NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Bosutinib for previously treated chronic myeloid leukaemia

This premeeting briefing is a summary of:

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

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

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

Key issues for consideration

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

Clinical effectiveness

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

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

Cost effectiveness

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

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

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

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

1 Background: clinical need and practice

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

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

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

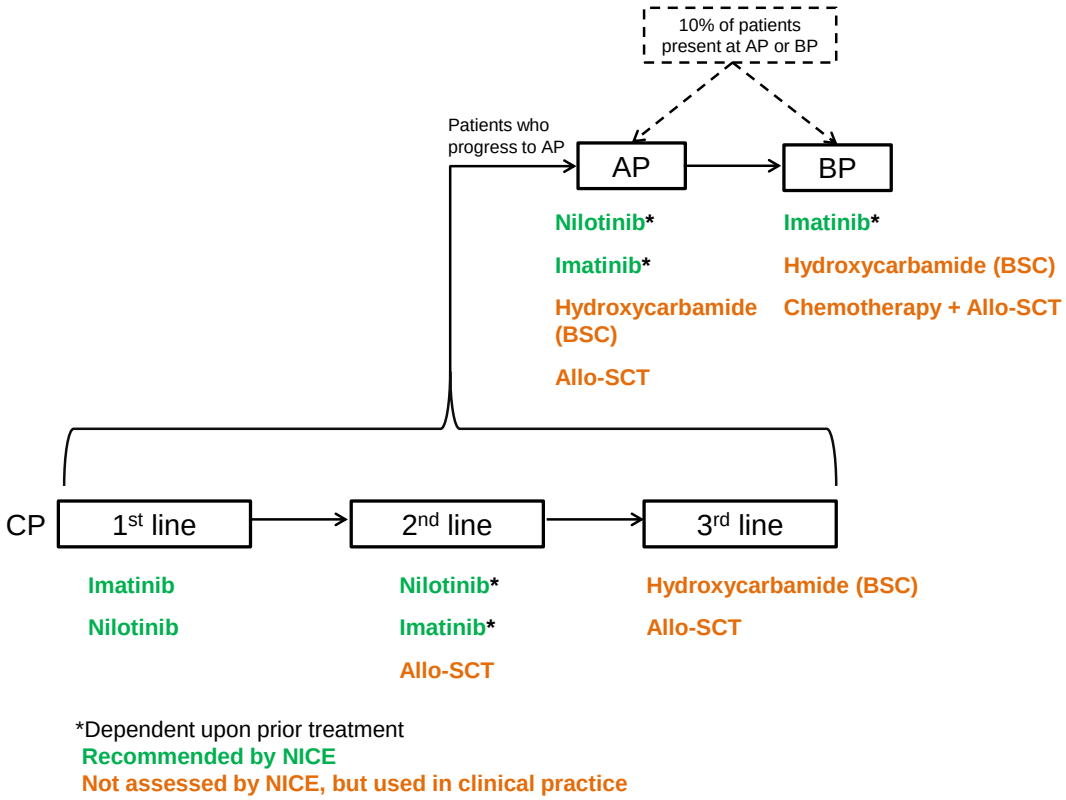
progress to an accelerated phase. During this phase, disease progression is more rapid, and immature blast cells in blood and bone marrow proliferate. Symptoms include bruising, bleeding and infections. The final phase is called the blast phase because a blast cell crisis occurs. This is a rapid increase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

