HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Committee Papers

Bosutinib for previously treated chronic myeloid leukaemia

The following documents are made available to the consultees and commentators:

1. **CDF rapid reconsideration committee meeting slides** prepared by NICE project team

2. **Company submission** from Pfizer

3. **Consultee submissions from;**
   - **Chronic Myeloid Leukaemia Support Group**
   - **Leukaemia Care**
   - **National Cancer Research Institute – Royal College of Physicians - Association of Cancer Physicians** (joint submission)
   - **The Royal College of Pathologists**

4. **Expert statements from;**
   - **Dr Jennifer Byrne** – Clinical expert nominated by The National Cancer Research Institute–Royal College of Physicians-Association of Cancer Physicians
   - **Professor Adam Mead** – Clinical expert nominated by The Royal College of Pathologists
   - **Russell Cooper** – Patient expert nominated by The Chronic Myeloid Leukaemia Support Group
   - **David Ryner** – Patient expert nominated by The Chronic Myeloid Leukaemia Support Group

5. **Evidence Review Group report** prepared by PenTAG

6. **Evidence Review Group report – company factual accuracy check & ERG responses**

7. **Erratum to the ERG Report** prepared by PenTAG

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

NICE National Institute for Health and Care Excellence

Bosutinib for previously treated Chronic Myeloid Leukaemia

Rapid reconsideration of TA299

Public observer slides

25th May 2016

Issues for consideration

- Does the new submission address the issues highlighted in TA299 final guidance?
- Is there still considerable uncertainty about the clinical benefit of bosutinib?
- What are the most plausible ICERs ?
- Could any further data collection address the uncertainties in this appraisal?

Disease Background: Chronic myeloid leukaemia (CML)

- Myeloproliferative disorder of pluripotent haematopoietic stem cells associated with chromosomal abnormality – commonly 22 - “Philadelphia chromosome” which produces the fused gene BCR-ABL (breakpoint cluster region and Abelson) coding for a tyrosine kinase that is continually active

- Approximately 560 - 800 new cases per year in UK (~2660 prevalent cases in England and Wales)

- Slowly progressive – 3 phases:
  - chronic phase (patients that stay in this phase have approximately normal life expectancy)
  - accelerated phase
  - blast crisis (transformation)

Marketing Authorisation

Bosutinib

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

- Oral agent
- Dose 500mg a day
- Second Generation-BCR – ABL/SRC tyrosine kinase inhibitor
- Common adverse effects
  - Gastrointestinal
  - Haematological
  - Rash

NICE scope decision problem (TA299)

Company's decision problem	
Population	Patients with Ph+ CML previously treated with ≥1 TKI and unsuitable imatinib/nilotinib/dasatinib "unmet need"
Intervention	Bosutinib 500mg daily
Comparators	Hydroxycarbamide (HU) ≈ Best Supportive Care (this was regarded as most relevant comparator) Allogeneic SCT (not considered to be relevant comparators) Interferon alfa
Outcomes	Survival – Overall/ Event free/ Progression free Response – haematological/cytogenetic/molecular Adverse events Health related QoL
Economic evaluation	Cost utility from NHS and PSS perspective

TA299: Evidence available

- Study 3000 (Bosutinib vs Imatinib RCT 1st line) not presented to Committee
- Study 200 - Single arm study (N=546) for 2nd and 3rd line chronic phase (CP), accelerated phase (AP) and blast phase (BP) CML
- Small proportion of study population (52 people) that was defined post hoc had unmet medical need (i.e. met MA indication, which was: patients previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options)
- Bosutinib showed efficacy for CP, AP, BP- outcomes of cytogenetic response (CP) and haematological response (AP&BP)

TA299 FAD: ICERs

	Company	ERG	Committee
Chronic phase (EoL not met)	£20,972 per QALY	£43,000 (HU survival 3.5ys) or £49,000 (HU survival 7ys) Up to £135k in scenario analysis	£43,000 per QALY £40,000 to £50,000 per QALY *
Accelerated phase (EoL)	£53,789	£65,000	£58,000 per QALY
Blast phase (EoL)	£59,191	£89,000	£60,000 per QALY

* taking into account the limited potential for post-bosutinib benefit and a proportion of people taking bosutinib after loss of complete cytogenetic response an estimated range of £40,000 to £50,000 was most plausible for Committee's decision making

TA299: Original Committee concerns

Clinical Effectiveness

- Limitations in study design, population size
- No direct comparisons of bosutinib with comparators
- Small studies, data from single arms, and modelled comparison with interferon alpha only for CP CML (same OS as HU)
- Study 200 data for bosutinib last line but 45% received subsequent treatment.
- Uncertainty in overall survival estimate for hydroxycarbamide
- Uncertainty surrounding extension to life estimates for bosutinib in AP and BP CML

Cost Effectiveness

- Modelling of post treatment benefit with bosutinib
- Bosutinib was not cost-effective

TA299: Company's assumptions in the model

- Patients in different studies are similar
- Majority of patients receive bosutinib third line
- Patients receive only hydroxycarbamide (HU) after bosutinib
- Response of "unmet need" population is same as overall population in Study 200
- Major Cytogenetic Response has same relation to Overall Survival as in population with high dose imatinib
- Response to "other" treatments in Kantarjian 2007 reflects response to HU
- SCT offers "cure"

TA299: Company's modelling of overall survival

- Overall survival estimate for bosutinib in CP based on surrogate outcome (Major cytogenetic response MCyR)
- Inferred from high dose imatinib study (Jabbour 2009) – in which subsequent treatments were available
- All people assumed to receive best supportive care after stopping bosutinib (which was hydroxycarbamide) and survival on hydroxycarbamide was overall survival minus time on treatment with bosutinib
- Survival in BSC arm assumed to be 3.5 years

TA299: ERG cumulative survival assumption

- Assumed that survival on hydroxycarbamide (HU) following bosutinib should be similar to survival on HU taken in same position in treatment pathway as bosutinib
- Overall survival is duration of treatment with bosutinib + survival estimate for BSC ie HU (adjusted for people who died while still taking bosutinib)
- Tested 2 survival estimates for HU
  - 3.5 years (same as company)
  - 7 years (based on extrapolation from Kantarjian 2007)

TA299: Committee considerations

- The cumulative modelling approach for overall survival was preferred over the surrogate approach
- Post-treatment benefit of 1 to 2 months was considered plausible
- Overall survival of 3.5 years with hydroxycarbamide was accepted
- End of Life criteria were not fulfilled for chronic phase
- End of Life criteria were fulfilled for accelerated and blast phase

TA299 Committee ICERs

	Committee's most plausible ICERs
Chronic phase (EoL not met)	£43,000 per QALY £40,000 to £50,000 per QALY *
Accelerated phase (EoL)	£58,000 per QALY
Blast phase (EoL)	£60,000 per QALY

* taking into account the limited potential for post-bosutinib benefit and a proportion of people taking bosutinib after loss of complete cytogenetic response an estimated range of £40,000 to £50,000 was most plausible for Committee's decision making

Company's new submission

- Use of cumulative approach to overall survival modelling (adding time on bosutinib treatment to the OS for hydroxycarbamide)
- This method assumes no post-treatment benefit
- Company states that because the Committee had considered there to be a plausible post-treatment benefit of 1 to 2 months, the resulting base-case ICERs are thought to be a "maximum upper bound" to the most likely ICER of bosutinib
- The most plausible overall survival estimate with hydroxycarbamide is assumed to be 3.5 years
- Use of utility values derived directly from the bosutinib pivotal study (Study200) in the base case (EQ-5D-3L utilities)
- Costs have been updated to reflect 2014/2015 values using inflation indices from the PSSRU 2015
- The new ICERs including the PAS were lower compared with TA299

ERG comments

- The ICERs from the new submission, when using the TA299 price, align reasonably well with Committee's most plausible ICERs → reasonable confidence in appropriateness of the model
- Small logic and implementation issues that, when addressed, had a small upwards impact on the ICERs of bosutinib
- There is considerable uncertainty regarding the relative effectiveness of bosutinib vs hydroxycarbamide, since it has not been estimated in comparative studies
- Company's new submission implicitly assumes that a given patient's life expectancy is extended exactly by the length of time they are treated with bosutinib – this duration may, however, be larger or smaller
- ICER is also sensitive to the uncertainty about length of overall survival on hydroxycarbamide

Issues for consideration

- Does the new submission address the issues highlighted in TA299 final guidance?
- Is there still considerable uncertainty about the clinical benefit of bosutinib?
- What are the most plausible ICERs ?
- Could any further data collection address the uncertainties in this appraisal?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

January 2016

1 Introduction

1 All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2 In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3 The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4 The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5 A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6 Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7 The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8 Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9 The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

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

The proposed patient access scheme applies to the entirety of this indication.

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

Prior to the introduction of tyrosine kinase inhibitors (TKIs), the median life expectancy for CML patients was around six to seven years (1), and while overall chronic phase CML survival rates have improved to the extent that patients may now expect a normal life expectancy (2), there remains a high unmet medical need for patients who are unable to take the currently approved TKIs. Bosutinib has demonstrated clinical benefit in a targeted subgroup of patients who have no disease modifying options currently available to them:

- Some patients may not respond to these therapies or may develop a resistance to them (due to genetic mutations) (3), (4), (5), (6).
- Some patients may not be able to tolerate them (i.e. the side-effects of the therapy are so severe or persistent that they can no longer continue treatment) (7).
- Some patients may have pre-existing medical conditions, which may pre-dispose them to an unacceptable risk based on adverse drug reactions associated with treatment with other TKIs (8).

The proposed patient access scheme improves the cost-effectiveness of bosutinib, and [redacted]. The new ICERs presented based on this patient access scheme, combined with the ERG's preferred assumptions, should be judged as the maximum upper bounds of bosutinib's cost-effectiveness, and demonstrate that bosutinib offers good value for money to the NHS.

With the patient access scheme, [redacted]

Molecule	Pack	Strength	Cost	Cost per tablet	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib (Bosulif®)	28 tablets	500mg	£3,436.67	£122.7/tablet	BNF, February 2016 (11)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

The proposed patient access scheme is a simple discount, which is conditional on the level of discount offered remaining confidential. It is proposed that NHS Trust procurement entities will purchase bosutinib at a discount applied to the invoice at the point of purchase.

3.4 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

- 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 proposed patient access scheme will apply to the full licensed population, as described in Section 3.1.

3.5 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The proposed scheme is not dependent upon any criteria and is simply applied as a discount at the point of invoice.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

The proposed scheme will apply to all NHS patients for whom bosutinib is indicated.

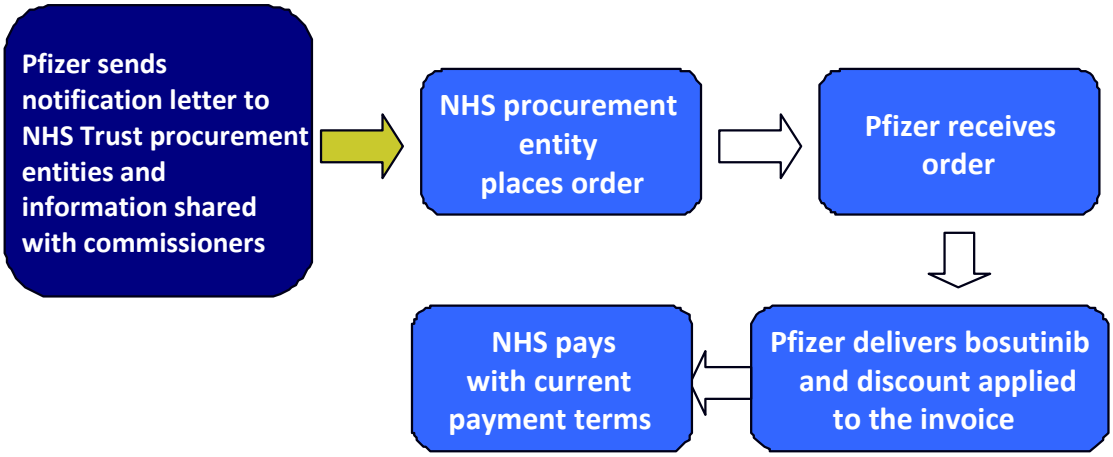
3.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

The discount will be applied at the point of invoice.

3.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will be applied at the point of invoice.

3.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

The proposed patient access scheme is conditional upon the receipt of positive NICE guidance for the use of bosutinib as treatment option for adult patients with chronic phase (CP), accelerated phase (AP) and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, and upon the treatment of the scheme as confidential.

Pfizer reserves the right, to change or terminate this Agreement with the consent of the Department of Health (such consent not to be unreasonably withheld) by giving no less than three (3) months' notice in writing. In the unlikely event that Pfizer exercises this right, Pfizer will use reasonable endeavours to discuss and work with the appropriate parties within the NHS and Department of Health to put in place an appropriate plan to manage the impact on NHS patients who are already receiving Bosulif under this scheme. For the avoidance of doubt, the main circumstances envisaged where Pfizer may terminate this scheme may include but are not limited to the withdrawal of NICE positive guidance in respect of Bosulif or a breach of this agreement which in Pfizer's reasonable opinion presents a significant risk of the discounted priced being referenced by another country.

3.11 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme taking into account current legislation.

3.12 If available, please list any patient access scheme/ commercial access agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Not applicable.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

Not applicable

4 Cost effectiveness

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

In technology appraisal guidance (TAG) 299 "*Bosutinib for previously treated chronic myeloid leukaemia*" (9) the most plausible incremental cost effectiveness ratios (ICERs) as judged by the Committee were:

- Chronic phase (CP): £43,000/QALY (section 4.18);
- Accelerated phase (AP): £58,000/QALY; End-of-Life criteria applicable (section 4.19, section 4.22);
- Blast phase (BP): £60,000/QALY; End-of-Life criteria applicable (section 4.19, section 4.22).

The assumptions reflected in these ICERs are discussed in detail below.

In TAG299, the Committee concluded that the key uncertainties in the estimates of cost-effectiveness were those related to the assumptions regarding bosutinib's expected survival benefit, namely: (1) the overall survival estimates for bosutinib and hydroxycarbamide after bosutinib; and (2) whether a post-treatment benefit would be expected with bosutinib.(section 4.11, TAG299 (9)).

To model the overall survival of patients on bosutinib, Pfizer originally presented the "surrogate approach". This method assumed a relationship between the surrogate outcome "major cytogenetic response" and "overall survival" using the same approach used by the assessment group in TA241, and attributed a considerable post-treatment benefit to bosutinib in chronic phase CML.

By contrast, the ERG presented the "cumulative survival approach". This method assumed that there was no post-treatment benefit for bosutinib patients, and derived OS by adding time on bosutinib treatment to the OS for hydroxycarbamide.

Both modelling approaches are associated with uncertainty. The ERG's "cumulative survival approach" assumed zero post-treatment benefit for patients on bosutinib. This assumption is counter to the position put forward by the CML Support Group (CMLSG) during the appraisal, which suggested that there might be a reduced disease load at the point of bosutinib discontinuation relative to disease load at the start of bosutinib treatment, and which the Committee considered plausible (section 4.14, TAG299 (9)). Conversely, the Committee agreed that the opportunity for a clinical benefit from bosutinib to persist beyond treatment would be limited in clinical practice, restricting the appropriateness of the "surrogate approach". Ultimately, although the exact magnitude of the anticipated clinical benefit associated with bosutinib after treatment discontinuation could not be quantified, the Committee agreed that on the basis of the presented evidence, post-treatment benefit could reasonably be argued to be 1 or 2 months (section 4.14, TAG299 (9)).

As a consequence of the above conclusion, the Committee's preferred modelling approach ("cumulative survival") necessarily represents a conservative estimate for the cost-effectiveness of bosutinib. In this submission, all new ICERs presented incorporate the necessary amendments to the model to adopt the "cumulative survival" methodology, and should therefore be judged as the maximum upper bounds of the most likely ICERs for bosutinib.

Further changes have been made to the model in light of the feedback provided in TAG299 (9), which reflect key conclusions made by the Committee. These are listed below, and summarised in Table 1:

- We have removed interferon alfa as a comparator in line with feedback in section 4.17 of TAG299 (9), which reflects that both the Committee and CMLSG agreed that interferon alfa is rarely used in the NHS in England.

- We have removed stem-cell transplant (SCT) as a comparator based on the Committee's feedback that SCT was an option for a minority of patients only, and would be likely to be used after all tyrosine kinase inhibitor options had failed (section 4.3 of TAG299 (9)). This aligned to the views of the CMLSG

during consultation that people would be likely to try all tyrosine kinase inhibitor options before SCT (TAG 4.15).

- Where relevant, we have assumed that the most plausible survival estimate for hydroxycarbamide in the chronic phase was 3.5 years, in line with the Committee's conclusion (section 4.13 of TAG299 (9)).

- Utility values derived directly from the bosutinib pivotal study (Study 200) are used as the base case in this resubmission. EQ-5D-3L utilities from Study 200 (scored using the UK tariff) became available during the original NICE appraisal (TA299), and were only incorporated in the final models submitted to NICE at the ACD response stage.

- Costs have been updated to reflect 2014/2015 values (based on NHS Reference Costs or inflation indices from PSSRU where appropriate).

Table 1 Assumptions in the economic model

Assumption	Original company model	Appraisal Committee's preferred assumption
Approach to survival modelling	Based on the "surrogate survival approach". This method assumed a relationship between the surrogate outcome "major cytogenetic response" and "overall survival" using the same approach used by the assessment group in TA241, and attributed a considerable post-treatment benefit to bosutinib in chronic phase CML	Based on the "cumulative survival approach" – implemented as the base case for Pfizer's new submission. This approach was proposed by the ERG, and preferred by the NICE Committee (TA299). This method derived OS by adding time on bosutinib treatment to the OS for hydroxycarbamide. It assumed that there was no post-treatment benefit for bosutinib patients, and therefore represents a conservative estimate for the cost-effectiveness of bosutinib. The "cumulative survival approach" was explored in the model for the ACD response by using the PFS times for each treatment in an ad hoc manner. Following the FAD, the "cumulative survival approach" method was implemented formally in modelling, taking in to account the effects of discounting. This revised model was then used for a SMC resubmission in 2014, and it is now utilised for this submission to NICE. The current model assumes that the most

Assumption	Original company model	Appraisal Committee's preferred assumption
		plausible survival estimate for hydroxycarbamide when taken third line or later is 3.5 years, in line with the Committee's conclusion. Any potential benefits following treatment discontinuation from bosutinib (1 or 2 months based on the Committee's feedback) are only explored in sensitivity analyses. Pfizer's revised modelling approach yields ICERs similar to those reported in TA299 (including the previously proposed PAS).
Survival estimates associated with hydroxy. in CP	OS for hydroxycarbamide in the chronic phase (3.5 years) was taken from a model used in TA241.	The Committee understood that the manufacturer's estimate was 3.5 years in the base-case analysis, compared with the ERG's estimate of 7 years. The Committee considered comments received from the CMLSG that, because the most likely line of treatment with bosutinib would be third or later, overall survival with hydroxycarbamide (if taken at this point in the treatment pathway) was more likely to be at the lower end of the 3.5-year to 7-year survival range The Committee was persuaded by the comment from the CMLSG and concluded that the most plausible survival estimate for hydroxycarbamide when taken third line or later was 3.5 years.
Comparators	Comparisons made against hydroxycarbamide, interferon alfa and stem cell transplant	Comparison with hydroxycarbamide is the only comparison included in this submission, as it was felt to be the most appropriate comparator by the Committee and ERG, as noted in the FAD. Interferon alfa has been removed as a comparator as both the Committee and CMLSG agreed that interferon alfa is rarely used in the NHS in England. Although SCT was listed in the final scope, during the appraisal it became apparent that this was not a comparator for bosutinib; eligible patients would have been already offered SCT. When bosutinib was compared to SCT, it was either

Assumption	Original company model	Appraisal Committee's preferred assumption
		dominant, or highly cost effective, depending on the assumptions used.
Costs	The original submission to NICE was made in 2012, and use NHS reference costs from 2010/2011.	The costs in the model have been updated to the latest NHS reference costs (2014/15). Other costs have been updated to current costs using inflation indices from the PSSRU 2015.
Utilities	The original submission to NICE used utilities from the IRIS study, a study of imatinib at an earlier treatment line	Utility values derived directly from the bosutinib pivotal study (Study 200) are used as the base case in this resubmission. EQ-5D-3L utilities from Study 200 (scored using the UK tariff) became available during the original NICE appraisal (TA299), and were only incorporated in the final models submitted to NICE at the ACD response stage. These utilities were also used in the 2013 SMC resubmission.

4.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published 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 company 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/ commercial access agreement. You must also complete the rest of this template.

N/A

4.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic

model which includes the patient access scheme/ commercial access agreement.

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

Although according to this indication, bosutinib may be used in second-, third- or fourth-line patients where current TKIs have been unsuccessful due to intolerance or are inappropriate due to mutations or existing co-morbidities, bosutinib is more likely to be used as a third- or fourth-line TKI, as previously suggested by the Committee (section 4.2, TAG299 (9)). Bosutinib therefore offers a valuable alternative in the management of CML across all phases, where treatment is based on unmet need rather than line of therapy in patients whose current options are limited to best supportive care.

The data for the licensed indication are derived from Study 200, an open-label, phase I/II single-arm study of 546 Ph+ CML patients. Study 200 had multiple cohorts including 288 patients with CP CML in second line, 118 patients with CP CML in third line and 76 and 64 patients in second line or later AP and BP CML respectively. The clinical efficacy of bosutinib in all three phases of the disease was evaluated as part of the original health technology appraisal in 2013 (TA299), where the Committee concluded that bosutinib had shown efficacy in Study 200 in terms of haematological and cytogenetic response (section 4.6, TAG299 (9)).

The main clinical effectiveness parameters used in this submission remain unchanged. The primary efficacy outcome for the chronic phase population was rate of major cytogenetic response by 24 weeks. A major cytogenetic response means that less than 35% of bone marrow cells test positive for the Philadelphia chromosome. The primary outcome for patients with advanced phase CML was rate of attainment or maintenance of overall haematological response by week 48. Overall haematological response was defined in the manufacturer's submission as any 1 of: complete haematological response, no evidence of leukaemia or a return to chronic phase. Secondary outcomes included complete cytogenetic response, complete haematological response, progression‐free survival and overall survival. For all

cohorts, analyses of the primary and secondary end points, except for progression‐free survival and overall survival, were carried out using the evaluable population. The evaluable population was defined as all enrolled patients who received at least 1 dose of bosutinib and had an adequate baseline efficacy assessment.

