NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

The **final scope and final stakeholder list** are available on the NICE website.

The following documents are made available to consultees and commentators:

1. **Company submission** from Novartis

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. CML Support Group
   b. Leukaemia Care
   c. Royal College of Pathologists and British Society for Haematology
   d. Royal College of Physicians

4. **Evidence Review Group report** prepared by prepared by CRD and CHE Technology Assessment Group

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Novartis

7. **Technical engagement response & expert statement from experts:**
   a. Professor Mhairi Copland, clinical expert nominated by the Royal College of Physicians and the Royal College of Pathologists
   b. Dr Dragana Milojkovic, clinical expert nominated by the Royal College of Physicians and the Royal College of Pathologists
   c. Graham Dickenson, patient expert nominated by Chronic Myeloid Leukaemia Support Group (CML Support)

8. **Technical engagement response from consultees and commentators:**
   a. Leukaemia Care
   b. *Joint response* from the Royal College of Physicians

9. **Evidence Review Group critique of company response to technical engagement** prepared by prepared by CRD and CHE Technology Assessment Group
   a. Main response
   b. MAIC response

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
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Abbreviations

Acronym	Definition
ABL1	Abelson
ACA	Additional chromosome abnormalities
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike's information criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic stem cell transplant
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
BCR	Breakpoint cluster region
BD	Twice-daily
BIC	Bayesian information criterion
BMA	Bone marrow aspirate
BP	Blast phase
CCA	Clonal chromosome abnormalities
CCyR	Complete cytogenetic response
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CHR	Complete haematological response
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CML	Chronic myeloid leukaemia
CP	Chronic phase
CRF	Case report form
CRUK	Cancer Research UK
CSR	Clinical study report
CyR	Cytogenetic response
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
ELN	European LeukemiaNet
EPAR	European public assessment report
EQ	EuroQol
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FISH	Fluorescence in situ hybridisation
GLM	Generalised linear model
GUS	β-glucuronidase
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio

Acronym	Definition
HRQoL	Health-related quality of life
HTA	Health technology assessment
IPD	Individual patient data
IRT	Interactive response technology
IS	International scale
ITC	Indirect treatment comparison
KM	Kaplan-Meier
MCyR	Major cytogenetic response
MDASI	M.D. Anderson Symptom Inventory
MMR	Major molecular response
MMRM	Mixed effect model repeated measure
MR	Molecular response
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OD	Once-daily
OR	Odds ratio
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PAS	Patient access scheme
PCyR	Partial cytogenetic response
PFS	Progression-free survival
PKS	Pharmacokinetic analysis set
PGIC	Patient global impression of change
Ph	Philadelphia chromosome
PK	Pharmacokinetic
PSA	Probabilistic sensitivity analysis
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RFS	Relapse free survival
RQ-PCR	Real-time quantitative polymerase chain reaction
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36-Item
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ classes
STAMP	Specifically targeting the ABL myristoyl pocket
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation

Acronym	Definition
TTF	Time to treatment failure
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

Executive summary

Chronic myeloid leukaemia

- Chronic myeloid leukaemia (CML) is a cancer of the blood characterised by the uncontrolled proliferation of myeloid cells in the bone marrow and subsequent release into peripheral blood (1-3).
- CML is defined by the presence of the Philadelphia chromosome (Ph) and assigned a phase depending on the number of immature blasts in the bone marrow or peripheral blood; chronic phase (CP), accelerated phase (AP), or blast phase (BP) (4). At diagnosis, 90–95% of patients with CML present in the CP (5-7) (the focus of this submission).
- Key symptoms of CML-CP include fatigue, weight loss, splenomegaly, and anaemia (8).
- NICE guidelines recommend tyrosine kinase inhibitors (TKIs) at all lines of therapy, with imatinib, dasatinib, or nilotinib recommended at first-line; and dasatinib, nilotinib, bosutinib, or ponatinib recommended in patients requiring second or later line therapy (9).
- Whilst the availability of TKIs has improved the life expectancy of patients with CML-CP (10), there remains an unmet need for patients in the third or later line treatment setting who are resistant to/intolerant of early-line TKI therapy.

Asciminib

- Asciminib is an orally bioactive BCR-ABL1 inhibitor specifically targeting the ABL myristoyl pocket (STAMP) inhibiting ABL1 kinase activity (11).
  - Asciminib is anticipated to be licensed for [redacted]

Clinical effectiveness of asciminib

The ASCEMBL randomised controlled trial (RCT) in patients with Ph+ CML-CP previously treated with two or more TKIs showed that asciminib 40 mg twice-daily (BD) (n=157) was associated with improved outcomes vs bosutinib 500 mg once-daily (OD) (n=76)[a] (12, 13).

- The study met its primary objective and showed a statistically significant and clinically relevant treatment difference at Week 24 in major molecular response (MMR) rate of 12.2% (95% CI: 2.19, 22.30, p-value: 0.029).
- Analysis of 48-week data showed that the time to achieve MMR was faster in patients treated with asciminib (median time to MMR: [redacted]) compared with bosutinib (median time to MMR: [redacted]).
- A higher proportion of asciminib-treated patients achieved a molecular response (MR) 4.5 vs bosutinib ([redacted], respectively) in the 48-week data-cut.
- Complete cytogenetic response (CCyR) rates at Week 48 were [redacted] in the asciminib arm vs [redacted] in the bosutinib arm. The CCyR rate by Week 48 was [redacted] in the asciminib arm compared with [redacted] in the bosutinib arm.

[a] The 24-week ASCEMBL CSR presents the primary analysis and provides baseline demographics and disease characteristics, the primary efficacy endpoint, all patient-related outcomes, pharmacokinetics, and resource utilisation (data cut-off: 25th May 2020) (12) (Sections B.2.6.1.3, B.2.6.1.16–B.2.6.1.20). All other efficacy and safety outcomes from the ASCEMBL trial are from the latest data-cut off (6th January 2021; 48-week data) (13, 14). All data from the 24-week primary analysis (data cut-off of 25th May 2020) are provided in Appendix M for completeness. Supporting safety evidence is also provided by Study X2101 (data cut-off: 6th January 2021) in Appendix N.

The Haematological Malignancy Research Network (HMRN) report details the findings of real-world disease management and outcomes in CML in England (supporting evidence) (14).

- There were [redacted] newly diagnosed cases of CML-CP in England between the 1st September 2004 and 31st August 2019 ([redacted] males, median age: [redacted] years).
- Most patients were initially treated with a TKI ([redacted] and [redacted] of patients received first-line imatinib).
- A total of [redacted] patients went onto receive a second-line TKI, and [redacted] patients received third-line or later therapy.
- Of the [redacted] patients treated with a first-line TKI, [redacted] patients [redacted] achieved a MMR or MR^2 response, and the median time to response was [redacted].
- A total of [redacted] patients received a third-line TKI. Of these, [redacted] patients [redacted] achieved a MMR or MR^2 response (median time to response was [redacted]
- Excluding the three patients with the T315I mutation, 5-year OS at third-line was [redacted]

A matching-adjusted indirect treatment comparison (MAIC) was conducted to compare the TTD for asciminib vs ponatinib, nilotinib, and dasatinib for the treatment of CML-CP patients who had received ≥2 prior TKIs (Appendix I).

- Post-MAIC, the observed TTD curve for asciminib [redacted] substantially vs ponatinib or dasatinib, [redacted] vs nilotinib.
- Median TTD for asciminib was not reached in the ASCEMBL trial. Post-MAIC with ponatinib, median TTD for asciminib was [redacted] compared with median TTD of [redacted] for ponatinib. Post-MAIC with nilotinib and dasatinib, median TTD was not reached.
- MAIC estimates suggest that asciminib offers improvements in both efficacy and safety compared with conventional TKIs (dasatinib, nilotinib, and ponatinib) in the target population.

Safety of asciminib

Safety data from ASCEMBL suggests that asciminib 40 mg twice daily (BD) has a better safety and tolerability profile than bosutinib 500 mg once-daily (OD) in patients with CML-CP treated with two or more TKIs (data cut-off: 6th January 2021) (15)

- Adverse events (AEs) were experienced by [redacted] of patients in the asciminib treatment group compared with [redacted] in the bosutinib treatment group.
- Exposure-adjusted incidence rates (per 100 patient treatment years [PTY]) of all grade AEs (irrespective of study treatment relationship) were [redacted] per 100 PTY and [redacted] per 100 PTY with asciminib and bosutinib, respectively.
- All categories of AEs were [redacted] frequent in the asciminib treatment group (with the exception of [redacted]
- Treatment discontinuation due to AEs was [redacted] in the asciminib arm compared with the bosutinib treatment arm [redacted] respectively).
- AEs requiring dose interruptions or dose adjustments were reported [redacted] frequently with asciminib than with bosutinib [redacted], respectively).

Cost-effectiveness of asciminib

- The economic analysis compares the lifetime costs and quality adjusted life expectancy of asciminib compared to bosutinib, ponatinib, nilotinib and dasatinib in patients with Ph+ CML-CP, previously treated with two or more TKIs.
- The approach to the modelling of OS following discontinuation of third-line treatment is based on the approach recommended by the ERG in TA401 (bosutinib), in which OS is the sum of TTD plus a fixed period of survival beyond third-line treatment.
- Data on TTD for ponatinib and bosutinib include patients in the fourth-line setting. While data for dasatinib and nilotinib do not include patients in the fourth-line setting, this is largely due to the evolution of the CML treatments over the last 10-15 years.
- At the patient access scheme (PAS) price for asciminib, and PAS price for nilotinib, results of the cost-effectiveness analysis showed that:
  - Compared with bosutinib, asciminib is associated with higher costs but also higher quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of [redacted] (probabilistic) per QALY gained ([redacted] deterministic).
  - Compared with dasatinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] (probabilistic) of per QALY gained ([redacted] deterministic).
  - Compared with nilotinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] (probabilistic) per QALY gained ([redacted] deterministic).
  - When comparing asciminib to ponatinib, asciminib is associated with lower costs and lower QALYs, resulting in an ICER for ponatinib (when compared to asciminib) of [redacted] (probabilistic) per QALY gained ([redacted] deterministic).
- Scenario analysis in which survival following discontinuation of third-line treatment is reduced generated lower ICERs. The presented cost-effectiveness analysis could, therefore, be regarded as a conservative proxy assessment of the cost-effectiveness of asciminib.

Added value of asciminib

Asciminib has been shown to provide a longer treatment duration compared with bosutinib, the comparator within the ASCEMBL trial, and the cost-effectiveness analysis has shown asciminib's potential to be cost-effective compared with all treatments, and in particular provide cost-savings compared to ponatinib. Asciminib is an important addition to the available treatments for CML in patients who have already progressed to third or later lines of treatment, offering improved outcomes vs bosutinib, dasatinib and nilotinib, and cost savings compared to ponatinib as well as an improved safety profile. Providing access to asciminib is a cost-effective decision compared with the majority of TKIs currently used in third-line and later treatment setting.

B.1 Decision problem, description of the technology, and clinical care pathway

B.1.1 Decision problem

This submission is for asciminib for treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) (third-line and later). The submission covers the technology's anticipated marketing authorisation for this indication. The company submission is generally consistent with the final National Institute for Health and Care Excellence (NICE) scope (16) and the NICE reference case, with differences outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with Ph+ CML-CP previously treated with two or more TKIs	As per NICE final scope	N/A
Intervention	Asciminib	As per NICE final scope	N/A
Comparator(s)	• Bosutinib • Dasatinib • Nilotinib • Ponatinib	As per NICE final scope	N/A
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates • Time to response • Adverse effects of treatment • Health-related quality of life	As per NICE final scope, with two additional outcome measures (MMR and TTD)	• MMR: Since the introduction of imatinib, nearly all imatinib-treated patients achieve normalised blood counts and most achieve a complete cytogenetic response. There is evidence that achieving a MMR predicts superior long-term clinical outcomes (24). • TTD: OS and PFS trial data from ASCEMBL are immature; TTD is an important clinical outcome and is used within the economic model to capture that overall survival is the sum of time on treatment and survival post-discontinuation of third-line treatment.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per NICE final scope	N/A

Source: NICE (2021) (16)
Abbreviations: CML, chronic myeloid leukaemia; CP, chronic phase; MMR, major molecular response; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation.

B.1.2 Description of the technology being appraised

The draft summary of product characteristics (SmPC) is presented in Appendix C.

Table 2 summarises the technology (asciminib) being appraised in this submission.

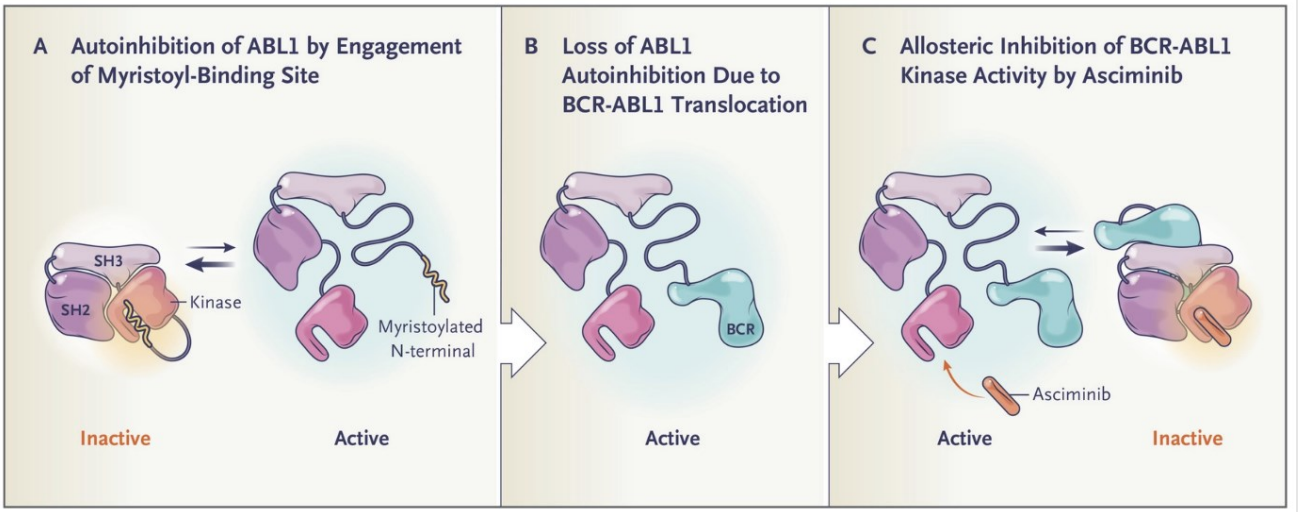
Table 2: Technology being appraised

UK approved name and brand name	Asciminib (Scemblix®)
Mechanism of action	Asciminib is an orally bioactive BCR-ABL1 inhibitor, specifically targeting the ABL myristoyl pocket (STAMP) inhibiting ABL1 kinase activity (11, 17). Asciminib acts as an allosteric inhibitor that binds a myristoyl site of BCR-ABL1, inhibiting kinase activity (18). As the myristoyl pocket has a distinct conformation, asciminib is selective for only ABL1, and potentially ABL2 kinases, with a low-nanomolar–range activity against unmutated BCR-ABL1 (18). Autoinhibition of the ABL1 kinase occurs through engagement of the myristoyl-binding site by the myristoylated N-terminal — a negative regulatory motif that locks the ABL1 kinase in the inactive state. On fusion of ABL1 to BCR, the myristoylated N-terminal is lost and the ABL1 kinase is activated. By allosterically binding the myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity (Figure 1) (18).
Marketing authorisation/CE mark status	A regulatory submission was made to the MHRA via the ACCESS consortium route on the 28/07/21 (19).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted] (17) .
Method of administration and dosage	• Asciminib is administered orally. Tablets should be swallowed whole and should not be broken, crushed, or chewed. Asciminib should be taken without food, and food consumption should be avoided for ≥2 hours before and 1 hour after administration (17). • Asciminib dosage was explored in a Phase I dose-escalation study (NCT02081378) (18).† o The recommended dose for patients with Ph+ CML-CP previously treated with ≥2 TKIs is 80 mg, available as a 2 x 40 mg dose regimen 12 hours apart [focus of this submission] or as an 80 mg once daily dose regimen.
Additional tests or investigations	No additional tests or investigations are needed compared with current clinical practice.
List price and average cost of a course of treatment	40 mg (6x10): [redacted] Daily cost: **List price (£)** | **mg/MU per pack** | **Daily dose (Mg/MU)** | **Daily cost (£)** [redacted] | 2,400.00 | 80.00 | [redacted]
Patient access scheme (if applicable)	40 mg (6x10): [redacted]

	Daily cost:			
	List price (£)	**mg/MU per pack**	**Daily dose (Mg/MU)**	**Daily cost (£)**
	[redacted]	2,400.00	80.00	[redacted]

†Phase I, multi-centre, open-label, dose escalation study in adult patients with Ph+ CML-CP/AP, previously treated with ≥2 different TKIs or who have relapsed disease with presence of T315i mutation after ≥1 TKI; and in adult patients with ALL and CML-BP relapsed/refractory to ≥1 prior TKI or intolerant of TKIs (18).
Abbreviations: ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BD, twice-daily; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; OD, once-daily; Ph+, Philadelphia chromosome-positive; RDI, relative dose intensity; TKI, tyrosine kinase inhibitor.

Figure 1: Binding of the myristoyl site of the BCR-ABL1 protein by asciminib



Source: Hughes et al. 2019 (18).

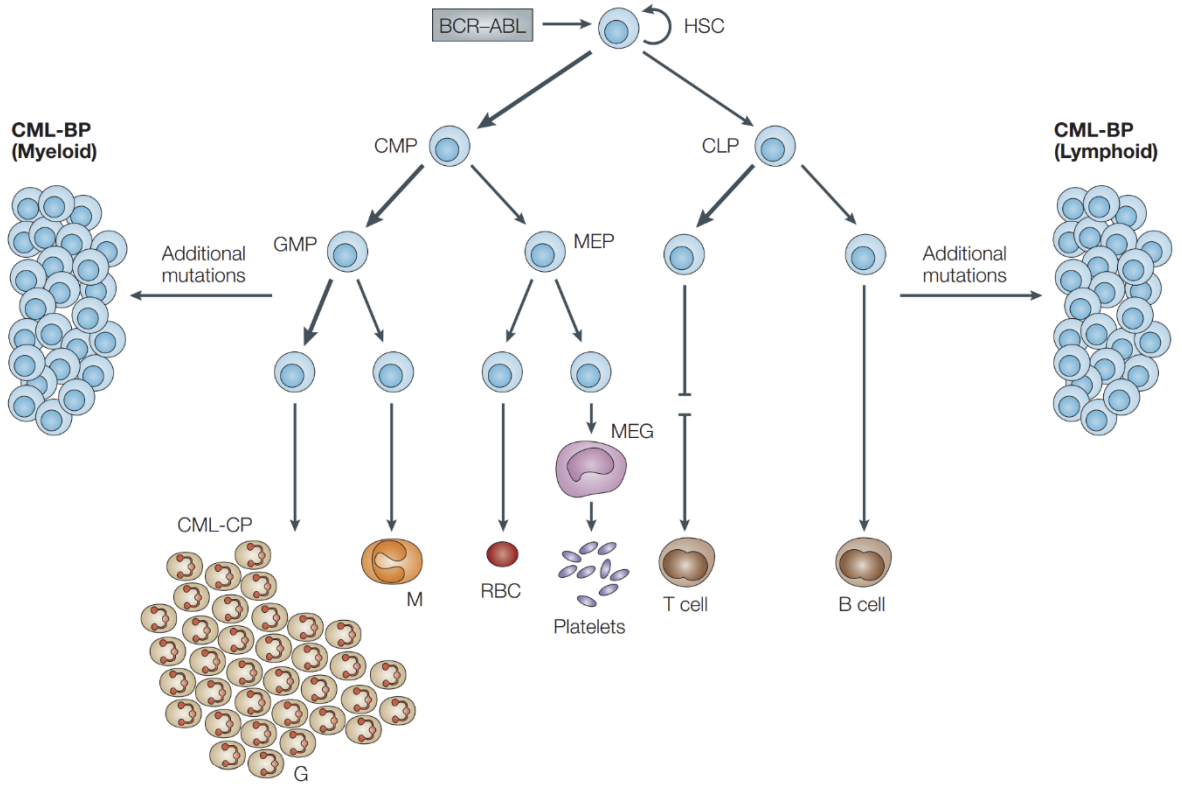
B.1.3 Health condition and position of the technology in treatment pathway

B.1.3.1 Disease overview

Chronic myeloid leukaemia (CML) is a cancer of the blood characterised by the uncontrolled proliferation of myeloid cells in the bone marrow and subsequent release into peripheral blood (1-3). CML is defined by the presence of the Philadelphia chromosome (Ph). Presence of the Ph is an acquired abnormality in haematopoietic stem cells (20), which results from a translocation between the long arms of chromosomes 9 and 22 [t(9;22)] (21). This translocation involves the ABL1 (Abelson) protooncogene on chromosome 9, and the breakpoint cluster region (BCR) gene on chromosome 22 (5). The molecular consequence of the t(9,22) translocation is the formation of the fusion protein BCR-ABL, an active cytoplasmic

tyrosine kinase that can activate multiple signal-transduction cascades driving the growth and differentiation of haematopoietic cells (20, 22, 23) (Figure 2).

Figure 2: The development of CML†



†CML is initiated by expression of the BCR–ABL fusion gene product in self-renewing, HSCs. HSCs can differentiate into CMPs, which then differentiate into GMPs; progenitors of G and M, and MEPs; progenitors of RBCs and MEGs, which produce platelets). HSCs can also differentiate into CLPs, which are the progenitors of lymphocytes such as T cells and B cells.
Source: Ren 2005 (24).
Abbreviations: BP, blast phase; CLP, common lymphoid progenitor; CML, chronic myeloid leukaemia; CMP, common myeloid progenitor; CP, chronic phase; G, granulocytes; GMP, granulocyte/macrophage progenitor; HSC, haematopoietic stem cell; M, macrophages; MEG, megakaryocyte; MEP, megakaryocyte/erythrocyte progenitor; RBC, red blood cell.

CML is classified into one of three phases depending on the number of immature blasts in the bone marrow or peripheral blood; chronic phase (CP), accelerated phase (AP), or blast phase (BP) (4). The criteria for classifying these phases are presented in Section B.1.3.4.1. At diagnosis, 90–95% of patients with CML present in the CP (5-7), and up to 50% of patients with CML-CP are asymptomatic and diagnosed by routine blood tests (14).

In the CP, mature granulocytes are still produced but there is an overproduction of myeloid cells in the peripheral blood (6, 25). If CP is not treated successfully, it can progress to AP and may be followed by BP, which is morphologically similar to acute

leukaemia: differentiation of myeloid and/or lymphoid cells stops, and immature blasts accumulate in the bone marrow and subsequently propagate tissues and organs (6). Typically, the disease course from the CP to more advanced stages (AP and BP) without treatment is 3.5–5 years (5, 26).

The only known risk factors for CML are high doses of ionizing radiation and occupational exposure to benzene, evidenced by the increased incidence of all leukaemia subtypes in atomic bomb survivors (27). There are no known genetic predispositions for CML, no known oncogenic viruses associated with CML, and disease onset is not generally considered to be preventable (27).

