810	6143
7a	Reducing the costs assumed post-progression in CP-CML or post allo-SCT for CP-CML patients to that of BSC.	21,717	18,688	21,712
7b	Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib.	21,584	18,555	21.039
8	Assuming life table data are probabilities not rates	18,226	15,211	4043
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	18,017	15,035	4096
9b	Assuming decrements of HRQoL between CP-CML and other CML states are maintained	17,920	14,954	4125
10	2a, 4,5,[TEXT DELETED] 7a, 8 and 9a, using the curves believed most credible by the company	23,059	18,308	27,649
11. ERG base case ICERs	As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a) As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,986 – 52,121 22,995 – 42,637	18,246 – 27,667 N/A	18,279 – Dominated N/A

The ERG base case ICERs are likely to be favourable to ponatinib as neither drug wastage nor treatment-related deaths are assumed

All analyses are changes from the company's base case unless stated. ♪ cost per QALY yielded

Table 4: Impact of the ERG's deterministic exploratory analyses in BP-CML

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,601	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	11,184 – 18,808	8,251 - Dominated
2	Recalculation of the survivor functions	15,812	157,193
3	Assuming drug wastage	18,022	Dominated
4	Incorporating a three-month stopping rule for bosutinib	21,910	Dominated
5	No half-cycle correction of intervention costs	18,396	Dominated
6	Including treatment-related deaths	16,665	Dominated
7	Assuming life table data are probabilities not rates	17,601	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	21,254	102,612
9 ERG base case ICER	As 8, but choosing alternative distributions in addition to those selected by the company (range)	17,066 – 22,545	4,004 - Dominated

Note: the ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

Note: the comparison of ponatinib with allo-SCT is the cost per QALY gained of allo-SCT compared with ponatinib (South-West quadrant).

Ponatinib typically dominates BSC

Note: All analyses are changes from the company's base case unless stated.

6.3 Exploratory analyses for patients known to be with, and without, the T315I mutation

The company did not present results for patients with, and without the T315I mutation.

The ERG believes that for patients known to have the T315I mutation the most appropriate comparison would exclude bosutinib. This results in an estimated ICER in CP-CML in the range £18,246 - £27,667 per QALY gained compared with BSC, and remaining uncertain compared with allo-SCT. In AP-CML, the ICER is estimated to be in the range £7475 - £18,005 per QALY gained compared with BSC, and remaining uncertain compared with allo-SCT. In BP-CML, ponatinib is estimated to dominate BSC, and the ICER is uncertain compared with allo-SCT.

8 OVERALL CONCLUSIONS

Clinical effectiveness

In the absence of direct comparative data with other treatments, the main evidence in the CS was derived from a phase II, industry-sponsored, single-arm, non-comparative, open-label, study. The efficacy (measured in terms of surrogate response measures e.g. MCyR, MaHR and CCyR) in the PACE study appears favourable, and the safety appears acceptable. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Whilst the study was generally well reported and conducted, single-arm studies are associated with an array of potential biases including a high risk of selection bias (due to the absence of randomisation), performance and detection bias (due to the absence of blinding). In addition, due to the absence of a controlled comparator group in the PACE study, inference of treatment effects (including magnitude) may be confounded and its ability to compare or demonstrate efficacy with other current treatments is limited. A further limitation to the robustness of the efficacy and safety data relate to the small subgroups that comprise the target population in the CS, including lack of statistical power for the subgroup assessments. The key uncertainties in the clinical evidence for CML relate to optimal dosing, duration of treatment and magnitude of treatment effect.

Cost-effectiveness

The ICER of ponatinib compared to the comparators within the scope is typically uncertain, particularly with respect to allo-SCT.

In CP-CML the ERG's estimate of the ICER of ponatinib is uncertain, ranging from £22,863 – £42,637 in comparison with bosutinib, from £18,136 – £27,501 in comparison with BSC and from £18,438 – dominated, but nearer the upper end, of the range, in comparison with allo-SCT.

In AP-CML the ERG's estimate of the ICER of ponatinib is expected to dominate bosutinib, to be below £18,000 compared with BSC, and from dominating – £63,701, but nearer the upper end of the range, in comparison with allo-SCT.

In BP-CML the ERG's estimate of the ICER of ponatinib is expected to be below £25,000 compared with bosutinib and ponatinib was estimated to dominate BSC. The ICER of allo-SCT compared with ponatinib is estimated to lie between £4004 and dominated, but nearer the lower end of the range.

a. Implications for research

There are no direct comparisons on the clinical and cost effectiveness of third-line ponatinib with other current treatments such as bosutinib in patients with CP-CML, AP-CML and BP-CML. Hence

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underestimated by the company. The results of the probabilistic sensitivity analyses were not considered robust by the ERG but were not amended.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of ponatinib for the treatment of Ph+ALL. No major limitations were noted. The PACE study was well-reported and conducted single-arm study and measured a range of clinically relevant outcomes. Few programming errors were found within the submitted model which was subjected to a cell-by-cell evaluation.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty in the evidence base relates to the lack of direct comparative data with other current treatments such as TKIs. In addition, although the PACE study population appears reflective of the Ph+ ALL population in England, the treatment pathway is not an absolute reflection of UK practice (patients received nilotinib in the PACE study, which is not used in the UK). Long-term safety and efficacy data are also lacking. The ERG believes that the uncertainty in the decision has been greatly underestimated by the company. The results of probabilistic sensitivity analyses were not considered robust by the ERG. The ERG believes that the central estimate produced by the company was considerably unfavourable to ponatinib, due to assumptions regarding OS that were not supported by clinical advice received by the ERG.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The exploratory analyses undertaken by the ERG are shown in Table 1 for those who can receive allo-SCT and **Error! Reference source not found.** for those who cannot receive an allo-SCT.