The primary uncertainties we seek to address in this resubmission are the Committee's concerns regarding the long-term survival associated with bosutinib. This is achieved by implementing the preferred ERG modelling assumptions and implementing the "cumulative survival approach" method as previously described to generate a maximum upper-bound of the most plausible ICERs for all phases of CML.

4.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'.

Not applicable. The scheme is simply applied as a discount.

Table 2 Costs associated with the implementation and operation of the patient access scheme (PAS)/ commercial access agreement (CAA)

	Calculation of cost	Reference source
Stock management		
Administration of claim forms		
Staff training		
Other costs…		
…		

…		
Total implementation/ operation costs		

4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable. The scheme is simply applied as a discount.

Table 32 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)/ commercial access agreement (CAA)

	Intervention without PAS/ CAA		**Intervention with PAS/ CAA**		**Reference source**
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
…					
…					
Total treatment-related costs					

Summary results

New base-case analysis

4.6 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

A suggested format is shown below (table 4).

CHRONIC PHASE

Table 4a New base-case cost-effectiveness results using the price as in the published technology appraisal (i.e. "cumulative survival approach", including previous PAS): chronic phase

	Bosutinib	Hydroxycarbamide
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 4b New base-case cost-effectiveness results using the patient access scheme/ commercial access agreement (i.e. "cumulative survival approach", including newly proposed PAS): chronic phase

	Bosutinib	Hydroxycarbamide
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

ACCELERATED PHASE

Table 4c New base-case cost-effectiveness results using the price as in the published technology appraisal (i.e. "cumulative survival approach", including previous PAS): accelerated phase

	Bosutinib	Hydroxycarbamide
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4d New base-case cost-effectiveness results using the patient access scheme/ commercial access agreement (i.e. "cumulative survival approach", including newly proposed PAS): accelerated phase

	Bosutinib	Hydroxycarbamide
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

BLAST PHASE

Table 4e New base-case cost-effectiveness results using the price as in the published technology appraisal (i.e. "cumulative survival approach", including previous PAS): blast phase

	Bosutinib	Hydroxycarbamide
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4f New base-case cost-effectiveness results using the patient access scheme/ commercial access agreement (i.e. "cumulative survival approach", including newly proposed PAS): blast phase

	Bosutinib	Hydroxycarbamide
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.7 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

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 5.

- Results based on "cumulative survival approach", incorporating the newly proposed patient access scheme

CHRONIC PHASE

Table 5a presents the base-case cost-effectiveness results for bosutinib in the treatment of chronic phase CML based on the "cumulative survival approach", including the new patient access scheme. As described in section 4.1, the "cumulative survival approach" conservatively assumes zero post-treatment benefit for bosutinib patients, and therefore results should be judged as the maximum upper bounds of the most likely ICERs associated with bosutinib.

We believe this analysis demonstrates that bosutinib represents a cost-effective use of NHS resources compared to hydroxycarbamide in CML patients previously treated with one or more TKI, and for whom other available TKIs are not an option. More importantly, we have adopted a conservative approach and these results do not incorporate the Committee's feedback on the reasonable 1 or 2 months of post-treatment benefit associated with bosutinib (section 4.14, TAG299 (9)), which would be expected to lead to a lower ICER.

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

Table 5a New base-case incremental results using the previous patient access scheme: Chronic Phase

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

ACCELERATED PHASE

Table 5b presents the base-case results for the AP model. As with the chronic phase model, these results are based on the "cumulative survival approach", and therefore represent most conservative upper bound estimate of ICER for bosutinib, which should be considered an end-of-life medicine for this sub-population (section 4.22, TAG299 (9)).

Table 5b New base-case incremental results using the patient access scheme: Accelerated Phase

AP	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

BLAST PHASE

Table 5c presents the base-case results for the AP model. As with the chronic phase model, these results are based on the "cumulative survival approach", and therefore represent the most conservative upper bound estimate of the ICERs for bosutinib, which should be considered an end-of-life medicine for this sub-population (section 4.22, TAG299 (9)).

Table 5c New base-case incremental results using the patient access scheme: Blast Phase

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

- Validation of results: Results based on “cumulative survival approach”, incorporating the previous patient access scheme (from TA299)

Results originally produced by the ERG, and subsequently reported in the TAG, have been use as a source of external validation for these model changes. As part of the original appraisal, the Committee discussed the most plausible ICER for bosutinib compared with best supportive care (noting its previous conclusion that it is appropriate to consider hydroxycarbamide as best supportive care; see section 4.1, TAG299 (9)). For the chronic phase, the Committee concluded that the most plausible ICER presented by the manufacturer and the ERG was £43,000 per QALY based on the cumulative survival approach (assuming 3.5 years of overall survival with hydroxycarbamide), within a range of £40,000 to £50,000 per QALY” (section 4.18, TAG299 (9)).

Table 5d below presents the results of Pfizer’s model adapted as described above to produced results based on a “cumulative survival approach” (that is, assuming no post-treatment benefit for bosutinib patients, where OS has been derived by adding time on bosutinib treatment to the 3.5 years OS for hydroxycarbamide). Results reported in Table 5d, which include the price for bosutinib considered as part of TA299, replicate the Committee’s most plausible ICER within a [redacted]% margin, and should therefore be accepted to demonstrate the validity of the structural changes implemented to incorporate the Committee’s preferred assumptions.

Table 5d New base-case incremental results using the price as in the published technology appraisal: Chronic Phase

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

For the accelerated phase and the blast phase, both of which were met NICE’s end of life criteria (section 4.22, TAG299 (9)), the Committee concluded that most plausible ICERs were £58,000 and £60,000 respectively (section 4.19, TAG299 (9)).

Results reported in Table 5e and Table 5f below detail the ICERs for accelerated phase CML and blast phase CML based on the “cumulative survival approach”, including the price for bosutinib considered as part of TA299. At [redacted] and [redacted] for accelerated phase CML and blast phase CML respectively, these results once again

align to the results produced by the ERG's model, and demonstrate the structural validity of the changes implemented in the model.

Table 5e New base-case incremental results using the price as in the published technology appraisal: Accelerated Phase

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5f New base-case incremental results using the price as in the published technology appraisal: Blast Phase

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

As stated above, all new ICERs presented incorporate the necessary amendments to the model to adopt the cumulative survival methodology, and should consequently be judged as the maximum upper bounds of the most likely ICERs for bosutinib.

- Validation of results: Comparison of Markov traces→ "Cumulative survival approach" (new submission) vs "surrogate survival approach" (TA299)

A comparison between the Markov traces for bosutinib based on the "cumulative survival approach" (used as part of this submission) and the "surrogate approach" (presented in TA299) is presented here to further illustrate the impact of the structural changes implemented in the model to incorporate the Committee's feedback. Figure 1 and Figure 2 demonstrate that no benefit has been assumed for bosutinib following treatment discontinuation, in line with the "cumulative survival approach". In contrast, Figure 3 and Figure 4 present the Markov traces associated with the "surrogate approach" as presented in TA299, where a relationship between the surrogate outcome "major cytogenetic response" and "overall survival" was assumed using the same approach presented by the assessment group in TA241. Figure 1 and Figure 2 should be interpreted as further evidence that the new results based on the "cumulative survival approach" represent the most conservative upper bound estimate of cost-effectiveness for bosutinib.

Figure 1 presents the Markov trace of the proportion of patients on bosutinib during CP, and demonstrates that no additional OS benefit has been assumed for bosutinib following treatment discontinuation.

Figure 1: Markov trace of bosutinib – cumulative survival approach –CIC

The Markov trace presented in Figure 2 demonstrates that the QALYs accrued by bosutinib are also restricted by the cumulative survival approach

Figure 2: Bosutinib QALYs accrued – cumulative survival approach - CIC

Figure 3 and Figure 4 present the Markov traces of the proportion of patients and QALYs accrued in each health state for bosutinib as presented in TA299, and it illustrates the additional benefit assumed by the surrogate approach.

Figure 3: Markov trace of bosutinib- surrogate approach (TA299) - CIC

Figure 4: Bosutinib QALYs accrued – surrogate approach (TA299) - CIC

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

Table 6a and Table 6b present scenario analyses exploring the impact of assuming one or two months of treatment benefit following discontinuation from bosutinib in the chronic phase, in line with the Committee's preferred assumptions. These analyses further demonstrate that bosutinib represents a cost-effective use of NHS resources compared to hydroxycarbamide by leading to lower estimates of the ICER, in CML patients previously treated with one or more TKI and for whom other TKIs are not an option.

Table 6a Scenario analysis: ICERs assuming 1 month post- treatment benefit (chronic phase)

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6b Scenario analysis: ICERs assuming 2 months post- treatment benefit (chronic phase)

	Discounted Totals			Discounted Incrementals			ICER
	Costs	QALYs	Life years	Costs	QALYs	Life years	
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic results based on 1,000 probabilistic simulations are presented in Table 7 for the chronic population, and compared to the deterministic results. The number of probabilistic simulations reflects the stability of the PSA results.

Table 7 Deterministic vs Probabilistic point estimates

	Total		Incremental		ICER	ICER v Hydroxycarbamide
	Cost	QALYs	Cost	QALYs		
Deterministic results						
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results						
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A probabilistic scatter plot is presented in Figure 1 below and a cost-effectiveness acceptability curves in Figure 2

Figure 1 Cost-effectiveness scatterplot – CIC

Figure 2 Cost-effectiveness acceptability curves - CIC

4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a 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

5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Documents submitted to PASLU as part of the PAS application have been included with this submission.

5.3 Details of outcome-based schemes

5.3.1 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.

5.3.2 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.

5.3.3 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.

5.3.4 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.

5.3.5 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.

5.3.6 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.

5.3.7 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.

5.3.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.3.9 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.

References

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(2) Kantarjian H, O'Brien S, Jabbour E et al. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood. 2012 Mar 1;119(9):1981-7

(3) Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011 Oct 27;118(17):4567-76

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(5) Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012 Apr 12;119(15):3403-12

(6) Redaelli S, Mologni L, Rostagno R et al. Three novel patient-derived BCR/ABL mutants show different sensitivity to second and third generation tyrosine kinase inhibitors. Am J Hematol. 2012 Nov;87(11):E125-8

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European Hematology Association (EHA). June 13–16, 2013. Stockholm, Sweden.

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(10) Baccarani M et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013; 122:872-884

(11) British National Formulary (BNF). Available at www.bnf.org. Accessed February 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

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.

A template that has had no responses added to any of its ten sections is six pages in length, we assume that restricting the 'length of our response' to ten pages discounts that already occupied before a response is added.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Chronic Myeloid Leukaemia Support Group (CMLSG)

Your position in the organisation: [redacted]

Brief description of the organisation:

(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.

CMLSG is the only UK registered charity (Reg No 1114037) with a sole focus on CML. It is patient lead with its Director and three of our Trustees being CML patients. Because of the rarity of CML (incidence 1 to 1.5 cases per 100,000), CMLSG operates primarily, but not exclusively, online. Our objective is to offer support, information and advocacy to CML patients and those that care for them, so that they can resume a life as close as possible to that lived before diagnosis. 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.

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 it like to live with the condition or what do carers experience when caring for someone with the condition?

The use of TKIs has transformed the outcomes for CML patients over the last 15 years. CML has moved from being an acute condition with a high mortality rate to a chronic, long term condition for the overwhelming majority of patients most of whom can expect a life expetancy near to the norm. For these patients living with the condition revolves around management of side effects (which can vary from patient to patient and differ between drugs over the course of an invidual's treatment) that accompany any drug based treatment.

For those patients unable to obatin an optimal response to the TKIs that are routinely avaiable in the NHS in England, the search for a TKI that can do so brings with it understandable anxiety and stress given that CML, without an effective treatment, remains a malignant condition. This anxiety is shared by those that care for them.

Given the high risks involved, all patients are fearful of the only non TKI treatment routinely available, Stem Cell Transplantation (SCT), and would regard it as a treatment of last resort after all TKIs have been either considered or used.

For those for whom an SCT would be considered, many would not qualify either because a matched donor cannot be located before the disease progresses, or their clinical profile disqualifies them.

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.

Given the invariably fatal outcome if left untreated, it is axiomatic that the primary outcome most important to patients is survival. Should an optimal response be obtained following treatment with a TKI that is routinely available

in the NHS in England, securing a quality to of life similar to that present before disease onset is the next most important priority for patients.

Third would be a resumption of public life within their social networks and community and including employment if applicable which, given the median age at diagnosis is 55, is a relevant consideration.

For carers, the greater the distance travelled along this three stage continuum the better, since this brings successive decreases in the caring burden placed upon 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?

Currently out of the five TKI based treatments, only two are routinely available in the NHS in England with NICE recommending both (standard dose) imatinib and nilotinib in first line (TA 251) and nilotinib in second line (TA 241).

By far the most pervasive treatment in first line is imatinib and approximately 60% of patients obtain an optimal response following imatinib use. When nilotinib is used in 2nd line, around 50% of patients are also able to obtain an optimal response.

For the rapidly diminishing number who do not obtain an optimal response to either imatinib or nilotinib; dasatinib, bosutinib and ponatinib are also available, but only via an application by their clinician to the the Cancer Drugs Fund (CDF) and then only if more restrictively defined criteria than those of each drugs EMA license are met.

For the remaining tiny number of patients left who are unable to obtain optimal response with any TKI, an SCT remains the only other treatment option.

Acceptability/non acceptability considerations revolve around the costs paid (of side effects experienced) set off against benefits gained (by securing an optimal response) with judgements on cost-benefit resolution being highly individual.

As an organisation our view is that the small number of patients who are either unable to tolerate, or are resistant to, imatinib and/or nilotinib should not be disadvantaged in the treatment options available to them by the highly conditional access provided by the CDF.

For example, Bosutinib has been the subject of six evaluations between (its CDF entry evaluation) May 2013 until September 2015 and has, over this period seen successive reductions in its access criteria.

Ponatinib is only available via application to the CDF for patients with the T315i mutation, with dasatinib being only available within the CDF to patients intolerant of imatinib and/or nilotinib.

This diminution of access has resulted in a clinical environment in England that is diverging from rather than converging towards the consensus position arrived at by leading European CML specialists in 2013 (ELNet/European Leukaemia Network Recommendations for the treatment of CML).

CMLSG's goal is to see both a convergence towards and compliance with ELNet recommendations become a routine reality for patients, with an aspiration that this Rapid Reconsideration marks one step towards that goal.

For the record we also support the four applications made to the CDF Panel in 2014 by two specialist clinicians which the Panel declined to score and instead opted for an action plan (in July 2014) it requested the NHSE Chemotherapy Clinical Reference Group (CRG) to implement. As of the date of this submission we are still waiting (twenty month later) for a response to our request in February 2016 for an update on progress.

Had these applications been successful, access in England would have moved much closer to the ELNet recommendations.

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.

The primary benefit is the possibility for patients whose clinicians consider it an appropriate treatment, to first obtain a Major Cytogenetic Response (MCyR) within the first three months of starting therapy, which constitutes the entry level optimal response for patients.

Second, bosutinib as a second generation (2G) TKI offers, with its fellow 2G class members, the possibility of a faster and deeper response towards the more developed optimal response sought by clinicians and patients, namely a Major Molecular response (MMR) within 6 - 12 months.

Third, bosutinib, like all TKIs, is sensitive to specific oncogene mutations (notably Y253H) whereas other TKIs are sensitive to other mutations with each TKI having a portfolio of ‘resistant mutations‘ they are sensitive to and of course the obverse.

Fourth, bosutinib treatment seems to cause fewer side effects for most patients. Effective clinical counter measures are now deployed in mitigation of its most common, but short-lived, side effect (diarrhoea). Cardio vascular side effects of some other TKIs that present the greatest clinical challenge to the management of CML are not seen with bosutinib, neither are the effects to the plural cavity.

Fifth, bosutinib is a once a day, oral, home based treatment which does not require a fasting regime prior to use. Visits to hospital units are regular but infrequent once an optimal response has been obtained.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Advantages compared to:

Imatinib: bosutinib use is capable of delivering a faster and deeper response which means an optimal response of MMR within 3 months is more likely.

Nilotinib : unlike nilotinib, bosutinib use is not associated with cardio vascular adverse events (AEs).

Dasatinib: bosutinib is not associated with the development of pleural effusion which is a more common and recurrent side effect of dasatinib.

Ponatinib: unlike ponatinib, bosutinib use is not associated with cardio vascular AEs.

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.

Please list any concerns patients or carers have about the treatment being appraised.

The most commonly articulated concern is with the onset of diarrhoea that frequently and very quickly manifests itself during the initial stage of treatment. However management of this side effect is now well developed and discontinuation of treatment highly unlikely. Once this stage has passed, this side effect ceases to be an issue for most patients.

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.

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.

Yes.

For patients who are not able to obtain an optimal response within 3 months (minimally MCyR) following treatment with other TKIs, or who are unable to tolerate treatment and who are not judged clinically fit to undertake an SCT or for whom a suitably HLA matched donor is not able to be identified; bosutinib represents the sole remaining treatment option that offers the possibility of securing an optimal response. For such patients, bosutinib offers a therapeutic response to their clear unmet need.

For some patients, bosutinib treatment represents the least worst option in terms of side effects. It is in effect their TKI of choice.

Are there any groups of patients who might benefit less from the

treatment than others? If so, please describe them and explain why.

Yes.

For patients with a clinical profile that includes any gastro intestinal problems bosutinib represents the last option of choice

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 - we will leave a response to his section to the clinical experts

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.

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.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes but with a qualifier ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Bosutinib treatment is innovative in so far as it has been proven to be clinically effective for a sub group of the CML patient population who are either resistant to or are unable to tolerate all other licensed TKIs.

It is not innovative in the sense that it represents a step change in approaches to the treatment of CML.

Are there any other issues that you would like the Appraisal Committee to consider?

One key development in the treatment of CML over recent years has been a focus on dose reduction and, in some cases, TKI treatment cessation for

patients who have achieved significant levels of optimal response and maintained such levels over time.

Two Clinical Trials are underway in the UK (SPIRIT III and DESTINY) that explore this (and other) issue (s).

Results from other studies elsewhere with a similar focus seem to confirm a significant number of patients that fall in this class can reduce their daily dosage without losing their optimal response and an even smaller group can also cease their treatment altogether again without a loss of response.

The scope for dose reduction across the CML patient population in England is not yet known neither is the size of the consequent reduction in TKI expenditure but it seems it would be considerable.

The same reduced expenditure situation applies with the expiry of the patent granted to Glivec (imatinib) in December 2016 and the consequent availability of generic imatinib at a significantly reduced price than that currently in place.

Since affordability issues seem an increasing concern for NICE we would argue the Committee should consider the impact of both of these issues on future 'whole population' treatment costs. In this case, the effect of the budget impact arising from bosutinib dose reduction and cessation on NHS resource use..

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- A clear unmet need exists for the very small number of patients resistant to or intolerant of all other licensed TKIs for whom bosutinib is judged to be an appropriate treatment by their clinicians and for whom an SCT is not considered a feasible treatment option.
- A sub set of the above unmet need patient population are those patients exhibiting specific mutations against which bosutinib is particularly effective. As with ponatinib, a mutation specific recommendation for use in

the NHS in England is possible should the capture in the first bullet be considered to be too broad.

- Of all the 2G (and third generation ponatinib) TKIs, bosutinib is the TKI likely to be best tolerated by most patients given the side effects following treatment, especially after the initial phase, tend to be mild making clinical management less onerous for busy medical professionals.
- Given bosutinib is very well tolerated, its once a day, oral, home based delivery regime adds to its appeal to patients as an effective drug that is easy to live with which in turn reduces the burden on those that care for them.
- The success in treating CML over the last 15 years has resulted in a current focus on securing the promise offered by personalised medicine for the patient population. The personalised medicine mantra of ‘the right drug, at the right dose, at the right time for the right patient’ neatly summarises the approach made possible by advances in the life (and information technology) sciences. We believe the treatment of CML leads the way in this approach to oncology and should be supported by a positive recommendation for its use in the NHS.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

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 syndrome, 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 all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line (including a Nurse Advisor)
- 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 purely on 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 wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our annual 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

(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:

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?

Chronic myeloid leukaemia (CML) is a rare form of leukaemia with approximately 700 people diagnosed in the UK each year (714 UK, 624 England, 33 Wales).

Untreated chronic myeloid leukaemia (CML) is a fatal disease. If left untreated, patients will progress through symptoms, which gradually increase in severity. These symptoms include chronic fatigue, anaemia, loss of appetite, loss of weight, progressive bleeding and bruising. If left untreated these symptoms will worsen until the patient reaches a point of immune-compromise where they can no longer fight infection and will succumb to their disease. Depending upon the state of the disease at diagnosis, if untreated, this could take between 3-5 years.

Due to the often gradual onset of symptoms, diagnosis can come as a complete shock. Patients living with CML report a significant emotional impact requiring emotional support. In particular, due to the small numbers affected by this condition, patients often report feeling “helpless” and “isolated”.

“Being diagnosed with leukaemia is very scary! Not just for me, but for my family as well.”

Such feelings do not remain with the patient alone but causes a “ripple effect” felt by their carers and families. Caregiver duties often include ensuring the patient attends medical appointments, ensuring the patient takes outpatient medication and to generally monitor their wellbeing and any changes in their condition. Furthermore, carers often spend time researching potential treatment options for their partner or relative, familiarising themselves with treatment side effects, remaining treatment options and patient outcomes. Any improvement in access to treatment for CML will therefore have a wider beneficial impact than just the patient group in question.

Before 2001, treatment options for CML were extremely limited, until the launch of tyrosine kinase inhibitors (TKIs) which revolutionised the treatment of CML. Patients diagnosed today that respond to first or second-line treatment with TKI's (imatinib, nilotinib or dasatinib) will enjoy a normal life-span with good quality of life. However, there are a small group of patients who fail to respond to, have developed resistance to, are unable to tolerate, or who are contra-indicated for these options. These patients have an unmet medical need as without access to further treatment, CML remains a potentially fatal disease.

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.

From a patient perspective, the most important treatment outcomes will include survival, response rates and quality of life (including symptom control and side effects of treatment.

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?