B.1.3.2 Epidemiology

According to Cancer Research UK (CRUK), leukaemia is the 12th most common cancer type in the United Kingdom (UK), and CML accounts for approximately 8.4% of all cases of leukaemia in adults in England (28, 29). In total, there are approximately 720 new cases of CML each year in England (28). In UK, approximately 44% of new CML cases occur in adults aged ≥65 years (2015–2017) (28). In the UK, 46% of chronic myeloid leukaemia cases are in females, while 54% are in males (28).

B.1.3.3 Burden of Disease

B.1.3.3.1 *Clinical burden*

B.1.3.3.1.1 Signs and symptoms

Fatigue is the most common and burdensome symptom reported among patients with CML-CP receiving TKI therapy (8). Other commonly reported symptoms include (8):

- Weight loss/loss of appetite
- Splenomegaly
- Skin rash
- Anaemia
- Sweating
- Drowsiness
- Abdominal fullness
- Sleep disturbances
- Muscle soreness/cramping

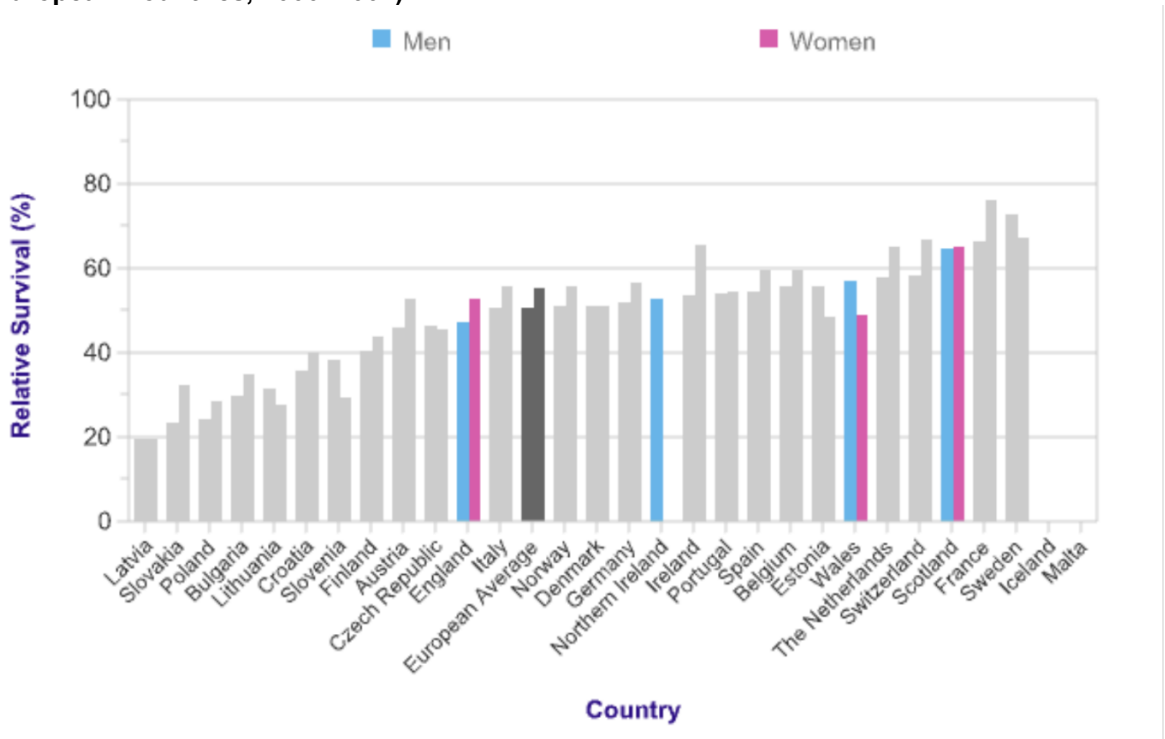
- Memory loss/difficulty in remembering

CML is also reported to interfere with general aspects of life, such as walking and other daily activities (8).

B.1.3.3.1.2 Mortality

In England, CML accounts for approximately 191 deaths per year; in 2018, there were an estimated 84 deaths in females and 107 deaths in males (30). The five-year relative survival for CML in England between 2000 and 2007 was 53% and 47% for males and females, respectively (31). Survival rates for patients with CML in England are comparable to those reported in other European countries (Figure 3). Tyrosine kinase inhibitors (TKI) have improved survival of patients with CML, with patients in CP having a 2-year survival of 98% (10). However, for those patients whose disease progresses to AP or BP, survival is poor and mean survival can be less than 24 months (5).

Figure 3: Age-standardised 5-year relative survival in patients with CML aged ≥15 years (European Countries, 2000–2007)



Source: Cancer Research UK (31).

B.1.3.3.2 *Humanistic burden*

Whilst TKIs have improved the disease outcomes of CML, patients receiving TKI therapy typically report worse quality of life (QoL) compared with the general

population (32). In a United States (US) study of 62 patients with CML and 62 age- and sex-matched controls, patients with CML reported significantly worse scores for physical, role, emotional, cognitive, and social functioning scales (all p<0.001; assessed via the Short Form 36-Item [SF-36]) (32). Furthermore, patients receiving TKIs were more likely to report clinically meaningful depression and fatigue (32).

Self-reported anxiety and depression were assessed in another study of 1,169 patients with CML receiving TKI therapy between 2016 and 2018 (China). Anxiety and depression were reported by 251 (22.4%) and 415 (37.1%) patients, respectively (33). Multivariate analyses revealed that being female, lower education level, comorbidities, advanced-line TKI-therapy, and longer TKI-therapy duration were significantly associated with more severe anxiety and/or depression (33).

The QoL of patients with CML receiving TKI therapy is important for treatment adherence. In a study of 221 patients with CML in India, QoL scores were significantly higher between adherent (n=99) and nonadherent (n=122) patients (mean ± standard error [SE]; 78.9±19.8 vs 64.4±24.7; p<0.001, higher scores denote worse QoL) (34). Studies examining adherence to TKIs have reported mixed results, with adherence ranging from 14% (35) to 104% (36) and the symptom burden being a common explanation for non-adherence (37).

B.1.3.3.3 *Economic burden*

The economic burden of CML is substantial when compared with that of other cancer types and the general population. A retrospective analysis of claims data in the US from 2000–2016 reported substantially higher costs among patients with CML ($82,054), compared with patients with other haematological cancers ($56,886) and the general population without cancer ($56,886) (38).

The economic burden of CML and the treatment of the disease is also compounded by TKI treatment failure. A retrospective analysis of claims data in the US between 2008 and 2011 compared mean all-cause follow-up healthcare resource utilisation and costs per episode in patients with CML who experienced TKI treatment failure (n=547) and patients who did not (n=547) (39). Patients with TKI failures had fewer TKI prescription fills, but utilised other services (primarily inpatient services, laboratory tests, and other services) to a significantly (p<0.05) greater degree compared with non-failures (39). Subsequently, patients with TKI failures incurred

higher medical costs than non-failures ($52,619 vs $18,180, respectively; p<0.05), and these costs were not outweighed by lower pharmacy costs; resulting in significantly higher overall costs ($103,857 vs $90,630, respectively; p<0.05) (2012 US dollars) (39). These results are consistent with another retrospective analysis of claims data in the US from 2008–2011, which reported that cost of failures increased with each line of TKI treatment failure (40).

B.1.3.4 Clinical pathway of care

Treatment recommendations for the management of CML are provided by NICE (9) (Section B.1.3.4.2). Other treatment guidelines relevant to England are also available from the following bodies and are generally consistent with the NICE guidelines:

- European Society for Medical Oncology (ESMO), 2017 (7)
- European LeukemiaNet (ELN) expert panel, 2020 (41)
- The British Society of Haematology, 2020 (42).

B.1.3.4.1 *Diagnosis and monitoring*

CML is diagnosed by peripheral blood counts and morphological investigation of bone marrow aspirates for cytogenetic analysis (7, 41, 42). Diagnosis is confirmed by the identification of the Ph or BCR-ABL1 transcripts, or both (7). Approximately 95% of patients exhibit the Ph (or a variant) that is visible on conventional cytogenetic analysis (42, 43). The remaining cases with a cryptic BCR-ABL1 fusion may be detected by fluorescence in situ hybridisation (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR). Diagnosis may also include a physical examination (e.g. of the spleen and liver). Detection of a BCR-ABL1 kinase domain mutations, emergence of additional chromosome abnormalities (ACA) in Ph+ cells, and bone marrow fibrosis can be predictors of adverse disease outcomes (7, 41, 42).

Following diagnosis, patients are assigned one of three disease phases: CP, AP, or BP. Approximately 95% of patients are diagnosed with CML in the CP (the focus of this submission) (44), which can last for several years and be asymptomatic for many patients (25, 45). Disease can progress to a faster-progressing AP, followed by transformation to BP. Progression to AP and BP are associated with burdensome symptoms, TKI therapy resistance, and poor survival outcomes (46, 47). Variable clinical and haematological definitions of AP and BP are provided by the World Health Organization (WHO) and ELN (7); the ELN definition of AP and BP are

provided in Table 3 due to these criteria being used in almost all clinical trials assessing the efficacy of TKIs (including ASCEMBL) (7, 41).

Table 3: ELN definitions of AP and BP

Clinical criteria	AP	BP
Blast cell count†	15–29%	≥30%
Basophil count†	>20%	–
Decreased Platelet count¶	Yes	–
CCA/Ph+	Present	–
Extramedullary involvement‡	–	Present

Source: ELN, 2017 and 2020 (7, 41).
†In peripheral blood or in the bone marrow; ‡excluding liver or spleen; including lymph nodes, skin, CNS, bone, and lung, ¶Persistent, unrelated to therapy.
Abbreviations: AP, accelerated phase; BP, blast phase; CCA, clonal chromosome abnormalities; ELN, European LeukemiaNet; Ph, Philadelphia chromosome.

Periodic molecular and cytogenic monitoring is recommended to assess patient response to TKI therapy. Assessment of molecular response is the strongest predictor of disease outcomes, and must be assessed according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts (7, 41, 42). BCR-ABL1 transcript levels ≤0.1% are defined as a major molecular response (MMR) (MR^3). BCR-ABL1 transcript levels ≤0.01%[b] and ≤0.0032%[c] are defined as a deep molecular response (MR) (MR^4 or $MR^{4.5}$, respectively). A complete cytogenetic response (CCyR) is defined by the absence of Ph+ metaphases or <1% BCR-ABL1 nuclei out of ≥200 cells (7).

B.1.3.4.1.1 Current treatment

TKIs remain the treatment of choice for all lines of therapy (7, 9, 41, 42). Whilst an allogeneic stem cell transplantation (allo-SCT) is potentially curative, it is not a therapeutic option for many patients due to patient/disease characteristics and matched donor availability (48).

Choice of first-line TKI therapy for the management of patients with CML-CP is guided by the disease phase and any pre-existing medical conditions, with imatinib being recommended for the majority of first-line patients (42). There are no studies comparing the efficacy of third and later line TKIs, hence, no treatment guidelines

[b] Or BCR–ABL not detectable with ≤10,000 ABL or 24 000 β-glucuronidase [GUS] transcripts.
[c] Or BCR–ABL not detectable with ≤32,000 ABL or 77,000 GUS transcripts.

provide well-defined treatment recommendations regarding the TKI of choice at sequent therapy line (7, 9, 41, 42). Consequently, the criteria for choice of second-line TKI in patients resistant to/intolerant of first-line therapy are almost entirely patient-related and depend on age, comorbidities, and the toxicity associated with first-line TKI therapy (41).

B.1.3.4.2 *NICE treatment guidelines*

NICE guidelines for the treatment of CML in adult patients are presented in Table 4 (9). Choice of therapy at third or later line is not well defined in the NICE treatment pathway for CML (9), and TKIs are recommended at all lines of therapy: imatinib, dasatinib, or nilotinib at first-line; and dasatinib, nilotinib, bosutinib, or ponatinib recommended in previously treated patients requiring second- or later line therapy (9).

The majority (89.6%) of patients with CML-CP in England receive first-line treatment with imatinib, followed by second-line treatment with nilotinib (58.2%) or dasatinib (29.3%) (HMRN, September 2004–August 2019; Section B.2.6.2)[d] (14).

[d] The HMRN region covers the former two adjacent UK Cancer Networks with a total population of 3.8 million (Yorkshire and the Humber & Yorkshire Coast Cancer Networks) and collects detailed information in all patients newly diagnosed with a haematological malignancy in the HMRN region.

Table 4: NICE treatment guidelines for CML

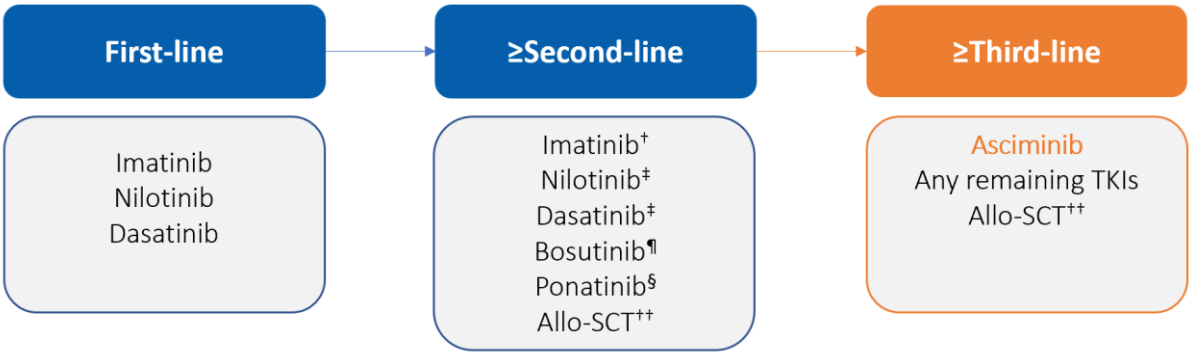
Guideline (Year)	Treatment	Recommendations
Untreated (first-line)		
TA426 (2016)	Dasatinib (Sprycel®) (2GTKI)	• Recommended for the treatment of untreated (first-line) Ph+ CML-CP
	Nilotinib (Tasigna®) (2GTKI)	
TA426 (2016) and TA70 (2003)	Imatinib (Glivec®) (1GTKI)	Recommended for: • The treatment of untreated (first-line) Ph+ CML-CP • Patients with Ph+ CML-CP who initially present in the AP or BP • Patients who present in the CP and then progress to the AP or BP if they have not received imatinib previously
Previously treated (second- or later line)		
TA425 (2016)	Dasatinib (Sprycel®) (2GTKI)	• Recommended for adult patients with CP or AP Ph+ CML who cannot have imatinib or are imatinib-resistant
	Nilotinib (Tasigna®) (2GTKI)	
TA401 (2016)	Bosutinib (Bosulif®) (2GTKI)	Recommended for patients with CP, AP, and BP Ph+ CML when: • Patients have previously received >1 TKI, and • Imatinib, nilotinib, and dasatinib are not considered appropriate
TA451 (2017)	Ponatinib (Iclusig®) (3GTKI)	Recommended for patients with CP, AP, and BP CML when: • Patients are resistant to dasatinib or nilotinib • Patients cannot tolerate dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate • Patients are positive for the T315I gene mutation

Source: NICE treatment pathway for CML (9).
Abbreviations: 1/2/3GTKI, first/second/third generation tyrosine kinase inhibitor; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; NICE, National Institute for Health and Care Excellence; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.

B.1.3.4.3 *Pathway of care and the proposed positioning of asciminib*

The clinical pathway of care for managing Ph+ CML-CP after two or more TKIs is presented in Figure 4; the proposed positioning of asciminib is included in the pathway.

Figure 4: Clinical pathway of care for managing Ph+ CML-CP (including the proposed positioning of asciminib)†



Source: NICE treatment pathway for CML (9).
†In clinical practice, imatinib is used for the treatment of second-line patients who are intolerant to a prior TKI therapy, but not in the case of prior TKI resistance; ‡Dasatinib and nilotinib are recommended for the treatment of patients with CML-CP who cannot have imatinib or their disease is imatinib-resistant; ¶Bosutinib is recommended for patients with CML-CP who have previously received >1 TKI and imatinib, nilotinib, and dasatinib are not considered appropriate; §Ponatinib is recommended for patients with CML-CP who are resistant to dasatinib or nilotinib, cannot tolerate dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or patients who are positive for the T315I gene mutation; ††Allo-SCT is used in clinical practice but is not part of the NICE clinical pathway of care.
Abbreviations: Allo-SCT, allogeneic stem cell transplantation; Ph+ CML-CP, Philadelphia chromosome positive chronic myeloid leukaemia-chronic phase.

B.1.3.5 Unmet need

Whilst the availability of several TKIs has improved the life expectancy of patients with CML-CP (10), there remains an unmet medical need for patients in the third-line or later treatment setting who are resistant to/intolerant of early-line TKI therapy (10, 49, 50).

The majority of patients with CML-CP in the UK receive first-line treatment with imatinib (14) (Section B.2.6.2). Among patients initiating first-line imatinib therapy in the UK, approximately 40% of patients experience loss of response within the first-year of treatment (14) (Section B.2.6.2). Approximately 30%–50% patients discontinue imatinib treatment within 5 years, with 5–7% of patients discontinuing treatment due to TKI intolerance and 15–20% due to TKI resistance (49, 51-53). Consequently, ≥25% of patients with CML switch TKIs at least once during their lifetime (54).

Each subsequent TKI therapy line can cause increased resistance, a lower treatment response, and decreased survival (49, 55). A retrospective study of 90 patients with CML (90% CML-CP) treated with first-line imatinib and second- or later line dasatinib or nilotinib reported worse long-term clinical outcomes with later lines of therapy (Brazil, January 2009–October 2017) (55). Five-year overall survival (OS) rates

reduced significantly from 83% with first-line therapy to 77% with third- or later line therapy (p=0.01) (55). Moreover, 8-year OS in patients who received three or more lines of treatment was significantly lower compared with those who continued to receive first-line imatinib therapy (22% and 83%, respectively p<0.01) (55). Poor treatment response and adverse disease outcomes are consistently reported in additional studies that have evaluated later-line TKI therapies (56-58).

Sequential TKI treatment can lead to the emergence of new mutations and currently available TKIs have limited sensitivity following the emergence of such mutations (49, 59). ABL1 kinase domain mutations are primarily responsible for secondary resistance to TKI therapy (60, 61). BCR-ABL1 kinase domain mutational analysis is routinely undertaken following an inadequate TKI response to guide selection of the most appropriate TKI; however, treatment options are limited (41). The most relevant predictor of disease progression is the kinetics of response to treatment (62); patients who do not achieve a reduction <10% BCR-ABL1 after 3 months with first-line imatinib and second generation TKIs have a higher risk of progression to AP, and if disease progresses to BP survival is generally less than 1 year (41, 45, 62-65).

TKI-related toxicity is of high importance in CML due to many patients requiring lifelong treatment (66). Currently available TKIs are associated with toxicities due to their lack of specificity and consequent off-target activities (49). In some patients, later-line TKI therapies are associated with a greater risk of adverse events (AEs), which may ultimately lead to treatment intolerance, long-term safety issues, and treatment discontinuation (49). Although most AEs initially occur early in the treatment course, the onset of some toxicities can occur months, or even years, after the start of therapy (66). Potential cardiovascular, metabolic, and pulmonary toxicities associated with TKI treatments range from being chronically problematic (e.g. hyperlipidaemia and pneumonitis) to potentially life-threatening (e.g. thrombosis and heart failure) (66). Notably, the safety profile of ponatinib is a concern, with ponatinib associated with cardiovascular and arteriothrombotic adverse events (some irreversible) (67). The risk:benefit must therefore be carefully evaluated and ponatinib is often only used in selected patients with fewer remaining treatment options (67, 68).

New treatment approaches are needed to improve disease control, prevent development of TKI resistance, prevent progression to advanced disease (AP and

BP), and alleviate TKI-related toxicity (50). In contrast to the currently available TKIs that target the BCR-ABL1 adenosine triphosphate (ATP) binding site, asciminib specifically targets the myristoyl pocket of BCR-ABL1. Asciminib does not interact with the ATP-binding site and therefore maintains activity against cells expressing clinically observed ATP-binding TKI-resistant mutations. It is anticipated that asciminib's novel mechanism will lead to lower rates of therapy resistance and off-target toxicity for patients resistant to/intolerant of early-line TKIs.

B.1.4 Equality considerations

It is not anticipated that the use of asciminib will be associated with any equality issues.

B.2 Clinical effectiveness

The ASCEMBL randomised controlled trial (RCT) in patients with chronic myeloid leukaemia (CML) in the chronic phase (CP) previously treated with ≥2 prior tyrosine kinase inhibitors (TKIs) showed that asciminib 40 mg twice-daily (BD) was associated with improved outcomes vs bosutinib 500 mg once-daily (OD) (primary evidence)[e] (12, 13)

- One RCT of asciminib (ASCEMBL) was identified. ASCEMBL included 233 adult patients with Philadelphia chromosome positive (Ph+) CML-CP previously treated with ≥2 prior TKIs. The trial arms were:
  - Asciminib 40 mg BD (n=157)
  - Bosutinib 500 mg OD (n=76)
- In the ASCEMBL trial, asciminib 40 mg BD was associated with improved clinical outcomes vs bosutinib 500 mg OD
  - The study met its primary objective and showed a statistically significant and clinically relevant treatment difference at Week 24 in major molecular response (MMR) rate of 12.2% (95% CI: 2.19, 22.30, p-value: 0.029).
  - Analysis of 48-week data showed that the time to achieve MMR was faster in patients treated with asciminib (median time to MMR: [redacted]) compared with bosutinib (median time to MMR: [redacted]).
  - A higher proportion of asciminib-treated patients achieved $MR^{4.5}$ vs bosutinib ([redacted], respectively) in the 48-week data-cut.
  - Complete cytogenetic response (CCyR) rates at Week 48 were [redacted] in the asciminib arm compared with [redacted] in the bosutinib arm. The CCyR rate by Week 48 was [redacted] in the asciminib arm compared with [redacted] in the bosutinib arm.

The Haematological Malignancy Research Network (HMRN) report details the findings of real-world disease management and outcomes in CML in England (supporting evidence) (14)

- There were [redacted] newly diagnosed cases of CML-CP in England between the 1st of September 2004 and the 31st of August 2019 ([redacted] median age of [redacted])
- Most patients were initially treated with a TKI ([redacted] received first-line imatinib)
- A total of [redacted] patients went onto receive a second-line TKI, and [redacted] patients received third-or later line therapy. [redacted] was treated with asciminib at tenth-line
- Of the [redacted] patients treated with a first-line TKI, [redacted] patients [redacted] achieved a

[e] The 24-week ASCEMBL CSR presents the primary analysis and provides baseline demographics and disease characteristics, the primary efficacy endpoint, all patient-related outcomes, pharmacokinetics, and resource utilisation (data cut-off: 25th May 2020) (12) (Sections B.2.6.1.3, B.2.6.1.16–B.2.6.1.20). All other efficacy and safety outcomes from the ASCEMBL trial are from the latest data-cut off (6th January 2021; 48-week data) (13, 14). All data from the 24-week primary analysis (data cut-off of 25th May 2020) are provided in Appendix M for completeness. Supporting safety evidence is also provided by Study X2101 (data cut-off: 6th January 2021) in Appendix N.

MMR or MR[2] response, and the median time to response was [redacted]

- A total of [redacted] were treated with a third-line TKI. Of these[redacted] patients [redacted] achieved a MMR or MR2 response, and the median time to response was [redacted].
- Excluding the three patients with the T315I mutation, 5-year OS at third-line was [redacted] and differed between choice of TKI therapy ([redacted] and [redacted] with bosutinib and ponatinib, respectively)

A matching-adjusted indirect treatment comparison (MAIC) was conducted to compare the TTD for asciminib vs the following comparators for the treatment of CML-CP patients who had received ≥2 prior TKIs: ponatinib, nilotinib, and dasatinib (Appendix I).