For patients who could receive allo-SCT, recalculation of the OS curve increased the ICER, as did removing the half-cycle correction of intervention costs, and the inclusion of drug wastage. Assuming that the OS for non-response (NR) is independent of whether a patient had received ponatinib, markedly reduced the ICER due to the additional costs of being alive in the NR state. The use of alternative curves to those selected by the company increased the uncertainty and increased the upper range of the ICER. These conclusions also applied to the model where people could not have allo-SCT, with the exclusion of the recalculation of the OS post-allo-SCT which was not relevant in this scenario.

If it is assumed that OS for people in the NR state is independent of whether the patient received ponatinib, as believed by the clinical expert to the ERG, the ICER for ponatinib in people who can receive allo-SCT ranges from dominant to £11,727 per QALY gained when compared with induction

chemotherapy, although the ERG notes the naïve indirect comparison used, and from £7892 - £31,696 compared with BSC. For patients who cannot receive allo-SCT the ICER for ponatinib is likely to dominate BSC.

No formal analyses were conducted for those patients known to have, or not have, the T315I mutation. Clinical advice provided to the ERG suggested that if it was known that the T315I mutation was present then induction chemotherapy would not be an appropriate comparator. Clinical advice suggested that if the T315I mutation was known not to be present then the ICERs compared with induction chemotherapy are likely to be less favourable to ponatinib, although the extent of the change is unknown.

Table 1: The impact of the ERG's deterministic exploratory analyses in patients suitable for allo-SCT

		Cost per QALY (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs induction chemotherapy**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	31,123	26,624
1	Recalculation of the OS post allo-SCT curve	57,140	53,603
2	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	23,838 – 52,559	14,203 – 45,218
3	Assuming drug wastage	32,499	26,944
4	No half-cycle correction of intervention costs	43,766	29,568
5	Including treatment related deaths	28,635	25,864
6	Removal of immortality for a small subset of patients	31,989	26,999
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,983
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,959
8	1, 3,4 and 6 using the curves believed most credible by the company	90,325	62,801
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	11,727	31,696
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant – 11,727	7,892 – 31,696

Allo-SCT, allogeneic stem cell transplant; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders; OS, overall survival; QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

disease or where the residual disease burden was less than 1/1000 at the time of transplant. For patients receiving BSC, it was assumed that there would be NR and the patient would remain in this state. For all treatments, death could occur at any time point.

5.2.2.1.1 Patients receiving ponatinib or induction chemotherapy

For patients receiving ponatinib or induction chemotherapy, the model simulates the response of patients to the treatment, which was assumed to occur in the first cycle only. It was assumed that patients would fall into one of two mutually exclusive and exhaustive states: remission (which incorporated either MyCR (ponatinib) or CR (induction chemotherapy) and NR.

For patients simulated to experience remission, the next event in the model (a term which has been used in the ERG report to identify the next event whilst excluding remaining in the same health state) would be allo-SCT, if appropriate. Following allo-SCT, the next event is death. For those who experience NR, and/or who are unsuitable for allo-SCT, the next event is death.

5.2.2.1.2 Patients receiving BSC

For patients receiving BSC, the only event possible is death.

2.1.1 Population

The population modelled is provided in Table 2.

Table 2: Characteristics of the hypothetical patients used in the Ph+ ALL model

	Initial Age (years)	Proportion male (%)	Source
Ph+ ALL	53.0	62.5	PACE[20]

2.1.2 Intervention and comparators

2.1.2.1 The comparators in Ph+ ALL

The intervention being appraised is ponatinib which is a third-generation antineoplastic protein kinase inhibitor administered orally. Further details are provided in Section **Error! Reference source not found.**.

2.1.2.2 Comparators in Ph+ ALL

Within Ph+ ALL, three strategies are compared: (i) ponatinib; (ii) induction chemotherapy; and (iii) BSC.

Table 3: The impact of the ERG's deterministic exploratory analyses in patients suitable for allo-SCT

		Cost per QALY (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs induction chemotherapy**	**Ponatinib vs BSC**
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3	Assuming drug wastage	32,499	26,944
4	No half-cycle correction of intervention costs	43,766	29,568
5	Including treatment related deaths	28,635	25,864
6	Removal of immortality for a small subset of patients	31,989	26,999
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,983
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,959
8	1, 3,4 and 6 using the curves believed most credible by the company	90,325	62,801
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	11,727	31,696
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant – 11,727	7,892 – 31,696

Allo-SCT, allogeneic stem cell transplant; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders; OS, overall survival; QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

6.1.3 Results for patients known to be with, and without, the T315I mutation

Based on clinical advice provided to the ERG it is believed that for patients known to have the T315I mutation the most appropriate comparison would exclude induction chemotherapy and would result in an ICER likely to lie in the range £7,892 to £31,696 per QALY gained. Based on this clinical advice, for patients known to not have the T315I mutation it is anticipated that the lower and upper values in the range in the cost per QALY gained compared with induction chemotherapy would increase, that is, become less favourable to ponatinib. However, the precise increase in these values is unknown.