The standard treatment for CML is a tyrosine kinase inhibitor (TKI). These include imatinib (Glivec®), nilotinib (Tasigna®), dasatinib (Sprycel®), bosutinib (Bosulif®) or ponatinib (Iclusig®). To date, only imatinib and nilotinib have been recommended for use by NICE. For those patients who respond to treatment with these options patients will achieve normal life expectancy with high quality of life.

A stem cell transplant is an option for fit patients who have exhausted other treatment choices but it is associated with high morbidity and mortality and requires a matching donor so it is only suitable for a very small group of patients.

Unfortunately, not all patients will respond to (or develop resistance/unable to tolerate/are contra-indicated) currently approved TKI options. However, dasatinib, bosutinib and ponatinib are currently available to patients via the

Cancer Drugs Fund. Should funding for these treatments be removed, options for patients in this setting will be limited (equivalent to those before the introduction of TKIs in 2001). Patients being considered eligible for bosutinib will have already exhausted their alternative treatment options. Patients in this setting would otherwise be likely to receive best supportive care with further progression of the disease and ultimately death.

In effect, a lack of access to these treatments would mean that patients in this setting are left without a realistic treatment option, unless bosutinib is available. It is imperative that on equity grounds treatment is provided for patients for whom, previous treatment is not effective, not tolerated, resistant to previous treatment, or contra-indicated due to pre-existing medical conditions.

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, over other NHS treatments in England.

By the time they become eligible for treatment with bosutinib they will have exhausted their other TKI options. As such, in the absence of bosutinib patients will be facing a fatal disease without access to a realistic treatment.

If patients continue to be able to access bosutinib (and respond to treatment) there are a number of potential benefits. Bosutinib is an oral preparation, which can be taken at home once a day, with food, and is convenient from both a patient and carer perspective. Patients responding to TKI's (including bosutinib) generally have excellent symptom control, with manageable side effects for most patients. Bosutinib also has a different side effect profile to previous options, so for those unable to tolerate previous options, bosutinib offers this key benefit (and is generally well tolerated). Some TKIs cannot be taken due to co-morbidities and adverse effects so this provides a further option. For example nilotinib may not be appropriate for patients with diabetes, because of its twice daily fasting requirement.

For patients that respond, they will expect to live as near normal a life as possible. Patients can maintain independence, self-care and dignity. 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.

For all CML patients and carers, knowing that there is a third line option treatment available (bosutinib) 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 bosutinib, for whom it could be the difference between survival or not, is obvious. Additionally this would avoid the experience of patients being told that there are realistically no further reimbursable treatment options. The psychological outlook of the patients, carers and the patients' extended family/friends and indeed all the healthcare professionals involved in the treatment of those patients would be impacted by the availability of this treatment 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.

N/A

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.

At present there are a few different treatment options in NHS England (approved by NICE or available via the CDF). They key concern about current NHS treatments is that access will be restricted should NICE decide not to recommend the use of bosutinib.

In this situation patients would be left facing a fatal disease without access to an effective treatment option. As not all patients respond to (or are able to tolerate) treatment with imatinib, nilotinib or dasatinib, it is imperative that there are numerous options available so that all patients can benefit.

Please list any concerns patients or carers have about the treatment being appraised.

Patients have reported side-effects from treatment with bosutinib, although these have generally been mild and manageable. Common side effects included diarrhoea, anaemia, low platelet levels, headaches, nausea and abdominal pain.

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.

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.

Patients who fail to respond to, have developed resistance to, are unable to tolerate, or who are contra-indicated for previous treatment options.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

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.

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.

Bosutinib has been assessed and recommended for use by the Scottish Medicines Consortium (SMC). If NICE were to not recommend its use and consequently prevent access to a drug which is currently available through the CDF, it would create unacceptable regional variation in access to treatment. These are the sort of 'postcode lotteries' that NICE was created to prevent, not create.

https://www.scottishmedicines.org.uk/SMC_Advice/Advice/910_13_bosutinib_Bosulif/bosutinib_Bosulif_Resubmission

Additionally, as bosutinib is currently available to patients via the CDF a decision not to recommend bosutinib and prevent access for future patients, but retaining access for existing patients, would be inequitable as patients would be discriminated against based upon the date they started treatment.

Finally, stem cell transplantation is an option for fit patients, but requires a matching donor. As such, it may create an equality issue for specific ethnic minorities (where finding a matched donor may be more problematic).

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.

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

As the first targeted therapies for CML, we consider all tyrosine kinase inhibitors (TKIs) to be innovative. TKIs (including bosutinib) have transformed the treatment of CML from a fatal disease into a chronic condition with normal life expectancy for those that respond to treatment.

Are there any other issues that you would like the Appraisal Committee to consider?

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.

- 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”. Without effective treatment, these symptoms will worsen until the patient reaches a point of immune-compromise where they can no longer fight infection and will succumb to their disease. Depending upon the state of the disease at diagnosis, this could take between 3-5 years.

- 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. It is imperative that on equity grounds that TKI treatment is provided for patients who fail, become resistant to, are unable to tolerate, or are contra-indicated to previous treatment options. It bosutinib is not recommended by NICE (and withdrawn from CDF funding) there will be limited alternative options. These patients represent an unmet medical need as they would be left facing a fatal disease without access to effective treatment.

- Bosutinib has demonstrated substantial efficacy, durable outcomes and acceptable tolerability, with mild and manageable side effects. Bosutinib is an oral preparation, which can be taken at home once a day, with food, and is convenient from a patient and carer perspective, reducing the need for hospital attendance and giving patients independence and dignity. Bosutinib also has a different side effect profile to previous options, so for those unable to tolerate previous options, bosutinib offers this key benefit. Some TKIs cannot be taken due to co-morbidities and adverse effects so this provides a further option. For example nilotinib may not be appropriate for patients with diabetes, because of its twice daily fasting requirement.

- For all CML patients, the knowledge that there is access to additional options (bosutinib) should they need it will have a huge impact on their psychological wellbeing, even though only a few will ever need to access the treatment. Although bosutinib may only be needed by a relatively small number of patients, it is a valuable treatment option for those who need it.

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] **submitting on behalf of**

Name of your organisation: NCRI-RCP-ACP

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Chronic myeloid leukaemia is currently treated with tyrosine kinase inhibitors (TKIs) in the NHS. 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. Eligible patients are also offered National Studies, that compare one TKI against a second or third line TKI (for eg the upcoming SPIRIT3 NCRI study, which will compare Imatinib against Dasatinib and Nilotinib as first line therapy).

Approximately 75- 80% of patients respond satisfactorily to Imatinib / Nilotinib and achieve complete cytogenetic responses, but the remaining 25% of patients either cannot tolerate the drugs due to side effects and toxicity, or are refractory to these drugs and fail to achieve adequate responses. One cause of a failure to respond is the acquisition of bcr-abl mutations which prevent the binding of, or block the action of the tyrosine kinase inhibitor. There are over 40 bcr-abl mutations reported in the literature, and there are known sensitivities of the different drugs to these mutations e.g. patients with a specific mutation may be much more likely to respond to one drug than another. The true efficacy of an individual TKI can be judged by the number of patients that continue to receive the drug after a number of years. After 7 years of first line imatinib therapy, only 60% of patients remain on imatinib for the reasons mentioned. 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.

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). 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 generally considered to have less activity than Nilotinib and is inactive in the presence of many of the known bcr-abl mutations. Unfortunately the other licensed 2nd line tyrosine kinase inhibitors, Dasatinib, Bosutinib, and Ponatinib have not been approved by NICE for 2nd line use.

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Since an increasing number of patients are now receiving Nilotinib as a 1st line treatment, alternative TKIs are required 2nd line agent in these patients. Furthermore as Nilotinib is generally accepted as a more potent bcr-abl inhibitor than Imatinib, with activity in many but not all the known mutations, it would be futile to switch patients who have failed Nilotinib to Imatinib.

Currently the only fully approved treatment options apart from Imatinib and Nilotinib are Interferon or allogeneic haemopoietic stem cell transplantation. Interferon has a low response rate of 10-15% and a significant side effect profile, limiting its usefulness as a realistic alternative treatment for CML. Allogeneic bone marrow transplantation depends on a suitable fully matched donor being identified, and on the performance status of the patient being adequate: effectively ruling out patients over the age of 70 years and many patients from ethnic minority backgrounds. Furthermore allogeneic bone marrow transplantation is a complex treatment with a 10-15% transplant-related mortality and a significant number of patients may develop graft versus host disease resulting in significant comorbidities and the need for ongoing immunosuppressive treatments.

Dasatinib is currently only available for a limited number of patients who are either refractory or intolerant of Imatinib and also intolerant of Nilotinib through the Cancer Drugs Fund. However patients who are resistant to Niltotinib are not eligible for Dasatinib via the CDF. There is currently no availability of Dasatinib in Scotland. Bosutinib is also available via the CDF for a limited number of patients who have to have demonstrated intolerance to both Nilotinib and Dasatinib. It is however not available for patients who are resistant (have failed to respond) to either or both of these drugs eg due to the presence of Nilotinib resistant mutations, even though there is evidence that a significant number of such resistant patients would respond to Bosutinib (Study 200)

A further problem with the current restriction to Imatinib and Nilotinib for the treatment of CML is that there emerging evidence of a significantly increased risk of arterial thrombotic events, increased blood glucose and hypercholesterolaemia in patients treated with Nilotinib. This appears to be particularly prevalent in patients who are diabetic or already have other risk factors for cardiovascular disease. Effectively there are a number of patients with these comorbidities for whom Nilotinib may be contra-indicated. Since these co-morbidities are more likely to exist in an elderly population there will emerge an element of discrimination in older patients who are then limited to Imatinib as the only safe treatment for their CML. Neither Bosutinib or Dasatinib treatment is associated with an increased risk of cardiovascular events and would be a safer alternative in such patients, though Dasatinib can be causal in the development of pleural effusions and may be contraindicated in patients with severe pre-existing lung disease.

The proposed technology, bosutinib would offer an alternative drug treatment for patients who could not tolerate Imatinib or Nilotinib, or for patients who are refractory to these drugs. Further advantages of bosutinib include once daily dosing (improvement of compliance) and the greatest selectivity for bcr-abl

(lack of c-kit and PDGFR inhibition), unlike the other TKIs. Off-target signalling is felt to be responsible for a number of the side-effects on other TKIs. Bosutinib may therefore be the safest choice of drug for patients who have failed or are intolerant of Imatinib and have significant cardiovascular risk factors and / or diabetes in whom Nilotinib may be contraindicated

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with a high Sokal score may be at higher risk of being refractory to Imatinib treatment.
Patients aged over 70 years old or from ethnic minority backgrounds are less likely to be able to benefit from the alternative treatment of allogeneic bone marrow transplantation.
Older patients who have cardiovascular risk factors and / or diabetes at higher risk of a significant side-effect of nilotinib (and alternative TKIs) due to their co-morbidities would benefit from the technology.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The use of bosutinib would be restricted to secondary care and specialist clinics. There would be no requirement for additional professional input.

The technology
If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Bosutinib is not yet widely available in the NHS. So far its use has been restricted to clinical trials and via the CDF for a restricted number of patients. It has always been used for its licensed indication i.e as a 2nd or 3rd line treatment for CML although there have been some trials of first line use.

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.

The ELN 2013 and the NCCN CML guidelines leave the decision for 2nd line treatment for patients resistant or intolerant of their first line therapy up to the clinican and recommend the use of either Nilotinib, Dasatinib or Bosutinib bosutinib. There is published data from the Study 200 which confirms the efficacy of Bosutinib as a second line agent after failure / intolerance to either Nilotinib or Dasatinib and indeed as a third line drug after failure / intolerance to both of these agents.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bosutinib for previously treated chronic myeloid leukaemia

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology will be straightforward to use once it becomes available since it is a simple once daily tablet taken as an out-patient. There are no required concomitant medications or other clinical requirements. It would certainly be much simpler for patients than the alternative treatments of BMT or interferon. Monitoring of treatment response is the same as for the other well established tyrosine kinase inhibitors.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Bosutinib treatment would be similarly monitored by bone marrow cytogenetics and regular q-PCR testing for bcr-abl as is standard for the other TKIs. No additional testing is necessary. Patients who are intolerant, or failing to respond (by ELN criteria definition) after 6 months of treatment, would be recommended to stop and other treatment options considered. Responding patients are currently recommended to continue the tyrosine kinase inhibitors indefinitely. However, there is currently interest in discontinuation of TKIs for patients who achieve complete molecular remissions as a proportion of these appear to remain disease free. Currently this should only be done in the context of a clinical trial, and only about 10% of CML patients are thought likely to have good enough responses to consider this approach but it is not yet standard practice.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials that have been done with bosutinib in the 2nd and 3rd line settings are comparable to those observed in routine clinical practice in the UK. The bosutinib trials were conducted in a similar way to the other TKI studies. The drug was shown to be effective in inducing complete cytogenetic remissions in 41% of patients who were resistant or intolerant of imatinib and in 21% of patients who had failed both imatinib and either nilotinib and dasatinib. Achievement of complete cytogenetic remission is associated with survival in CML patients so is a valid predictor of long term outcome.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The studies report a low level incidence of adverse reactions to the drug which are rarely above Grade 2 and can usually be managed with supportive measures. Some of these side effects appear to be self limiting e.g. those related to GI toxicity. Importantly, all the side-effects are reversible, which is sometimes not the case with alternative TKIs. No new side effects have subsequently become apparent.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There would be no significant issues in terms of the delivery of care for these patients if the technology was approved. There are no specific educational or training requirements for NHS staff and no additional resources would be required. A positive NICE guidance would allow equity of access to all patients requiring the technology.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

The approval of this technology would allow additional treatment options to be made available for older/unfit patients and those from ethnic minorities who are currently unable to benefit from allogeneic haemopoietic stem cell transplantation which is currently the only existing alternative treatment for those who fail or are intolerant of both Imatinib and Nilotinib.
Furthermore, allowing clinicians the option of choosing Bosutinib as an alternative 2nd line treatment instead of Nilotinib for patients with comorbidities (in particular those with diabetes and/or cardiovascular disease) who are at high risk of/experiencing significant peripheral vascular disease, ischaemic heart disease or cerebrovascular disease on Nilotinib will have significant benefits for these patients and the health service with regards to future morbidity and medical interventions required.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

Your name: [redacted]

Name of your organisation:

NCRI CML Working Party, Royal College of Physicians, 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)?

√ 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)?

Professor of Haematology and Honorary Consultant Haematologist

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No

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) is a triphasic disease characterised by the presence of the Philadelphia chromosome which itself contains the fusion oncogene BCR-ABL1. This gene encodes a dysregulated tyrosine kinase with enhanced auto-phosphorylation. The majority of patients (>90%) present in the relatively stable chronic phase (CP) but without treatment the disease progresses to a terminal blast crisis (BC), usually through an intermediate stage known as acceleration. CML-BC is uniformly fatal with a life expectancy of less than 5 years. The true incidence of CML in the UK is unknown but is probably just less than 1 per 100,000 population per annum. However, the prevalence of the disease has increased considerably in recent years because of the highly significant improvements in treatment.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

The prognosis of CML has changed so dramatically since 2000 that the majority of patients now have a normal life expectancy and this is solely due to the introduction of the tyrosine kinase inhibitors (TKI) that target the causative oncoprotein, Bcr-Abl1. The first of these was imatinib (1999), followed by the second generation agents dasatinib (2006), nilotinib (2007) and bosutinib (2010), and most recently the third generation drug, ponatinib. All the TKI rapidly normalise the blood count (complete haematological remission-CHR) in patients presenting in chronic phase. It also induces a considerable reduction in tumour load as evidenced by the loss of cells containing the Philadelphia chromosome when the bone marrow was examined by conventional chromosome analysis. This state is known as complete cytogenetic remission (CCyR) and is achieved in approximately 75% of patients after 18 months of treatment with imatinib, but more rapidly and in a higher percentage of patients treated initially with dasatinib or nilotinib. 40-60% of patients achieve a greater reduction in tumour load as indicated by the detection of the RNA encoding BCR-ABL1 only by highly sensitive molecular methodology (RT-PCR). This state is known as major molecular remission (MMR). In approximately 5% of patients the RT-PCR for BCR-ABL1 becomes negative indicating complete molecular remission (CMR).

Practice across the UK is largely uniform. Outside the context of a clinical trial, most patients presenting in CP are treated with imatinib although nilotinib is available and is often used for patients with poor prognostic features at diagnosis (using the Sokal/Hasford/EUTOS prognostic scores for CP). Excellent guidelines have been provided by an expert consensus group from the European Leukemia Net (ELN), first published in 2006 with revisions in 2009 and 2013. A further update is in preparation. These guidelines permit any of imatinib, dasatinib and nilotinib as first line treatment and set out milestones for response (which by definition include both depth of response and the time to that response).

For patients in England who fail their first line therapy for resistance or intolerance, further treatment in the UK is not straightforward. For the patient who starts treatment with imatinib, they can currently receive nilotiinib second line through normal commissioning. In fact the only drug they can get second line is nilotinib even if they have failed imatinib with a nilotinib resistant mutation (see later). This latter situation will inevitably result in failure due to resistance but bosutinib and dasatinib are only available for nilotinib intolerance. In summary the patient who fails imatinib with a nilotinib resistant mutation currently has no further treatment option.

For a patient who fails first line imatinib therapy due to resistance or intolerance, and who subsequently fails nilotinib due to resistance, there is no further drug treatment available, even though one or other of bosutinib or dasatinib will rescue 20-25% of these patients. In England patients who fail first line imatinib therapy due to resistance or intolerance, and subsequently fail nilotinib due to intolerance, can access dasatinib. However dasatinib is not available at all in Scotland. In England, patients can only be given bosutinib (which has equivalent efficacy to dasatinib and nilotinib in second and third line settings) if they are resistant or intolerant to imatinib, intolerant to nilotinib and subsequently intolerant to dasatinib.

For the patient who receives nilotinib first-line and fails due to resistance, there is no further drug therapy available.

Patients who are defined as intolerant to TKI, which by definition suggests that their disease is sensitive to TKI, have a number of TKI options. Unfortunately current drug availability requires them to move sequentially through drugs that might not be the most appropriate choice for the patient given pre-existing co-morbidities. The ideal situation would be the ability to choose the most appropriate drug for each patient.

None of these situations is satisfactory in 2016: with five drugs available we ought to be able to find a treatment that is both effective and tolerable for more than 85% pf patients who present in CP, and give them a near normal life expectancy. The remaining 15% will potentially benefit from allo-SCT but should not be offered this treatment with its inherent risk of death, without trying alternative TKI.

In large part the illogical and inappropriate pathway of TKI usage dictated by current NICE and CDF decisions has arisen from the sequential availability of the various drugs and the resulting independent evaluations of their relative place in management, not to mention their relative costs, This situation has been further complicated by the relatively recent emergence of potentially serious side effects of the second and third generation TKI, which require consideration not only of potential efficacy but also of the pre-existing co-morbidities of the individual patient.

The only other effective therapy for CML is allogeneic stem cell transplantation (allo-SCT) which carries considerable risk of mortality and in survivors, long-term morbidity, and should now be reserved for those patients who fail multiple TKI or who present in the more advanced phase. Prior to the introduction of imatinib the standard of care for the majority of patients with chronic phase CML was a life-long combination of hydroxycarbamide and interferon. Busulphan, an alkylating agent, was commonly used until the late 1980s and although this remains a useful cytotoxic agent in some situations, it became a less popular choice for early phase disease because of toxicity. With optimal use of interferon, approximately 10-15% of patients achieved CCyR. Patients who obtained a CCyR or even a partial cytogenetic response (> 65% Ph-negative) experienced a statistically significant improvement in survival compared to those with lesser or no cytogenetic responses. Unfortunately interferon is a poorly tolerated drug with both short and long-term side effects and in retrospect was probably used less frequently in elderly patients. The overall survival of patients treated with interferon is 6-7 years but the median survival of those who achieved CCyR on interferon is greater than 10 years. Exact data for patients in CCyR on interferon is no longer available as many converted to imatinib when it became available. These data remain critically important because they reflect the ability to use CCyR as an accurate prediction of long-term survival.

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?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

The goal of therapy has gradually changed over the past 15 years from immediate disease control, to an acceptance that most patients will have a prolonged life expectancy as long as they take TKI daily for life, to the realisation that some patients have such deep responses that they might eventually be able to stop TKI without disease recurrence. Several studies have shown that about 40% of patients with sustained deep molecular responses (currently about 30% of all patients) can discontinue treatment indefinitely. This has resulted in four broad patient groups:

1. Patients who present in acceleration or blast crisis (about 5-10%) who require immediate treatment with the most potent TKI, and ideally further management by allogeneic stem cell transplantation (allo-SCT) .

2. Patients presenting in CP who do not respond optimally to imatinib and require rigorous molecular monitoring and early change to another more potent TKI, to try to establish a deep response and avoid allo-SCT (about 20-25%).

3. Patients presenting in CP who respond well to imatinib but who do not achieve sustained deep molecular responses, and who might benefit from a change in TKI to deepen the response and/or abrogate the side effects of TKI (about 55-60%). This is the group where management strategies should focus on optimising quality of life to allow a return to normal daily activities.

4. Patients presenting in CP who achieve sustained deep molecular responses and can stop treatment (currently about 10-15%), normally after about 8 years of treatment with one or other TKI.

The groups that are likely to require an alternative TK to maintain maximum benefit (in terms of both efficacy and tolerability) are groups 2 and 3. These are the groups where access to bosutinib will be beneficial. As there are 4 alternative drugs to imatinib, there will be a mixture of drug usage, largely determined by the biology of the disease (determined by individual drug sensitivity), prior co-morbidities which might preclude certain drugs, and the emergence of side effects.

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)?

Specialist clinics in secondary or tertiary care, staffed by consultant haematologists and supported by clinical nurse specialists. Many patients who are responding well and whose medical team follow the ELN guidelines can be managed in secondary care. Others who are failing to respond adequately should be referred to a tertiary care centre with expertise in the management of difficult situations.

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?

See above. Although both imatinib and nilotinib are approved for first line therapy, most patients receive imatinib, unless there are prognostic indicators at the time of diagnosis that suggest a more potent drug should be used early in treatment. As far as I am aware the TKI are always used for their licensed indications.

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.

Physicians across the world have used the European LeukemiaNet (ELN) guidelines published in 2006 and updated in 2009 and 2013. There are similar guidelines from the US National Comprehensive Cancer Network.