- Post-MAIC, the observed TTD curve for asciminib [redacted] when matched to ponatinib or dasatinib, while it [redacted] when matched to nilotinib.
- Median TTD for asciminib was not reached in the ASCEMBL trial. Post-MAIC with ponatinib, median TTD for asciminib was [redacted] compared with median TTD of [redacted]for ponatinib. Post-MAIC with nilotinib and dasatinib, median TTD was not reached.
- MAIC estimates suggest that asciminib offers improvements in both efficacy and safety compared with conventional TKIs (dasatinib, nilotinib, and ponatinib) in the target population.

B.2.1 Identification and selection of relevant studies

Appendix D presents the full details of the process and methodology used to identify and select the clinical evidence relevant to the technology being appraised.

A systematic literature review (SLR) was conducted[f] to identify relevant clinical effectiveness studies in patients with CML-CP. Studies identified are listed in Table 5. The SLR identified a Phase I dose-escalation study for asciminib (X2101, NCT02081378) (18, 69, 70); a Phase III randomised controlled trial (RCT) study of asciminib vs bosutinib (ASCEMBL, NCT03106779) (abstract) (11); a Phase III randomised controlled trial (RCT) study of asciminib vs bosutinib (ASCEMBL, NCT03106779) (abstract) (11); and publications of asciminib under the compassionate use programme in Spain (71-73).

An internal clinical study report (CSR) detailing 24-week results from ASCEMBL is also available (data cut-off: 25th May 2020) (12), as well as two internal reports presenting efficacy and safety from the latest data cut of the ASCEMBL trial and Study X2101 (safety only) (data cut-off of 6th January 2021; 48-week data) (13, 15). In addition, an internal document that details the findings of real-world disease management and outcomes in CML by the Haematological Malignancy Research Network (HMRN) is available (14).

[f] Conducted on the 9th of November 2020 and updated on the 13th of May 2021.

Table 5: Studies identified by the clinical effectiveness SLR†

Study	Intervention/s									
	Asciminib	Bosutinib	Ponatinib	Dasatinib	Nilotinib	Imatinib	Omacetaxine	Olverembatinib	PF-114	Allogenic-SCT
ASCEMBL (11)	✓	✓								
X2101 (18, 69, 70)	✓									
Luna 2020 (71-73)	✓									
PACE (58, 74-78)			✓							
PEARL (79)			✓							
OPTIC (78, 80-84)			✓							
Cortes 2012 (85)			✓							
Tojo 2017 (86)			✓							
Khan 2017 (87)		✓	✓	✓	✓	✓				
Swaminathan 2018 (88)			✓							
OITI (89)			✓							
Chan 2020 (90)			✓							
Sasaki 2020 (91)		✓	✓	✓	✓	✓				
Khoury 2012 (57, 92-98)		✓								
BYOND (99-108)		✓								
Garcia-Gutierrez 2019 (109)		✓								
Tiribelli 2018 (110)		✓								
Takahashi 2017 (111, 112)		✓								
Cortes 2019 (113)		✓								
Giles 2010 (114)					✓					
Tan 2019 (115)				✓						
Rossi 2013 (116)				✓	✓					
Ibrahim 2010‡ (56)				✓	✓					

Study	Intervention/s									
	Asciminib	Bosutinib	Ponatinib	Dasatinib	Nilotinib	Imatinib	Omacetaxine	Olverembatinib	PF-114	Allogenic-SCT
Ongoren 2017 (117)				✓	✓					
Garg 2009 (118)				✓	✓					
Ribeiro 2015 (119)				✓	✓					
Garcia-Gutierrez 2012‡ (120)				✓	✓					
CML-203 (121-123)							✓			
Jiang 2019 (124)								✓		
Turkina 2018 (125)									✓	
Lee 2014 (126)										✓
Devos 2021 (127)			✓							
Gugliotta 2020 (128)			✓	✓	✓	✓				
Chitanava 2021 (129)		✓	✓	✓	✓					
Latagliata 2021 (130)		✓								
TOPASE (131)			✓							

†Two additional studies were identified as part of the SLR, but these are not included here as they exclusively enrolled patients positive for the T315I mutation, which is not relevant to this submission; ‡Patients received dasatinib and/or nilotinib.
Abbreviations: SCT, stem cell transplant; SLR, systematic literature review.

B.2.2 List of relevant clinical effectiveness evidence

The Phase III ASCEMBL RCT is considered the primary evidence in the submission. The 24-week ASCEMBL CSR presents the primary analysis and provides baseline demographics and disease characteristics, the primary efficacy endpoint, all patient-related outcomes, pharmacokinetics, and resource utilisation (data cut-off: 25th May 2020) (12) (Sections B.2.6.1.3, B.2.6.1.16–B.2.6.1.20). All other efficacy and safety outcomes from the ASCEMBL trial are from the latest data-cut off (6th January 2021; 48-week data) (13, 15). All data from the 24-week primary analysis (data cut-off of 25th May 2020) are provided in Appendix M for completeness. Supporting safety evidence is also provided by Study X2101 (data cut-off: 6th January 2021) in Appendix N.

Supporting evidence provided by the real-world study by the HMRN (12, 14). The Phase I study (X2101, NCT02081378) results are not presented in this submission as it was a first-in-human dose escalation study (18, 69, 70). The publications by Luna et al. 2020 are not considered relevant to this submission due to its geography (Spain) and most patients receiving ≥3 prior TKI therapies before initiating asciminib (71-73).

B.2.2.1 Primary evidence

The ASCEMBL trial provides clinical effectiveness evidence for asciminib 40 mg twice daily (BD) within the indication being appraised (adult patients with Ph+ CML-CP previously treated with ≥2 prior TKIs) (12, 13). Details of this study are provided in Table 6, Section B.2.3.1 (methodology), Section B.2.6.1 (clinical effectiveness), and Section B.2.10 (adverse reactions).

Table 6: Clinical effectiveness evidence – ASCEMBL

Study	ASCEMBL (NCT03106779/CABL001A2301)				
Study design	Phase III, open-label, active-controlled, multi-centre RCT (2:1)				
Population	Adult patients with Ph+ CML-CP previously treated with ≥2 prior TKIs				
Intervention(s)	Asciminib (40 mg BD) (n=157)				
Comparator(s)	Bosutinib (500 mg OD) (n=76)				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Pivotal trial comparing the efficacy and safety of asciminib 40 mg BD vs bosutinib 500 mg OD				
Reported outcomes specified in the decision problem	• MMR at 24 weeks (primary endpoint) • MMR at 96 weeks • Cytogenic response rate (complete, partial, major, minor, minimal, no response) at all scheduled time points including 24, 48, and 96 weeks • MMR at all scheduled data collection time points • Time to MMR • Duration of MMR • Time to CCyR • Duration of CCyR • TTF • PFS • OS • Safety of asciminib vs bosutinib • Safety of asciminib when administered after bosutinib failure				
All other reported outcomes	• Trough plasma concentrations, PK parameters				

Source: Novartis (2021) (12, 13)
Abbreviations: ATP, adenosine triphosphate; BD, twice-daily; CCyR, complete cytogenic response; CML, chronic myeloid leukaemia; CP, chronic phase; MMR, major molecular response; PFS, progression-free survival; PK, pharmacokinetic; Ph+, Philadelphia chromosome-positive; OD, once-daily; OS, overall survival; RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure.

B.2.2.2 Supporting evidence

An internal document that details the findings of real-world disease management and outcomes in CML by the HMRN provides supporting evidence. The HMRN real-world study describes the disease management and complete treatment pathways for CML-CP with a focus on those treated with ≥2 TKIs. Details of this evidence are provided in Table 7, Section B.2.3.2 (methodology), and Section B.2.6.2 (clinical effectiveness).

Table 7: Clinical effectiveness evidence – HMRN real world evidence

Study	HMRN real-world disease management and outcomes in CML				
Study design	Disease registry (population-based cohort) study				
Population	Adult patients with newly diagnosed CML-CP (ICD-0–3: 9875/3) by HMDS (1st September 2004–31st August 2019) ([redacted])				
Intervention(s)	• Asciminib (n=1)				
Comparator(s)	• Imatinib ([redacted]) • Dasatinib ([redacted]) • Nilotinib ([redacted]) • Bosutinib ([redacted]) • Ponatinib ([redacted]) All outcomes are reported by treatment line and type of treatment				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	✓
	No	✓		No	
Rationale for use/non-use in the model	Study investigating the real-world disease management, complete treatment pathway and outcomes of CML-CP				
Reported outcomes specified in the decision problem	• Response (MMR, ≤1% BCR-ABL1 or MR[2] or CCyR) • Time to response • OS • PFS • TTD • Duration of disease state				
All other reported outcomes	• Proportion of subjects with T315I mutation in patients who have not responded to treatment				

Source: HMRN (2021) (14).
Abbreviations: CCyR, complete cytogenic remission; CML, chronic myeloid leukaemia; CP, chronic phase; HMDS, haematological malignancy diagnostic service; HMRN, haematological malignancy research network; ICD-0-3, Classification of Diseases for Oncology, third edition; MMR, major molecular response; MR, molecular response; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 ASCEMBL – primary evidence

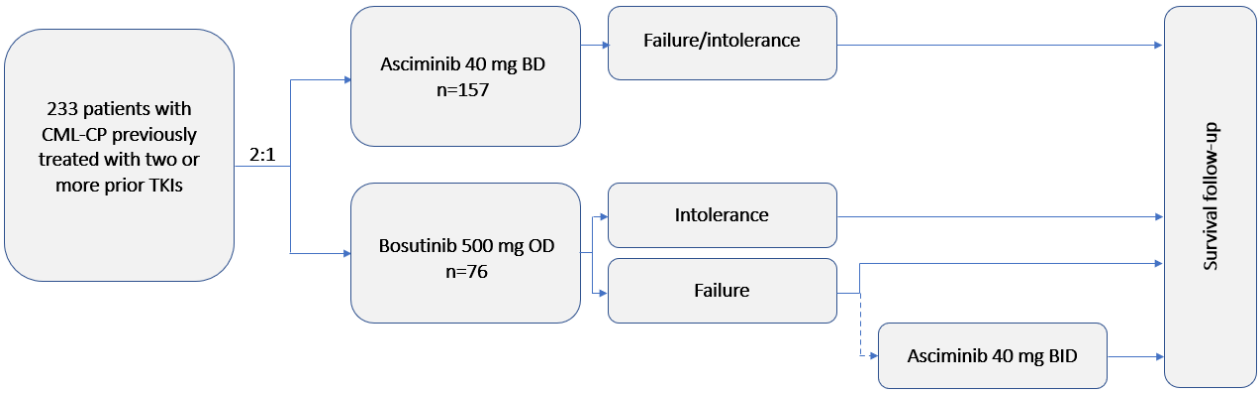
B.2.3.1.1 *Trial design*

ASCEMBL (CABL001A2301) is a Phase III, randomised, multi-centre, open-label study, which evaluated the efficacy and safety of asciminib 40 mg BD vs bosutinib 500 mg once-daily (OD) in adult patients with Ph+ CML-CP previously treated with ≥2 prior TKIs. Patients with CML-CP were enrolled in the study from 87 centres in 25 countries worldwide. Patients were randomised to receive either asciminib 40 mg BD or bosutinib 500 mg OD (Section B.2.3.1.2).

Patients with documented treatment failure (not meeting adapted efficacy criteria from 2013 ELN recommendations (132) [Section B.2.4.1.4.1] in either treatment arm) discontinued study treatment. Patients in the bosutinib treatment arm meeting treatment failure criteria had the option to switch to asciminib treatment within 96 weeks after the last patient was randomised to the study.[g] Patients received treatment for up to 96 weeks after the last patient received the first dose, or up to 48 weeks after the last patient had switched to asciminib treatment (whichever was longer, unless patients had discontinued study treatment earlier). A schematic of the study design is presented in Figure 5.

[g] The efficacy data collected after the switch from patients switching to asciminib following bosutinib failure were analysed separately as exploratory endpoints and not included for primary and secondary study endpoints.

Figure 5: Study design of ASCEMBL



Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; CML, chronic myeloid leukaemia; CP, chronic phase; OD, once-daily; TKI, tyrosine kinase inhibitor.

The ASCEMBL trial is currently ongoing (a 96-week analysis is planned, and data are expected in Quarter 2 2022) (Section B.2.11). This submission presents the 24-week analysis of the primary endpoint, patient-related outcomes, pharmacokinetics, and resource utilisation (data cut-off: 25th May 2020) (12) (Section B.2.6.1.3). All other efficacy and safety outcomes from the ASCEMBL trial are from the latest data-cut off (6th January 2021; 48-week data) (13, 15). Patients who discontinued study treatment at any time during the study will be assessed for survival and progression to AP/BP for up to 5 years from the date when the last randomised patient received the first dose (irrespective of treatment switch for patients failing bosutinib).

B.2.3.1.2 *Randomisation*

At baseline, patients were randomised in a 2:1 ratio to receive either asciminib 40 mg BD or bosutinib 500 mg OD. Due to cytogenetic response level to previous treatment being correlated with better outcomes, randomisation was stratified by cytogenetic response (CyR) status (133, 134):

- Major cytogenetic response (MCyR) (complete or partial)
  - Complete cytogenetic response (CCyR): No Ph+ metaphases
  - Partial cytogenetic response (PCyR): 1%–35% Ph+ metaphases
- No MCyR (minor, minimal, or none)
  - Minor: 36%–65% Ph+ metaphases
  - Minimal: 66%–95% Ph+ metaphases
  - None: >95% Ph+ metaphases

B.2.3.1.3 *Eligibility criteria*

The study population consisted of patients with CML-CP who had prior treatment with ≥2 ATP binding site TKIs. Key eligibility criteria are presented in Table 8.

Table 8: Key eligibility criteria in ASCEMBL

Inclusion criteria	Exclusion criteria
• Male or female ≥18 years of age with a diagnosis of CML-CP, who had received prior treatment with ≥2 ATP binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib), and were treatment failure or intolerant to the most recent TKI • Adequate liver and renal function as defined per laboratory values • ECOG PS of ≤2 • Electrolytes (as per central laboratory tests) within normal limits or corrected to be within normal limits with supplements prior to first dose of study medication • Avoiding consumption of grapefruit, Seville oranges, or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications‡. • Evidence of typical BCR-ABL1 transcript (e14a2 and/or e13a2) at the time of screening.	• Known presence of the T315I or V299L mutation at any time prior to study entry • Known second CP of CML after previous progression to AP/BP • Previous treatment with a haematopoietic SCT or patient planning to undergo allo-SCT • Presence of cardiac or cardiac repolarisation abnormality, including history of MI, angina pectoris, CABG, clinically significant cardiac arrhythmias, risk factors for TdP, concomitant medication(s) with a "Known risk of TdP" • Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol† • History of acute pancreatitis (within 1 year of study entry or past medical history of chronic pancreatitis), acute or chronic liver disease, infections (HIV, HBV, HCV), impaired GI function or GI disease, other active malignancy within 3 years prior to study entry¶ • Known presence of significant congenital or acquired bleeding disorder unrelated to cancer • Treatment with moderate or strong inducers/ inhibitors of CYP3A that cannot be discontinued ≥1 week prior to study treatment commencement • Previous treatment with or known/ suspected hypersensitivity to asciminib/bosutinib or any of its excipients • Participation in a prior investigational study within 30 days prior to randomisation or within 5 half-lives of the investigational product • Pregnant or nursing (lactating) women, and women of child-bearing potential§

Source: Novartis (2021) (12).
†E.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension); ‡orange juice was allowed; ¶with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively; §unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of asciminib and one month after last dose of bosutinib.
Abbreviations: AP, accelerated phase; ATP; adenosine triphosphate; BP, blast phase; CABG, coronary artery bypass graft; CML, chronic myeloid leukemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; HBV, chronic hepatitis B; HCV, chronic hepatitis C; HIV, human immunodeficiency virus; MI, myocardial infarction; PS, performance status; SCT, stem cell transplant; TdP, Torsades de Pointes; TKI, tyrosine kinase inhibitor.

B.2.3.1.4 *Trial drugs and concomitant medications*

Intervention: The intervention was asciminib 40 mg BD provided as tablets to be taken orally. Asciminib was taken in a fasted state; food was to be avoided for ≥2 hours before the dose and for ≥1 hour after the dose (water was permitted).

Selection of the asciminib 40 mg BD dosing schedule was based on the PK, efficacy, and safety data available from the Phase I dose escalation study (X2101, NCT02081378) (18, 69, 70). In Study X2101, patients with CML-CP previously treated with ≥2 prior TKIs received increasing doses of oral asciminib monotherapy (10 mg–200 mg on a continuous BD schedule). The maximum tolerated dose for asciminib monotherapy in patients with CML-CP was not achieved; based on the totality of available data, the 40 mg BD dose was selected as the recommended dose.

Comparator: The study comparator was bosutinib 500 mg OD provided as tablets to be taken orally in a fed state.

B.2.3.1.4.1 Permitted dose adjustments and interruptions of study treatment

Dose escalation of asciminib beyond the standard dose of 40 mg BD was not permitted. Dose escalation of bosutinib to 600 mg daily was permitted in patients who were taking 500 mg daily, did not have ≥grade 3 AEs and who:

- did not reach complete haematological response (CHR) by Week 8, or
- did not reach complete cytogenetic response (CCyR) by Week 12.

For patients who were unable to tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated to allow patients to continue study treatment Table 9.

Table 9: Dose reduction steps for asciminib and bosutinib

Dose levels	Asciminib	Bosutinib
Starting dose level	40 mg tablet BD (total daily dose 80 mg)	500 mg (1 x 500 mg tablet OD)
Dose level –1	20 mg tablet BD (total daily dose 40 mg)	400 mg (4 x 100 mg tablet OD)
Dose level –2	Not allowed	300 mg (3 x 100 mg tablet OD)

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; OD, once-daily.

B.2.3.1.4.2 Concomitant medications

The use of any concomitant medication/therapies deemed necessary for the supportive care of the patient were permitted; except those specifically prohibited (Table 10).

Table 10: Prohibited concomitant medications for patients on asciminib and bosutinib

Asciminib	Bosutinib
• Other anticancer drugs[†] • Strong CYP3A4/5 inhibitors/ inducers, and strong UGT1A/2B inducers • Drugs with a "Known", "Possible" or "Conditional" risk of TdP[‡] • Herbal preparations/medications	• Other anticancer drugs • Strong or moderate CYP3A inhibitors/inducers • pH altering medications

Source: Novartis (2021) (12).
[†]The administration of any other anticancer agents including chemotherapy and biologic agents is not permitted except for anti-cancer treatments of newly diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of patients. These patients may remain in the current study after consultation with Novartis; [‡]If concomitant administration of drugs with a "Known risk of TdP" was required and could not be avoided, then study drug was to be interrupted. If, based on the investigator assessment and clinical need, study treatment was to be resumed, close ECG monitoring was advised. If during the study, concomitant administration of a drug with "Possible risk" or "Conditional risk of TdP" was required, based on the investigator assessment and clinical need, study treatment could be continued under close ECG monitoring to ensure patient safety.
Abbreviations: ECG, electrocardiogram; TdP, Torsades de Pointes.

B.2.3.1.5 *Outcomes specified in the scope/used in the model*

Outcomes specified in the scope relate to primary and secondary endpoints in the trial. Descriptions of study assessments are provided in Table 11.

- **Primary outcome:** MMR rate at 24 weeks while on study treatment without meeting any treatment failure criteria (Section B.2.4.1.4.1) prior to 24 weeks.
- **Key secondary outcome**: MMR rate at 96 weeks while on study treatment without meeting any treatment failure criteria (Section B.2.4.1.4.1) prior to 96 weeks (data not presented as part of this submission[h]).
- **Other secondary outcomes:** Additional MMR outcomes, cytogenic response, time to treatment failure (TTF), progression free survival (PFS), OS, and safety.
- **Exploratory outcomes:** Efficacy in the switch analysis population, pharmacokinetic (PK) analyses, biomarkers, PROs, and resource utilisation.

[h] The ASCEMBL trial is currently ongoing with a 96-week analysis planned. This submission presents the results of the 24-week and 48-week data cuts.

Table 11: Study assessments

Study assessment	Description
Assessments specified in the scope	
MMR, response rate, time to response	Molecular response • Rate of MMR (MMR defined as a ≥3.0 log reduction in BCR-ABL1 transcripts compared with the standardised baseline equivalent to ≤0.1% BCR-ABL1/ABL % by IS†) • Time to MMR • Duration of MMR‡
	Cytogenic response • Defined as complete (CCyR), partial (PCyR), major (MCyR), minor (mCyR), or minimal response and no response‡ • Time to CCyR • Duration of CCyR¶
PFS	PFS during the time from randomisation to the earliest occurrence of documented disease progression to AP/BP or the date of death from any cause
OS	OS during the time from randomisation to the date of death
Disease progression	TTF from time of randomisation to an event of treatment failure§
Adverse effects of treatment	Type, frequency and severity of AEs, changes in laboratory values that fall outside the pre-determined ranges, clinically notable ECG, and other safety data (vital signs, physical examination)
HRQoL	Measure the impact of treatment on PROs, including CML-specific symptoms, patient QoL, and impact on work productivity and activity impairment with the following measures/questionnaires: • MDASI-CML • EQ-5D-5L • WPAI • PGIC
Other assessments	
PK	Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F
Biomarkers	• Biomarker assessments in bone marrow samples • Characterisation of low-level mutations in BCR-ABL1 gene • Cytokine analysis • Pharmacogenetics or drug metabolism genetics

Study assessment	Description
Assessments specified in the scope	
Resource utilisation	Including, hospitalisation, emergency room, GP, specialist, and urgent care visits

Source: Novartis (2021) (12).
†Patients not achieving MMR or missing PCR evaluations were considered 'nonresponders'; patients discontinuing treatment prior to 24 weeks or meeting any treatment failure criteria (Section B.2.4.1.4.1) prior to 24 weeks were considered as not having achieved MMR; ‡CCyR: 0% Ph+ metaphases, PCyR: >0 to 35% Ph+ metaphases, MCyR: 0 to 35% Ph+ metaphases, mCyR: >35 to 65% Ph+ metaphases, minimal: >65 to 95% Ph+ metaphases, none: >95 to 100% Ph+ metaphases; ¶Defined as the time from the date of first documented MMR/CCyR to the earliest date of loss of MMR/CCyR, progression to AP or BP, or CML-related death; §Treatment failure defined as: No CHR or >95% Ph+ metaphases at 3 months post-randomisation or thereafter; BCR-ABL1 ratio >10% IS and/or >65% Ph+ metaphases at 6 months post-randomisation or thereafter; BCR-ABL1 ratio >10% IS and/or >35% Ph+ metaphases at 12 months post-randomisation or thereafter; Loss of CHR, CCyR or PCyR at any time after randomisation; Detection of new BCR-ABL1 mutations that potentially cause resistance to study treatment at any time after randomisation; Confirmed loss of MMR in two consecutive tests; New clonal chromosome abnormalities in Ph+ cells: clonal chromosome abnormalities (CCA)/Ph+: at any time after randomisation; Discontinuation from randomised treatment for any reason.
Abbreviations: AE, adverse event; AP, accelerated phase; AUC, area under the curve; BP, blast phase; CCyR, complete cytogenetic response; CL/F, clearance; Cmax, maximum concentration; CML, chronic myeloid leukaemia; ECG, echocardiogram; IS, international scale; MCyR, major cytogenetic response; mCyR, minor molecular response; MDASI, M.D. Anderson Symptom Inventory; MMR, major molecular response; OS, overall survival; PCR, polymerase chain reaction; PCyR, partial cytogenetic response; PFS, progression-free survival; PGIC, patient global impression of change; Ph+, Philadelphia chromosome positive; PK, pharmacokinetic; PRO, patient related outcome; QoL, quality of life; Tmax; time to maximum concentration; TTF, time to treatment failure; WPAI, work productivity and activity impairment

B.2.3.1.5.1 Primary endpoint: MMR rate at 24 weeks

Treatment goals in CML have evolved over time with the introduction of imatinib in 2001, now nearly all imatinib-treated patients achieve normalised blood counts and most achieve a CCyR. There is evidence that achieving a major molecular response (MMR) predicts superior long-term clinical outcomes (e.g. PFS) (135). Additionally, achieving a MMR (BCR-ABL1 ≤0.1%) predicts a CML-specific survival close to normal as disease progression is uncommon once this level of cytoreduction has been achieved (136, 137).