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

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

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

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



2 The technology

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

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

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

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

3 Remit and decision problem(s)

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

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

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

Population

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

Comparators

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

Outcomes

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

4 Clinical-effectiveness evidence

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

Study 200 population and follow up

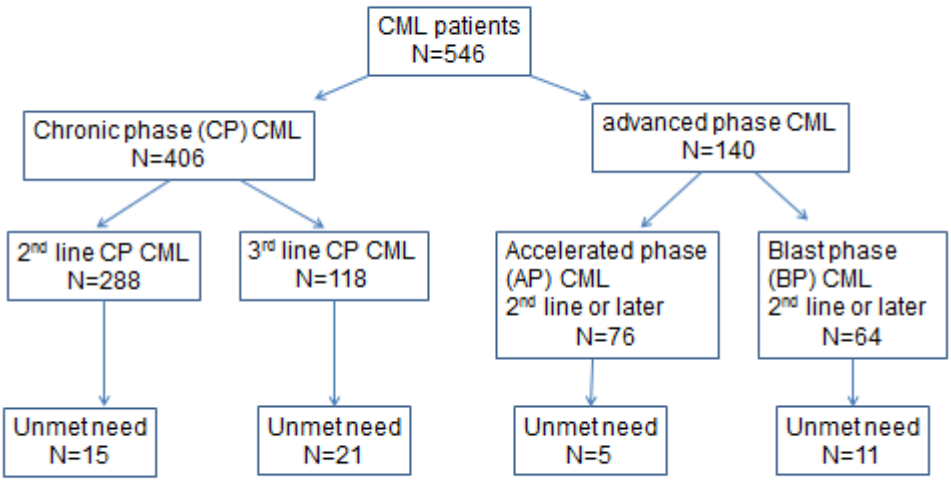
4.2 Part 1 of Study 200 was a dose-escalation study in 18 patients to determine a dose for part 2 and was not considered further within the Manufacturer's submission. Part 2 of Study 200 studied the efficacy and safety of 500mg once daily bosutinib in 570 Ph+ patients with resistance

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

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

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

Figure 2: unmet medical need population in Study 200



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

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

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

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

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

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

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

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

Efficacy of bosutinib from Study 200

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

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

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

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

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

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

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

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

Efficacy estimates for comparator treatments from systematic review

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

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

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

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

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

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

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

Safety of bosutinib and comparator treatments

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

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

Quality of life with bosutinib from Study 200

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

Evidence Review Group comments

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

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

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

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

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

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

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

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

5 Comments from other consultees

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

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

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

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

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

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

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

6 Cost-effectiveness evidence

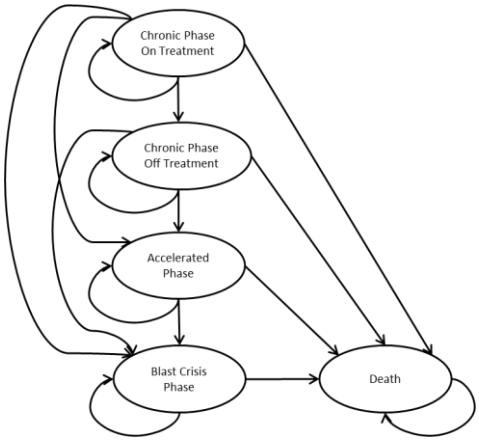
6.1 The manufacturer performed a systematic review to identify cost effectiveness studies in CML patients previously treated with one or more tyrosine kinase inhibitor but did not identify any economic evaluations of bosutinib in refractory CML. The search identified three publications relating to the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

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

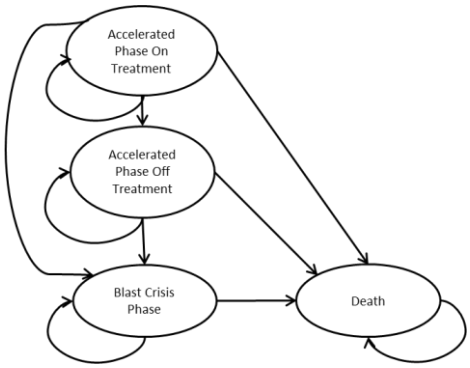
stage, the ERG identified an error in the model relating to the overall survival estimate for bosutinib in the chronic phase model. The manufacturer submitted an updated model with this error corrected and presented their amended base case and sensitivity analyses. All results for the chronic phase model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

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

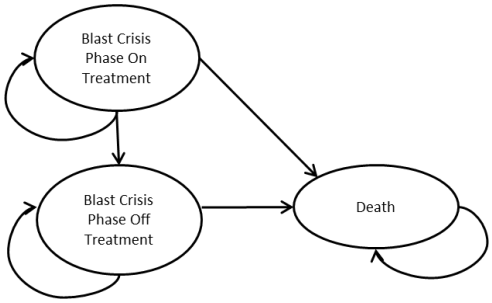
Chronic phase



Accelerated phase model



Blast crisis phase model



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Utility values presented are for a 56 year old patient.

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

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

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

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

Manufacturer's scenario analyses

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

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

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

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

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

Evidence review group comments on the cost effectiveness estimates

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

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

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

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

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

Blast phase	0.5	[redacted]	na

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

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

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

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

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

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

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

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

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

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

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

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

Chronic phase CML

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

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

Accelerated phase CML

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

Blast phase CML

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

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

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

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

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

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

7 End-of-life considerations

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

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

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

8 Equalities issues

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

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

9 Innovation

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

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

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

Related Technology Appraisals:

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

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

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

Related Guidelines:

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

The European Public Assessment report is available from:

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