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?

As indicated above, the majority of patients with CML will enjoy a near-normal life expectancy if we can achieve deep responses and long-term drug tolerability. All of the second generation drugs, bosutinib, dasatinib and nilotinib, can induce CCyR in patients resistant to imatinib (as defined by the failure to achieve ELN milestones). With longer follow-up from the initial Phase II studies it seems that not only are the majority of responses durable, but also that the majority of patients with CCyR also achieve MMR. Both CCyR and MMR are associated with long survival times.

However, it is possible that the patient who responds to dasatinib, for instance, might not necessarily respond to bosutinib or nilotinib, and vice versa. In other words, because we do not understand the reasons for resistance in the majority of patients, we cannot predict which of the drugs will induce the deepest and most durable response. The exception is that a small number of patients develop resistance to one or other of the TKI because of a mutation in the DNA encoding BCR-AB\l1, that changes the shape of the resulting Bcr-Abl1 protein and disturbs the binding of the oncoprotein and the drug. At present we are experiencing the unsatisfactory position of having to give nilotinib to patients failing imatinib because of a nilotinib resistant mutation, because this is the only agent currently approved for second line therapy.

In addition one of our biggest challenges is to find a drug that allows good quality of life for our patients, particularly because most patients will have to take their drugs for life. The median age of onset of CML is 55-60 years with a wide age range, such that most patients will literally experience decades of treatment. Although the side effects of the TKI largely fall within the same spectrum, it is quite remarkable that a side effect on one drug does not necessarily recur on an alternative agent.

Having said that the side effects tend to fall within the same spectrum of disorders, each drug has a particular side effect profile that is not (or rarely) seen with the others. Examples include pleural effusions and pulmonary arterial hypertension with dasatinib, arterial thrombotic events, hypertension, induction of diabetes and poor control of pre-existing diabetes with nilotinib, hepatitis with bosutinib and arterial thrombotic events, hypertension and pancreatitis with ponatinib. This results in the not uncommon position of tryingto choose a drug according to the pre-existing co-morbidities of the patient. Giving nilotinib or ponatinib to a long-tern smoker with hypertension and a history of ischaemic heart disease is likely to result in further medical problems, as is giving dasatinib to a patient with pre-existing chronic obstructive airways disease or bosutinib to a patient with cirrhosis. There is no doubt that the TKI have saved the lives of patients with CML but are beginning to result in additional disease burden that could be avoided with better initial drug selection. Of course there will be patients in whom the best drug in terms of efficacy is not the best drug in terms of co-morbidity but at this stage, the decision will be based on a careful evaluation of the risk-benefit.

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.

As has been mentioned several times previously the majority of patients will receive the TKI on a daily basis for life. At present a small proportion of patients have been able to discontinue treatment after several years. This proportion will increase. First, those patients who have been treated long enough to be offered the opportunity to stop treatment, are those who responded well to imatinib, because if they had poor responses, the other drugs were not yet available. This would have included not only patients in who imatinib was ineffective but also those who could not tolerate the drug long-term. Now, we can recognise the patient with a lower chance of responding to imatinib, as early as 3-6 months after initiation of treatment and by prescribing the alternative TKI, can give these patients deep responses and eventually offer them an opportunity to stop. Patients who were unable to tolerate imatinib long-term now change to a more acceptable agent and will eventually achieve deep responses: some of these will also be offered an opportunity to stop. Finally the chance of achieving deep and durable responses is higher if nilotinib or dasatinib are used as initial therapy (the first line study on bosutinib is currently underway and it is possible that similar results will emerge) and the expectation is that more of these patients will be able to stop treatment. This statement might seem to contrast with my earlier opinion that most patients are treated with imatinib at diagnosis and the reason for this is the fact that we can now recognise imatinib poor responders very early in their disease course. The expectation (as yet unproven) is that a change to a more potent agent as early as 3 months after diagnosis will give similar results to giving the more potent agent immediately from diagnosis. This approach is likely to be the most cost-effective as about 50-55% of patients will both respond to, and tolerate imatinib in the long-term. As generic imatinib will be available in the UK from December 2016, this will reduce the overall drug budget, as the more expensive and more potent agents can be reserved for those who are now known to need them.

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?

All the second generation agents (bosutinib, dastinib and nilotinib) induce CCyR in about 40% of those who are resistant, and 50% of those who are intolerant to imatinib, Having given these results, which are derived from the phase II studies of these drugs for imatinib failure, it is important to remember the circumstances in which the Phase II studies were conducted. By the time they became available. some patients with imatinib resistance and/or intolerance had been waiting months or years for an alternative agent. It could be argued that those patients with aggressive disease may have progressed and died before the trial were open, and thus the result of the trials was biased to patients with easily controllable disease. In this case the trial results over estimate the potential responses. Alternatively, it can be argued that by keeping the patients on imatinib when it was clearly not working optimally, allowed the development of drug resistance and disease progression, and that by the time the trial opened, the patient was highly unlikely to respond. In this case the trial results underestimate the potential benefit of the second generation drugs.

The outcome of these studies was measured in terms of CCyR and MMR. These are surrogate markers of survival and appear to be highly predictive. The difficulty of using survival as an endpoint in CML trials is that the survival is now so good, that the numbers of patients to be included in the studies would be very large and the duration of the trial would be very long. Such studies are not attractive to funders and the treatment algorithm has usually changed long before the trial ends.

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?

I have discussed the side effects extensively in the previous section. Although all the TKI cause side effects in a similar spectrum, each has an individual side effect profile that can make that drug more or less suitable for any individual patient.

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.

Studies are underway for the 'real-world' experience of bosutinib and will be available in abstract form by August 2016, in order to be submitted for presentation at the 2016 meeting of the American Society of Hematology (ASH). A publication should follow shortly. My personal experience of bosutinib in second, third or fourth line settings is that it is well tolerated and induces excellent responses in about 40% of those who have failed one prior drug and 20-25% of those who have failed 2 or more prior drugs. Every patient salvaged and given an excellent prognosis with one or other of the TKI is a patient who does not have to be subjected to allo-SCT

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)?

No additional resources or education would be necessary, especially if patients who have failed more than two TKI were to be referred to a specialist CML centre.

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;

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TA299 - Bosutinib for previously treated chronic myeloid leukaemia

- 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.

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 that some 40% of the patients with resistance to imatinib and/or nilotinib, 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.

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Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **Royal College of Physicians and NCRI CML Working Party** and consequently I will not be submitting a personal statement.

Name: .....Jennifer Byrne.....

Signed: .....  .....

Date: .....3/5/16.....

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Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **The Royal College of Pathologists** and consequently I will not be submitting a personal statement.

Name: Adam Mead

Signed: .....

.....

Date: 27th May 2016

Appendix K – patient expert statement declaration form

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Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by the Chronic Myeloid Leukaemia Support Group and consequently I will not be submitting a personal statement.

Name: RUSSELL COOPER

Signed: [signature]

Date: 19 MAY 2016.

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CDF rapid reconsideration process

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by the Chronic Myeloid Leukaemia Support Group and consequently I will not be submitting a personal statement.

Name: .....David Ryner.....

Signed:

.....

Date: 23rd May 2016.....

Bosutinib for previously-treated chronic myeloid leukaemia

A Single Technology Appraisal Review

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
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EX1 2LU

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Date completed

27/04/2016

Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Tristan Snowsill	Critiqued the company's economic evaluation. Developed and implemented ERG exploratory analyses. Designed, conducted and screened scoping searches. Wrote the report apart from the Clinical effectiveness chapter. Compiled and edited the report and provided overall project management.
Linda Long	Led the critique of the clinical effectiveness evidence and contributed to the writing and editing of the report.
Claudius Rudin	Provided clinical advice on chronic myeloid leukaemia and its management within the NHS. Reviewed and revised a draft version of the report.

Please refer to the International Committee for Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts submitted to Biomedical Journals see http://www.icmje.org/

Use of confidential data

Any 'commercial in confidence' data provided by the company, and specified as such, is highlighted in blue and underlined in the review. Any 'academic in confidence' data provided by companies, and specified as such, is highlighted in yellow and underlined in the review.

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Abbreviations

ACD	Appraisal Consultation Document
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
AP	Accelerated phase
BP	Blast phase
CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMLSG	Chronic Myeloid Leukaemia Support Group
CP	Chronic phase
CP2L	Chronic phase (2nd line)
CP3L	Chronic phase (3rd line)
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol Five Dimensions
ERG	Evidence Review Group
FACT-Leu	Functional Assessment of Cancer Therapy – Leukaemia
FAD	Final Appraisal Determination
HC	Hydroxycarbamide
HCHS	Hospital and Community Health Services
HU	Hydroxyurea (hydroxycarbamide)
HRQL or HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM or K-M	Kaplan–Meier

MCyR	Major cytogenetic response
MMR	Major molecular response
$MR^{4.5}$	4.5 log reduction in BCR-ABL transcripts
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OHR	Overall haematological response
OS	Overall survival
PAS	Patient Access Scheme
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SCT	Stem cell transplant
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor

1 Summary

In January 2013, NICE issued the Final Scope for a Single Technology Appraisal of bosutinib for previously treated chronic myeloid leukaemia (CML). In March 2013, Pfizer and other consultees made submissions to NICE and these were reviewed by the Evidence Review Group (ERG), PenTAG. The submission included a proposed patient access scheme.

Following consultation on the Appraisal Consultation Document, a Final Appraisal Determination was produced, indicating that NICE had not recommended bosutinib for previously treated CML (TA299).[1]

Bosutinib was subsequently added to the Cancer Drugs Fund (CDF), and was therefore available to patients in England meeting the eligibility criteria.

All cancer drugs that were previously appraised by NICE and are currently funded through the current CDF are being re-considered by NICE.

Companies are instructed that their new evidence submission should focus on cost-effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health or as a commercial access arrangement with NHS England.

Companies are also instructed that:

- Cost-effectiveness analyses must use the assumptions that determined the most plausible ICERs in the published guidance;
- Only in exceptional circumstances and with prior written agreement with NICE should new clinical evidence be included.

1.1 Critique of the decision problem in the company submission

The company's submission addresses a narrower decision problem than the NICE Final Scope and the company's original submission to TA299, because two comparators have been omitted: interferon alfa and allogeneic stem cell transplantation. The removal of interferon alfa was felt to be justifiable, whereas the removal of stem cell transplant was not adequately justified.

The ERG concluded (based on the cost-effectiveness results in TA299) that the removal of stem cell transplant has not led to a biased representation of the cost-effectiveness of bosutinib for previously treated CML.

1.2 Clinical effectiveness evidence

The company has not included additional clinical effectiveness evidence.

1.2.1 Clinical effectiveness evidence submitted by the company in TA299

The clinical evidence for bosutinib in previously treated CML comes from a Phase 1/2, single-arm, multicentre trial: Study 200. In particular, the company's submission focused on the 3rd line chronic phase (CP) CML cohort and the accelerated phase (AP) and blast phase (BP) cohorts, excluding the 2nd line CP CML cohort.

The 3rd line CP CML cohort included 118 patients, while the AP and BP cohorts included 76 and 64 patients respectively.

Table 1 shows the main efficacy results of Study 200 as submitted in TA299.

Table 1: Summary of clinical effectiveness results from Study 200

Cohort	Response% (95% CI)			Kaplan–Meier OS% (95% CI)	
	CHR	*MCyR*	*CCyR*	*1 year*	*2 years*
CP3L	73.1 (64.2, 80.8)	40.9 (31.6, 50.7)	31.8 (23.3, 41.4)	91.4 (84.6, 95.3)	84.0 (75.8, 89.6)
AP	34.8 (23.7, 47.2)	39.0 (28.0, 50.8)	29.9 (20.0, 41.4)	76.0 (64.7, 84.2)	65.6 (53.4, 75.4)
BP	15.0 (7.1, 26.6)	32.8 (21.6, 45.7)	25.0 (15.0, 37.4)	43.8 (31.3, 55.6)	35.4 (23.8, 47.3)

Key: AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematological response; CI, confidence interval; CP3L, third line chronic phase; MCyR, major cytogenetic response; OS, overall survival
Source: Hoyle et al. (2013)[2]

Responses were achieved or maintained in some patients with mutations which were believed to confer resistance to nilotinib and dasatinib (Y253, E255, F317 and F359), but bosutinib did not appear to have efficacy in patients with the T315I mutation.

Adverse events were mainly restricted to gastrointestinal toxicities and in the majority of cases these toxicities were mild or moderate in severity.

EQ-5D data were collected in Study 200. The mean EQ-5D utilities, averaged mostly over the first two years of treatment, were [redacted], [redacted] and [redacted] in the CP 2nd-line, 3rd-line, AP and BP populations respectively.

The main weakness of the clinical effectiveness evidence for bosutinib is that no comparative evidence was identified. Additionally, only 52 of the 546 patients in Study 200 were identified as strictly meeting the marketing authorisation for bosutinib. There is also significant uncertainty surrounding overall survival estimates from Study 200 as patients were able to receive active treatments for CML after discontinuing bosutinib, but no adjustment for treatment switching was attempted.

The clinical evidence for hydroxycarbamide was claimed to be from a study of CML patients following imatinib failure,[3] but this is a poor evidence source (since only a minority of patients in the identified subgroup received hydroxycarbamide), and it was not interpreted correctly by the company.

1.2.2 Scoping review conducted by the ERG for this review

The ERG conducted a scoping review to identify any evidence which could supplant or supplement the evidence considered in TA299. Two publications were identified which gave additional results from Study 200, but other studies were either not relevant to the decision problem, or had significantly smaller sample sizes than Study 200.

Study 200 remains the best published source for estimates of the efficacy and safety of bosutinib in the licensed population.

1.3 Summary of cost-effectiveness evidence submitted by the company

The company have submitted a cost-effectiveness model which is adapted from the model submitted in TA299.

The main differences from the TA299 model are:

- Newly proposed patient access scheme;
- Cumulative survival approach adopted for overall survival;
- Interferon alfa and stem cell transplant removed as comparators;
- Revised medical management, monitoring and costs resource use;
- Health state utility values estimated from Study 200;
- Costs updated to 2014/15 prices.

As shown in *Table 2*, the incremental cost-effectiveness ratios (ICERs) from the current submission, when using the TA299 PAS, align reasonably well with the Committee's most plausible ICERs from TA299, which the company reasonably claims gives confidence in the appropriateness of the model.

Table 2: Incremental cost-effectiveness ratios from TA299 and current submission with list price, TA299 PAS and currently proposed PAS

Model	CP	AP	BP
TA299 (Pfizer)			
List price	[redacted]	[redacted]	[redacted]
TA299 PAS	[redacted]	[redacted]	[redacted]
Current PAS	[redacted]	[redacted]	[redacted]
TA299 (ERG)			
List price	[redacted]	[redacted]	[redacted]
TA299 PAS	[redacted]	[redacted]	[redacted]
Current PAS	[redacted]	[redacted]	[redacted]
TA299 (NICE)			
List price	NA	NA	NA
TA299 PAS	£43,000	£58,000	£60,000
Current PAS	NA	NA	NA
Current (Pfizer)			
List price	[redacted]	[redacted]	[redacted]
TA299 PAS	£42,068	£62,231	£60,859
Current PAS	[redacted]	[redacted]	[redacted]

Key: AP, accelerated phase; BP, blast phase; CP, chronic phase; ERG, Evidence Review Group; PAS, Patient Access Scheme

1.4 Summary of the ERG's critique of the cost-effectiveness evidence submitted

Only small logic and implementation issues were identified in the company's current submission. These had a small upwards impact on the ICERs of bosutinib.

There is considerable uncertainty regarding the relative effectiveness of bosutinib versus hydroxycarbamide, since it has not been estimated in any comparative studies.

The cumulative survival approach employed in the submission assumes that life expectancy following discontinuation of bosutinib treatment is equal to life expectancy in the absence of bosutinib treatment, i.e., a given patient's life expectancy is extended exactly by the length of time they are treated with bosutinib. There are reasons why the extension may be less than or greater than this duration.

There is also uncertainty about the expected overall survival for patients receiving hydroxycarbamide third line. The cost-effectiveness of bosutinib is sensitive to this assumption even when the cumulative survival approach means that incremental undiscounted life years gained are not affected.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

The economic evaluation submitted by the company produces ICERs which are similar to the Committee's most plausible ICERs from TA299 when the PAS from TA299 is used in the model.

The ERG has also checked for implementation errors in the model and found very few, and those identified had only a small impact on the ICERs of bosutinib.

1.5.2 Weaknesses and areas of uncertainty

The current submission does not include interferon alfa and stem cell transplantation as comparators.

The cost-effectiveness of bosutinib is sensitive to assumptions about the relative effectiveness of bosutinib versus hydroxycarbamide, and the absolute effectiveness of hydroxycarbamide. There is considerable uncertainty about both of these quantities.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

Corrections to the implementation of the company's submission result in ICERs for bosutinib of [redacted], [redacted] and [redacted] per QALY for chronic phase, accelerated phase and blast phase patients respectively.

When additional survival benefit is assumed post-discontinuation, the ICER for chronic phase patients decreases to [redacted] per QALY when three months' additional benefit is assumed, but increases to [redacted] per QALY when one month less benefit is assumed.

Alternative estimates for the overall survival for hydroxycarbamide gave ICERs for bosutinib in chronic phase patients of [redacted] and [redacted] per QALY.

2 Background

This is the ERG critique of the company submission for rapid reconsideration of bosutinib for previously-treated chronic myeloid leukaemia (CML). The previous guidance is NICE TA299.

The company was not required to submit a description of the underlying health problem or an overview of current service provision. *Table 3* provides a brief overview.

Table 3: Overview of underlying health problem and current service provision

Disease	Leukaemia is a form of cancer affecting blood. Chronic myeloid leukaemia (CML) is characterised by excessive proliferation of white blood cells (mainly granulocytes) in the bone marrow, and an initial slow disease progression.
Incidence	Annual incidence rate: 1.0 per 100,000 population (1.2 per 100,000 men, 0.8 per 100,000 women) Expected UK cases per year: 580
Population	M:F rate ratio: 1.6 Median age at diagnosis: 59.1
Survival	5-year relative survival: 89.1%
Natural history	CML has three phases: chronic (CP), accelerated (AP) and blast (BP), each corresponding to increasing leukaemic blast counts in the blood and bone marrow and clinical severity. Blast is a term which describes an immature blood cell of any type. Normally, a blast will develop into a mature blood cell, but in CML these cells are abnormal and do not fully develop, becoming known as leukaemic blasts. Approximately 90% of patients are diagnosed while in CP, 9% in AP and 1% in the BP. If left untreated, the average time a patient would remain in CP, AP and BP is 3–5 years, 6–24 months and 6 months, respectively.
Applicable NICE guidance	TA70: Imatinib is recommended as an option for treating CML[4] TA241: Nilotinib is recommended as an option for patients with CML whose treatment with imatinib failed due to resistance or intolerance (dasatinib and high-dose imatinib are not recommended)[5] TA251: Nilotinib is recommended as an option for treating newly-diagnosed CML (dasatinib is not recommended)[6]
Current service provision	Our clinical expert (CR) has advised that newly-diagnosed patients are offered imatinib and nilotinib as treatment options, and the majority prefer first-line treatment with imatinib because of its simpler administration. Patients will typically then receive nilotinib or imatinib as second-line treatment (whichever they did not receive first-line). Third- and fourth-line treatment will often be with dasatinib (via the CDF), followed by bosutinib (via the CDF). If patients have the T315I mutation they are unlikely to receive any TKI except ponatinib (via the CDF). If patients are found to be intolerant to TKIs, treatment with reduced doses is sometimes attempted. After TKI options have been exhausted, stem cell transplant will be offered to patients for whom it would be clinically appropriate.

Key: AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; CDF, Cancer Drugs Fund; F, female; M, male; TKI, tyrosine kinase inhibitor

Sources: Rogers et al. (2012),[7] Haematological Malignancy Research Network[8] and Pfizer submission to TA299

3 Critique of company's definition of decision problem

Table 4 provides a summary of the decision problem as described in the Final Scope for TA299 and in the company submission.

Table 4: Summary of decision problem

Definition	NICE Final Scope (TA299)	Company decision problem
Population	Adults with previously treated chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia	Adults with chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia previously treated with one or more tyrosine kinase inhibitor (TKI) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options
Intervention	Bosutinib	Bosutinib
Comparators	• Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML) • Hydroxycarbamide • Interferon alfa • Best supportive care	Hydroxycarbamide
Outcomes	• Overall survival • Event-free survival • Progression-free survival • Time to progression • Response rates: cytogenetic, haematological and molecular, including time to response and duration of response • Time to treatment failure • Adverse effects of treatment • Health-related quality of life	As NICE Final Scope plus rates of transformation from chronic phase to accelerated phase and accelerated phase to blast base CML

3.1 Population

The population in the company's decision problem matches the marketing authorisation. The clinical evidence (Study 200) is broadly reflective of the population in the decision problem, although only a minority of patients were deemed to have "unmet clinical need" (i.e., unsuitable for treatment with imatinib, nilotinib and dasatinib).[2]

Subgroups were considered for chronic, accelerated and blast phase patients. Our clinical expert has suggested that patients with a history of intolerance to other tyrosine kinase inhibitors (TKIs) are qualitatively different to patients with a history of resistance, as they are likely to have been treated for less time, but are also at increased risk of intolerance to bosutinib.

3.2 Intervention

The intervention is bosutinib, matching the NICE Final Scope.

3.3 Comparators

The final scope lists the following comparators:

- Allogeneic stem cell transplantation (with or without leukaemia-style chemotherapy depending on phase of CML);
- Hydroxycarbamide;
- Interferon alfa;
- Best supportive care.

In the company's submission the decision problem considers only a single comparator: hydroxycarbamide.

The ERG considers the exclusion of allogeneic stem cell transplantation is unjustified (see *Section 3.3.1*), that the exclusion of interferon alfa is appropriately justified (see *Section 3.3.3*), and that for certain patients, additional comparators may also be appropriate (see *Sections 3.3.5 and 3.3.6*), although any analyses of these would not meet the NICE reference case.

3.3.1 Allogeneic stem cell transplantation

The company's submission states that stem cell transplantation (SCT) was removed as a comparator with the following reasoning (source: Pfizer submission, pages 12–13):

> We have removed stem-cell transplant (SCT) as a comparator based on the Committee's feedback that SCT was an option for a minority of patients only, and would be likely to be used after all tyrosine kinase inhibitor options had failed (section 4.3 of TAG299). This aligned to the views of the CMLSG during consultation that people would be likely to try all tyrosine kinase inhibitor options before SCT (TAG 4.15).