The primary endpoint in ASCEMBL was MMR at 24 weeks while on study treatment without meeting any treatment failure criteria[i]. MMR was defined as a ≥3.0 log

[i] Treatment failure was based on adapted ELN criteria for failure of second-line treatment: No CHR or >95% Ph+ metaphases at 3 months after randomisation or thereafter; BCR-ABL1 ratio >10% IS and/or >65% Ph+ metaphases at 6 months after randomisation or thereafter; BCR-ABL1 ratio >10% IS and/or >35% Ph+ metaphases at 12 months after randomisation or thereafter; Loss of CHR, CCyR or PCyR at any time after randomisation; Detection of new BCR-ABL1 mutations that potentially cause resistance to study treatment at any time after randomisation; Confirmed loss of MMR in two consecutive tests; New clonal chromosome abnormalities in Ph+ cells: clonal chromosome abnormalities (CCA)/Ph+: at any time after randomisation; Discontinuation from randomised treatment for any reason

reduction in BCR-ABL1 transcripts from the standardised baseline equivalent to ≤0.1% BCR-ABL1 or percent of BCR-ABL1 transcripts vs control gene (on the IS). BCR-ABL1 transcript levels ≤0.1% are defined as a MMR (MR^3). BCR-ABL1 transcript levels ≤0.01% (MR^4) and ≤0.0032% ($MR^{4.5}$) are defined as a deep MR.

B.2.3.1.5.2 EQ-5D-5L

EQ-5D-5L is a two-part standardised instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems (or unable to perform the activity). The EQ VAS records the respondent's self-rated health on a vertical, VAS where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'. The health states derived from the descriptive system can be summarised into a single index score that provides a simple measure of health for clinical and economic appraisal.

Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period were included in the change from baseline analyses. Missing data items in a scale were handled according to the manual for each instrument. No imputation was applied if the total or subscale scores are missing at a visit. EQ-5D-5L data was were collected in ASCEMBL (12, 138) at baseline, and then at Weeks 4, 8, 12, 16, 24, 36, 48, and 96. These were mapped onto EQ-5D-3L responses, as suggested by NICE, using the mapping algorithm developed by van Hout and colleagues (139, 140). This is aligned with NICE's preferred approach that the EQ-5D-3L should be used for reference-case analyses until further research is undertaken to better understand the impact of adopting the EQ-5D-5L, as per their position statement last updated in October 2019 (141), as well as the proposals in the recent methods review consultation (142). A repeated measures model for longitudinal data was used to estimate differences between treatment arms. The repeated measures model included terms for treatment arm, treatment status (on/off), time, baseline value as main effects, and an interaction term for treatment by time (results presented in Section B.2.6.1.18). Data were also

examined with a generalised linear model (GLM). Data were insufficient to support analysis by progression status or proximity to death.

B.2.3.1.6 *Baseline demographic characteristics*

Details of the baseline demographic characteristics are provided in Table 12. The mean age of patients in the study was 51 years. Most patients were White (74.7%) and almost all patients (98.7%) had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The two treatment arms were well-balanced for the demographic characteristics assessed, with only small differences observed in ethnicity and sex. There were fewer Hispanic/Latino patients in the asciminib arm (9.6%) compared with the bosutinib arm (22.4%), and the proportion of males was higher in the asciminib arm (52.2%) compared with the bosutinib arm (40.8%).

Table 12: Baseline demographic characteristics

Demographic variable	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)	All patients (N=233)
Age (years) mean ± SD	51.0 ± 13.49	51.0 ± 13.95	51.0 ± 13.61
Age category, n (%)			
18–<65 years	128 (81.5)	61 (80.3)	189 (81.1)
65–<75 years	25 (15.9)	13 (17.1)	38 (16.3)
≥75 years	4 (2.5)	2 (2.6)	6 (2.6)
<65 years	128 (81.5)	61 (80.3)	189 (81.1)
≥65 years	29 (18.5)	15 (19.7)	44 (18.9)
Sex (female), n (%)	75 (47.8)	45 (59.2)	120 (51.5)
Ethnicity, n (%)			
Hispanic or Latino	15 (9.6)	17 (22.4)	32 (13.7)
Not Hispanic or Latino	102 (65.0)	43 (56.6)	145 (62.2)
Not reported	23 (14.6)	11 (14.5)	34 (14.6)
Unknown	17 (10.8)	5 (6.6)	22 (9.4)
BMI, kg/m^2			
N	152	76	228
mean ± SD	27.9 ± 6.52	27.4 ± 7.16	27.7 ± 6.73
ECOG performance status, n (%)			
0	126 (80.3)	62 (81.6)	188 (80.7)
1	28 (17.8)	14 (18.4)	42 (18.0)
2	2 (1.3)	0	2 (0.9)
Missing	1 (0.6)	0	1 (0.4)

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; OD, once-daily; SD, standard deviation.

B.2.3.1.7 *Baseline disease characteristics*

Median time since initial diagnosis was 3.8 years and 5.1 years in the asciminib and the bosutinib arms, respectively. Disease history regarding extramedullary involvement was well balanced (Table 13).

Table 13: Baseline disease characteristics

Disease history	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)	All patients (N=233)
Time since initial diagnosis of CML (years)			
Mean ± SD	6.2 ± 5.75	7.0 ± 5.63	6.5 ± 5.71
Any extramedullary involvement, n (%)			
Yes	8 (5.1)	4 (5.3)	12 (5.2)
Location of extramedullary involvement - n (%)			
Spleen	8 (5.1)	4 (5.3)	12 (5.2)
Liver	1 (0.6)	1 (1.3)	2 (0.9)

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; CML, chronic myeloid leukaemia; OD, once-daily; SD, standard deviation.

B.2.3.1.7.1 Bone marrow aspirate analysis at baseline

Based on the randomisation data collected in the interactive response technology (IRT) system, 46 patients (29.3%) in the asciminib arm and 22 patients (28.9%) in the bosutinib arm were in MCyR at baseline. However, according to baseline bone marrow aspirates, 28.0% of patients in the asciminib arm and 27.6% of patients in the bosutinib arm were classified as MCyR. Some patients had a missing MCyR status at baseline due to either a missing bone marrow aspirate (BMA), a BMA with insufficient quality, or with less than 20 metaphases examined (22.3% in the asciminib arm and 11.8% in the bosutinib arm) (Table 14).

Table 14: Bone marrow aspirate analysis at baseline (FAS)

BM evaluation	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
Blasts (%) in BM		
N	139	69
Mean ± SD	1.42 ± 1.698	1.76 ± 2.192
Blasts (%) in BM category, n (%)		
0%	34 (21.7)	9 (11.8)
>0–<5%	97 (61.8)	56 (73.7)
≥5–<15%	8 (5.1)	4 (5.3)
≥15%	0	0
Missing	18 (11.5)	7 (9.2)
Promyelocytes (%) in BM		
N	134	68
Mean ± SD	3.55 ± 4.175	2.81 ± 2.989
Blasts + promyelocytes (%) in BM (derived)		
N	140	71
Mean ± SD	4.81 ± 4.556	4.40 ± 3.932
Any other chromosomal abnormalities in Ph+ metaphases, n (%)		
Yes	16 (10.2)	16 (21.1)
No	129 (82.2)	58 (76.3)
Missing	12 (7.6)	2 (2.6)
Any other chromosomal abnormalities in Ph- metaphases, n (%)		
Yes	11 (7.0)	9 (11.8)
No	134 (85.4)	65 (85.5)
Missing	12 (7.6)	2 (2.6)
Ph+ metaphases (%) in BM		
N	122	67
Mean ± SD	61.63 ± 39.481	64.37 ± 38.754
Percentage Ph+ metaphases category, n (%)		
>95%	41 (26.1)	25 (32.9)
>65%–95%	26 (16.6)	13 (17.1)
>35%–65%	11 (7.0)	8 (10.5)
>0%–35%	25 (15.9)	16 (21.1)
0%	19 (12.1)	5 (6.6)
Missing	35 (22.3)	9 (11.8)
Major cytogenetic response, n (%)		
Yes	44 (28.0)	21 (27.6)
No	78 (49.7)	46 (60.5)
Missing†	35 (22.3)	9 (11.8)

Source: Novartis (2021) (12).
†Includes BMA missing, BMA with insufficient quality and BMA with less than 20 metaphases examined
Abbreviations: BD, twice daily; BM, bone marrow; FAS, full analysis set; Ph- Philadelphia chromosome negative; Ph+ Philadelphia chromosome positive; OD, once-daily; SD, standard deviation.

B.2.3.1.7.2 BCR-ABL1 gene mutations

At Week 1 Day 1, the proportion of patients with ≥1 mutation in the BCR-ABL1 oncoprotein was 12.7% in the asciminib arm compared with 13.2% of patients in the bosutinib arm. T315I mutations were observed in three patients (1.9%) in the asciminib arm and one patient (1.3%) in the bosutinib arm, and V299L mutation was observed in one patient (1.3%) in the bosutinib arm (Table 15). As per exclusion criteria, these patients were discontinued from the study.

Table 15: BCR-ABL1 gene mutation status by the central laboratory (Week 1 Day 1) (FAS)

Mutation	Asciminib 40 mg BD (N=157) n (%)	Bosutinib 500 mg OD (N=76) n (%)	All patients (N=233) n (%)
F317L	3 (1.9)	2 (2.6)	5 (2.1)
T315I	3 (1.9)	1 (1.3)	4 (1.7)
Y253H	3 (1.9)	0	3 (1.3)
F359V	3 (1.9)	0	3 (1.3)
G250E	2 (1.3)	0	2 (0.9)
E255K	2 (1.3)	0	2 (0.9)
E255V	1 (0.6)	1 (1.3)	2 (0.9)
M244V	0	2 (2.6)	2 (0.9)
E459K	1 (0.6)	0	1 (0.4)
E462K	1 (0.6)	0	1 (0.4)
F359C	1 (0.6)	0	1 (0.4)
F359I	0	1 (1.3)	1 (0.4)
F486S	1 (0.6)	0	1 (0.4)
L248V	1 (0.6)	0	1 (0.4)
Q252H	0	1 (1.3)	1 (0.4)
R473Q	0	1 (1.3)	1 (0.4)
V299L	0	1 (1.3)	1 (0.4)
W478R	1 (0.6)	0	1 (0.4)
Patients with any mutation	**20 (12.7)**	**10 (13.2)**	**30 (12.9)**
Patients with multiple mutations	**3 (1.9)**	**0**	**3 (1.3)**

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; FAS, full analysis set; OD, once-daily.

B.2.3.1.7.3 Relevant medical history and ongoing conditions

Overall, 91.1% of patients in the asciminib arm and 94.7% in the bosutinib arm had at least one medical condition. A higher number of cardiac disorders (19.7% vs 10.5%, respectively) and respiratory, thoracic, and mediastinal disorders (24.8% vs 19.7%, respectively) were reported in patients in the asciminib arm compared with the bosutinib arm. In contrast, there were fewer surgical and medical procedures

(25.5% vs 42.1%, respectively), gastrointestinal disorders (26.1% vs 38.2%, respectively), vascular disorders (43.3% vs 52.6%, respectively), immune system disorders (3.2% vs 10.5%, respectively), and endocrine disorders (5.1% vs 10.5%, respectively) in patients in the asciminib arm relative to the bosutinib arm.

B.2.3.1.8 *Prior antineoplastic medications*

Patients were heavily pre-treated, with approximately half of the patients receiving study treatment as third-line therapy. In the asciminib arm 52.2% of patients received asciminib as third-line therapy and 47.8% as fourth- or later line, while 39.5% received bosutinib as third-line therapy and 60.5% as fourth- or later line. Most patients entered the study due to lack of efficacy with their last TKI therapy (Table 16).

Table 16: Prior antineoplastic therapy (FAS)

	Asciminib 40 mg BD (N=157)	**Bosutinib 500 mg OD (N=76)**	**All patients (N=233)**
Prior TKIs, n (%)			
Dasatinib	131 (83.4)	65 (85.5)	196 (84.1)
Imatinib	130 (82.8)	63 (82.9)	193 (82.8)
Nilotinib	104 (66.2)	56 (73.7)	160 (68.7)
Ponatinib	23 (14.6)	18 (23.7)	41 (17.6)
Other	5 (3.2)	4 (5.3)	9 (3.9)
Radotinib	4 (2.5)	2 (2.6)	6 (2.6)
Number of prior TKIs, n (%)			
2	89 (56.7)	33 (43.4)	122 (52.4)
3	53 (33.8)	33 (43.4)	86 (36.9)
4	14 (8.9)	7 (9.2)	21 (9.0)
≥5	1 (0.6)	3 (3.9)	4 (1.7)
Number of lines of prior TKI therapy, n (%)			
2	82 (52.2)	30 (39.5)	112 (48.1)
3	44 (28.0)	29 (38.2)	73 (31.3)
4	24 (15.3)	10 (13.2)	34 (14.6)
≥5	7 (4.5)	7 (9.2)	14 (6.0)
Reason to discontinue last TKI, n (%)			
Lack of efficacy	95 (60.5)	54 (71.1)	149 (63.9)
Lack of tolerability	59 (37.6)	22 (28.9)	81 (34.8)
Other	3 (1.9)	0	3 (1.3)
Prior non-TKI therapies			
No	101 (64.3)	51 (67.1)	152 (65.2)
Yes	56 (35.7)	25 (32.9)	81 (34.8)

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; FAS, full analysis set; OD, once-daily; TKI, tyrosine kinase inhibitor.

B.2.3.1.9 *Concomitant medications*

In total, 86.5% and 96.1% of patients required concomitant medications in the asciminib and bosutinib treatment arms, respectively. The concomitant medications by Anatomical Therapeutic Chemical (ATC) class that were reported more frequently in the bosutinib arm relative to asciminib arm (with a ≥10% relative difference) included:

- Alimentary tract and metabolism (65.4% in the asciminib arm vs 82.9% in the bosutinib arm)
- Systemic hormonal preparations, excluding sex hormones and insulins (14.1% in the asciminib arm vs 26.3% in the bosutinib arm).

In contrast, medications belonging to musculoskeletal system (46.2% vs 26.3%, respectively) and anti-infectives for systemic use (36.5% vs 22.4%, respectively) were reported more frequently in the asciminib arm compared with the bosutinib arm.

B.2.3.2 HMRN real world evidence – supporting evidence

B.2.3.2.1.1 Study design

The Haematological Malignancy Research Network (HMRN) is an ongoing population-based cohort, which was established in 2004 to provide robust, generalisable data to inform clinical practice and research. The HMRN region covers the former two adjacent UK Cancer Networks with a total population of 3.8 million (Yorkshire and the Humber & Yorkshire Coast Cancer Networks) and collects detailed information about all haematological malignancies diagnosed in the region. This is done for all patients newly diagnosed with a haematological malignancy in the HMRN region. CML diagnosis is based on the demonstration of a BCR-ABL fusion transcript expressed by the Ph by real-time quantitative polymerase chain reaction (RQ-PCR) and/or the demonstration of t(9;22)(q34;q11) by conventional karyotyping or interphase FISH. As per standard practice, response to therapy is monitored using either molecular and/or cytogenetic tests.

B.2.3.2.1.2 Data collection

Data collection was initiated 6 months after date of diagnosis; research nurses working to agreed operating procedures and data standards visited each of the 14 hospitals in the region and abstracted a core clinical dataset from the patients'

medical records. The information collected included demographic details, baseline blood count data, and first-line treatment. Further data abstraction from medical records provided information on subsequent treatment lines. Information on date and cause of death were obtained from the National Health Service (NHS) Central Register.

B.2.3.2.1.3 Data analysis and study outcomes

Analysis included adult (≥18 years) patients newly diagnosed with CML-CP between the 1st of September 2004 and the 31st of August 2019 whilst resident in the HMRN region and treated within the network. Patients were described in terms of their baseline demographic and prognostic characteristics, and each patient's treatment pathway characterised from date of diagnosis to date of death or, for patients still alive, end of follow up. Reported outcomes are described in Table 17.

Table 17: Outcomes reported in HMRN real world evidence

Outcome	Methodology
Disease response	MMR ≤0.1% BCR-ABL1, or MR^2 (≤1.0% BCR-ABL1), or CCyR. Time to response was measured from treatment initiation to achieving MMR/MR^2; and DOR was measured from the date a MMR/MR^2 was achieved to loss of response for each treatment line
TTD	Time from treatment initiation to the date of discontinuation or death; TTD also reported for all patients censoring at the end of follow-up for those patients still on treatment
OS†	Time (years) from treatment initiation (i.e. index date) to death from any cause
PFS‡	Initiation of treatment (i.e. the index date) to the earliest documentation of disease progression to AP/BC or date of death from any cause
Duration of disease	Time spent in AP and BP was defined from date of disease progression to remission, or date of death if remission was not achieved

Source: HMRN (2021) (14).
†Patients who did not die within the study observation period were censored on the last date they were known to be alive, according to national central register; ‡For patients who did not have disease progression or died, the last date of follow-up of the medical records was used as the censor date.
Abbreviations: AP, advanced phase; BP blast phase; CCyR, complete cytogenetic response; HMRN, Haematological Malignancy Research Network; MMR, major molecular response; MR, molecular response; OS, overall survival; PFS, progression-free survival; TTD, time-to-discontinuation.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 ASCEMBL – primary evidence

The 24-week ASCEMBL CSR presents the primary analysis and provides baseline demographics and disease characteristics, the primary efficacy endpoint, patient-related outcomes, pharmacokinetics, and resource utilisation (data cut-off: 25th May 2020) (12) (Section B.2.6.1.3). All other efficacy and safety outcomes from the ASCEMBL trial are from the latest data-cut off (6th January 2021; 48-week data) (13). All data from the 24-week primary analysis (data cut-off: 25th May 2020) are provided in Appendix M for completeness.

B.2.4.1.1 *Analysis sets*

The following analysis sets were defined in the trial:

- **Full analysis set (FAS):** all randomised patients
- **Safety set:** all patients who received at least one dose of study treatment
- **Pharmacokinetic set (PKS):** all patients who provided at least one evaluable PK concentration[j]
- **MMR responder set:** a subset of the FAS and included patients who achieved MMR at any time on study treatment (used for duration of MMR and time to MMR)
- **CCyR analysis set:** a subset of the FAS and included patients who were not in CCyR at baseline (used for CCyR rates at and by scheduled time points)
- **CCyR responder set:** a subset of the FAS and included patients who were not in CCyR at baseline and achieved CCyR at any time on study treatment (used for duration of CCyR and time to CCyR)
- **Switch analysis set:** a subset of the FAS and included patients who switched from bosutinib to asciminib and received at least one dose of asciminib

The efficacy data collected after the switch from patients switching to asciminib following bosutinib failure were analysed separately as exploratory endpoints and will not be included for primary and secondary study endpoints.

[j] Blood samples for patients providing full PK profiles were capable of serial PK sampling over 12 hours. Sparse PK samples were taken from all other patients on asciminib.

B.2.4.1.2 *Summary of hierarchical testing*

Hypothesis testing for the primary and key secondary endpoints followed a hierarchical testing approach to preserve overall alpha level of 5% (two-sided). Since the test of the primary endpoint was significant, the key secondary endpoint will be tested at the 5% significance level at the 96-week analysis time-point (not part of this submission).

B.2.4.1.3 *Hypothesis objective*

To demonstrate that asciminib 40 mg BD was superior to bosutinib 500 mg OD with respect to MMR rate at 24 weeks.

B.2.4.1.4 *Statistical analysis of primary endpoint*

The analysis of the primary variable was based on the FAS. The null hypothesis was that the efficacy of asciminib (40 mg BD) was superior to bosutinib 500 mg OD in patients with CML-CP, previously treated with ≥2 TKIs. This was determined as MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria (Section B.2.4.1.4.1) prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications. MMR was defined as a ≥3.0 log reduction in BCR-ABL1 transcripts compared to the standardised baseline equivalent to ≤0.1% BCR-ABL1/ABL% by international scale (IS) as measured by RQ-PCR. Patients discontinuing treatment due to any reason and patients meeting any treatment failure criteria prior to 24 weeks were considered as not having achieved MMR at 24 weeks. The Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the randomisation stratification factor (MCyR vs no MCyR at screening), was used to compare MMR rate between the asciminib and bosutinib arms, at the two-sided 5% level of significance. Multiple supplementary and sensitivity analyses were performed to assess the overall robustness of the primary efficacy results.

B.2.4.1.4.1 Treatment failure criteria

Treatment failure was based on adapted ELN criteria for failure of second-line treatment (132):

- No CHR or >95% Ph+ metaphases at 3 months after randomisation or thereafter

- BCR-ABL1 ratio >10% IS and/or >65% Ph+ metaphases at 6 months after randomisation or thereafter
- BCR-ABL1 ratio >10% IS and/or >35% Ph+ metaphases at 12 months after randomisation or thereafter
- Loss of CHR, CCyR or PCyR at any time after randomisation
- Detection of new BCR-ABL1 mutations that potentially cause resistance to study treatment at any time after randomisation
- Confirmed loss of MMR in two consecutive tests
- New clonal chromosome abnormalities in Ph+ cells: clonal chromosome abnormalities (CCA)/Ph+: at any time after randomisation
- Discontinuation from randomised treatment for any reason.

B.2.4.1.5 *Statistical analysis of secondary endpoints*

The key secondary endpoint is MMR rate at 96 weeks while on study treatment, without meeting any treatment failure criteria prior to 96 weeks. The ASCEMBL trial is currently ongoing, and this submission presents the results from the 24-week and 48-week data cut-offs; thus, the key secondary endpoint is not included.

No confirmatory statistical testing of non-key secondary efficacy endpoints was performed; however, nominal p-values were presented. A summary of the approach taken for other secondary endpoints is presented in Table 18.

Table 18: Summary of the secondary endpoint statistical analyses in ASCEMBL

Outcome	Analysis overview
MMR and CCyR rate at and by time points	For each endpoint, the rate and the associated 95% CI based on the Clopper-Pearson method were presented by treatment group. CIs for the differences in any response rates between treatment groups were provided using the Wald method. Statistical testing was performed via CMH chi-square tests stratified by the randomisation strata. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% CI was also provided. The same analysis of the MMR rate was performed using the number of patients with adequate follow-up as the denominator, i.e. for each time point (Week X), only patients randomised at least X weeks prior to the cut-off date were considered. In addition, the cumulative incidence of MMR/CCyR by treatment group was graphically displayed by an increasing step function.
Cytogenetic response at and by time points	Cytogenetic response was based on the percentage of Ph+ metaphases in the bone marrow, and the following summaries were presented: • Frequency and percentage of all cytogenetic response categories by treatment arm • Shift table comparing baseline and best post-baseline cytogenetic response categories by treatment All assessments of cytogenetic response categories were listed by treatment arm.
Time to response (MMR and CCyR)	The time to response variables were presented by descriptive statistics and by KM method. An additional analysis of time to MMR was performed considering discontinuation from treatment due to any reason, without prior achievement of MMR as a competing risk. Time to MMR was censored at the last molecular assessment date on treatment prior to or at the cut-off date, if no events/competing risk occurred before or at the cut-off date or the EOT. The estimated cumulative incidence rates and 95% CI at 24, 48, 72 and 96 weeks were presented for each treatment arm. The cumulative incidence curve was plotted.
Duration of response (MMR and CCyR)	Duration of MMR/CCyR was analysed by KM method and graphically displayed by KM plots. The estimated rates of patients who are still responding at various time points was also be provided using KM method.
TTF, PFS, and OS	TTF, PFS, and OS were estimated and graphically displayed using the KM approach on the FAS. The estimated rates by KM method at various time points are provided and the endpoints were compared between the two treatment groups using stratified log-rank test stratified by the randomisation strata. The hazard ratio and 95% CIs were computed from a stratified Cox model.

Source: Novartis (2021) (12).
Abbreviations: CCyR, complete cytogenetic response; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EOT, end of treatment; FAS, full analysis set; KM, Kaplan-Meir; MMR, major molecular response; OS, overall survival; PCR, polymerase chain reaction; PFS, progression free survival; Ph+, Philadelphia chromosome positive; TTF, time to failure.

B.2.4.1.6 *Sample size and power calculation*

It was assumed that asciminib has a 20% higher MMR rate at 24 weeks than bosutinib, i.e. 35% compared with 15%, resulting in an odds ratio (OR) of 3.05. The assumed bosutinib rate of 15% was based on the results of a previous trial evaluating bosutinib therapy in patients treated with ≥2 prior TKIs (94).

To test the null hypothesis – that the MMR rate at 24 weeks is equal in the two treatment arms – a total of 222 patients were needed (i.e. 148 patients in the asciminib arm and 74 patients in the bosutinib arm with a 2:1 randomisation ratio), based on a two-sided 5% level of significance and with 90% power.

If the primary analysis of MMR rate at 24 weeks was statistically significant, the key secondary endpoint MMR rate at 96 weeks was to be tested, with the overall alpha controlled at the 5% two-sided level using a gatekeeping strategy.[k]

B.2.4.1.7 *Discontinuation of study treatment and premature patient withdrawal*

A patient would be considered withdrawn if he/she stated an intention to withdraw, failed to return for visits, or became lost to follow-up for any other reason. For outcomes with a specific time-point, patients discontinuing the randomised treatment prior to a specific time point due to any reason were considered non-responders for that time point.

For patients who discontinued treatment in the treatment period or switch treatment period for reasons other than death, lost to follow-up, or withdrawal of consent, the patient would enter the survival follow-up phase. Survival visit assessments (survival, antineoplastic therapies, stem cell transplant and progression) were to be performed every 12 weeks until documented death, lost to follow-up, withdrawal of consent or until the end of the study.

[k] The ASCEMBL trial is currently ongoing with a 96-week analysis planned. This submission presents the results of the 24-week and 48-week data cuts.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Appendix D contains the quality assessment of each of the trials identified in the SLR.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 ASCEMBL – primary evidence

B.2.6.1.1 *Analysis sets*

The analysis sets and the numbers of patients in each analysis set are presented in Table 19. All randomised patients were included in the FAS. One patient in the asciminib arm was excluded from the Safety set after developing cytopenia after randomisation and subsequently did not receive study treatment.

Table 19: Analysis sets (all randomised patients)

Analysis set	Asciminib 40 mg BD (N=157) n (%)	Bosutinib 500 mg OD (N=76) n (%)	All patients (N=233) n (%)
Full analysis set	157 (100.0)	76 (100.0)	233 (100.0)
Safety set	156 (99.4)	76 (100.0)	232 (99.6)
PK analysis set	149 (94.9)	NA	NA
MMR responder set	54 (34.4)	14 (18.4)	68 (29.2)
CCyR analysis set	103 (65.6)	62 (81.6)	165 (70.8)
CCyR responder set	44 (28.0)	19 (25.0)	63 (27.0)
Switch analysis set	NA	22 (28.9)	NA

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; CCyR, complete cytogenetic response; FAS, full analysis set; MMR, major molecular response; NA, not applicable; OD, once-daily; PK, pharmacokinetic.

B.2.6.1.2 *Patient disposition*

The ASCEMBL study enrolled 233 patients with CML-CP from 87 centres in 25 countries worldwide. Of these, 157 patients were randomised to treatment with asciminib and 76 to treatment with bosutinib. As of the 6th of January 2021 data cut-off, [redacted] patients [redacted] continued to receive treatment. Twice the proportion of patients were ongoing in the asciminib arm [redacted] relative to the bosutinib arm [redacted] at data cut-off. Full details of patient disposition are provided in Table 20.

Table 20: Patient disposition (FAS)

	Asciminib 40 mg BD (N=157) n (%)	Bosutinib 500 mg OD (N=76) n (%)	All patients (N=233) n (%)
Treated	[redacted]	[redacted]	[redacted]
Treatment ongoing†	[redacted]	[redacted]	[redacted]
Discontinued from treatment	[redacted]	[redacted]	[redacted]
<Week 24	[redacted]	[redacted]	[redacted]
≥Week 24 and <Week 48	[redacted]	[redacted]	[redacted]
≥Week 48 and <Week 96	[redacted]	[redacted]	[redacted]
≥Week 96	[redacted]	[redacted]	[redacted]
Reason for discontinuation			
Lack of efficacy	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Patient/guardian decision	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (13)
Abbreviations: BD, twice-daily; FAS, full analysis set; NA, not applicable; OD, once-daily.

The countries with the largest enrolments were the Russian Federation (n=33, 14.2%), the US (n=22, 9.4%), Brazil (n=19, 8.2%), Germany (n=18, 7.7%), France (n=17, 7.3%), and Japan (n=16, 6.9%).

At the 25th of May 2020 data-cut, 22 patients randomised to bosutinib switched to asciminib treatment after meeting lack of efficacy criteria as per protocol; 12 of the 22 patients (54.5%) were ongoing at the time of data cut-off. Ten patients discontinued: seven due to lack of efficacy (31.8%), two patients due to adverse events (AEs) (9.1%), and one patient due to physician decision (4.5%). As of the 6th of January 2021 data-cut, a further [redacted] patients had switched from bosutinib to asciminib due to lack of efficacy.

B.2.6.1.3 *Primary endpoint: MMR rate at 24 weeks*

The primary endpoint objective was reached; the MMR rate at 24 weeks was significantly higher in the asciminib arm compared with the bosutinib arm while on study treatment without meeting any treatment failure criteria (treatment different of 12.2%, [95% confidence interval [CI]: 2.19, 22.30; p=0.029]), demonstrating superiority (Table 21).

Table 21:MMR rate at 24 Weeks (FAS)

	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
Response, n (%)	40 (25.48)	10 (13.16)
95% CI for response†	(18.87, 33.04)	(6.49, 22.87)
Unstratified difference in response rate (vs bosutinib) (%)	12.32	–
95% CI for difference in response rate‡	(2.11, 22.53)	–
Common risk difference (%)¶	12.24	–
95% CI for difference	(2.19, 22.30)	–
CMH test p-value§	0.029	–

Source: Novartis (2021) (12).
†Clopper-Pearson 95% 2-sided CI; ‡Wald 95% 2-sided CI; ¶The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method; §CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomisation data).
Abbreviations: BD, twice-daily; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; MMR, major molecular response; OD, once-daily.

B.2.6.1.3.1 Sensitivity analyses of primary endpoint

Results of the predefined sensitivity analyses were consistent with the primary analysis. Discrepancies noted in Section B.2.3.1.7.1 between stratum assigned at IRT and that derived based on bone marrow aspirate data as reported in the case report form (CRF) had no significant impact on the primary analysis of the primary endpoint (Table 22). The imputation rule in case of missing PCR evaluations at Week 24 was not used in the primary analysis as no patient with missing Week 24 assessment had both a 16-week and a 36-week assessment indicating MMR. Consequently, the results from the analysis of the primary endpoint not using the imputation rule were the same as those from for the primary analysis (Table 22).

The primary endpoint assessment was missed for two patients due to the COVID-19 pandemic (considered non-responders). The results from the sensitivity analysis excluding patients with a planned Week 24 visit after the start of the COVID-19 pandemic were consistent with the results from the primary analysis.

Table 22: Sensitivity analyses of MMR rate at 24 weeks (FAS)

		Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
By stratum recorded in the CRF	Response, n (%)	40 (25.48)	10 (13.16)
	95% CI for response†	(18.87, 33.04)	(6.49, 22.87)
	Unstratified difference in response rate (vs bosutinib) (%)	12.32	–
	95% CI for difference in response rate‡	(2.11, 22.53)	–
	Common risk difference (%)¶	11.54	–
	95% CI for difference	(1.73, 21.34)	–
	CMH test p-value§	0.037	–
Missing PCR evaluations - without the imputation rule	Response, n (%)	40 (25.48)	10 (13.16)
	95% CI for response†	(18.87, 33.04)	(6.49, 22.87)
	Unstratified difference in response rate (vs bosutinib) (%)	12.32	–
	95% CI for difference in response rate‡	(2.11, 22.53)	–
	Common risk difference (%)††	12.24	–
	95% CI for difference	(2.19, 22.30)	–
	CMH test p-value‡‡	0.029	–

Source: Novartis (2021) (12).
†Clopper-Pearson 95% 2-sided CI for response rate.
‡Wald 95% 2-sided CI.
¶The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on CRF data) and its 95% CI were estimated using the Mantel-Haenszel method.
§CMH 2-sided test was stratified by baseline major cytogenetic response status (based on CRF data).
††The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomised data) and its 95% CI were estimated using the Mantel-Haenszel method.
‡‡CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomisation data).
Abbreviations: BD, twice daily; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CRF, case report form; FAS, full analysis set; MMR, major molecular response; OD, once-daily; PCR, polymerase chain reaction.

B.2.6.1.4 *Key secondary endpoint: MMR rate at 96 weeks*

The key secondary endpoint is MMR rate at 96 weeks while on study treatment, without meeting any treatment failure criteria prior to 96 weeks. The ASCEMBL trial is currently ongoing, and the key secondary endpoint to be performed at the 96-week analysis is not included in this submission (data expected in Quarter 2 of 2022).

B.2.6.1.5 *Secondary endpoint: MMR rate at and by all scheduled data collection time points*

The MMR rate at each scheduled time point was higher for the asciminib arm compared with the bosutinib arm, with the clinical benefit of asciminib reflected by

more than [redacted] improvement in MMR rates compared with bosutinib at Week 48; [redacted] in the asciminib arm compared with [redacted] in the bosutinib arm, corresponding to a common treatment difference (after adjusting for baseline MCyR status) of [redacted]) (Table 23).

The MMR rate by each scheduled time point (patients who achieved MMR at or before the specified visit) was higher for the asciminib arm compared with the bosutinib arm (Table 23). The MMR rate by Week 12 was 19.1% (95% CI: 13.28, 26.14) in the asciminib arm and 9.2% (95% CI: 3.78, 18.06) in the bosutinib arm. By Week 24, rates had increased to 27.4% (95% CI: 20.58, 35.07) in the asciminib arm and 14.5% (95% CI: 7.45, 24.42) in the bosutinib arm. By Week 48, these rates had increased to [redacted] in the asciminib arm compared with [redacted] in the bosutinib arm. By the data cut-off, the cumulative MMR rate was [redacted] in patients treated with asciminib and [redacted] in patients treated with bosutinib.

Table 23: MMR rate at and by scheduled time points (FAS)

	At time points		By time points	
	Asciminib 40 mg BD (N=157)	**Bosutinib 500 mg OD (N=76)**	**Asciminib 40 mg BD (N=157)**	**Bosutinib 500 mg OD (N=76)**
Week 24				
Response, n (%)	40 (25.48)	10 (13.16)	43 (27.39)	11 (14.47)
95% CI for response†	(18.87, 33.04)	(6.49, 22.87)	(20.58, 35.07)	(7.45, 24.42)
Unstratified difference in response rate (vs bosutinib) (%)	12.32	–	12.91	–
95% CI for difference in response rate‡	(2.11, 22.53)	–	(2.37, 23.46)	–
Common risk difference (%)¶	12.24	–	12.85	–
95% CI for difference	(2.19, 22.30)	–	(2.40, 23.29)	–
CMH test p-value§	0.029	–	–	–
Week 48				
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for response†	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified difference in response rate (vs bosutinib) (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for difference in response rate‡	[redacted]	[redacted]	[redacted]	[redacted]
Common risk difference (%)¶	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for difference	[redacted]	[redacted]	[redacted]	[redacted]

	At time points		By time points	
	Asciminib 40 mg BD (N=157)	**Bosutinib 500 mg OD (N=76)**	**Asciminib 40 mg BD (N=157)**	**Bosutinib 500 mg OD (N=76)**
Week 60				
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for response[†]	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified difference in response rate (vs bosutinib) (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for difference in response rate[‡]	[redacted]	[redacted]	[redacted]	[redacted]
Common risk difference (%)[¶]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for difference	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (13)
[†]Clopper-Pearson 95% 2-sided CI; [‡]Wald 95% 2-sided CI; [¶]The common risk difference after adjusting for stratum: major baseline cytogenetic response status (based on randomisation data) and its 95% CI were estimated using the Mantel-Haenszel method; [§]CMH 2-sided test was stratified by baseline major cytogenetic response status based on randomisation data.
Abbreviations: BD, twice-daily; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; MMR, major molecular response; OD, once-daily.

B.2.6.1.6 *Secondary endpoint: Time to MMR adjusting for competing risk*

The probability of achieving MMR by Week 24 was 25.0% (95% CI: 18.5%, 32.1%) and 12.0% (95% CI: 5.8%, 20.5%) in the asciminib arm and the bosutinib arm, respectively. The probability of achieving MMR by Week 48 was [redacted] in the asciminib arm and [redacted] in the bosutinib arm (Figure 6).

Figure 6: Cumulative incidence curve of MMR (FAS)

Source: Novartis (2021) (13)
Abbreviations: FAS, full analysis set; MMR, major molecular response.

B.2.6.1.7 *Secondary endpoint: Time to MMR*

Among patients who achieved MMR, responses were achieved faster in patients treated with asciminib (median time to MMR: [redacted] compared with bosutinib (median time to MMR: [redacted]) (Table 24).

Table 24: Time to first MMR among patients who achieved MMR (MMR responder set)

Time to MMR (week)	Asciminib 40 mg BD	Bosutinib 500 mg OD
Original SCE		
N	54	14
Mean ± SD	19.0 ± 14.40	22.8 ± 18.37
Median	12.7	14.3
30-day update		
N	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]

Source: Novartis (2021) (13)
Abbreviations: BD, twice-daily; MMR, major molecular response; OD, once-daily; SCE, summary of clinical efficacy; SD, standard deviation.

B.2.6.1.8 *Secondary endpoint: Duration of MMR*

Most patients who achieved MMR continued in MMR: only [redacted] patients [redacted] in the asciminib arm subsequently lost their response. Loss of response was observed in [redacted] in the bosutinib arm. The Kaplan-Meier (KM) estimated proportion of patients maintaining their MMR for ≥[redacted] was [redacted]) in the asciminib arm vs [redacted] in the bosutinib arm.

B.2.6.1.9 *Secondary endpoint: BCR-ABL1 ratio (% IS) categories at Week 48*

At Week 48, patients in the asciminib arm had [redacted] responses compared with patients on bosutinib. BCR-ABL1 IS ≤0.01% (MR^4 or better) was observed in [redacted] of patients receiving asciminib and [redacted] of patients receiving bosutinib, with [redacted] asciminib-treated patients achieving a grade of $MR^{4.5}$ [redacted] (Table 25).

Consistent with the [redacted] improvement in MMR rate in patients on asciminib as compared with those receiving bosutinib [redacted] (Table 21), the percentage of patients receiving asciminib with BCR-ABL1 IS ≤1% at Week 48 was [redacted] than that observed in patients on bosutinib [redacted] regardless of the BCR-ABL1 IS baseline level. At Week 24, these percentages were 49.0% (77 patients) in the asciminib arm and 23.7% (18 patients) in the bosutinib arm.

Table 25: BCR-ABL1 ratio (% IS) categories at Weeks 24, 48, and 60 (FAS)

Category	Asciminib 40 mg BD (N=157) n (%)	Bosutinib 500 mg OD (N=76) n (%)
Week 24		
≤0.0032%	14 (8.9)	1 (1.3)
>0.0032%–≤0.01%	3 (1.9)	3 (3.9)
>0.01%–≤0.1%	23 (14.6)	6 (7.9)
>0.1%–≤1%	37 (23.6)	8 (10.5)
>1%–≤10%	21 (13.4)	12 (15.8)
>10%	23 (14.6)	17 (22.4)
Missing	36 (22.9)	29 (38.2)
Ongoing without treatment failure	4 (2.5)	4 (5.3)
Ongoing with treatment failure	9 (5.7)	3 (3.9)
Discontinued due to lack of efficacy/PD/death	7 (4.5)	7 (9.2)
Discontinued due to other reasons	16 (10.2)	15 (19.7)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (13).
Abbreviations: BD, twice-daily; FAS, full analysis set; OD, once-daily.

B.2.6.1.10 *Secondary endpoint: CCyR rate at and by scheduled time points*

The CCyR rate at Week 48 (based on patients who were not in CCyR at baseline) was [redacted] in the asciminib arm and [redacted] in the bosutinib arm, corresponding to a common treatment difference (after adjusting for baseline MCyR status) of [redacted] (Table 26). At Week 24, the CCyR rate was 40.8% in the asciminib arm compared with 24.2% in the bosutinib arm.

The CCyR rate (based on patients who were not in CCyR at baseline) by Week 24 was 40.8% in the asciminib arm compared with 24.2% in the bosutinib arm (Table 26). The CCyR rate by Week 48 was [redacted] in the asciminib arm compared with [redacted] in the bosutinib arm (Table 26). By the 48-week data-cut, cumulative CCyR rates were [redacted] (compared with 42.7% at the time of the 24-week data-cut) in the asciminib arm and [redacted] (compared with 30.7% at the time of the 24-week data-cut) in the bosutinib arm.

Table 26: CCyR rate at and by scheduled time points

	At time-point		By time-point	
	Asciminib 40 mg BD (N=103)	**Bosutinib 500 mg OD (N=62)**	**Asciminib 40 mg BD (N=103)**	**Bosutinib 500 mg OD (N=62)**
Week 24				
Response, n (%)	42 (40.78)	15 (24.19)	42 (40.78)	15 (24.19)
95% CI for response†	(31.20, 50.90)	(14.22, 36.74)	(31.20, 50.90)	(14.22, 36.74)
Unstratified difference in response rate (vs bosutinib) (%)	16.58	–	16.58	–
95% CI for difference in response rate‡	(2.31, 30.86)	–	(2.31, 30.86)	–
Common risk difference (%)¶	17.30	–	17.30	–
95% CI for difference	(3.62, 30.99)	–	(3.62, 30.99)	–
CMH test p-value§	0.019	–	0.019	–

	At time-point		By time-point	
	Asciminib 40 mg BD (N=103)	**Bosutinib 500 mg OD (N=62)**	**Asciminib 40 mg BD (N=103)**	**Bosutinib 500 mg OD (N=62)**
Week 48				
Response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for response†	[redacted]	[redacted]	[redacted]	[redacted]
Unstratified difference in response rate (vs bosutinib) (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for difference in response rate‡	[redacted]	[redacted]	[redacted]	[redacted]
Common risk difference (%)¶	[redacted]	[redacted]	[redacted]	[redacted]
95% CI for difference	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (13).
†Clopper-Pearson 95% 2-sided CI.
‡Wald 95% 2-sided CI.
¶The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomisation data) and its 95% CI were estimated using the Mantel-Haenszel method.
§CMH 2-sided test was stratified by baseline major cytogenetic response status based on randomisation data. Nominal p-values are presented for descriptive purpose only.
Abbreviations: BD, twice-daily; CI, confidence interval; CCyR, complete cytogenetic response; CMH, Cochran-Mantel-Haenszel; OD, once-daily.

B.2.6.1.11 *Secondary endpoint: Time to CCyR*

Time to CCyR among patients who achieved CCyR was comparable between the two treatment arms, with medians of approximately [redacted] (Table 27).

Table 27: Time to CCyR (CCyR responder set)†

Time to CCyR (weeks)	Asciminib 40 mg BD (N=49) n (%)	Bosutinib 500 mg OD (N=22) n (%)
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]

Source: Novartis (2021) (13).
†Bone marrow was assessed at screening and after that every 24 weeks up to Week 96. Consequently, no patients who were not in CCyR at screening can be in CCyR before Week 24.
Abbreviations: BD, twice-daily; CCyR, complete cytogenetic response; OD, once-daily; SD, standard deviation.

B.2.6.1.12 *Secondary endpoint: Duration of CCyR*

Most patients who achieved CCyR continued to be in CCyR at their last assessment. Subsequent loss of response was reported in [redacted] patient each in the asciminib (of 49 patients) and the bosutinib (of 22 patients) arms, respectively. The KM estimated

proportion of patients maintaining their CCyR for ≥48 weeks was [redacted] in the asciminib arm vs [redacted] in the bosutinib arm. The KM estimated median duration of CCyR [redacted]

B.2.6.1.13 *Secondary endpoint: Time to treatment failure*

The KM analysis of the time to treatment failure among all subjects is presented in Figure 7 and Table 28. The probability of treatment failure was [redacted] in the bosutinib arm compared with the asciminib arm [redacted]. The KM estimated proportion of patients without treatment failure by the 48-week data-cut was [redacted] in the bosutinib arm [redacted] compared with the asciminib arm [redacted] The median time to treatment failure [redacted] for the bosutinib arm and [redacted] in the asciminib arm.

Figure 7: KM plot of time to treatment failure (FAS)

Source: Novartis (2021) (13).
Abbreviations: FAS, full analysis set; KM, Kaplan-Meier; NE, not estimable.

Table 28: KM estimates of time to treatment failure (FAS)

	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
Number of patients with event, n	[redacted]	[redacted]
Percentage of patients with events (n/N) (%)	[redacted]	[redacted]
Maximum follow-up, years	[redacted]	[redacted]
Median follow-up, years	[redacted]	[redacted]
Time to event (year)		
KM percentiles (95% CI)		
25th	[redacted]	[redacted]
50th	[redacted]	[redacted]
75th	[redacted]	[redacted]
KM % event-free (95% CI)†		
1 year	[redacted]	[redacted]
2 year	[redacted]	[redacted]

Source: Novartis (2021) (13).
†Event free probability estimate is the estimated probability that a patient will not have an event prior to the specified time point. Event free probability estimates are obtained from the KM survival estimates for all treatment groups; CIs for KM percentiles are based on Brookmeyer and Crowley (1982) (143). CIs for KM estimates of % event free are based on Greenwood formula.
Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; NE; not estimable.