While the ERG agrees that it is likely SCT would not be an option for the majority of patients, the remainder of the justification provided is not logical.

In TA299, the ERG's preferred base case used SCT as a comparator for patients for whom SCT would be appropriate, and it was assumed that SCT would be the next line of treatment for those patients after they stopped treatment with bosutinib; conversely, patients for whom SCT would be inappropriate would have hydroxycarbamide as a comparator, and that patients would receive hydroxycarbamide after bosutinib discontinuation.[1]

The decision problem in the economic evaluation should be to consider the relative costs and outcomes in a world where bosutinib is available to patients and in a world where it is not available. When bosutinib is not available, certain patients will receive SCT, and where bosutinib is available, those patients will receive bosutinib before SCT (aligned with the views of the CMLSG as summarised by the company).

In TA299, the Committee concluded that the most likely ICER for bosutinib versus best supportive care was £43,000 per QALY.[1] The ERG estimates for the ICERs of bosutinib followed by SCT versus SCT were marginally lower than the corresponding ICERs for bosutinib followed by hydroxycarbamide versus hydroxycarbamide.

On this basis, it seems unlikely that excluding SCT as a comparator has artificially removed results demonstrating worse cost-effectiveness. The ERG believes that, although not

adequately justified, the removal of SCT from the decision problem has not introduced any bias.

3.3.2 Hydroxycarbamide

Hydroxycarbamide (previously termed hydroxyurea) is an antineoplastic drug which is used when patients do not have TKI treatments available (or when the CML diagnosis is not yet confirmed). It is generally not considered to be a disease-modifying treatment, but as an approximation to best supportive care.[1]

3.3.3 Interferon alfa

Interferon alfa is currently rarely used in the UK to treat CML.[1] The inclusion of interferon alfa as a comparator may result in worse cost-effectiveness estimates for bosutinib.

3.3.4 Best supportive care

In NICE TA299, best supportive care was not included as a comparator as hydroxycarbamide was accepted to represent best supportive care.[1] The same approach has been adopted in the current submission and the ERG believe this to be appropriate.

3.3.5 Low-dose imatinib

Our clinical advisor (CR) has stated that patients who are intolerant to standard-dose imatinib and subsequently intolerant to nilotinib and dasatinib (or are unable to be treated with dasatinib, which has not received a positive NICE recommendation[5, 6]) could attempt treatment with low-dose imatinib to reach a tolerable dose with some therapeutic effect.

This comparator was not included in the NICE Scope and the ERG is not aware of any evidence for the efficacy of low-dose imatinib in this subgroup.

3.3.6 Ponatinib

Ponatinib is licensed for the treatment of chronic, accelerated, or blast phase chronic myeloid leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib or nilotinib, and for whom subsequent treatment with imatinib is not clinically appropriate.[9, 10]

Following consultation on a draft remit and a scoping workshop, NICE considered that an appraisal of ponatinib for chronic myeloid leukaemia would not be appropriate, noting the very small population size.[11] There is therefore no NICE guidance on ponatinib. Ponatinib is currently included in the Cancer Drugs Fund for patients who have the T315I mutation.[12]

Ponatinib was not included in the NICE Scope and the ERG is not aware of any evidence to support an analysis including ponatinib.

3.4 Outcomes

The outcomes in the company submission match the outcomes described in the scope. Overall survival estimates from Study 200 were immature.

4 Clinical effectiveness

As is standard in the CDF rapid reconsideration process, no new clinical effectiveness evidence was submitted by the company.

In this section, the ERG summarises the evidence previously submitted in NICE TA299, as well as a scoping review undertaken by the ERG to ensure that there is no significant and relevant clinical effectiveness evidence other than that previously submitted in TA299.

4.1 Clinical effectiveness evidence submitted by the company in NICE TA299

4.1.1 Summary of clinical effectiveness evidence submitted by the manufacturer

> The clinical effectiveness evidence of bosutinib (Bosulif®) in treatment of adult patients with Ph+ CML was reviewed. The entire clinical evidence for bosutinib comes from a single arm, Phase I/II multi-centre trial, Study 200. Because no RCT evidence was identified, separate clinical effectiveness evidence was submitted for the Scope defined comparators. Thirteen non-randomised comparator studies were included.
>
> —Hoyle et al. (2013)[2] (p. 23)

4.1.1.1 Bosutinib

> Study 200 (Phase II) examined the efficacy and safety of bosutinib 500mg daily in 546 Ph+ CML patients with previous imatinib failure. Patients in all three phases of Ph+ CML were recruited; second line CP (N=288), third line CP (N=118), AP (N=76) and BP (N=64). In addition, based on EMA recommendation, a subgroup of patients previously treated with one or more TKI and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options (population of unmet clinical need) was identified and analysed post hoc. Baseline characteristics across all phases of the disease and lines of treatment are summarised in [*Table 5*].
>
> In the complete population of Study 200, bosutinib was associated with good cytogenetic and haematological response rates and overall survival [*Table 6*]. However, the OS data from Study 200 for CP patients is very immature. Cytogenetic and haematological responses were also observed among participants with mutations that would confer the use of nilotinib or dasatinib inappropriate [*Table 7*]. Apart from the BP subpopulation, cytogenetic rates reported in the full Study 200 population are somewhat lower that the rates reported in the unmet clinical need population. For example, MCyR was 60%, 42.9%, 60% and 18.2% for second and third line CP and AP and BP unmet clinical need population respectively. However these response rates are based on very small sample sizes (N=3–21) and are therefore uncertain.
>
> —*Ibid*. (pp. 23–24)

Table 5: Study 200 baseline patient characteristics

Population	Age (years) [Median (range)]	Male [N (%)]	CML duration (years) [Median (range)]	IM duration (years) [Median (range)]	ECOG performance status N (%)		
					0	*1*	*2*
CP2L (n=288)	53.0 (18–91)	154 (53%)	3.6 (0.1–15.1)	2.2 (<0.1–8.8)	219[a] (77%)	65[a] (23%)	1[a] (<1%)
CP3L (N=118)	56.0 (20–79)	53 (45%)	6.7 (0.6–18.3)	2.7 (0.02–6.6)	86 (74%)	31 (26%)	NA
AP (N=76)	50.5 (18–83)	42 (55%)	5.06 (1.11–22.06)	NR	41 (54%)	33 (43%)	2 (3%)
BP (N=64)	48.5 (19–82)	41 (64%)	3.08 (0.35–14.46)	NR	22 (34%)	28 (44%)	14 (22%)
Unmet clinical need (N=52)[b]	58 (19-81)	31 (605)	NR	NR	22 (42%)	27 (52%)	3 (6%)

Key: AP, accelerated phase; BP, blast phase; CP2L, second line chronic phase; CP3L, third line chronic phase; ECOG, Eastern Cooperative Oncology Group performance status; IM, imatinib; N, number of participants; NR, not reported

Notes: a, Information taken from Cortes (2012)[13]; b, Information taken from EPAR

Table 6: Study 200 cytogenetic and haematological response rates for full Study 200 population

	Evaluable population			
	MCyR March 2011	*CCyR March 2011*	*CHR March 2011*	*K-M estimates of OS at 2 years*
CP2L	53.4%	41.4%	84.7%	90.6%[a]
CP3L	38.9%	30.6%	73.3%	84.0%[a]
AP	34.8%	24.6%	34.8%	65.6%[b]
BP	29.6%	20.4%	15%	35.4%[c]

Key: AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematological response; CP2L, second line chronic phase; CP3L, third line chronic phase; K-M, Kaplan–Meier; MCyR, major cytogenetic response; OS, overall survival

Notes: a, 24 month minimum follow-up, median OS had not yet been reached; b, 12 month minimum follow-up, median OS had not yet been reached; c, 18 month minimum follow-up, median OS for BP patients was 11.1 months

Table 7: Study 200 response rates by baseline mutation

Mutation	CP2L CHR [n/N %]	CP2L MCyR [n/N %]	CP3L CHR [n/N %]	CP3L MCyR [n/N %]	AP & BP CHR [n/N %]	AP & BP MCyR [n/N %]
Y253	2/2 100%	2/2 100%	5/6 83%	4/6 67%	1/7 14.3%	2/7 28.6%
E255	0/2 0%	2/3 67%	NA	NA	0/4 0%	1/3 33.3%
F317	4/4 100%	3/4 75%	4/8 50%	1/7 14%	0/9 0%	0/6 0%
F359	8/9 89%	4/9 44%	0/2 0%	1/2 50%	0/2 0%	1/2 50%

Key: AP, accelerated phase; BP, blast phase; CP2L, second line chronic phase; CP3L, third line chronic phase; n, numbers of participants with response; N, number of participants with mutation; NA, not applicable

> Bosutinib was found to have an acceptable safety profile across all phases of the disease and lines of treatment. Low rates of transformation to the next phase of CML were observed on bosutinib treatment for both chronic and advanced phase populations [*Table 8*]. Adverse events were mainly restricted to gastrointestinal toxicities [*Table 8*] and in the majority of cases these toxicities were mild in severity. The most common haematological events across all phases of the disease and lines of treatments in both the chronic and advanced phases of the disease were thrombocytopenia, neutropenia and anaemia. Severe cases of anaemia seemed to be more pronounced at the more advanced stages of the disease [*Table 8*]. The profile of AE associated with bosutinib appears to be more similar to those associated with nilotinib than with dasatinib. In comparison, the most commonly reported dasatinib AE were headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombopenia and anaemia.[7] In addition, the clinical effectiveness of bosutinib appears to be mainly seen in patients with previous intolerance to TKI.
>
> —Hoyle et al. (2013)[2] (pp. 25–26)

Table 8: Study 200 safety

	CP2L	CP3L	AP	BP
Rates of disease transformation to the next phase of CML	3.8%	4%	6.4%	NA
Treatment discontinuation	58% (36 months minimum follow-up)	76% (24 months minimum follow-up)	NR	NR
Treatment discontinuation due to AE	23%	22%	23.7%	9.4%
Diarrhoea	85.3%	82.4%	85.5%	65.6%
Nausea	45.5%	48.7%	44.7%	50%
Vomiting	36.7%	39.5%	44.7%	39.1%
Rash	36%	26.9%	32.9%	31.3%
Thrombocytopenia Grade 3/4	24%	25.4%	32.9%	26.6%
Neutropenia Grade 3/4	18%	14.4%	14.5%	20.3%
Anaemia Grade 3/4	13%	5.1%	30.3%	18.8%

Key: AE, adverse event; AP, accelerated phase; BP, blast phase; CP2L, second line chronic phase; CP3L, third line chronic phase; NA, not applicable; NR, not reported

> EQ-5D data were collected in Study 200. The mean EQ-5D utilities, averaged mostly over the first two years of treatment, were [redacted] in the CP 2nd-line, 3rd-line, AP and BP populations respectively.
>
> —*Ibid*. (p. 26)

4.1.1.2 Hydroxycarbamide

Two studies reported on hydroxycarbamide.[3, 14]

> In summary, the clinical effectiveness evidence for the comparator treatments is very poor. Hydroxycarbamide was considered to be a proxy for best supportive care. Participants in the comparator studies appear to be younger, and most of the comparator studies are small and the outcomes reported vary. Pfizer describe the [hydroxycarbamide] comparator studies as "not strictly eligible" (p89 Pfizer submission) for inclusion […]. This further highlights the difficulty inherent to such naïve comparisons and impedes any comparisons of Study 200 with comparator studies.
>
> The [chronic phase] cost-effectiveness model used data from Kantarjian (2007)[3] for the clinical effectiveness of [hydroxycarbamide] […]. Of particular importance for the model are:
>
> [Overall survival for hydroxycarbamide in chronic phase] of 77% at year 2 and 70% at year 3 in Kantarjian (2007)[3]
>
> No safety data were reported for [hydroxycarbamide].
>
> —Hoyle et al. (2013)[2] (pp. 26–27)
>
> [No] literature was identified on utilities for CML patients taking hydroxycarbamide
>
> —*Ibid*. (p. 133)

4.2 Critique of the clinical effectiveness evidence submitted by the company in TA299

> First, the main weakness of the clinical effectiveness evidence is the fact that no RCT evidence was identified. The only clinical evidence for bosutinib comes from Study 200, a Phase I/II multi-centre trial conducted in North America, the European Union, Eastern Europe, Africa and Asia. Study 200 is a single arm, open-label, 2-part, efficacy and safety study of bosutinib in patients with Philadelphia positive CML. Similarly, the evidence for comparator treatments comes from 13 non-randomised comparator studies.
>
> Second, the bosutinib licence is intended for treatment of adult patients with CP, AP and BP Ph+ CML patients previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. However only 52 of the 546 patients in Study 200 fulfilled the criteria for this unmet need population.
>
> Third, Pfizer do not state the nature of treatments given after bosutinib failure. This means that the relevance of the OS data from Study 200 is uncertain, because many patients may have proceeded to take a different TKI on bosutinib failure. Also, the OS data in CP is very immature, which means that it is difficult to estimate mean OS, a key driver of the cost-effectiveness of bosutinib.
>
> Fourth, we cannot stress enough, that the naïve comparison of the single arm Study 200 with non- randomised comparator studies is predisposed to bias. The evidence for the two comparator treatments, HU and SCT, is taken from small studies with populations that mostly did not meet the unmet need criteria.
>
> —Hoyle et al. (2013)[2] (p. 27)

4.3 Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook a scoping review to identify any supporting evidence to answer the decision problem published since NICE TA299.

4.3.1 Methods

4.3.1.1 Literature review

Searches were adapted from the systematic review searches designed by Pfizer and conducted on 21st January 2013. As summarised in *Table 9* and detailed in *Appendix 1*, the ERG scoping searches were less restrictive for population, but were more restrictive for interventions and publication date.

Table 9: Scoping searches performed in TA299 and in ERG scoping review

Search group	Pfizer TA299	ERG scoping review	Comparison
Population	• Chronic myeloid leukaemia and • Refractory to or intolerant of imatinib	• Chronic myeloid leukaemia	ERG less restrictive
Interventions	• Bosutinib or	• Bosutinib	ERG more restrictive

	• Hydroxycarbamide or • Stem cell transplantation or • Interferon alfa or • Best supportive care		
Outcomes	(Not used)	(Not used)	Identical
Study design	• Systematic review or • Meta-analysis or • Clinical trial or • Observational study	• Systematic review or • Meta-analysis or • Clinical trial or • Observational study	Identical
Date range	• From inception	• Since 2012[a]	ERG more restrictive

Key: ERG, Evidence Review Group
Notes: [a]Date limit applied to EMBASE, MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations

Searches were run on 7th April 2016 on the following databases (platforms):

- EMBASE (Ovid);
- MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations (Ovid);
- Cochrane Library (Wiley Online Library): Cochrane Central Register of Controlled Trials; Health Technology Assessment Database; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effect; Cochrane Methodology Register; NHS Economic Evaluation Database.

Results were combined and deduplicated automatically with EndNote X7 (Thomson Reuters, NY) and also manually deduplicated.

Records were categorised according to their:

- Publication type: journal article, abstract, other;
- Included intervention: bosutinib, not bosutinib;
- Population: adults with newly-diagnosed CML, adults with previously-treated CML, adults with CML (mixed line or unspecified), mixed population including adult CML, other;
- Study design: primary (tiers 1–5), secondary (tiers 1–2), economics, other [see *Table 10*, *page 25*].

Records were then classified as follows:

- Include: RCT of bosutinib in newly-diagnosed CML;
- Include: RCT of bosutinib in previously-treated CML;
- Include: Non-RCT of bosutinib in previously-treated CML;
- Include: Systematic review of the above;
- Exclude: All other studies and all abstracts.

Multiple publications from single studies were then grouped together.

4.3.1.2 Trial registries

Several trial registries were searched, including ClinicalTrials.gov and Pfizer's registry of clinical study report synopses (see *Appendix 2*).

4.3.2 Results

Searches of bibliographic databases yielded 110 records, of which 11 were removed as duplicates, leaving 99 records. The characteristics of these records are shown in *Table 10*.

Table 10: Studies identified through bibliographic databases

Studies	N
Total	99
Publication	
Journal article	61
Abstract	27
Other	11
Intervention	
Bosutinib	80
Not bosutinib	19
Population	
Adults with newly-diagnosed CML	14
Adults with previously-treated CML	18
Adults with CML (multiple lines or line unspecified)	39
Mixed population including adults with CML	15
Other	13
Study design	
Primary (Tier 1): Randomised controlled trials	6
Primary (Tier 2): Controlled clinical trials, before-and-after studies, interrupted time series	0
Primary (Tier 3): Cohort study, case–control study, cross-sectional survey	8
Primary (Tier 4): Case series	13
Primary (Tier 5): Case studies, surveys of clinicians	1
Secondary (Tier 1): Systematic reviews with or without meta-analyses (direct, indirect or network)	20
Secondary (Tier 2): Non-systematic reviews, opinion	39
Economics: Model-based economic evaluations, trial-based economic evaluations, systematic reviews of economic evaluations	6
Other: In silico studies, in vitro studies, animal studies, other	6

Key: CML, chronic myeloid leukaemia; N, number of records

Trial registry searches yielded 48 records, of which 22 were removed as duplicates, leaving 26 records. Ten of these records were deemed to correspond to includable studies (*Table 11*).

Table 11: Trials identified through trial registry searching

Study identifier (other identifiers)	Title	Recruitment	Results	Publications
RCTs of bosutinib in newly-diagnosed adult CML				
BELA (Study 3000, NCT00574873, EUCTR2007-003780-50, 3160A4-3000, B1871008)	Compare bosutinib to imatinib in subjects with newly diagnosed chronic phase Philadelphia chromosome positive CML	Closed: Completed	Results available	Cortes 2012[13] Gambacorti-Passerini 2014[15] Brümmendorf 2015[16]
AV001 (NCT02130557, EUCTR2013-005101-31)	A multicenter Phase 3, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed chronic phase chronic myelogenous leukemia	Closed: Active, not recruiting	No results available	
Non-RCTs of bosutinib in previously-treated adult CML				
Study 200 (NCT00261846, EUCTR2005-004230-40, 3160A4-200, B1871006)	A Phase 1/2 study of bosutinib (SKI-606) in Philadelphia chromosome positive leukemias	Closed: Completed	Results available	Cortes 2011[17] Khoury 2012[18] Trask 2012[19] Gambacorti-Passerini 2014[20] Kantarjian 2014[21]
NCT00811070 (3160A4-2203, B1871007)	Study evaluating SKI-606 (Bosutinib) in Japanese subjects with Philadelphia chromosome positive leukemias	Closed: Completed	Results available	Nakaseko 2015[22]
NCT02228382 (B1871039, EUCTR2013-003250-25)	A Phase 4 safety and efficacy study of bosutinib (Bosulif®) in patients with Philadelphia chromosome positive chronic myeloid leukemia previously treated with one or more tyrosine kinase inhibitors	Open: Recruiting	No results available	
NCT02445742 (BOS-IIG-01)	CML treated with bosutinib after relapse	Open: Recruiting	No results available	
EUCTR2013-000691-15	An open-label bosutinib treatment extension study for subjects with chronic myeloid leukemia (CML) who have previously participated in bosutinib studies B1871006 or	Closed: Active, not recruiting	No results available	

	B1871008		
Bosutinib Dose Optimization Study - BODO-Study (EUCTR2014-005531-13)	Multicenter, open-label single arm phase II study testing the tolerability and the efficacy of Bosutinib step-in dosing in Chronic Phase CML patients intolerant or refractory to previous Nilotinib or Dasatinib therapy	Closed: Active, not recruiting	No results available
NCT02546375 (B1871052)	A Retrospective Observational Research Study To Describe The Real World Use Of Bosutinib In The UK And Netherlands	Closed: Active, not recruiting	No results available
BOSTRO (EUCTR2013-004323-37)	Single nucleotide polymorphism association with response and toxic effects in patients with Ph+ CP-CML treated with bosutinib after relapse or intolerance to previous treatment	Open: Recruiting	No results available

Key: CML, chronic myeloid leukaemia; CP, chronic phase; Ph+, Philadelphia chromosome positive; RCT, randomised controlled trial

4.3.2.1 Updated results from Study 200

Two studies were identified which reported further results from Study 200. One study reported results for the chronic phase chronic myeloid leukaemia patients,[20] while the other reported results for patients in the accelerated and blast phase chronic myeloid leukaemia when recruited (the study also reports results for patients with acute lymphoblastic leukaemia).[23]

4.3.2.1.1 Gambacorti-Passerini et al. 2014 (chronic phase patients)

Overall survival

> Median OS was not reached; the 2-year Kaplan-Meier estimate for OS was 91%
>
> —Gambacorti-Passerini et al. 2014[20] (p. 738)

Progression-free survival

Median PFS was not reached; the 2-year Kaplan-Meier estimate of PFS was 81% […] Disease progression included transformation to AP/BP CML, which occurred in 11 patients during bosutinib treatment. Among imatinib-resistant patients, four patients transformed to AP with a time to transformation ranging from 415 to 630 days after bosutinib initiation and 6 patients transformed to BP with a time to transformation ranging from 42 to 476 days after bosutinib initiation. One imatinib-intolerant patient transformed to AP 246 days after bosutinib initiation; with continued bosutinib treatment, this patient returned to CP and regained a confirmed CHR.

—*Ibid.* (p. 738)

Haematological, cytogenetic and molecular responses

The cumulative response rates to bosutinib were as follows: 85% achieved/maintained complete haematological response and 59% achieved/maintained major cytogenetic response (including 48% with complete cytogenetic response) and 35% achieved major molecular response. Responses were durable, with 2-year estimates of retaining response >70%. Two-year probabilities of progression-free survival and overall survival were 81% and 91%, respectively.

—*Ibid.* (p. 732)

Bosutinib demonstrated high rates of cumulative MCyR in imatinib-resistant (58%; including a 46% CCyR rate) and imatinib-intolerant (61%; including a 54% CCyR) patients.

—*Ibid*. (p. 738)

Responses were durable, with Kaplan-Meier median durations of CHR, MCyR and MMR were not reached for imatinib-resistant or imatinib-intolerant patients […] The 2-year Kaplan-Meier estimates of retaining a response remained >70% in the overall population for all three response types, although estimates were generally higher for imatinib-intolerant versus imatinib-resistant patients.