B.2.6.1.14 *Secondary endpoint: Progression-free survival*

The median follow-up time for PFS was [redacted] in the asciminib arm and [redacted] in the bosutinib arm. At the 48-week data-cut, the KM estimated PFS rate was [redacted] for the asciminib arm and [redacted] for the bosutinib arm.

B.2.6.1.15 *Secondary endpoint: Overall survival*

The median follow-up time for OS was [redacted] in [redacted] patients [redacted] randomised to the asciminib arm died [redacted] on-treatment and [redacted] during survival follow-up) and [redacted] in the bosutinib arm died [redacted], on-treatment). Further details on patients who died are presented in Section B.2.10.1.2.5. At the 48-week data-cut, the KM estimated OS rate was [redacted] for the asciminib arm and [redacted] for the bosutinib arm.

B.2.6.1.16 *Exploratory endpoint: Patient-reported outcomes*

Compared with bosutinib, treatment with asciminib was generally associated with better improvements in disease-related symptoms, health-related quality of life (HRQoL), and work productivity and activity impairment at Week 24.

B.2.6.1.17 *Exploratory endpoint: MDASI-CML*

At Week 24, completion of the M.D. Anderson Symptom Inventory (MDASI)-CML questionnaire demonstrated a slight decrease in the mean total severity score compared with baseline in both treatment arms, indicating an improvement in symptom burden. The median change from baseline was –0.4 and –0.3 in the asciminib and the bosutinib treatment arm, respectively. The median change in total interference score was –0.3 vs –0.2, respectively.

Between-treatment differences for the change in severity and interference scores between the asciminib and bosutinib treatments evaluated using a linear mixed effect model was –0.65 (95% CI: –1.01, –0.29) compared with –0.16 (95% CI: –0.67, 0.36), respectively.

B.2.6.1.18 *Exploratory endpoint: EQ-5D-5L*

Data were available up to 96 weeks from baseline. A summary of the data is presented in Table 29.

Table 29: EQ-5D-5L at baseline and follow-up to 96 weeks

Timepoint	Asciminib 40 mg BD (N=157)		Bosutinib 500 mg OD (N=76)	
	Completion rate, n (%)	Mean (SD)	Completion rate, n (%)	Mean (SD)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
96†	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (144) (12).
†96-week data is provided by a small number of patients with longer follow-up data.
Abbreviations: BD, twice-daily; OD, once-daily.

Analysis with GLM or a mixed effect model repeated measure (MMRM) gave very similar results. Both indicated that the intercept and baseline EQ-5D-5L value were [redacted]. The results of the MMRM including treatment status (on/off) are shown in Table 30.

Table 30: Health state utility estimates derived from the MMRM model including treatment status

Health State	N patients	N observations	LS mean Utility (SE) [95% CI]
On-treatment: Asciminib	[redacted]	[redacted]	[redacted]
On-treatment: Bosutinib	[redacted]	[redacted]	[redacted]
On-treatment	[redacted]	[redacted]	[redacted]
Off-treatment	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed effect model repeated measure; SE, standard error.

B.2.6.1.19 *Exploratory endpoint: WPAI-CML*

At Week 24, the Work Productivity and Activity Impairment (WPAI)-CML questionnaire scores indicated an improvement (i.e. decreased score) in productivity loss associated with CML, with a greater improvement (in terms of mean change and standard deviation [SD] from baseline) associated with asciminib treatment compared to the bosutinib treatment.

Table 31: WPAI-CML at Week 24 (FAS)

	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
Completion rate, n (%)	123 (78.5)	64 (84.0)
Percent work time missed due to CML, n (%)	–8.2 (29.49)	–3.2 (8.78)
Percent impairment while working due to CML, n (%)	–11.5 (28.43)	–5.8 (25.75)
Percent overall work impairment due to CML, n (%)	–10.3 (31.87)	–8.0 (26.49)
Percent activity impairment due to CML, n (%)	–9.4 (26.21)	–3.1 (23.41)

Source: Novartis (2021) (12).
Abbreviations: BD, twice-daily; OD, once-daily.

Between-treatment differences for the WPAI-CML change over time evaluated using a linear mixed effect model was 6.74 (95% CI: –7.64, 21.11).

B.2.6.1.20 *Exploratory endpoint: PGIC*

The Patient Global Impression of Change is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale where one (1) equals very much improved and seven (7) equals very much worse. The compliance rates of completing the PGIC questionnaire at Week 24 was 82.3% in the asciminib arm vs 82.0% in the bosutinib arm. The PGIC score indicated greater improvements over time in overall health status as perceived by patients with asciminib compared with

bosutinib; at Week 24, twice the proportion of patients reported improvement in CML symptoms (Table 32).

Table 32: PGIC† at Week 24 (FAS)

	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
Completion rate, n (%)	129 (82.3)	62 (82.0)
Level 1, %	16.9	8.0
Level 2, %	32.3	18.0
Level 3, %	8.5	16.0
Level 4, %	20.0	34.0
Level 5, %	3.8	6.0
Level 6, %	0.8	0.0
Level 7, %	0.0	0.0

Source: Novartis (2021) (12).
†The PGIC uses a seven-point scale where level 1 equals very much improved and level 7 equals very much worse
Abbreviations: BD, twice-daily; OD, once-daily.

B.2.6.1.21 *Resource utilisation*

The proportion of patients utilising any healthcare resource (including hospitalisation, emergency room visit, general practitioner visit, specialist visit, urgent care visit) was lower in the asciminib treatment arm (24.2%) compared with the bosutinib treatment arm (36.8%) (Table 33).

Table 33: Proportion of patients using any healthcare resource (FAS)

Healthcare resource use	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
Any resource used	38 (24.2)	28 (36.8)
Hospitalisation	22 (14.0)	14 (18.4)
Emergency room visit	3 (1.9)	4 (5.3)
General practitioner visit	7 (4.5)	5 (6.6)
Specialist visit	17 (10.8)	10 (13.2)
Urgent care visit	0	4 (5.3)

Source: Novartis (2021) (145)
Abbreviations: BD, twice-daily; OD, once-daily.

B.2.6.1.22 *Pharmacokinetic results*

Plasma concentrations of asciminib increased rapidly and appeared to decline in a bi-phasic manner. After oral administration of asciminib 40 mg BD, the absorption was rapid with a median Tmax of 1.97 hours (Table 34). The geo-mean of peak plasma concentration of asciminib (Cmax) was 931 ng/mL (coefficient of variation [CV]% geo-mean: 46.7%), geo-mean of area under the curve (AUC)last was

5,120 ng*hr /mL (CV% geo-mean: 47.8%), geo-mean of AUC0-12 was 5,760 ng*hr/mL (CV% geo-mean: 34.0%). Moderate inter-patient variability (CV%) of exposure was observed ranging from 34% to 47% for AUC and Cmax. The trough concentrations (Ctrough) of asciminib were similar throughout study visits (i.e. median 250 ng/mL).

Table 34: PK parameters for asciminib on Week 2 Day 1 (PKS, full sampling group†)

Parameter	Asciminib N=14
AUC0-12h (ng*hr/mL)	
n	13
Mean (SD)	6,070 (2,090)
CV%	34.5
Geo-mean	5760
Geo-CV%	34.0
Median	5,410
Min-Max	3,480–10,700
AUClast (ng*hr/mL)	
n	14
Mean (SD)	5,580 (2,260)
CV%	40.5
Geo-mean	5120
Geo-CV%	47.8
Median	5,130
Min-Max	1,810–10,300
CL/F (L/hr)	
n	13
Mean (SD)	7.29 (2 .34)
CV%	32.0
Geo-mean	6.94
Geo-CV%	34.0
Median	7.39
Min-Max	3.73–11.5
Cmax (ng/mL)	
n	14
Mean (SD)	1,010 (419)
CV%	41.3
Geo-mean	931
Geo-CV%	46.7
Median	939
Min-Max	389–1,850

Parameter	Asciminib N=14
Ctrough (ng/mL)	
n	10
Mean (SD)	324 (139)
CV%	43.0
Geo-mean	297
Geo-CV%	47.2
Median	284
Min-Max	145–551
Tlast (hr)	
n	14
Mean (SD)	10.7 (1.77)
CV%	16.5
Geo-mean	10.6
Geo-CV%	19.9
Median	11.2
Min-Max	6.33-12.2
Tmax (hr)	
n	14
Mean (SD)	1.76 (0.668)
CV%	37.9
Geo-mean	1.65
Geo-CV%	39.4
Median	1.97
Min-Max	0.983–3.33

Source: Novartis (2021) (12).
†Blood samples for patients providing full PK profiles were capable of serial PK sampling over 12 hours. Sparse PK samples were taken from all other patients on asciminib.
Abbreviations: AUC, area under the curve; CL/F, clearance; Cmax, peak concentration; Ctrough, trough concentration; Tlast, time to the last detectable concentration; Tmax, time to peak concentration; CV%, coefficient of variation; geo, geometric; hr, hour; max, maximum; min, minimum; PAS, pharmacokinetic analysis set; PK, pharmacokinetic; SD, standard deviation.

B.2.6.2 HMRN real world evidence – supporting evidence

B.2.6.2.1 *Baseline demographics and disease characteristics*

In total, there were [redacted] newly diagnosed cases of CML-CP between the 1st of September 2004 and the 31st of August 2019 ([redacted]). The performance status of most patients was [redacted]) and whilst hepatomegaly was [redacted] splenomegaly affected [redacted] Median follow-up time was [redacted].

The majority of patients were initially treated with a TKI ([redacted]). The remaining [redacted] either received hydroxycarbamide only [redacted] or were treated with a supportive/palliative

intent only ([redacted]); these patients were generally [redacted] with a median age of [redacted]. A total of [redacted] patients went onto receive a second-line TKI, and [redacted] patients received third- or later line therapy (Table 35). The highest number of treatment lines received was [redacted]). [redacted] patients received an allograft during the treatment pathway, [redacted] of which were after disease progression to AP or BP.

Table 35: TKI by treatment line

	1L	2L	3L	4L	5L	6L	7L	8L	9L	10L
Total, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at treatment, mean (SD), years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment										
Imatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: HMRN (2021) (14).
Abbreviations: L, line; SD, standard deviation; TKI, tyrosine kinase inhibitor.

B.2.6.2.2 *Outcomes*

B.2.6.2.2.1 Disease response

A total of [redacted] patients were treated with a first-line TKI, of these, [redacted] patients [redacted] achieved a MMR or MR[2] response, and median time to response was [redacted]. Of these, [redacted] patients [redacted] achieved a MMR and [redacted] patients [redacted]) an MR[2]. In total, [redacted] patients lost their response, and the median time to loss of response was [redacted].

A total of [redacted] were treated with a third-line TKI. Of these, [redacted] patients [redacted] achieved a MMR or MR[2] response, and the median time to response was [redacted]. Of these, [redacted] patients [redacted] achieved a MMR and [redacted] patients [redacted]) an MR[2] only. In total, [redacted] patients [redacted] lost their response, and the median time to loss of response was [redacted].

B.2.6.2.2.2 Time to treatment discontinuation

Median time on first-line TKI therapy was [redacted], this decreased to a median of [redacted] in those who had discontinued treatment. Time to treatment discontinuation (TTD) decreased to a mean of [redacted] at second-line [redacted] at third-line (Table 36), and [redacted] at fourth-line.

In total, [redacted] switched TKIs between second- and fourth-line of therapy. The most common reason for switching was lack or loss of response ([redacted]). A relatively high proportion switched as they were unable to tolerate the therapy (second-line: [redacted] third-line: [redacted] fourth-line: [redacted]).

Table 36: Time to treatment discontinuation for third-line treatment

	Total n, (%)	Discontinued n, (%)	Total Mean TTD, years (95% CI)	Discontinued Mean TTD, years (95% CI)
Third-line				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]

Source: HMRN (2021) (14).
Abbreviations: CI, confidence interval; TTD, time to treatment discontinuation.

B.2.6.2.2.3 Overall survival

Excluding the three patients with the T315I mutation, 5-year OS at third-line was [redacted] and differed between choice of TKI therapy (5-year OS was [redacted] and [redacted] with bosutinib and ponatinib, respectively). OS at 5-years was poorer in those who did not achieve a MMR ([redacted]) compared with those who did achieve a MMR ([redacted]) (Table 37).

Five-year OS at third-line, including the three patients with the T315I mutation, was [redacted] and also differed between choice of TKI therapy (5-year OS was [redacted] and [redacted] with bosutinib and ponatinib, respectively). By fourth-line TKI therapy, 5-year OS had reduced to [redacted] (including those with the T315I mutation; OS at fourth-line excluding patients with the T315I mutation is not available).

Table 37: OS from start of third-line treatment by regimen excluding patients with the T315I mutation

	Total	Alive	Dead	5-year survival, % (95% CI)	10-year survival, % (95% CI)
Third-line					
Total, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR					
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR at 6 months					
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR at 12 months					
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: HMRN (2021) (14).
Abbreviations: CI, confidence interval; MMR, major molecular response; OS, overall survival.

B.2.6.2.2.4 Progression-free survival

PFS was defined from the initiation of treatment (i.e. the index date) to the earliest documentation of disease progression to AP/BP or date of death from any cause.

Similar trends were seen for PFS compared to OS. In total, [redacted] patients progressed from CML-CP to AP ([redacted]) or BP [redacted]). The median time spent in AP/BP was [redacted]) and the corresponding mean was [redacted]. The median time for those in AP was [redacted]) with a respective mean of [redacted]).The median time for those BP was [redacted]) and the mean was [redacted]). At third-line, [redacted] patients progressed: AP [redacted]), BP ([redacted]) and the mean time in state was [redacted]) (Table 38).

Table 38: PFS from start of third-line treatment excluding patients with the T315I mutation

	Total	PFS		5-year PFS, % (95% CI)	10-year PFS, % (95% CI)
		Yes	No		
Third-line					
Total, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR					
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR at 6 months					
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMR at 12 months					
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

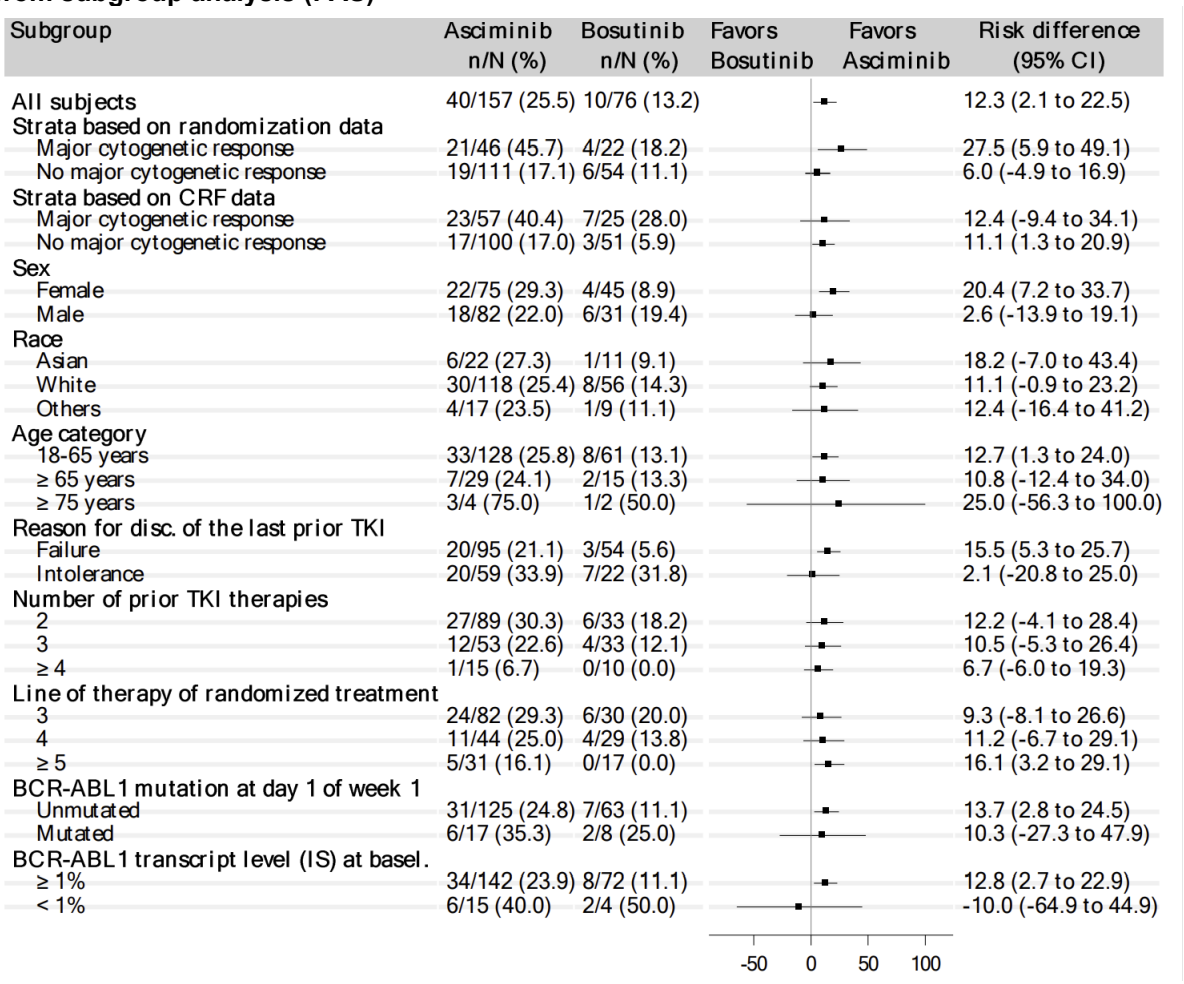
Source: HMRN (2021) (14).
Abbreviations: CI, confidence interval; MMR, major molecular response; PFS, progression free survival.

B.2.7 Subgroup analyses

B.2.7.1 Subgroup analysis of the primary endpoint in ASCEMBL

Subgroup analyses demonstrated a homogeneous and consistent treatment effect in favour of asciminib across most major demographic and prognostic subgroups (Figure 8). The MMR rate at 24 Weeks was higher in patients receiving asciminib regardless of baseline cytogenetic response (MCyR or no MCyR) or the detection of BCR-ABL1 mutations. The subgroup analysis by line of therapy of randomised treatment confirmed the benefit of asciminib in patients previously treated with two or more TKIs. A consistent treatment benefit with regards to MMR rate at 24 Weeks, was observed with asciminib compared with bosutinib whether given as third-line therapy (29.3% vs 20.0%, respectively), fourth-line therapy (25.0% vs 13.8%, respectively), or fifth- or later line therapy (16.1% vs 0%, respectively). Variability in the treatment effect was observed for some subgroups, i.e. sex (with higher difference in MMR rate between asciminib and bosutinib in females compared with males), and in reasons for discontinuation of last prior TKI (with higher difference in MMR rate between asciminib and bosutinib in patients resistant to their last TKI compared with intolerance). A limited number of patients with BCR-ABL <1% precludes drawing any conclusion for this subgroup.

Figure 8: Forest plot of risk difference with 95% confidence interval for MMR rate at 24 weeks from subgroup analysis (FAS)



Source: Novartis (2021) (12).
Abbreviations: CI, confidence interval; FAS, full analysis set; IS, international scale; MMR, major molecular response; TKI tyrosine kinase inhibitor.

B.2.8 Meta-analysis

A meta-analysis was not conducted as there is only one trial of asciminib in CML.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Objective

In the absence of direct evidence comparing asciminib with the comparators defined in the final scope, a matching-adjusted indirect treatment comparison (MAIC) was conducted to compare the TTD for asciminib vs the following comparators for the treatment of CML-CP patients who have received ≥2 prior TKIs:

- Ponatinib
- Nilotinib

- Dasatinib

Time to treatment discontinuation is the main focus of the MAIC, as these data are used to estimate OS in the cost-effectiveness analysis. The cost-effectiveness analysis assumes a fixed survival of 7 years following discontinuation of treatment, there is a fixed period of time until death, irrespective of third line treatment tried and of subsequent treatments. This assumption has been previously used in TA401 (146).

B.2.9.2 Methodology

B.2.9.2.1 *Study selection*

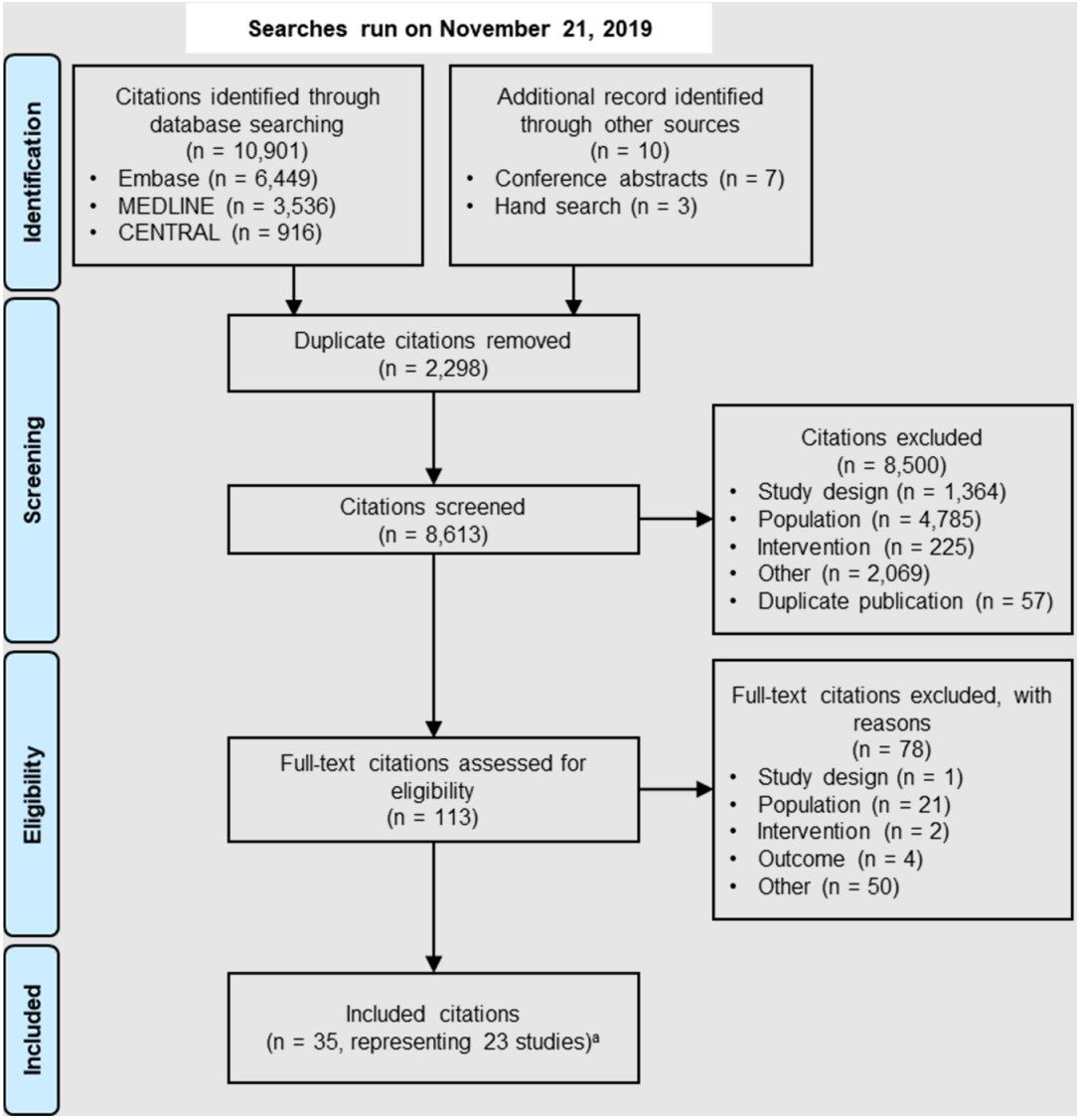
An SLR was conducted in November 2020 to identify studies of TKIs and other interventions of interest in patients with CML-CP who had received ≥2 prior TKIs and who did not harbour the T315I mutation. The SLR identified [redacted] studies ([redacted] citations) reporting various outcomes in the target population. In addition to the studies identified in the SLR, the unpublished ASCEMBL trial was also included. Of the identified publications, [redacted] studies were included in the current analysis [redacted] ([redacted] studies were excluded from the analysis based on pre-defined eligibility criteria). Of note, no RCT comparing interventions in a head-to-head fashion was identified in the target population. Study selection criteria can be seen in Table 39. With the study selection flow diagram in Figure 9.

Table 39: Study selection criteria for MAIC

Criteria	Description	
Population	*Inclusion criteria:* Studies reporting outcomes for adult (≥18 years) CP-CML patients where ≥75% of patients had prior experience with ≥2 TKIs and did not harbour the T315I mutation *Exclusion criteria:* Studies with mixed population where <75% of patients matched the target population AND patient characteristics were not reported for target population†	
Interventions	Ponatinib Dasatinib Nilotinib	Imatinib Homoharringtonine (omacetaxine) Hydoxycarbamide
Comparators	Placebo or best supportive care Any intervention of interest	
Outcomes	Time to treatment discontinuation and responses (CCyR and MMR at 6-months and 12-months)	
Study design	*Inclusion criteria:* Interventional studies (randomised or non-randomised) Observational studies (prospective or retrospective) Cross-sectional studies *Exclusion criteria:* Phase I trials Dose-ranging, dose-finding, and dose-escalating trials	

†Mixed populations were defined as a mix of target patients and those with <2 prior lines of TKI and/or with advanced phase disease.
Abbreviations: Allo-SCT, allogeneic stem cell transplantation; CP-CML, chronic phase chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation.

Figure 9: Study selection flow diagram of the systematic literature review



Of the included studies from Figure 9, [redacted] studies were excluded, with their reasons summarised in Table 40. See Appendix I for full details.

Table 40: Excluded study reasons

Exclusion reason	Number of studies
Interventions were not of interest or population were different	5
Populations where <80% of patients matched the target population and did not report baseline characteristics for the target population	4
Did not report outcomes for >20 participants in the target population.	2
Did not report patient characteristics for interventions of interest	3
Phase I trials	2
Did not have outcome of interest	3

The remaining [redacted] studies are listed in Table 41. Omacetaxine was not considered in the economic model and is not discussed further.

Table 41: Included studies

Comparator	Outcome	Study
Ponatinib	TTD/response	[redacted]
Nilotinib	TTD	[redacted]
Dasatinib	TTD	[redacted]
Omacetaxine	TTD/response	[redacted]

Abbreviations: TTD, time to treatment discontinuation.

B.2.9.2.2 *Outcomes extracted*

KM curves for TTD was not available for any comparator, only median treatment duration was available. The median treatment durations for each comparator were:

- Ponatinib: [redacted]
- Nilotinib: [redacted]
- Dasatinib: [redacted]

Response was also an outcome of the MAIC. However, the focus of this summary remains on TTD, as this is used in the economic model (response is not used). More details on the MAIC can be found in Appendix I.

B.2.9.2.3 *Matching-adjusted indirect treatment comparison*

In the absence of RCTs forming a connected network, it was not feasible to perform an anchored indirect treatment comparison (ITC) (or network meta-analysis) to evaluate the comparative efficacy of asciminib vs relevant interventions. No RCT

comparing interventions in a head-to-head fashion was identified in the target population. ASCMEBL is the first head to head trial in this disease area. Unanchored ITCs were therefore used to estimate the relative treatment effects between asciminib and the competing interventions with independent (non-randomised) studies that did not share a common comparator arm.

Given the availability of individual patient data for the 'index' trial (ASCEMBL) evaluating the efficacy of asciminib, it was possible to adjust for between-study differences in the distribution of patient factors that may influence the outcome and/or treatment effects using a population-adjusted indirect comparison (PAIC). MAICs reflect a method for PAIC, which uses the individual patients data (IPD) from the index intervention (i.e. asciminib) and aggregate data for the studies of competing interventions to weight the IPD to better match the 'target population' as defined by the population in the aggregate data publications (148). Initially, a logistic propensity score model was used to estimate weights for the IPD from the index trial so that the weighted mean baseline characteristics matched those observed for the target population. These weights were then applied to the index treatment to predict the observed outcomes in the target population. The estimation of these propensity weights was complicated by the lack of IPD in the competitor trial; a modified likelihood reweighting approach was employed which estimates weights from a logistic regression model:

$$\log(w_i) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X}_i$$

For each patient i, with covariates Xi, in the index set, standard regression techniques could not be employed to generate weights as the full distribution of covariates was not available for the target trial. Following the NICE recommendations, the method of moments approach was used to balance the mean covariate values across populations (56). The weights were obtained by minimising:

$$\sum_{i=1}^{N} \exp\left(\boldsymbol{\alpha}_1^T \boldsymbol{X}_i\right)$$

The weighting scheme was based only on the covariates and was therefore independent of the outcome. While this implies that the weights can be used on any scale, all treatment comparisons must be conducted on the appropriate scale of the outcome, as the comparisons assume additivity.

The validity of the MAIC model depends upon the overlap between the IPD and the aggregate data population. When there is little overlap between the populations, the estimates are heavily influenced by relatively few individuals. Therefore, it was important to evaluate the distribution of the patient characteristics and the effect of the weighting to assess the appropriateness of the weights. The weights were first rescaled relative to the unit weights of the original dataset based on sample size (N), which facilitates the interpretation of the distribution of weights:

$$\widetilde{w_i} = \frac{w_i N}{\sum_i^N w_i}$$

Patients with rescaled weights greater than one provide more information when matched to the target population than they did in the index population, and vice versa for patients with weights less than one.

A measure of the extent of overlap is represented by the effective sample size (ESS). Signorovitch et al. (149) suggest that the ESS of the pseudo-population formed by weighting the AB population can be approximated by:

$$\mathrm{ESS} = \frac{\left(\sum_{t=1}^{T}\sum_{i=1}^{N} w_{it}\right)^2}{\sum_{t=1}^{T}\sum_{i=1}^{N} w_{it}^2}$$

ESS is an adjustment of the sample size that accounts for the weighting of the observations, and the resulting correlations between estimated responses. As with the typical sample size, a large value is preferable as the larger sample contains more information.

The methods of logistic propensity score modelling to estimate weights for the IPD from ASCEMBL were consistent with recommendations from the Decision Support Unit commissioned by NICE (148, 150).The variables included in the propensity score analyses were identified from two sources (a targeted review identified prognostic factors in the target population and clinical experts informed the priority for the relevant prognostic factors) (151).

B.2.9.2.4 *Patient inclusion/exclusion criteria across the included studies*

IPD on baseline demographic/disease characteristics and patient outcomes in the ASCEMBL trial were obtained internally. Data on baseline demographic/disease characteristics and outcomes for patients receiving comparator therapies were

obtained from identified study publications (58, 114, 121, 147). Of the identified prognostic factors, data on best cytogenetic response to the last TKI were not available within the ASCEMBL IPD. Furthermore, patients harbouring the T315I mutation were excluded from ASCEMBL whereas the cohort considered from the PACE trial had patients with the T315I mutation, and therefore adjustments were not possible for this prognostic factor. The following patient characteristics were considered for inclusion as covariates in the propensity model: 1) number of prior TKIs received before study entry; 2) resistance to prior TKIs; 3) intolerance of prior TKIs; 4) cytogenetic response status of patients at study entry; 5) mutation status; 6) ECOG performance score at study entry; 7) age at study entry; 8) gender; and 9) race. The latter four characteristics were not retained in any final models due to problems with convergence or insufficient ESS.

B.2.9.2.4.1 Asciminib vs ponatinib

The PACE trial included patients who were resistant or intolerant to dasatinib or nilotinib, or who had the BCR-ABL1T315I mutation regardless of prior TKI use. Cohort A had 203 patients who were receiving third-line or subsequent therapy and Cohort B had 67 patients with the T315I mutation. Only Cohort A was of interest, but median treatment duration was given for 270 patients, which included cohort A and cohort B. [redacted], therefore, cohort A+B was used for the MAIC (58). As the ASCEMBL trial excluded patients with T315I mutation it was not possible to match on this characteristic for the purpose of the MAIC.

In the ASCEMBL trial, patients with a CCyR at baseline were included; unlike in PACE. In total, there were 157 patients receiving asciminib, 19 of which were known to have CCyR at baseline and for 35 of which the CCyR status was not known. CCyR information can be imputed based on the BCR-ABL ratio information captured at baseline (BCR-ABL1 ≤1% is equivalent to a CCyR (152). After imputation, 133 patients could be included in the analysis after excluding 24 patients who either had CCyR at baseline or who had a BCR-ABL ratio less ≥1%. Thus multiple scenarios can be considered: CCyR information can be imputed based on the BCR-ABL ratio information captured at baseline (BCR-ABL1 ≤1% is equivalent to a CCyR) (152). Of the 35 patients with missing CCyR at baseline, 5 had an imputation. In total, 133

patients could be included in the analysis after excluding 24 patients who either had CCyR at baseline or who had a BCR-ABL ratio less ≥1% indicating a CCyR. Hence, the following scenarios were considered:

[redacted]

To investigate further, TTD KM curves were compared for asciminib patients with and without CCyR at baseline. The hazard ratio for patients with CCyR compared with patients who did not have CCyR was [redacted]), which demonstrates that CCyR at baseline is an important prognostic factor for time on treatment (Figure 10).

A second comparison was undertaken in which patients lacking information on CCyR were compared with patients without CCyR at baseline (Figure 11). The KM curves are [redacted], and the HR is [redacted]). This result would suggest that the majority of patients lacking information on CCyR did not have a CCyr at baseline. The two analyses support the selection of scenario 3, in which missing CCyR was imputed on the basis of BCR-ABL ratio and patients with CCyR at baseline excluded (19 known + 5 imputed).

As a robustness check, a third comparison was undertaken between patients without CCyR at baseline and patients in with a CCyR at baseline after imputation of missing CCyR using BCR-ABL ratio. The hazard ratio for those patients with CCyR after imputation compared with patients who did not have CCyR was [redacted] which supports the exclusion of patients with a known or imputed CCyR at baseline (Figure 12).

Hence, following investigation of the data, missing baseline CCyR was imputed using BCR-ABL ratio and patients were excluded with known or imputed CCyR at baseline (scenario 3). The remaining data consisted of 133 patients. Results with the scenarios 1 and 2 are provided in Appendix I.

Figure 10: KM curves for TTD for asciminib patients segregated by CCyR at baseline

Abbreviations: CCyR, complete cytogenetic response; KM, Kaplan-Meier; TTD, time to treatment discontinuation

Figure 11: KM curves for TTD for asciminib comparing patients with no CCyR vs patients with CCyR or no cytogenetic information

Abbreviations: CCyR, complete cytogenetic response; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 12: KM curves for TTD for asciminib comparing patients without CCyR and with CCyR after imputation based on BCR-ABL ratio.

Abbreviations: CCyR, complete cytogenetic response; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

B.2.9.2.4.2 Asciminib vs nilotinib

To compare asciminib with nilotinib, evidence from Giles et al. 2010 was included in the analysis (121). The inclusion/exclusion criteria of Giles et al. was similar to that of ASCEMBL trial; therefore, no additional filtering was required and all 157 patients from ASCEMBL were included in the analysis.

B.2.9.2.4.3 Asciminib vs dasatinib

Data from Rossi et al. 2013 were used to compare asciminib and dasatinib (116). Both the studies had similar inclusion/exclusion criteria, therefore all 157 patients from ASCEMBL were included in the analysis. Whilst the study also had data on nilotinib in third-line patients, the median treatment duration was available for the dasatinib cohort only (116).

B.2.9.2.5 *Patient baseline characteristics*

Patient baseline demographic/disease characteristics that were used in the matching procedure included all those characteristics reported in the respective comparator study that could be reliably calculated for patients in ASCEMBL. Baseline characteristics were selected after consulting an expert clinician and included prior TKI therapy, resistance to/intolerance of TKIs, and cytogenic response (full list provided in Appendix I).

Of the identified prognostic factors, data on best cytogenetic response to the last TKI were not available within the ASCEMBL IPD. Furthermore, patients harbouring the T315I mutation were excluded from ASCEMBL and therefore adjustments were not possible for this prognostic factor. The remaining variables were examined to ensure that there was sufficient overlap between the populations, and to ensure that models were numerically stable. The weights were examined to ensure that no weights were excessively large, in which case variables leading to extreme weights were either modified in terms of number of levels adjusted for (e.g. the ‘number of mutations’ covariate was adjusted for two levels [0 vs ≥1]) or removed from the MAIC weightings. Propensity score models were chosen to maximise ESS and the set of variables included in the model. If the algorithm used to estimate the weights did not converge using the full set of characteristics, variables were removed in stepwise fashion according to their clinical relevance (low priority variables, such as race,

gender and age, were removed first) and imbalance across studies (least imbalanced covariate were removed first) until convergence was achieved.

B.2.9.3 Results

Base-case results are presented in Sections B.2.9.3.1–B.2.9.3.3, additional scenarios for asciminib vs ponatinib are presented in the Appendix I.

B.2.9.3.1 *Asciminib vs ponatinib*

The model was not able to converge with all baseline characteristics, therefore, the least important characteristics were removed.[l] The scenario with highest ESS was selected and used for the base case (matched characteristics reported in Table 42 and TTD before and after weighting) (Figure 13).

Table 42: Comparison of baseline characteristics before and after MAIC with PACE (ponatinib)

Characteristics	Ponatinib	Asciminib	
Study	[redacted]	[redacted]	[redacted]
Patients/ESS	[redacted]	[redacted]	[redacted]
2 prior TKIs	[redacted]	[redacted]	[redacted]
Resistant to nilotinib/dasatinib	[redacted]	[redacted]	[redacted]
Intolerant only (nilotinib/dasatinib)	[redacted]	[redacted]	[redacted]
PCyR at baseline	[redacted]	[redacted]	[redacted]

Abbreviations: MAIC, matching-adjusted indirect treatment comparison; PCyR, partial cytogenetic response; TKI, tyrosine kinase inhibitors.

[l] Characteristic removed included: race (White), male, median age 60, ECOG = 0, no mutation, and one mutation.

Figure 13: TTD KM curves before (red) and after (black) MAIC with PACE (ponatinib)

Abbreviations: KM, Kaplan-Meier; MAIC, matching-adjusted indirect treatment comparison; TTD, time to treatment discontinuation.

Post-MAIC with ponatinib, median TTD for asciminib was [redacted] as compared to median TTD of [redacted] for ponatinib.

B.2.9.3.2 *Asciminib vs nilotinib*

The model did not converge with all baseline characteristics, therefore the least important characteristics were removed.[m] In all scenarios, patients with near zero weight were relatively high (n=75). Patient characteristics before and after matching are reported in Table 43 and the TTD KM curve before and after matching is shown in Figure 14.

Table 43: Comparison of baseline characteristics before and after MAIC with Giles et al. 2010 (nilotinib)

Characteristics	Nilotinib	Asciminib	
Study	[redacted]	[redacted]	[redacted]
Patients/ESS	[redacted]	[redacted]	[redacted]
MCyR at baseline	[redacted]	[redacted]	[redacted]
Resistant to dasatinib	[redacted]	[redacted]	[redacted]
Intolerant to dasatinib	[redacted]	[redacted]	[redacted]
2 prior TKIs	[redacted]	[redacted]	[redacted]

Abbreviations: MAIC, matching-adjusted indirect treatment comparison; mCyR, major cytogenetic response; TKI, tyrosine kinase inhibitors.

[m] Characteristic removed included: median age 62, ECOG = 0, no mutation, one mutation, resistant to imatinib, and intolerant to imatinib.

Figure 14: TTD KM curves before (red) and after (brown) MAIC with Giles et al. 2010 (nilotinib)

Abbreviations: KM, Kaplan-Meier; MAIC, matching-adjusted indirect treatment comparison; TTD, time to treatment discontinuation.

Post-MAIC with nilotinib, median TTD was not reached.

B.2.9.3.3 *Asciminib vs dasatinib*

The model did not converge with all baseline characteristics, therefore the least important characteristics were removed.[n] The scenario with highest ESS was selected and used for the base case (Table 44 and Figure 15).

Table 44: Comparison of baseline characteristics before and after MAIC with Rossi et al. (dasatinib)

Characteristics	Dasatinib	Asciminib	
Study			
Patients/ESS			
Nilotinib resistance			
2 prior TKIs			

Abbreviations: MAIC, matching-adjusted indirect treatment comparison; TKI, tyrosine kinase inhibitors.

[n] Characteristic removed included: male, median age 60, no mutation, one mutation, imatinib resistance, imatinib intolerance, nilotinib intolerance.

Figure 15: TTD KM curves before (red) and after (brown) MAIC with Rossi et al. 2013 (dasatinib)

Abbreviations: KM, Kaplan-Meier; MAIC, matching-adjusted indirect treatment comparison; TTD, time to treatment discontinuation.

Post-MAIC with dasatinib, median TTD was not reached.

B.2.9.4 Discussion and conclusions

Comparison of characteristics of the patients in ASCEMBL showed [redacted] differences with those of patients in the comparator studies. Matching on all selected characteristics was not possible. Hence, the characteristics considered most important were prioritised. Matching generated weighted ASCEMBL patients sets in which the selected characteristics closely matched the comparator studies. After weighting, the observed TTD curve for asciminib did not shift substantially when matched to PACE (ponatinib) or to Rossi et al. 2013 (dasatinib), and shifted modestly upwards when matched to Giles et al. 2010 (nilotinib).

With regard to the estimated ESS values, Phillippo et al. 2019 identified 16 MAICs in oncology technology appraisals published by NICE between 2010 and 2018. Of the nine studies that reported ESS, the median was 80.0 (range: 4.0–335.5), with a median reduction in ESS from the original sample size of 74.2% (range: 7.9%–94.1%) (153), which is consistent with a recently published MAIC of ponatinib versus bosutinib in the third-line CML-CP population (154). In the current analysis, the ESS estimates were similar to the existing estimates in the literature with respect to relative reductions.

Median TTD for asciminib was not reached in the ASCEMBL trial. Post-MAIC with ponatinib, median TTD for asciminib for patients was [redacted] compared with

median TTD of [redacted] for ponatinib. Post-MAIC with nilotinib and dasatinib, median TTD was not reached.

The methods of logistic propensity score modelling to estimate weights for the IPD from ASCEMBL were consistent with recommendations from the Decision Support Unit commissioned by NICE (148, 150).The variables included in the propensity score analyses were identified from two sources (a targeted review identified prognostic factors in the target population and clinical experts informed the priority for the relevant prognostic factors). Although the methods used for the MAICs align with existing recommendations, it is important to highlight the limitations of cross-study comparisons. Specifically, the analysis was limited to study-level aggregate data from the publications of the comparator studies. In the absence of IPD from the comparator studies, it is challenging to evaluate the extent of bias in the treatment effect estimates and it is likely that some confounding variables remained unbalanced. While every attempt was made to ensure a robust approach to the selection of prognostic factors included in the propensity model, it is unclear whether all relevant differences in patient characteristics were captured. The analysis was also limited by the baseline characteristics that were reported, as well as the definitions used in the external studies. Finally, it is important to highlight the risk of bias given that any unreported or unknown differences in patient or study characteristics (and/or any treatment effect modifiers) were not accounted for in the analyses.

In conclusion, despite the known limitations of unanchored MAICs, estimates suggest asciminib offers improvements in both efficacy and safety compared with conventional TKIs (dasatinib, nilotinib, and ponatinib) in the target population, after weighting to match characteristics of patients in the target population.

B.2.10 Adverse reactions

Safety data from ASCEMBL suggests that asciminib 40 mg twice daily (BD) has a better safety and tolerability profile than bosutinib 500 mg once-daily (OD) in patients with CML-CP who had previously been treated with two or more tyrosine kinase inhibitors (TKIs) (Safety analysis set as of the 6th of January 2021 data cut-off, primary evidence) (15)

- Adverse events (AEs) were experienced by [redacted] of patients in the asciminib treatment group compared with [redacted] in the bosutinib treatment group.
- Exposure-adjusted incidence rates (per 100 patient treatment years [PTY]) of all grades AEs (irrespective of study treatment relationship) were [redacted] and [redacted] with asciminib and bosutinib, respectively.
- All categories of AEs were [redacted] frequent in the asciminib treatment group ([redacted]).
- The most commonly reported grade ≥3 AEs (occurring in ≥5% of patients) included [redacted]
- Treatment discontinuation due to AEs was [redacted] in the asciminib arm compared with the bosutinib treatment arm ([redacted] respectively).
- AEs requiring dose interruption or dose adjustments were reported [redacted] frequently with asciminib than with bosutinib [redacted] and [redacted] respectively).

B.2.10.1 ASCEMBL – primary evidence

Safety evidence is available from the latest data cut of the ASCEMBL trial (Safety analysis set as of the 6th of January 2021 data cut-off, 48-week data) (15). Safety data from the primary analysis (data cut-off of 25th May 2020) are provided in Appendix M for completeness. Supporting safety evidence is also provided by Study X2101 (data cut-off: 6th January 2021) (Appendix N).

B.2.10.1.1 *Extent of exposure*

B.2.10.1.1.1 Patient exposure

The median duration of exposure to study drug was approximately [redacted] in the asciminib treatment group [redacted] compared with the bosutinib

treatment group [redacted] range: [redacted] (Table 45). Total exposure was [redacted] patient-years and [redacted] patient-years for patients randomised to the asciminib treatment group and the bosutinib treatment group, respectively.

Table 45: Duration of exposure to study drug (Safety set)

	Asciminib 40 mg BD (N=156)	Bosutinib 500 mg OD (N=76)
Duration of exposure, weeks		
Mean ± SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Duration of exposure categories, n (%)		
<24 weeks	[redacted]	[redacted]
≥24 weeks	[redacted]	[redacted]
≥48 weeks	[redacted]	[redacted]
≥96 weeks	[redacted]	[redacted]
≥144 weeks	[redacted]	[redacted]
Patient treatment time, year	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: BD, twice-daily; OD, once-daily; SD, standard deviation.

B.2.10.1.1.2 Dose intensity

The median dose intensities were [redacted] range: [redacted] (range: [redacted] for the asciminib and bosutinib treatment groups, respectively. Overall, [redacted] of patients had a relative dose intensity (RDI) of [redacted] in the asciminib treatment group compared with [redacted] in the bosutinib treatment group [redacted].

B.2.10.1.1.3 Dose adjustments and permanent discontinuations

Patients with ≥1 dose interruptions, ≥1 dose reductions, ≥1 dose increases, and permanent discontinuations were [redacted] frequent in the asciminib treatment group compared with the bosutinib treatment group [redacted]) (15).