—*Ibid*. (p. 734)

Bcr-Abl kinase domain mutations

A total of 212 patients were assessed for Bcr-Abl kinase domain mutations at baseline: 79 (37%) patients had ≥1 mutation, including 11 (5%) patients who had ≥2 mutations. Forty-two unique point mutations were identified, several of which have been associated with resistance to imatinib in the clinical setting […] the most frequent mutations were M351T, F359V, and T315I (n = 9 each). As a whole, patients with ≥1 mutation had response rates (CHR, 83%; MCyR, 58%) that were similar to those observed for patients without baseline mutations (CHR, 90%; MCyR, 59%). When patients with the T315I mutation were excluded, the response rates for patients with a mutation were 91% for CHR and 62% for MCyR.

—*Ibid*. (p. 734)

Among patients with ≥1 baseline Bcr-Abl kinase domain mutation (n = 79) versus those without a baseline mutation (n = 133), the 2-year Kaplan-Meier estimates were generally lower for PFS (70% [95% CI, 57–80] vs 85% [95% CI, 77–91]) and OS (81% [95% CI, 70–88] vs 95% [95% CI, 89–97]).

—*Ibid*. (p. 738)

Safety and adverse events

The majority of both older (aged ≥65 years) and younger (aged <65 years) patients experienced only maximum grade 1/2 events, although certain types of TEAEs were reported more frequently among older patients, particularly vomiting, constitutional symptoms, pleural effusions, and dyspnea

—*Ibid.* (p. 738)

In the total population, the most common toxicities were primarily gastrointestinal adverse events (diarrhea [84%], nausea [45%], vomiting [37%]) which was primarily mild to moderate, typically transient, and first occurred during early treatment. Thrombocytopenia was the most common grade 3 or 4 haematological laboratory abnormality (24%).

—*Ibid*. (p. 732)

Thrombocytopenia was the TEAE most frequently leading to treatment interruption […] and dose reduction

—*Ibid*. (p. 737)

Cardiac TEAEs (i.e., cardiac disorders and electrocardiogram investigations) were reported in 39 (14%) patients, including 6% with a grade ≥3 cardiac event; few (n = 13 [5%]) had an event considered treatment related by the investigator.

—*Ibid*. (pp. 737–738)

Adverse events were the second most common reason for death (N=10 [3%]).

[Only] one death was considered treatment related (due to febrile neutropenia 78 days after the last bosutinib dose). Five (2%) patients (all imatinib-resistant) died within 30 days of their last bosutinib dose. Of these, three deaths were attributed to AEs unrelated to bosutinib (acute renal failure, pneumonia, cardiac failure).

—*Ibid*. (p. 738)

4.3.2.1.2 Gambacorti-Passerini et al. 2015 (advanced leukaemia)

The authors report efficacy and safety outcomes for the advanced leukaemia cohort in Study 200.[23] All patients had been enrolled at least four years prior to the data cut-off. The study reports data for accelerated phase (N=79) and blast phase CML (N=64), as well as for acute lymphoblastic leukaemia (ALL); the ALL results are not reported here (stripped from block quotations and sentences adapted as necessary for readability).

14 (18%) AP CML and 2 (3%) BP CML patients were still receiving bosutinib at 4 years, compared with 38 (48%) and 8 (13%) at 1 year (1 year = 48 weeks). Time from last enrolled patient's first dose to the data cutoff for AP CML and BP CML cohorts was 49.2 and 54.5 months, respectively; median (range) duration of follow-up from bosutinib initiation to last contact was 28.4 (0.3–88.6) and 10.4 (0.4–79.9) months.

—Gambacorti-Passerini et al. 2015[23] (p. 756)

Overall survival

As of the data cut-off, a total of 30 (38%) treated patients with AP CML had died; median OS had not yet been reached; Kaplan-Meier estimated OS (95% CI) was 78% (67%–86%) at 1 year and 59% (46%–69%) at 4 years with 38% censored before year 4. Among treated patients with BP CML, 44 (69%) had died, with a median OS (95% CI) of 10.9 (8.7–19.7) months, Kaplan-Meier-estimated OS (95% CI) was 42% (30%–54%) at 1 year and 23% (10%–39%) at 1 year and 23% (10%–39%) at 4 years with 28% censored before year 4.

—*Ibid*. (p. 764)

Transformation-free survival

The cumulative incidence (95% CI) of on-treatment transformation to BP CML in the AP CML cohort was 4% (1%–12%); 79% discontinued without on-treatment transformation before year 4. Three AP CML patients had on-treatment transformation to BP CML (two patients with second-line and one with ≥third-line bosutinib), which occurred 164, 315, and 744 days after treatment initiation.

—*Ibid*. (p. 764)

Haematological, cytogenetic and molecular responses

Among AP and BP patients, 57% and 28% newly attained or maintained baseline overall haematological response (OHR); 40% and 37% attained/maintained major cytogenetic response (MCyR) by 4 years (most by 12 months). In responders at 1 versus 4 years, Kaplan-Meier (KM) probabilities of maintaining OHR were 78% versus 49% (AP) and 28% versus 19% (BP); KM probabilities of maintaining MCyR were 65% versus 49% (AP) and 21% versus 21% (BP).

—*Ibid*. (p. 755)

Haematological and cytogenetic response rates appeared higher in the second-line versus ≥third-line in both the AP and BP CML cohort

—*Ibid*. (p. 758)

[Bosutinib] demonstrates a durable response, with ~50% of AP responders maintaining a response at 4 years. Moreover, ~25% of BP responders maintained response to treatment at 1 year.

—*Ibid*. (p. 767)

Bcr-Abl kinase domain mutations

Sixty-two (78%) AP and 53 (83%) BP patients had mutation assessment at baseline. There were 16 and 13 unique mutations in 32 (52%) AP and 28 (53%) BP patients, including 2 (3%) AP and 6 (11%) BP patients who had ≥2 mutations. Mutations occurring in more than five patients (AP and BP cohorts) included T315I (AP, N=3; BP, N=10), F317L (AP, N=4; BP, N=4), G250E (AP, N=4; BP, N=2), and Y253H (AP, N=3; BP, N=4).

In the AP CML cohort, OHR and MCyR rates were 57% (n = 16/28) and 39% (n = 11/28) in patients with ≥1 mutation (62% [n = 16/26] and 44% [n = 11/25], respectively, excluding T315I), versus 62% (n = 18/29) and 43% (n = 12/28) without a mutation. Among the 11 AP patients with ≥1 baseline mutation who had an MCyR, 10 newly attained an MCyR whereas only 1 (with a G321R mutation) maintained an MCyR from baseline while on bosutinib treatment.

In the BP CML cohort, OHR and MCyR rates were 27% (n = 7/26) and 17% (n = 4/23) in patients with one mutation or more (35% [n = 6/17] and 20% [n = 3/15] respectively, excluding T315I), versus 25% (n = 6/24) and 45% (n = 9/20) without a mutation.

Responses were broadly achieved across baseline Bcr-Abl kinase domain mutations for AP and BP CML patients, except for patients with T315I for whom only one response was achieved.

Among 45 patients who were assessed for mutations at baseline and on-treatment, 13 had an emergent mutation at treatment discontinuation (AP CML, 4/24 [17%]; BP CML, 9/21 [43%]).

—*Ibid*. (p. 761)

Safety and adverse events

Most permanent treatment discontinuations (72% [n = 120]) occurred within the first year of treatment; fewer patients in the AP CML cohort permanently discontinued (52% [n = 41]) within the first year compared with patients in the BP CML (88% [n = 56]) cohort.

—*Ibid*. (p. 756)

Most common AEs (AP, BP) were gastrointestinal (96%; 83%), primarily diarrhea (85%; 64%), which was typically low grade (maximum grade 1/2: 81%; 59%) and transient, with no discontinuation due to diarrhea. Serious AEs occurred in 44 (56%) AP and 37 (58%) BP patients, most commonly pneumonia (n = 9) for AP and pyrexia (n = 6) for BP; 11 and 13 died within 30 days of last dose (2 considered bosutinib-related [AP] per investigator).

—*Ibid*. (p. 755)

Overall, serious AEs (SAEs) occurred in 59% (99/167) of patients; the most frequently occurring individual SAEs (≥5% of patients overall) included pneumonia (10%), pyrexia (7%), febrile neutropenia (6%), thrombocytopenia (6%), disease progression (5%), headache (5%), and pleural effusion (5%). […]

Adverse events as the primary reason for discontinuation occurred more frequently in AP CML (30% [n = 4]) versus the BP CML (6% [n = 4]) patients including discontinuations after year 4. Across the cohorts, the most common AE leading to treatment discontinuation was thrombocytopenia (n = 6); in general, most discontinuations due to AEs occurred during the first year of treatment.

—*Ibid*. (p. 764)

4.3.2.2 Additional RCT and non-RCT evidence

4.3.2.2.1 Study 3000 / BELA: RCT of bosutinib vs. imatinib in 1st line CML

Three studies[13, 15, 16] were identified in our scoping search relating to the BELA trial, a randomised controlled trial that evaluates bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia (CP CML).

The first paper (Cortes et al. 2012[13]) describes the design of the BELA trial, an ongoing, open-label, randomized, multinational phase 3 study. 502 patients, enrolled in 31 countries, were randomly assigned 1:1 to bosutinib 500 mg per day or imatinib 400 mg per day.

The complete cytogenetic response (CCyR) rate at 12 months was not different for bosutinib (70%; 95% CI, 64% to 76%) versus imatinib (68%; 95% CI, 62% to 74%; two-sided P=0.601); and so the study did not achieve its primary end point. The major molecular response (MMR) rate at 12 months was higher with bosutinib (41%; 95% CI, 35% to 47%) compared with imatinib (27%; 95% CI, 22% to 33%; two-sided P < 0.001). Time to CCyR and MMR was faster with bosutinib compared with imatinib (two-sided P < 0.001 for both). On-treatment transformation to accelerated/blast phase occurred in four patients (2%) on bosutinib compared with 10 patients (4%) on imatinib. A total of three CML-related deaths occurred on the bosutinib arm compared with eight on the imatinib arm. The safety profiles of bosutinib and imatinib were distinct; gastrointestinal and liver-related events were more frequent with bosutinib, whereas neutropenia, musculoskeletal disorders, and edema were more frequent with imatinib.

—Cortes et al. (2012)[13] (p. 3486)

The second paper:

> [Brummendorf et al.] assessed the efficacy and safety of bosutinib 500 mg/d (n = 250) versus imatinib 400 mg/d (n = 252) after >24 months from accrual completion in newly diagnosed chronic phase (CP)-CML […]. Cumulative complete cytogenetic response (CCyR) rates by 24 months were similar (bosutinib, 79%; imatinib, 80%); cumulative major molecular response (MMR) rates were 59% for bosutinib and 49% for imatinib. Responses were durable; 151/197 vs. 172/204 and 125/153 vs. 117/131 responders remained on treatment and maintained CCyR and MMR, respectively. Since the 12 month primary analysis, no new accelerated-/blast-phase transformations occurred with bosutinib, four occurred with imatinib. Early response (BCR-ABL1/ABL1 ≤ 10%, 3 months) was associated with better CCyR and MMR rates by 12 and 24 months (both arms). Gastrointestinal events and liver function test elevations were more common, and neutropenia, musculoskeletal events and oedema were less common with bosutinib. Discontinuation due to adverse events were more common with bosutinib versus imatinib (most common being alanine aminotransferase elevation: 4% vs. <1%); most occurred within the first 12 months. Cardiovascular adverse events were similar in both arms. Bosutinib continues to demonstrate good efficacy and manageable tolerability in newly diagnosed CP-CML patients.
>
> —Brümmendorf et al. (2015)[16] (p. 69)

The third paper (Gambacorti-Passerini et al. 2014[15]):

> Bosutinib, an orally active, Src/Abl tyrosine kinase inhibitor, has demonstrated clinical activity and acceptable tolerability in chronic phase chronic myeloid leukemia (CP CML). This updated analysis of the BELA trial assessed the safety profile and management of toxicities of bosutinib versus imatinib in adults with newly diagnosed (≤6 months) CP CML after >30 months from accrual completion. Among patients randomized to bosutinib 500 mg/d (n = 250) or imatinib 400 mg/d (n = 252), 248 and 251, respectively, received ≥1 dose of study treatment. Adverse events (AEs; any grade) with bosutinib versus imatinib were significantly more common for certain gastrointestinal events (diarrhea, 70% vs. 26%; P < 0.001; vomiting, 33% vs. 16%; P < 0.001), alanine aminotransferase (33% vs. 9%; P < 0.001) and aspartate aminotransferase (28% vs. 10%; P < 0.001) elevations, and pyrexia (19% vs. 12%; P = 0.046). AEs significantly less common with bosutinib included edema (periorbital, 2% vs. 14%; P < 0.001; peripheral, 5% vs. 12%; P50.006), musculoskeletal (myalgia, 5% vs. 12%; P = 0.010; muscle cramps, 5% vs. 22%; P < 0.001; bone pain, 4% vs. 11%; P = 0.003), increased creatine phosphokinase (8% vs. 20%; P < 0.001), neutropenia (13% vs. 30%; P < 0.001), and leukopenia (9% vs. 22%; P < 0.001). Between-group differences in the incidence of cardiac and vascular AEs were not significant. Diarrhea was typically transient, mostly Grade 1/2, occurring early during treatment, and was manageable with antidiarrheal medication.
>
> —Gambacorti-Passerini et al. (2014)[15] (p. 947)

4.3.2.2.2 Study evaluating SKI-606 (Bosutinib) in Japanese subjects with Philadelphia chromosome positive leukemias

This study is similar to Study 200 but is smaller and includes only in Japanese patients.[22] There were 46 patients in Part 2 of the study (efficacy study), of whom only 11 had previously been treated with two TKIs (i.e., 3rd line patients). The primary endpoint for Part 2

was the cumulative MCyR rate by week 24 for the chronic phase 2nd line cohort. Secondary endpoints for the 3rd line cohort were: MCyR (response rate, time to response, duration of response and maintenance of existing response), confirmed OHR, progression-free survival, time to treatment failure and overall survival. Other outcomes (including molecular response) were included as investigative efficacy endpoints.

At the time of the study report, 9/11 3rd line patients were still receiving bosutinib, none had progressed, died or been lost to follow-up. Six of the 3rd line patients had a CCyR at baseline. The cumulative MCyR rate at 24 weeks was 18%.

4.3.2.2.3 Spanish compassionate use registry

This study reports a case series of 30 patients with chronic phase CML receiving bosutinib as 4th line TKI.[24]

After median follow-up 11.5 months the following results were observed:

- Two of 15 patients without a baseline CCyR achieved a CCyR;
- Fifteen of 15 patients with a baseline CCyR maintained their CCyR;
- One patient died;
- Ten other patients discontinued bosutinib.

4.3.2.2.4 Other identified studies with results available

Primary studies identified but not described above are shown in *Table 12*. None of these studies was able to provide useful information relating to bosutinib in chronic myeloid leukaemia.

Table 12: Other identified primary studies with results available

Study	Study design	Number of patients treated with bosutinib
Anonymous 2014[25,a]	Retrospective case series	52
Milojkovic 2012[26]	Cohort study	3
Lang 2015[27]	Retrospective cohort study	1
Nicolini 2013[28]	Matched pair analysis	1

Notes: a, Full text could not be retrieved, data extracted from abstract

Five systematic reviews including bosutinib were identified,[29-33] but none of these included studies of bosutinib in CML which had not already been identified (*Table 13*).

Table 13: Secondary studies of bosutinib

Study	Design	Outcomes of interest	Bosutinib studies	Key relevant findings[a]
Efficace 2013[29]	Systematic review and narrative synthesis	Patient-reported outcomes	• Trask 2013[34] • Trask 2012[19]	2nd line therapy with bosutinib provides clinically meaningful HRQOL benefit over time in imatinib-intolerant patients but not in imatinib-resistant patients
Ferdinand 2012[30]	Systematic review and narrative synthesis	Efficacy and safety	• BELA • Study 200	"Current evidence from single-arm studies in the second-line setting confirm that nilotinib, dasatinib, and bosutinib are valuable treatment options for the significant subgroup of patients who are intolerant or resistant to imatinib treatment."
Firwana 2016[31]	Systematic review, direct meta-analyses and network meta-analyses	MMR, MR4.5, OS, PFS	• BELA	None
Gurion 2013[32]	Systematic review and meta-analysis	CCyR, MMR, transformation to AP/BP, mortality	• BELA	None
Stansfield 2013[33]	Systematic review and narrative synthesis	Efficacy, safety and pharmacokinetics	• BELA • Study 200 • Abbas 2012[35]	"In the second-line setting, bosutinib is effective in some patients with CML resistant or intolerant to imatinib, dasatinib, and/or nilotinib, but it is not effective in patients whose disease expresses the T315I point mutation in BCR-ABL."

Key: AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; HRQOL, health-related quality of life; MMR, major molecular response; MR4.5, 4.5-log reduction in BCR-ABL transcripts from baseline; OS, overall survival; PFS, progression-free survival

Notes: a, Only findings directly relevant to the decision problem are included

4.4 Conclusions of the clinical effectiveness section

The company did not submit additional clinical effectiveness evidence.

The ERG performed a scoping review to identify any new relevant results or studies, and found results from Study 200 published since TA299. The ERG also summarised the results of the BELA study, the only completed RCT of bosutinib in chronic myeloid leukaemia.

Study 200 demonstrates that bosutinib has efficacy in the licensed population and has an acceptable safety profile.

The BELA study demonstrates that bosutinib is effective in treating newly-diagnosed chronic myeloid leukaemia, although statistical significance in the primary endpoint was not reached in the comparison against imatinib. There is some evidence to suggest bosutinib may have greater efficacy than imatinib in this population. A new RCT is being conducted in this population which will use MMR at 12 months as the primary efficacy endpoint.

There are no comparative studies of bosutinib in the licensed population, so there is significant uncertainty about the relative effectiveness of bosutinib versus the comparators listed in the NICE Final Scope.

5 Cost-effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

The company has not submitted a new review of cost-effectiveness evidence.

In TA299 the company submitted a review which identified no studies investigating the cost-effectiveness of bosutinib in refractory CML, and this was accepted by the ERG.[2]

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 14: Critical appraisal against NICE reference case

NICE reference case[36] requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	P	Population limited for consistency with marketing authorisation (as in TA299), and patients assumed to receive bosutinib as 3rd line TKI
Comparator	As listed in the scope developed by NICE	N	Relevant comparators excluded (see *Section 3.3*, *page 17*)
Perspective on costs	NHS and PSS	Y	
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Y	
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Y	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Y	
Synthesis of evidence on outcomes	Based on a systematic review	Y	
Measure of health benefits	Health effects should be expressed in QALYs The EQ-5D is the preferred measure of health-related quality of life in adults	Y	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Y	

Source of preference data for valuation of changes in HRQL	Representative sample of the UK population	Y
Discount rate	3.5% p.a. for costs and health effects	Y
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y

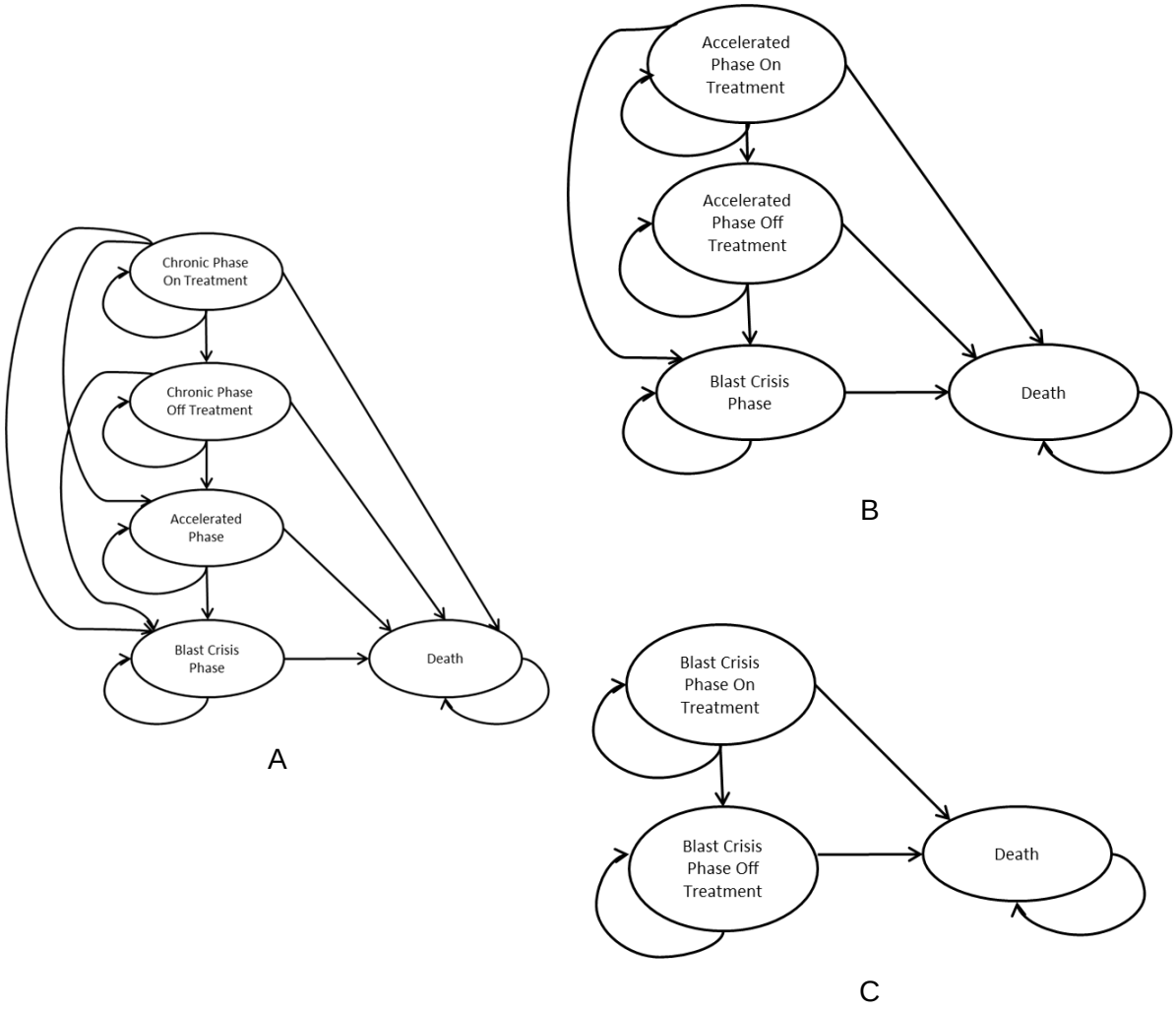
Key: EQ-5D; EuroQol 5 Dimensions; HRQL, health-related quality of life; N, No; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; QALY, quality-adjusted life year; P, Partial; p.a., per annum; PSS, personal social services; U, Unclear; Y, Yes

5.2.2 Model structure

5.2.2.1 Survival partition

A survival partition model was utilised in the company submission in NICE TA299, with health states as shown in *Figure 1*.[1] All patients were assumed to receive hydroxycarbamide in all health states except for bosutinib patients in the "On Treatment" state, who were assumed to receive bosutinib. Hydroxycarbamide patients did not transition to the "Off Treatment" health state, but directly progressed to the next disease phase or death.

Figure 1: Model structure diagram



Key: A, Chronic phase cohort; B, Accelerated phase cohort; C, Blast phase cohort

The model did not allow for AP and BP patients to return to chronic phase, although this is a possibility for patients receiving active treatment.

In the company submission for TA299, state membership was estimated by first assigning a proportion of the cohort to the death state to match the treatment- and cohort-specific overall survival curve. Then a proportion of the cohort was assigned to the blast phase state such that patients spend 6 months in this state, and a proportion was similarly assigned to the accelerated phase for 10 months. Finally, a treatment- and cohort-specific treatment duration curve was used to assign patients to the “On Treatment” and “Off Treatment” states.

This approach led to a significant post-treatment benefit from bosutinib, which the ERG and Committee considered to be overly optimistic.[1] The ERG conducted an exploratory analysis, the “cumulative survival approach”, as described in *Section 5.2.2.2*.

5.2.2.2 Cumulative survival approach

The cumulative survival approach assumes that there is no post-discontinuation benefit from bosutinib treatment, and that after patients discontinue bosutinib they should experience the same outcomes as patients initially treated with hydroxycarbamide.

This approach does not rely on overall survival estimates, which are subject to significant uncertainty and confounding due to subsequent active treatments which are not modelled. This approach instead makes use of the treatment duration estimates, which are expected to be reflective of the benefit patients receive specifically due to taking bosutinib.

Undiscounted outputs (costs, life years and QALYs) are estimated as shown in *Table 15*.

Table 15: Calculation of undiscounted outputs in the cumulative survival approach

Model phase	Hydroxycarbamide	Bosutinib
Chronic Phase On Treatment	A	B
Chronic Phase Off Treatment	—	A
Accelerated Phase	C	C
Blast Phase	D	D
Death	E	E
Adverse Events	F	G

Key: A, Chronic Phase On Treatment from SP model, HC arm; B, Chronic Phase On Treatment from SP model, bosutinib arm; C, Accelerated Phase from SP model, HC arm; D, Blast Phase from SP model, HC arm; E, Death from SP model, HC arm; F, Adverse Events from SP model, HC arm; G, Adverse events from SP model, bosutinib arm; HC, hydroxycarbamide; SP, survival partition

5.2.2.2.1 Discounted outputs

Discounted outputs (costs, life years and QALYs) are calculated by applying a discounting factor to the undiscounted outputs for each model state. The discounting factor is calculated assuming that the entire cohort spends exactly the mean time in each state, i.e., that the whole cohort transitions at the same time. This is an approximation, but the ERG believes it is unlikely to affect the ICER.

Equation (1) gives the formula for the discounted life years in each state, where the states are numbered in the order the cohort is assumed to progress. For patients starting in the chronic phase, the states are: 1) Chronic phase on treatment; 2) Chronic phase off treatment; 3) Accelerated phase; 4) Blast phase.

$$\text{Discounted life years in state } i = \int_{a_i}^{b_i} (1+r)^{-t}\,\mathrm{d}t = \int_{a_i}^{b_i} \frac{-e^{-\ln(1+r)t}}{\ln(1+r)}\,\mathrm{d}t = -\left(\frac{e^{-\ln(1+r)b_i} - e^{-\ln(1+r)a_i}}{\ln(1+r)}\right) \quad (1)$$

Where $a_i = \sum_{j=1}^{i-1} t_j$ and $b_i = \sum_{j=1}^{i} t_j$, t_j is the mean undiscounted life years in state j and r is the annual discount rate

The discount factor for costs and QALYs is then calculated as the ratio of the discounted life years to the undiscounted life years for a given health state.

The discounted costs of palliative care are discounted assuming that they occur exactly at the time of mean overall survival.

5.2.3 Population

The population is unchanged from the submission to TA299:

> Bosutinib is indicated for patients with Ph^+ CML in the chronic, accelerated or blast phase who have failed one or more TKIs and for whom imatinib, nilotinib and dasatinib are considered inappropriate.
>
> Pfizer estimate that each year, 80 of the 631 annual CML cases in England and Wales will be eligible to receive bosutinib, and of these 12 (15%) will be eligible to receive it second-line (following imatinib failure), 19 (24%) will be eligible to receive it third-line (following failure of imatinib and nilotinib), and 49 (61%) will be eligible to receive it fourth-line (Pfizer submission [TA299], Section 8.1, pp188-189).
>
> Pfizer suggest that the third-line chronic phase cohort in Study 200 is most representative of the intended population, and hence this forms the basis of the population in the CP model and for many other parameters in the CP model.
>
> All patients in the CP model were assumed to start treatment at age 54 years, which was the mean baseline age in the third-line CP cohort of Study 200 (Pfizer submission, Section 7.3.2, p124). All patients in the AP and BP models were assumed to start treatment aged 50 and 47 years respectively, which were the mean baseline ages in the AP and BP cohorts of Study 200 (Pfizer submission [TA299], Section 7.3.2, p124).
>
> Pfizer assumed equal proportions of males and females in the patient population.
>
> No assumptions were made in the model about previous treatments, although Study 200 evaluated patients who received imatinib first-line, followed by nilotinib and/or dasatinib. Some patients in Study 200 had previous interferon use (52% of third-line CP cohort, 50% of AP cohort and 30% of BP cohort) and some patients had previously received stem cell transplants (8% of third-line CP cohort, 9% of AP cohort and 6% of BP cohort).
>
> There were no subgroups in any of the models.
>
> —Hoyle et al. (2013)[2] (p. 115)

In TA299, the ERG noted the possibility that bosutinib might in clinical practice be used significantly 2nd-line, on the basis that nilotinib would displace imatinib as 1st-line therapy and that patients resistant to nilotinib would be unlikely to benefit from 2nd-line imatinib. Third-line usage was maintained as the base case, with second-line usage included as a scenario analysis.

The Committee concluded that bosutinib would be likely to be a third- or fourth-line tyrosine kinase inhibitor,[1] and this seems to reflect current clinical practice.

The ERG again note the lack of subgroups in any of the models. The inclusion of subgroups according to the reason for discontinuing previous TKIs would, in the ERG's view, be of value, since patients' response to and tolerability of bosutinib are influenced by this.

5.2.4 Interventions and comparators

As noted in *Section 3.3* (*page 17*), the current submission does not include interferon alfa or allogeneic stem cell transplant, both of which were included as comparators in TA299.[1]

While the ERG considers the exclusion of interferon alfa to be justified, the removal of allogeneic stem cell transplant is not justified. Nevertheless, the removal of allogeneic stem cell transplant is not thought likely to result in significant bias in the cost-effectiveness results.

5.2.5 Perspective, time horizon and discounting

The perspectives on costs and outcomes match the NICE reference case, i.e., NHS and PSS for costs, and direct health effects on patients (no effects on carers included).

The model uses a lifetime (50 years) time horizon.

Costs and QALYs are discounted at 3.5% per annum, and life years are undiscounted.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness in the model is determined by overall survival and the time to transformation to AP and BP (except in the BP cohort).

Time to transformation to AP and BP is not estimated directly from Study 200, but is calculated such that patients spend 10 months on average in AP and six months in BP. These durations were based on previous NICE technology appraisals in chronic myeloid leukaemia.

5.2.6.1 Overall survival

5.2.6.1.1 Bosutinib

The company submission for NICE TA299 extrapolated overall survival from short term outcomes in Study 200. A surrogate relationship between MCyR and overall survival was used for the CP cohort, while observed overall survival was extrapolated with an exponential survival distribution for the AP and BP cohorts.

These overall survival estimates were not robust, and they lacked face validity, since a significant post-treatment benefit was assumed as a consequence. One of the key reasons why overall survival was overestimated was that many patients in Study 200 (and in the study from which the surrogate relationship was derived), had further active treatment after discontinuing the present line of treatment. This confounds the estimate of overall survival and biases it upwards compared to survival in patients whose only treatment option after bosutinib discontinuation is hydroxycarbamide.

The ERG in NICE TA299 proposed instead that since treatment duration was observed in the trial, it would be more realistic to assume that patients would receive bosutinib until it no longer benefited them, and then they would receive hydroxycarbamide. The cumulative survival approach (see *Section 5.2.2.2*, *page 40*) is based on this assumption and was used by the Committee as its basis for decision making.

In the current submission, the company have incorporated the cumulative survival approach into their base case.

5.2.6.1.2 Hydroxycarbamide

Overall survival for patients treated with hydroxycarbamide (i.e., not receiving bosutinib) was estimated to be 3.5 years for CP patients, 16 months for AP patients and 6 months for BP patients.

In NICE TA299 the Committee considered the possibility that overall survival for patients treated with hydroxycarbamide could be longer than 3.5 years. The Committee concluded that overall survival was likely to be at the lower end of the range 3.5–7 years, and used 3.5 years as the base case value.

Despite the fact that alternative assumptions regarding overall survival with hydroxycarbamide also affect predicted overall with bosutinib (with the cumulative survival approach), the cost-effectiveness of bosutinib is still influenced significantly by this parameter, which is poorly estimated (see *Section 5.3.3*, *page 53* and *Section 6.3*, *page 57*).

5.2.7 Health related quality of life

The current submission uses quality of life data from Study 200, which was collected while patients remained on bosutinib treatment. This was measured using the EQ-5D (-3L) and valued using the UK tariff.

In the model, utility is assumed to be dependent on disease phase (chronic phase, accelerated phase and blast phase), age, and whether the patient is receiving bosutinib. It is implemented as a phase- and treatment-dependent utility multiplier applied to age-dependent general population utility (see *Table 16*).

Table 16: Utilities and utility multipliers in the economic model

Treatment	Chronic phase	Accelerated phase	Blast phase
Mean utility			
Bosutinib	[redacted]	[redacted]	[redacted]
Hydroxycarbamide	[redacted]	[redacted]	[redacted]
Utility multiplier			
Bosutinib	[redacted]	[redacted]	[redacted]
Hydroxycarbamide	[redacted]	[redacted]	[redacted]

The derivation of these is not described, since these were not used in the base case in TA299. The utilities for hydroxycarbamide appear to be taken from the mean utilities at screening. The utilities for bosutinib appear to be the weighted average of mean utilities, excluding screening.

While it is common to use more advanced statistical analyses (e.g., generalised estimating equations) to account for within-patient correlation and unbalanced data, a simple weighted average is likely to be sufficient in this case. More likely to be an issue is that patients with worse health-related quality of life may be less likely to report, even though they continue to receive the treatment.

In conclusion, the ERG believes the utility values chosen by the company are a reasonable basis for the base case.

5.2.8 Resources and costs

Resources and costs are the same as those included in TA299 apart from the following:

- A revised patient access scheme for bosutinib (see *Section 5.2.8.1.2*, *page 45*);
- Unit costs updated to 2014/15 prices, based on the following sources:

- NHS reference costs 2014 to 2015[37]
- Unit costs of health and social care 2015[38]: costs were inflated using the hospital and community health services (HCHS) pay and prices index of 293.1 (2014/15)

5.2.8.1 Drug acquisition

5.2.8.1.1 Resource use

Treatment duration

Patients treated with hydroxycarbamide receive hydroxycarbamide until death.

The treatment duration for bosutinib in the chronic phase was estimated by fitting a lognormal curve to individual patient data from Study 200, as shown in *Figure 2*. The lognormal curve was selected since it had the lowest Akaike Information Criterion value of the models fitted and was judged to have face validity. The same approach was also used for patients starting in the accelerated and blast phases.

Figure 2: Treatment discontinuation in Study 200

This parametric model would lead to median treatment duration (for patients starting in the chronic phase) of [redacted] and mean treatment duration of [redacted], except that the On Treatment state membership is capped to match overall survival and to obtain 10 months and 6 months duration in the accelerated and blast phase states, so the mean treatment duration output from the model is [redacted].

After discontinuing bosutinib, patients receive hydroxycarbamide until death.

Average daily dose

In the company's base case, the average daily dose of bosutinib is the licensed dose of 500 mg per day. A scenario analysis is included in the model to use dosing from Study 200, in which the average daily dose of bosutinib is:

- [redacted]
- [redacted]
- [redacted]

5.2.8.1.2 Unit costs

Bosutinib

The company have proposed a patient access scheme for bosutinib in the form of a simple confidential discount.

The list price of bosutinib is £3,436.67 per 28 tablets (500 mg).[10]

[redacted]

Hydroxycarbamide

The company assume a cost of £10.55 for a pack of 100 × 500 mg tablets. The ERG note that the current BNF price for hydroxycarbamide is £10.47,[10] while the Commercial Medicines Unit eMIT database estimates the average cost to be £8.77.[39]

The ERG checked the impact of using these alternative costs and found there was a negligible impact on the ICERs for bosutinib.

5.2.8.2 Drug administration

The company assume no drug administration costs for bosutinib or hydroxycarbamide, since these are both taken orally by patients at home.

5.2.8.3 Medical management, monitoring and tests

The current submission uses the ERG's preferred medical management, monitoring and tests resource use from TA299 (see *Table 17*).

Table 17: Costs of medical management, monitoring and tests

Resource	Resource use (per month)			Unit costs
	CP (Bosutinib)	*CP (HC)*	*AP and BP*	*(2014/15 prices)*
Nurse-led outpatient appointments	0.00	0.00	0.50	£92.00
Haematologist / Oncologist-led outpatient appointments	0.33[a]	0.72	1.30	£150.00
Hospital in patient-ward days	0.00	0.00	1.72	£383.28
Hospital in patient - ICU days	0.00	0.00	0.10	£1,331.27

Key: AP, accelerated phase; BP, blast phase; CP, chronic phase; HC, hydroxycarbamide; ICU, intensive care unit
Notes: a, Plus two appointments at time 0
Source: NHS reference costs 2014 to 2015[37]

5.2.8.4 Adverse events

The current submission includes costs of adverse events for patients receiving bosutinib (£580.13) but not for patients receiving hydroxycarbamide. The company indicated in TA299 that this leads to a conservative estimate of the costs associated with bosutinib, although this represents less than 1% of the incremental costs associated with bosutinib.

In TA299 the ERG noted that the methodology employed assumed the same costs for CP, AP and BP patients, even though the evidence suggests that costs would be doubled for AP and BP compared to CP. The ERG concluded this would not have a significant impact on cost-effectiveness and so no further analyses have been conducted in this review.

5.2.8.5 Palliative care

The current submission uses a cost of £6,160 for death based on a cost of £5,401 reported by Addicott and Dewar (2008)[40] and inflated from 2007/08 prices. The ERG are content that this is an appropriate cost.

5.2.9 Cost effectiveness results

Throughout, life years are presented undiscounted (unless otherwise stated) and costs and QALYs are presented discounted (unless otherwise stated).

The deterministic cost-effectiveness results presented by the company are given in *Table 18*. These indicate that bosutinib is associated with ICERs of [redacted], [redacted] and [redacted] per QALY in the chronic, accelerated and blast phase cohorts respectively.

Table 18: Deterministic cost-effectiveness results (company current submission; currently proposed patient access scheme)

Cohort	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Chronic phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Accelerated phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blast phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

5.2.9.1 Chronic phase

Table 19 and *Table 20* provide the key disaggregated outcomes from the company's current submission for chronic phase patients.

Table 19: Key outcomes for bosutinib in chronic phase patients (company current submission; currently proposed patient access scheme)

Outcome	Life years	QALYs	Costs
Chronic Phase On Treatment	[redacted]	[redacted]	[redacted]
Chronic Phase Off Treatment	[redacted]	[redacted]	[redacted]
Accelerated Phase	[redacted]	[redacted]	[redacted]
Blast Phase	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life year

Table 20: Key outcomes for hydroxycarbamide in chronic phase patients (company current submission; currently proposed patient access scheme)

Outcome	Life years	QALYs	Costs
Chronic Phase On Treatment	[redacted]	[redacted]	[redacted]
Chronic Phase Off Treatment	[redacted]	[redacted]	[redacted]
Accelerated Phase	[redacted]	[redacted]	[redacted]
Blast Phase	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life year

5.2.9.2 Accelerated phase

Table 21 and *Table 22* provide the key disaggregated outcomes from the company's current submission for accelerated phase patients.

Table 21: Key outcomes for bosutinib in accelerated phase patients (company current submission; currently proposed patient access scheme)

Outcome	Life years	QALYs	Costs
Accelerated Phase On Treatment	[redacted]	[redacted]	[redacted]
Accelerated Phase Off Treatment	[redacted]	[redacted]	[redacted]
Blast Phase	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life year

Table 22: Key outcomes for hydroxycarbamide in accelerated phase patients (company current submission; currently proposed patient access scheme)

Outcome	Life years	QALYs	Costs
Accelerated Phase On Treatment	[redacted]	[redacted]	[redacted]
Accelerated Phase Off Treatment	[redacted]	[redacted]	[redacted]
Blast Phase	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life year

5.2.9.3 Blast phase

Table 23 and *Table 24* provide the key disaggregated outcomes from the company's current submission for blast phase patients.

Table 23: Key outcomes for bosutinib in blast phase patients (company current submission; currently proposed patient access scheme)

Outcome	Life years	QALYs	Costs
Blast Phase On Treatment	[redacted]	[redacted]	[redacted]
Blast Phase Off Treatment	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life year

Table 24: Key outcomes for hydroxycarbamide in blast phase patients (company current submission; currently proposed patient access scheme)

Outcome	Life years	QALYs	Costs
Blast Phase On Treatment	[redacted]	[redacted]	[redacted]
Blast Phase Off Treatment	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life year

5.2.10 Sensitivity analyses

5.2.10.1 Univariate sensitivity analyses

The company have neither presented univariate sensitivity analyses in the current submission nor in their submission for TA299 (although some scenario analyses presented in TA299 only involved changing one parameter value).

5.2.10.2 Scenario analyses

5.2.10.2.1 Previously proposed patient access scheme (TA299)

The company present the results of the current submitted model using the previously proposed patient access scheme, which formed the basis of the Committee's decision in TA299. The previously proposed patient access scheme was a simple discount of [redacted], compared to the currently proposed patient access scheme using a simple discount of [redacted].

Table 25 gives the deterministic cost-effectiveness results in this scenario. These indicate that bosutinib is associated with ICERs of £42,068, £62,231 and £60,859 per QALY in the chronic, accelerated and blast phase cohorts respectively. These compare to the Committee's most plausible ICERs of £43,000 (range £40,000 to £50,000), £58,000 and £60,000 per QALY.[1]

Table 25: Deterministic cost-effectiveness results (company current submission; previously proposed patient access scheme)

Cohort	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Chronic phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,068
Accelerated phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,231
Blast phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,859

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

5.2.10.2.2 Prolonged post-treatment overall survival benefit

The company conducted scenario analyses for chronic phase patients where up to three months' additional overall survival benefit is assumed compared to the base case cumulative survival approach. *Table 26* shows the impact on cost-effectiveness as the duration of post-treatment overall survival benefit is increased. In TA299 the Committee concluded that "on the presented evidence any benefit could more reasonably be argued to be 1 or 2 months".[1] [redacted]

Table 26: Deterministic cost-effectiveness results as overall survival benefit is adjusted (company current submission; currently proposed patient access scheme)

Extension	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Base case							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+2 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+3 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

5.2.10.3 Probabilistic sensitivity analysis

In the current submission, the company present only the results of probabilistic sensitivity analysis (PSA) in chronic phase patients. The cost-effectiveness scatterplot (*Figure 3*) indicates there is good agreement between the deterministic and probabilistic analyses. It also indicates that bosutinib is most likely to be more expensive and more effective than hydroxycarbamide. The ICER for bosutinib is estimated to be [redacted] per QALY, compared to [redacted] per QALY in the deterministic analysis.

The cost-effectiveness acceptability curves (*Figure 4*) show that at a willingness-to-pay threshold of £20,000 (£30,000) per QALY, the probability bosutinib is cost-effective is [redacted] ([redacted]).

Figure 3: Cost-effectiveness scatterplot

Key: QALY, quality-adjusted life year
Source: Pfizer submission (2016), Figure 1

Figure 4: Cost-effectiveness acceptability curves

Key: HU, hydroxycarbamide (hydroxyurea); QALY, quality-adjusted life year
Source: Pfizer submission (2016), Figure 2

The current submission does not include PSA for accelerated or blast phase cohorts.

The ERG note that a number of uncertainties are not reflected in the PSA:

- The post-treatment survival benefit due to bosutinib (exactly zero in the PSA);

- Other structural uncertainty, e.g., curve fitting and extrapolation of treatment duration.

As a result, although the probabilistic results are in line with the deterministic results, this should not be seen as a full exploration of the uncertainty in the decision problem.

For this reason, the ERG have not attempted to PSA for the accelerated or blast phase cohorts.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Modelling hydroxycarbamide with the cumulative survival approach

The model submitted by the company estimated costs and outcomes for bosutinib using the cumulative survival approach, but used the survival partition model for the costs and outcomes of hydroxycarbamide. This was an unjustified asymmetry in the model, since the cumulative survival approach relies on an approximation for discounting. The ERG applied the same methodology for costs and outcomes for hydroxycarbamide as used for bosutinib.

5.3.2 Corrections to scenario analyses

A number of implementation issues were identified with the scenario analyses described in *Section 5.2.10.2.2* (*page 50*). These related to the calculation of undiscounted outcomes (not reported) and discounted outcomes (reported). The adjustments to the discounted outcomes did not account for discounting of the extra overall survival.

The company submission assumes that the additional overall survival is spent in the Chronic Phase Off Treatment state, so the ERG applied discounting assuming this extra time occurred at the mean treatment duration of bosutinib (i.e., immediately following discontinuation). This resulted in a discount factor of [redacted].

5.3.3 Alternative overall survival estimates for hydroxycarbamide in chronic phase

To explore the sensitivity of the cost-effectiveness results to the overall survival estimate for hydroxycarbamide, the ERG conducted two scenario analyses: one in which overall survival was 2 years, and one in which overall survival was 5 years.

5.4 Conclusions of the cost-effectiveness section

The company submission adapts the submission from TA299 to incorporate the Committee's preferred assumptions from TA299 and a newly proposed patient access scheme.

The current submission also removes two comparators which were included in TA299: interferon alfa and allogeneic stem cell transplant. The removal of interferon alfa was felt to be justifiable, whereas the removal of stem cell transplant was not adequately justified. The ERG concluded that the removal of stem cell transplant has not led to a biased representation of the cost-effectiveness of bosutinib.

The submission estimates the cost-effectiveness of bosutinib in the three phases of chronic myeloid leukaemia (chronic phase, accelerated phase, blast phase), but has not estimated the cost-effectiveness of bosutinib according to whether patients discontinued prior treatments mainly due to resistance or intolerance.

There is considerable uncertainty regarding the relative effectiveness of bosutinib versus hydroxycarbamide, since it has not been estimated in any comparative studies.

The cumulative survival approach employed in the submission assumes that life expectancy following discontinuation of bosutinib treatment is equal to life expectancy in the absence of bosutinib treatment, i.e., a given patient's life expectancy is extended exactly by the length of time they are treated with bosutinib. There are reasons why the extension may be less than or greater than this duration.

The extension may be less because patients will be older after discontinuing bosutinib (by [redacted] on average) and therefore their life expectancy would normally be expected to be reduced due to increased mortality rates from other causes and increased risk of comorbidities. The extension may also be less because clinicians are likely to continue bosutinib treatment while there is still a treatment effect (especially if bosutinib is the last line of treatment available), and could potentially continue to use bosutinib until progression or transformation into accelerated phase CML.

On the other hand, the extension may be greater since disease load may on average be reduced from baseline, although evidence has not been presented that this was the case in Study 200.

Sections 6.2 and *6.3* demonstrate that the cost-effectiveness of bosutinib is sensitive to assumptions about the relative effectiveness of bosutinib versus hydroxycarbamide, and the absolute effectiveness of hydroxycarbamide. There is considerable uncertainty about both of these quantities.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The only change proposed by the ERG for the base case analysis is as described in *Section 5.3.1* (*page 53*). Corrections were also made to a set of scenario analyses.

6.1 Modelling hydroxycarbamide with the cumulative survival approach

Table 27 shows the cost-effectiveness results when hydroxycarbamide is modelled with the cumulative survival approach. The ICERs in the company submission, for reference, are [redacted], [redacted] and [redacted] per QALY in the chronic, accelerated and blast phase cohorts respectively. This change has slightly increased the ICERs, most notably for chronic phase patients.

Table 27: Deterministic cost-effectiveness results when hydroxycarbamide is modelled with the cumulative survival approach

Cohort	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Chronic phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Accelerated phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blast phase							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

6.2 Scenario analyses for prolonged post-treatment overall survival benefit

Corrections to the implementation of these scenario analyses, combined with the change described in *Section 6.1 above*, lead to the results shown in *Table 28*. The impact of these corrections is that the ICER decreases more slowly as the post-treatment benefit is increased compared to the company's analyses. The ERG has also included a scenario in which overall survival is extended by one month *less* than the treatment duration; it can be seen that the change in ICER is nonlinear with respect to the change in overall survival.

Table 28: Scenario analyses for prolonged post-treatment overall survival benefit (including ERG corrections)

Extension	**Total**			**Incremental**			**ICER (£/QALY)**
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Base case							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+2 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+3 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
−1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

6.3 Sensitivity analysis for overall survival of hydroxycarbamide

Table 29 demonstrates that the ICER of bosutinib is sensitive to the assumed overall survival of hydroxycarbamide, even though this does not affect relative effectiveness in terms of overall survival.

Table 29: Sensitivity analysis for overall survival of hydroxycarbamide (including ERG corrections)

Extension	**Total**			**Incremental**			**ICER (£/QALY)**
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Base case							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HC OS = 2 years							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HC OS = 5 years							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: HC, hydroxycarbamide; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year

7 End of life

In TA299, the Committee concluded that the end-of-life criteria had been met for bosutinib for patients in the accelerated and blast phases.[1]

The ERG at the time expressed reservations that the life expectancy for patients in the accelerated phase (in the absence of bosutinib) would be less than 24 months, and also suggested that the assumptions made in the reference case economic modelling were not robust.[2] The ERG is not aware of any new data addressing the first point. The robustness of the economic modelling has been improved by replacing the surrogate survival method with the cumulative survival approach, but it is important to note that the cumulative survival approach is based on an assumption about post-treatment overall survival benefit which is informed only by clinical opinion. It has also been demonstrated that the cost-effectiveness results are sensitive to the assumed overall survival for patients receiving hydroxycarbamide, which has also not been estimated robustly.

8 Overall conclusions

The company submission closely reflects the conclusions of the Committee in TA299, and incorporates the main elements of the ERG preferred base case from TA299.

The company submission also includes a newly proposed patient access scheme.

The ERG has suggested only one change to the base case analysis, which leads to a small increase in the ICERs for bosutinib across the cohorts.

The cost-effectiveness of bosutinib is sensitive to assumptions about the relative effectiveness of bosutinib versus hydroxycarbamide, and the absolute effectiveness of hydroxycarbamide. There is considerable uncertainty about both of these quantities.

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Appendix 1. Bibliographic database searches

Embase

Platform: Ovid

Date: 7 April 2016

Database issue: **Embase** 1974 to 2016 April 06

Searcher: Tristan Snowsill

Hits: 68

#	Searches	Results
1	exp chronic myeloid leukemia/	35133
2	exp myeloid leukemia/	75384
3	chronic.mp. or exp CHRONIC DISEASE/	1427906
4	2 and 3	43403
5	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	44533
6	1 or 4 or 5	47531
7	exp bosutinib/	1448
8	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1491
9	7 or 8	1491
10	exp Meta Analysis/	106326
11	((meta adj analy$) or metaanalys$).tw.	116854
12	(systematic adj (review$1 or overview$1)).tw.	96636
13	or/10-12	208155
14	cancerlit.ab.	671
15	cochrane.ab.	51599
16	embase.ab.	51811
17	(psychlit or psyclit).ab.	962
18	(psychinfo or psycinfo).ab.	12133
19	(cinahl or cinhal).ab.	15740
20	science citation index.ab.	2532
21	bids.ab.	497
22	or/14-21	82182
23	reference lists.ab.	12278
24	bibliograph$.ab.	16864
25	hand-search$.ab.	5622
26	manual search$.ab.	3438
27	relevant journals.ab.	978
28	or/23-27	35257
29	data extraction.ab.	14973
30	selection criteria.ab.	23946
31	29 or 30	37511

32	review.pt.	2144706
33	31 and 32	17941
34	letter.pt.	930870
35	editorial.pt.	504294
36	animal/	1738059
37	human/	16851237
38	36 not (36 and 37)	1305907
39	or/34-35,38	2725538
40	13 or 22 or 28 or 33	248992
41	40 not 39	241263
42	Clinical trial/	859375
43	Randomized Controlled Trial/	399308
44	Randomization/	69785
45	Single blind procedure/	21793
46	Double blind procedure/	129735
47	Crossover procedure/	46580
48	Placebo/	285330
49	Randomi?ed controlled trial$.tw.	132543
50	RCT.tw.	19819
51	Random allocation.tw.	1543
52	Randomly allocated.tw.	24535
53	Allocated randomly.tw.	2117
54	(allocated adj2 random).tw.	831
55	Single blind$.tw.	17384
56	Double blind$.tw.	166735
57	((Treble or Triple) adj blind$).tw.	560
58	Placebo$.tw.	235331
59	Prospective study/	327591
60	or/42-59	1573827
61	Case study/	37145
62	Case report.tw.	311944
63	Abstract report/ or letter/	973598
64	or/61-63	1315780
65	60 not 64	1532589
66	Clinical study/	120496
67	Case control study/	103095
68	Family study/	11285
69	Longitudinal study/	86066
70	Retrospective study/	455407
71	Prospective study/	327591
72	Randomized controlled trials/	94384
73	71 not 72	324908
74	Cohort analysis/	236674
75	(Cohort adj (study or studies)).mp.	161292
76	(Case control adj (study or studies)).tw.	92551
77	(follow up adj (study or studies)).tw.	51771

78	(observational adj (study or studies)).tw.	88664
79	(epidemiologic$ adj (study or studies)).tw.	84956
80	(cross sectional adj (study or studies)).tw.	116166
81	or/66-70,73-80	1540834
82	41 or 65 or 81	2801166
83	6 and 9 and 82	277
84	limit 83 to yr="2012 -Current"	68

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations

Platform: Ovid

Date: 7 April 2016

Database issues: **MEDLINE** 1946 to March Week 5 2016; **MEDLINE In-Process & Other Non-Indexed Citations** April 06, 2016

Searcher: Tristan Snowsill

Hits: 31+3

#	Searches	MEDLINE	MEDLINE In-Process & Other Non-Indexed Citations
1	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	17104	0
2	exp Leukemia, Myeloid/	83789	0
3	exp Chronic Disease/ or chronic.mp.	987511	72600
4	2 and 3	24600	0
5	(chronic adj1 myel* adj1 leuk?emia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	25613	1274
6	1 or 4 or 5	29763	1274
7	(bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	251	43
8	Randomized controlled trials as Topic/	102386	0
9	Randomized Controlled Trial/	411978	586
10	Random allocation/	86260	0
11	Double blind method/	134422	0
12	Single blind method/	21619	0
13	Clinical trial/	498624	396
14	exp Clinical Trials as Topic/	290438	0
15	or/8-14	981318	694
16	(clinic$ adj trial$1).tw.	225701	26795
17	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	131485	9134
18	Placebos/	33206	0
19	Placebo$.tw.	162234	11840
20	Randomly allocated.tw.	17603	2369
21	(allocated adj2 random).tw.	707	22

22	or/16-21	432709	40508
23	15 or 22	1122991	40928
24	Case report.tw.	198972	33017
25	Letter/	878310	31252
26	Historical article/	329039	0
27	Review of reported cases.pt.	0	0
28	Review, multicase.pt.	0	0
29	or/24-28	1393988	63798
30	23 not 29	1093782	40661
31	Epidemiologic studies/	7079	0
32	exp case control studies/	769481	0
33	exp cohort studies/	1517858	0
34	Case control.tw.	83237	8818
35	(cohort adj (study or studies)).tw.	98944	14257
36	Cohort analy$.tw.	4156	541
37	(Follow up adj (study or studies)).tw.	38409	2340
38	(observational adj (study or studies)).tw.	49968	9131
39	Longitudinal.tw.	147040	18735
40	Retrospective.tw.	296548	38294
41	Cross sectional.tw.	181737	31748
42	Cross-sectional studies/	211263	0
43	or/31-42	2067448	109235
44	Meta-Analysis as Topic/	14733	0
45	meta analy$.tw.	73514	14410
46	metaanaly$.tw.	1425	156
47	Meta-Analysis/	63705	183
48	(systematic adj (review$1 or overview$1)).tw.	62463	15435
49	exp Review Literature as Topic/	8506	0
50	or/44-49	139911	24076
51	cochrane.ab.	34828	7240
52	embase.ab.	34734	7900
53	(psychlit or psyclit).ab.	855	29
54	(psychinfo or psycinfo).ab.	8328	3107
55	(cinahl or cinhal).ab.	11735	2370
56	science citation index.ab.	2123	233
57	bids.ab.	357	28
58	cancerlit.ab.	579	24
59	or/51-58	54749	13178
60	reference list$.ab.	10666	1416
61	bibliograph$.ab.	11864	1387
62	hand-search$.ab.	4117	665
63	relevant journals.ab.	774	104
64	manual search$.ab.	2506	420
65	or/60-64	26819	3568
66	selection criteria.ab.	21119	1800
67	data extraction.ab.	10554	1666

68	66 or 67	29958	3355
69	Review/	2031739	60604
70	68 and 69	21357	891
71	Comment/	615742	42127
72	Letter/	878310	31252
73	Editorial/	374840	23687
74	animal/	5826564	0
75	human/	15825995	0
76	74 not (74 and 75)	4189112	0
77	or/71-73,76	5513243	87464
78	50 or 59 or 65 or 70	167876	29458
79	78 not 77	157340	28578
80	30 or 43 or 79	3004171	167552
81	6 and 7 and 80	54	5
82	limit 81 to yr="2012- Current"	31	3

Cochrane Library

Platform: Wiley Online Library

Date: 7 April 2016

Issues: Cochrane Central Register of Controlled Trials : Issue 3 of 12, March 2016; Health Technology Assessment Database : Issue 1 of 4, January 2016; Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2016; Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015; Cochrane Methodology Register : Issue 3 of 4, July 2012; NHS Economic Evaluation Database : Issue 2 of 4, April 2015

Searcher: Tristan Snowsill

Hits: 8

#	Searches	Results
1	[mh "Leukemia, Myelogenous, Chronic, BCR-ABL Positive"]	367
2	[mh "Leukemia, Myeloid"]	1612
3	[mh "Chronic Disease"]	11942
4	chronic	81200
5	#3 or #4	81200
6	#2 and #5	450
7	chronic near/1 myel* near/1 leuk?emia	184
8	#1 or #6 or #7	560
9	bosutinib or PF-5208763 or PF5208763 or SKI-606 or SKI606 or SKI-758 or SKI758	32
10	#8 and #9	8

Combined search results

Database	Hits
Embase	68
MEDLINE	31
MEDLINE In-Process & Other Non-Indexed Citations	3
Cochrane Library	(8)
Cochrane Central Register of Controlled Trials	5
Health Technology Assessment Database	3
Database of Abstracts of Reviews of Effect; Cochrane Methodology Register; NHS Economic Evaluation Database	0
Subtotal	110
Automatic deduplication	−4
Manual deduplication	−7
Total	99

Appendix 2. Trial registry searches

ClinicalTrials.gov

Type	Interventional Studies
Condition	Chronic myeloid leukemia
Intervention	Bosutinib
Date	6 April 2016
Searcher	Tristan Snowsill
Hits	12

EU Clinical Trials Register

Search terms	("myeloid" OR "myelogenous") AND ("bosutinib" OR "SKI-606" OR "SKI-758")
Date	6 April 2016
Searcher	Tristan Snowsill
Hits	7

ISRCTN

Search terms	Bosutinib
Date	6 April 2016
Searcher	Tristan Snowsill
Hits	2

ICTRP

Search terms	Condition=leukemia Intervention=bosutinib
Date	6 April 2016
Searcher	Tristan Snowsill
Hits	19

Pfizer Clinical Study Report Synopses

Generic Name	Bosutinib
Date	6 April 2016
Searcher	Tristan Snowsill
Hits	8

Combined results

Trial registry	N
ClinicalTrials.gov	12
EU Clinical Trials Register	7
Pfizer Clinical Study Report Synopses	8
WHO ICTRP	19
ISRCTN	2
Subtotal records	*48*
Manual deduplication	*−22*
Total records	26

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

TA299 - Bosutinib for previously treated chronic myeloid leukaemia

You are asked to check the ERG report from PenTAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 12 May 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.

Issue 1 Summary of cost-effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Within the description of the changes to the model submitted as part of this appraisal, , the ERG report states the following (page 13 of 70): "*The main differences from the TA299 model are:* • *Newly proposed patient access scheme;* • *Cumulative survival approach adopted for overall survival;* • *Interferon alfa and stem cell transplant removed as comparators;* • *<u>Revised medical management, monitoring and costs resource use</u> ;* • *Health state utility values estimated from Study 200;* • *Costs updated to 2014/15 prices*"	Pfizer request that the underlined text be removed.	The costs in the model were updated either to the latest NHS reference costs (2014/15) or by using the inflation indices from the PSSRU 2015, as appropriate. No additional changes were implemented regarding the medical management, monitoring or resource use associated with the treatment of these patients	The resource use for medical management, monitoring and tests included in the current submission are not the same as those used in the company submission in TA299. In TA299 the ERG suggested that the resource use estimates should be revised in line with TA251 (lowering the ICER of bosutinib) and ICERs including this assumption were used by the Committee in estimating a most plausible ICER for bosutinib. The current submission incorporates the resource use estimates suggested by the ERG in TA299 and therefore the resource use is revised compared to the TA299 submission. **<u>No action taken.</u>**

Issue 2 Newly proposed patient access scheme

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Within section 5.2.10.2.1, the ERG report states the following (page 49 of 70): "The company present the results of the current submitted model using the previously proposed patient access scheme, which formed the basis of the Committee's decision in TA299. The previously proposed patient access scheme was a simple discount of [redacted]; compared to the currently proposed patient access scheme using a simple discount of [redacted].	Pfizer request that the value of the newly proposed discount be updated to [redacted], in line with section 5.2.10.2.1	The value cited in section 5.2.10.2.1 is incorrect	**Erratum issued (#2).**

Issue 3 Prolonged post-treatment overall survival benefit

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.10.2.2 of the ERG report indicates that "the company conducted scenario analyses for chronic phase patients where up to three months' additional overall survival benefit is assumed compared to the base case cumulative survival approach. Table 26 shows the impact on	Pfizer request that the underlined text be updated to reflect that scenario analyses for chronic phase patients where conducted assuming no more than two months' additional overall survival benefit	As part of the abbreviated submission Pfizer presented scenario analyses exploring the impact of assuming one or two months of treatment benefit following discontinuation from bosutinib in the chronic phase, in line with the Committee's preferred assumptions (see page 30 of 40). The current wording may be read	The ERG confirm that the company did not report the scenario analysis with three months' additional survival benefit, but note that this scenario analysis was conducted and included in the executable model. **Erratum issued (#3).**

cost-effectiveness as the duration of post-treatment overall survival benefit is increased. In TA299 the Committee concluded that "on the presented evidence any benefit could more reasonably be argued to be 1 or 2 months"		as though three months' benefit was also assumed.	

Issue 4 Clinical effectiveness evidence submitted by the company in NICE TA299

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.1.1 of the ERG report indicates: "For example, MCyR was 60%, 42.9%, 60% and 18.2% for second and third line CP and AP and BP unmet clinical need population respectively. However these response rates are based on very small sample sizes (N=3–21) and are therefore uncertain	Pfizer request that the underlined text be updated to from 3 to 5.	The range of sample sizes cited for the unmet need group on page 19 should read: (N= 5-21 There were 5 subjects in the unmet need post hoc analysis group and this was the smallest of the post hoc groups. The range is N= 5-21. This range is comprised of the following numbers per line/phase: CP2L = 15, CP3L=21, AP= 5, BP= 11. Reference: Committee for Medicinal Products for Human Use (CHMP) Product Assessment Report (EMA/70979/2013), Jan 2013. Page 55/87 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002373/WC500141745.pdf	**Erratum issued (#1).**

Issue 5 Prolonged post-treatment overall survival benefit

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG undertook a scoping review to identify any supporting evidence to answer the decision problem published since NICE TA299. Searches were adapted from the systematic review searches designed by Pfizer (dated 21st January 2013) and were run on 7th April 2016 The ERG review did not identify two relevant papers; an additional paper with updated results on Study 200 and an evaluation cardiac and vascular toxicity in patients treated with bosutinib It should be noted that the literature search was not updated in the submission because of the explicit instruction that the submission should focus only on cost-effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health or as a commercial access arrangement with NHS England.	If the ERG wishes to present an update of the literature review, please inclusion the following papers: Section 4.3.2.1 Brummendorf T, Cortes J, Khoury H, Kantarjian H, Dong-Wook K, Schafhausen P, Conlan, M, Shapiro M, Turnbull K, Leip E, Gambacorti-Passerini C, Lipton J. Factors influencing long-term efficacy and tolerability of bosutinib in chronic phase chronic myeloid leukaemia resistant or intolerant to imatinib. British Journal of Haematology, 2016, 172, 97–110 Section 4.3.2.2 Cortes J, Khoury J, Kantarjian H, Brümmendorf T, Mauro M, Matczak E, Pavlov D, Aguiar J, Fly K, Dimitrov S, Leip E, Shapiro M, Lipton J, Durand JB, Gambacorti-Passerini C. Long-Term Evaluation of Cardiac and Vascular Toxicity in Patients With Philadelphia Chromosome–Positive Leukemias Treated With Bosutinib. AJH 2016. E-pub doi:10.1002/ajh.24360	Brunmmendorf et al provide a 48month update to Study 200, data snapshot (15 May 2013) which was not identified in the literature search (conducted 7th April 2016) but should be included as was published in advance of this date. Cortes et al evaluate the long term cardiac and vascular toxicity from Study 3000 and Study 200 and again was available (as an e-publication) in advance of the literature search.	The ERG have checked the search results from when they were conducted (7th April 2016) and can confirm that the two studies highlighted by the company were not returned by any databases. Brummendorf et al. is now indexed in Medline In-Process (it was not on 7th April 2016), while Cortes et al. is not currently indexed in Medline, Medline In-Process or Embase. It is a known limitation of systematic review using bibliographic databases that publications are not immediately indexed. **No action taken.**

Bosutinib for previously-treated chronic myeloid leukaemia

A Single Technology Appraisal Review

Errata

ID	Page	Section	Correction
1	18	4.1.1.1 Bosutinib	Second paragraph, penultimate line, change “N=3–21” to “N=5–21”
2	48	5.2.10.2.1 Previously proposed patient access scheme (TA299)	First paragraph, last line, change [redacted] to [redacted]
3	49	5.2.10.2.2 Prolonged post-treatment overall survival benefit	Insert after first sentence: “The company only reported the scenarios with one and two months’ additional overall survival benefit.”

Use of confidential data

Any ‘commercial in confidence’ data provided by the company, and specified as such, is highlighted in blue and underlined in the review. Any ‘academic in confidence’ data provided by companies, and specified as such, is highlighted in yellow and underlined.