B.2.10.1.2 *Adverse reactions*

B.2.10.1.2.1 Overview of adverse events

Overall, AEs were experienced by [redacted] of patients in the asciminib treatment group compared with [redacted] in the bosutinib treatment group (15). All categories of AEs were [redacted] frequent in the asciminib treatment group, with the exception of

[redacted] This included a [redacted] percentage of patients with [redacted] treatment-related AEs, grade ≥3 AEs, and patients who discontinued treatment due to AEs in the asciminib treatment arm compared with the bosutinib arm (Table 46).

The proportion of patients in the bosutinib treatment group continuing treatment [redacted] %) was considerably [redacted] than in the asciminib treatment group [redacted] leading to a substantial difference in duration of treatment between both groups. Consequently, AEs by exposure-adjusted incidence rates may also be of value for comparisons between asciminib and bosutinib. Exposure-adjusted incidence rates (per 100 patient treatment years [PTY]) of all grades AEs (irrespective of study treatment relationship) was [redacted] and [redacted] in asciminib and bosutinib treatment groups, respectively. Exposure-adjusted incidence rates over time suggest that the occurrence of AEs [redacted] with longer duration of asciminib treatment (Table 47) (15).

Table 46: Overview of AEs (Safety set)

Category	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Fatal SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to dose adjustment/interruption	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: AE, adverse event; SAE, serious adverse event.

Table 47: Overview of AEs by exposure-adjusted incidence rates† (Safety set)

Category	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (IR per 100 PTY)	Grade ≥3 n (IR per 100 PTY)	All grades n (IR per 100 PTY)	Grade ≥3 n (IR per 100 PTY)
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in 100 PTY is counted up to the first qualifying event (or end of time at risk for patients without event).
Abbreviations: AE, adverse event; IR, exposure-adjusted incidence rate; PTY, patient treatment years; SAE, serious adverse event.

B.2.10.1.2.2 AEs by system organ class

The most reported AEs in the asciminib and bosutinib arms were [redacted], respectively. Full AEs by system organ class (SOC) are presented in Table 48. A [redacted] proportion of patients reported [redacted] with asciminib vs bosutinib. In contrast, events within the following SOCs were reported [redacted] frequently with asciminib: [redacted] The following grade ≥3 SOCs were reported [redacted] frequently with asciminib vs bosutinib: [redacted] in the asciminib treatment group vs the bosutinib group.

Table 48: AEs by primary system organ class and grading (Safety set)

Primary system organ class	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations†	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Congenital, familial and genetic disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]	[redacted]
Product issues	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
†Within the Investigations SOC, 2 patients with missing grades were not included in the in-text table.
Abbreviations: AE, adverse event; BD, twice-daily; OD, once-daily; SOC, system organ class.

B.2.10.1.2.3 AEs by preferred term

The most commonly reported AEs occurring in ≥10% of patients included [redacted] in the asciminib arm; [redacted] in the bosutinib arm (Table 49).

The most reported grade ≥3 AEs (occurring in ≥5% of patients) included [redacted] in the asciminib arm, [redacted] in the bosutinib arm.

Table 49: Adverse events by preferred term and grading occurring in ≥5% of patients in either treatment group (Safety set)

Preferred term	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with at least one event	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice-daily; OD, once-daily.

B.2.10.1.2.4 Serious adverse events

The incidence of individual SAEs was low for both treatment groups. SAEs were reported in a [redacted] proportion of patients in the asciminib treatment group [redacted] compared with the bosutinib treatment group [redacted] The most commonly reported SAEs were [redacted]; all other SAEs were reported as [redacted] cases (Table 50). [redacted] in the asciminib treatment group compared with [redacted] in the bosutinib treatment group had SAEs that were suspected to be treatment-related by the Investigator.

Table 50: Serious adverse events by preferred term and grading (Safety set)

Preferred term	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with at least one event	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial ischaemia	[redacted]	[redacted]	[redacted]	[redacted]
Postoperative wound infection	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: BD, twice-daily; OD, once-daily.

B.2.10.1.2.5 Deaths

Of the 232 patients treated in the study, four patients (2.6%) from the asciminib treatment group and one patient (1.3%) from the bosutinib treatment group died. Two out of the four deaths in the asciminib treatment group (1.3%) occurred during survival follow-up and were due to underlying disease.

'On-treatment' deaths (i.e. deaths while receiving study medication or within the initial 30 days of discontinuing therapy) were reported for three patients: two patients (1.3%) in the asciminib treatment group and one (1.3%) in the bosutinib treatment group. The causes of death were embolism arterial and ischemic stroke in the asciminib treatment group; and septic shock in the bosutinib treatment group (Table 51).

Table 51: On-treatment deaths by preferred term (Safety set)

Preferred term	Asciminib 40 mg BD (N=156) n (%)	Bosutinib 500 mg OD (N=76) n (%)
On-treatment deaths	2 (1.3)	1 (1.3)
Primary reason: Study indication	0	0
Primary reason: Other	2 (1.3)	1 (1.3)
Embolism arterial	1 (0.6)	0
Ischaemic stroke	1 (0.6)	0
Septic shock	0	1 (1.3)

Source: Novartis (2021) (15).
Abbreviations: BD, twice-daily; OD, once-daily.

B.2.10.1.2.6 Adverse events over time

Overall, the first occurrences of AEs in the asciminib treatment arm were primarily observed within the first [redacted] of therapy [redacted] The incidence of [redacted] during Weeks 8–24 and Weeks 24–48 of asciminib treatment either [redacted] over time.

B.2.10.1.2.7 Events suspected to be drug-related

The proportion of patients with AEs suspected to be treatment related was [redacted] in the asciminib treatment group [redacted] compared with the bosutinib treatment group [redacted] The most reported treatment-related AEs (occurring in ≥10% of patients) by preferred term included [redacted] in the asciminib arm, [redacted] in the bosutinib arm (Table 52).

Table 52: Treatment-related adverse events by preferred term occurring in at least 5% of patients in either treatment group (Safety set)

Preferred term	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with ≥1 event	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice-daily; OD, once-daily.

B.2.10.1.2.8 Adverse events leading to treatment discontinuation

The proportion of patients with AEs leading to treatment discontinuation was [redacted] in the asciminib treatment group compared with the bosutinib treatment group [redacted] respectively). The most frequently occurring AEs leading to treatment discontinuation in the asciminib arm were [redacted] and the most frequently occurring AEs leading to treatment discontinuation in the bosutinib arm [redacted] (Table 53).

Grade ≥3 AEs leading to treatment discontinuation were reported [redacted]% of patients in the asciminib treatment group compared with [redacted] for the bosutinib treatment group.

Table 53: Adverse events leading to discontinuation of study treatment by preferred term and grading (Safety set)

Preferred term	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of patients with ≥1 event	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
Cerebral disorder	[redacted]	[redacted]	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increase	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Diffuse large B-cell lymphoma	[redacted]	[redacted]	[redacted]	[redacted]
Drug eruption	[redacted]	[redacted]	[redacted]	[redacted]
Hydrothorax	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice-daily; OD, once-daily.

B.2.10.1.2.9 Adverse events of special interest

A substantially [redacted] proportion of patients in the asciminib treatment group compared with the bosutinib treatment group experienced adverse events of special interest (AESIs) of all grades for [redacted] respectively [redacted] respectively).

Additionally, a substantially [redacted] proportion of patients in the asciminib treatment group compared with the bosutinib treatment group experienced AESIs of grade ≥3

for [redacted] respectively [redacted] respectively [redacted] respectively). The proportion of patients experiencing all other AESIs were comparable between the two treatment groups [redacted] (Table 54).

Table 54: Overview of adverse events of special interest (safety set)

Preferred term	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Myelosuppression	[redacted]	[redacted]	[redacted]	[redacted]
GI toxicity	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity (including laboratory terms)	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatic toxicity	[redacted]	[redacted]	[redacted]	[redacted]
Oedema and fluid retention	[redacted]	[redacted]	[redacted]	[redacted]
Ischemic heart and CNS conditions	[redacted]	[redacted]	[redacted]	[redacted]
QTc prolongation	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive toxicity	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure (clinical events)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Novartis (2021) (15).
Abbreviations: BD, twice-daily; CNC, central nervous system; GI, gastrointestinal; OD, once-daily; QTc, duration of the QT interval.

B.2.11 Ongoing studies

The ASCEMBL trial is currently ongoing, with data from the 96-week analysis expected in Quarter 2 of 2022. Three additional studies are currently ongoing; all four ongoing studies are described in Table 55.

Table 55: Ongoing studies

Trial	NCT number	Start date and expected finish date	Trial design	Comparators	Population	Outcomes in Scope
	NCT02081378	April 24, 2014 – March 14 2024	Phase I	1. Asciminib + imatinib 2. Asciminib + nilotinib 3. Asciminib + dasatinib	Adult patients with CML and Ph+ ALL who are relapsed or refractory to or are intolerant of TKIs, and of asciminib+nilotinib, asciminib+imatinib and asciminib+dasatinib in Ph+ CML patients who are relapsed or refractory to TKIs	• AE
ASC4MORE	NCT03578367	November 22, 2018 – November 23, 2022	Phase II, multi-centre, open-label, randomised study	1. Imatinib 2. Nilotinib	Adult patients with Ph+ CML-CP, previously treated with first-line imatinib for ≥1 year and have not achieved DMR	• MR4.5
Frontline Asciminib Combination in Chronic Phase CML	NCT03906292	August 19, 2019 – November 2022	Phase II, multi-centre, open-label, non-randomised, parallel cohort study	1. Imatinib 2. Nilotinib 3. Dasatinib	Adult patients with newly diagnosed CML-CP	• Deep molecular response (DMR^4) • MMR • AE • PFS • OS

Trial	NCT number	Start date and expected finish date	Trial design	Comparators	Population	Outcomes in Scope
ASCEMBL / CABL001A2302	NCT04948333	November 15, 2021 – June 29, 2025	Phase IIIb, multi-centre, open-label, single-group study	–	Adult patients with Ph+ CML-CP, previously treated with ≥2 TKIs (patients resistant/intolerant to previous treatment)	• MMR • Safety and • Duration of CCyR and MMR • PFS • OS • TTF • PROs and QoL

Abbreviations: AE, adverse event; CML, chronic myeloid leukemia; CP, chronic phase; CCyR, complete cytogenetic response; DMR, deep molecular response; MMR, major molecular response; OS, overall survival; PFS, progression free survival, Ph+, Philadelphia chromosome positive; PRO, patient related outcome; QoL, quality of life; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

B.2.12 Innovation

TKIs are the treatment of choice for all lines of therapy for patients with CML-CP (7, 9, 41, 42). The availability of several TKIs has considerably improved the prognosis for patients with CML (10); however, discontinuation of first- and second-line therapies due to resistance or intolerance is not uncommon (49, 51-53). For patients requiring third-line and later therapy, treatment options are limited and not well-defined (9).

Sequential TKI therapy is often accompanied by the emergence of new mutations (49). In contrast to other available TKIs that target the adenosine triphosphate (ATP)-binding site, asciminib is a first in-class specifically targeting the ABL myristoyl pocket (STAMP) inhibitor of the BCR-ABL1 kinase (18). Because of this novel mechanism of action, asciminib maintains activity against BCR-ABL1 with ATP-site resistance mutations (18), unlike currently available TKIs that have limited sensitivity following the emergence of such mutations (49).

Patients in the CP progressing on second and later line TKI therapy represent an extremely challenging patient population. It is estimated that approximately 5–10% of patients with CML-CP eventually progress to AP while on treatment (45), and if disease progresses to BP survival is generally less than 1 year (41). The most relevant predictor of progression is the kinetics of response to treatment (62); patients who do not achieve a reduction <10% BCR-ABL1 after 3 months with first-line imatinib and second generation TKIs have a higher risk of progression to AP and reduced survival (45, 62-65).

Asciminib's novel mechanism of action is expected to lead to superior selectivity compared with current TKIs, and subsequently increase effectiveness with fewer off-target effects. Its favourable tolerability profile may therefore enable the treatment of patients who are intolerant of currently available TKIs, including patients for whom ponatinib is not considered suitable due to the risk of irreversible cardiovascular AEs (67, 68).

In conclusion, asciminib offers improved activity in patients resistant to previous TKIs and its safety profile may enable the treatment of patients who are intolerant of currently available TKIs. Thus, asciminib provides clinicians with a new treatment option for patients who have discontinued two or more prior TKI therapies.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Clinical trial programme

The ASCEMBL trial is an ongoing Phase III, open-label, active-controlled multi-centre trial (12). An open-label study design was considered appropriate due to inherent differences in the conditions for drug administration for the two treatment arms, namely that bosutinib needs to be taken with food, whereas asciminib needs to be taken fasted. Blinding with double dummy treatments would have been challenging and carries inherent risks of dosing errors and reduced patient compliance. The ASCEMBL trial recruited 233 patients from 87 sites across 27 countries. Of these, five sites were in the UK: three in England, one in Wales, and one in Scotland. Prior treatments received by patients upon study entry were reflective of clinical practice in England, with >93% of patients having received ≥2 prior TKIs routinely used in England: dasatinib, imatinib, nilotinib, and ponatinib (12). The ASCEMBL trial compared asciminib with a comparator reflective of clinical practice in England, bosutinib. Bosutinib is currently taken by approximately 24% of third-line patients with CML in England (14).

The HMRN CML audit report included all [redacted] new adult patients with CML from Yorkshire and the Humber & Yorkshire Coast Cancer Networks between the 1st of September 2004 and the 31st of August 2019, a total population of 3.8 million (14). In total, [redacted] patients with CML received treatment with a TKI; imatinib was the most common first-line TKI ([redacted]), nilotinib was the most common second-line therapy ([redacted]), and dasatinib was the most common third-line therapy ([redacted]) (14). These patient numbers are reflective of clinical practice, although may have been influenced by the availability of treatments, as imatinib was the only drug available in 2004–2005, nilotinib was introduced from 2006, and dasatinib in 2007 (at second-line) (14). In total, [redacted] patients received a third- or later line of therapy, with one patient receiving 10 lines. As such, the HMRN results provide real world evidence of clinical practice and outcomes in England.

B.2.13.2 Efficacy

ASCEMBL met its primary objective and showed a statistically significant and a clinically relevant treatment difference in MMR rate at Week 24 with asciminib compared with bosutinib (12.2% [95% CI: 2.19, 22.30; p=0.029]). Notably, subgroup analysis of the primary endpoint demonstrated the efficacy of asciminib irrespective of the number of prior lines of treatment with TKIs. A [redacted] in MMR rate with asciminib [redacted] compared with bosutinib [redacted] therefore supports the clinical benefit of asciminib in a patient population treated with two or more TKIs with limited treatment options [redacted] of patients receiving asciminib or bosutinib as third-line therapy and [redacted]% of patients receiving asciminib or bosutinib as fourth- or later line) (13).

The level of acceptable response to third- or later line treatment is not well-defined for patients with CML-CP by clinical guidelines; however, a BCR-ABL1 IS >1% or a cytogenetic response less than complete is considered inadequate for optimal survival at second-line (7, 41, 49). In the ASCEMBL trial, at Week 48, [redacted] (13) [redacted] is clinically relevant in the third- or later line treatment setting where the use of remaining TKIs may be limited, and the option of allogeneic stem cell transplantation carries high risk of morbidity and mortality.

B.2.13.3 Safety

ASCEMBL trial participants were randomised in a 2:1 ratio; more patients were allocated to the asciminib arm in order to better define the safety profile of the experimental therapy, since the tolerability of bosutinib is well-documented (155). The ASCEMBL trial demonstrated that asciminib has a better safety and tolerability profile than bosutinib. A [redacted] proportion of patients receiving asciminib experienced treatment-related AEs [redacted] respectively). Exposure-adjusted incidence rates (per 100 PTY) of all grades AEs (irrespective of study treatment relationship) were [redacted] with asciminib [redacted] compared with bosutinib [redacted] Furthermore, AEs leading to treatment discontinuation were [redacted] in the asciminib arm than the bosutinib arm [redacted], respectively) (15).

On-treatment deaths in the asciminib arm occurred in two (1.3%) patients (ischemic stroke and arterial embolism; neither suspected to be caused by treatment), and

there was one (1.3%) death with bosutinib (septic shock; suspected to be caused by treatment) (15).

B.3 Cost effectiveness

Summary

- Asciminib was compared to bosutinib, ponatinib, nilotinib, and dasatinib in a *de novo* cost-effectiveness analysis
- The analysis considers the effectiveness and cost-effectiveness of asciminib in a third-line and later population as aligned with the marketing authorisation, and data from the pivotal ASCEMBL trial which assessed patients at third-line and beyond. The supporting economic analysis also focuses on a third-line and later population.
- The approach to the modelling of OS following discontinuation of treatment is based on the approach recommended by the ERG in TA401 (bosutinib), in which OS is the sum of TTD plus a fixed period of survival beyond third-line treatment. Data on TTD were informed by clinical trials including ASCEMBL, and single arm trials for non-ASCEMBL comparators, HMRN analysis, and standard cost sources. Data on TTD for ponatinib and bosutinib include patients in the fourth-line setting. Data for dasatinib and nilotinib do not include patients in the fourth-line setting; this is largely due to the evolution of the CML treatments over the last 10–15 years.
- At list prices for asciminib and all comparators, results of the cost-effectiveness analysis showed that:
  - Compared with bosutinib, asciminib is associated with higher costs but also higher QALYs, resulting in an incremental (probabilistic) cost-effectiveness ratio (ICER) of [redacted] per QALY gained [redacted] per QALY gained - deterministic).
  - Compared with dasatinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of £93,467 (probabilistic) per QALY gained [redacted] per QALY gained - deterministic).
  - Compared with nilotinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] (probabilistic) per QALY gained [redacted] per QALY gained - deterministic).
  - When comparing asciminib to ponatinib, asciminib is associated with lower costs and lower QALYs, resulting in an ICER for asciminib (when compared to ponatinib) of [redacted] (probabilistic) saved per QALY lost [redacted] saved per QALY lost - deterministic).
- At the PAS price for asciminib when comparing asciminib to: bosutinib; ponatinib; and dasatinib (with comparators at their list prices), and at the PAS price for both asciminib and nilotinib (which is known to Novartis) when comparing asciminib to nilotinib, results of the cost-effectiveness analysis showed that:
  - Compared with bosutinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of £2,767 (probabilistic) per QALY gained (£3,192 per QALY gained - deterministic).
  - Compared with dasatinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of £3,665 (probabilistic) per QALY gained

(£3,180 per QALY gained - deterministic).
    - Compared with nilotinib, asciminib is associated with higher costs but also higher QALYs, resulting in an ICER of £49,001 (probabilistic) per QALY gained (£49,584 per QALY gained - deterministic).
    - When comparing asciminib to ponatinib, asciminib is associated with lower costs and lower QALYs, resulting in an ICER for asciminib (when compared to ponatinib) of £261,615 (probabilistic) saved per QALY lost (£253,193 saved per QALY lost - deterministic).
- Results were robust to parameter and scenario uncertainty when assessed via the sensitivity analyses, and probabilistic and deterministic ICERs were congruent. Parameters that had the most influence on outcomes were the duration of post third-line treatment survival by treatment arm, HSUVs, and RDI.
- Further, scenario analysis in which survival following discontinuation of third-line treatment is reduced generated lower ICERs. The presented cost-effectiveness analysis could, therefore, be regarded as a conservative assessment of the cost-effectiveness of asciminib.

B.3.1 Published cost-effectiveness studies

B.3.1.1 Identification of studies

An SLR was conducted to identify cost-effectiveness studies relevant to the decision problem from the published literature. A complete description of the search strategy is presented in Appendix G.

B.3.1.2 Description of identified studies

The SLR identified 29 unique studies from 34 publications, and 16 unique health technology assessments (HTAs) (from 22 HTA reports and five publications). The studies included in the SLR were conducted across 14 countries, with most studies conducted in the US (n=8), followed by China (n=5). Three studies reported data from multiple countries. No study reported data from England.

B.3.2 Economic analysis

No existing economic evaluations of asciminib were identified in the cost-effectiveness SLR (Section B.3.1), therefore a *de novo* cost-effectiveness model was developed.

There are a number of technology appraisals (TAs) evaluating the use of TKIs in the treatment of CML (146, 156, 157). Across these TAs, two main approaches have been used to extrapolate trial data and estimate lifetime costs and quality adjusted life expectancy. Both approaches address the relatively long life expectancy of patients with CML responding to treatment with a TKI, and the consequent immaturity of PFS and OS data. The simplest approach, applied in TA401 (bosutinib) assumes a fixed duration of life expectancy following discontinuation of treatment with a TKI (146). The alternative approach utilises data on cytogenic response as a surrogate measure of progression. This approach was applied in TA451 (ponatinib). Data from the BMS-034 trial of dasatinib in patients resistant/intolerant to imatinib, were utilised to link treatment response to progression rates (158). These data were used to estimate progression as a function of response to treatment with ponatinib (157).

The original manufacturer's submission for bosutinib (TA401) also estimated progression using response to treatment as a function, using proxy data. This approach was criticised by the evidence review group (ERG), who raised a number of concerns. The chief concern was the suitability of the data linking treatment outcomes with progression. These data were obtained from a second-line population and are likely to represent an optimistic estimate of progression in a third-line population. The available data are also limited to summary statistics at 6 month intervals to 4 years. At 4 years, PFS for patients with either a CCyR or a MCyR was 94%. Such data are clearly insufficient to support extrapolation of the rate of progression with any confidence.

Following criticisms of their original approach to estimating progression, the manufacturer revised their analysis to assume a fixed duration of survival following discontinuation of third-line treatment. This approach ensured consistency across treatment arms with regard to the duration of survival following the end of treatment with a TKI and the commencement of best supportive care (assumed to be hydroxycarbamide). This assumption also implies no post treatment benefit, which can be considered conservative. This submission applies the same approach to extrapolating outcomes as that applied in the revised bosutinib submission. However, since that submission, available TKI treatments have expanded to include ponatinib, and few patients are treated with hydroxycarbamide, except to stabilise

them prior to TKI treatment. The improvement in treatment options would indicate that data used to extrapolate outcomes in both the bosutinib and ponatinib submissions is likely to underestimate PFS. In this submission, the estimate of OS following discontinuation of third-line treatment was revised in the light of clinical opinion and real world evidence from HMRN.

B.3.2.1 Patient population

The population for this analysis are adult patients with Ph+ CML-CP, previously treated with two or more TKIs. This is in line with the population considered in ASCEMBL (the pivotal clinical trial; Section B.2.3.1), the anticipated marketing authorisation, and the final scope issued by NICE (16).

It is important to note that elements of the analysis are more applicable to a third line population, such as when compared to nilotinib or dasatinib, which are trials in third line populations. In addition survival post-discontinuation is more representative of a third line population. However this was necessary because of paucity of data, and this data is likely to be generalisable to later lines.

This approach aligns with the approach taken in the previous submission for bosutinib (TA401) in which data were presented for bosutinib in a third-line population and results were considered generalisable to a third-line and later population by the committee.

Please note, for clarity, from here on, the treatments compared when patients enter the model are referred to as third-line treatment, however this is taken to mean the treatment for people who have previously tried two or more TKI treatments.

B.3.2.2 Model structure

The model captures progression of CML through the three main phases: the CP, AP and BP. The CP is represented by two health states capturing time on third-line treatment and time in CP after discontinuation of third-line therapy. AP and BP are represented by a single state each. The health state structure also contains two sub-models for patients who receive an allo-SCT, which can occur in a proportion of patients either at discontinuation of third-line treatment (in the CP), or at progression to AP or progression to BP (in progressed disease). The allo-SCT sub-models

include two states capturing relapse free and post relapse survival. Figure 16 presents a schematic of the economic model. Patients progressing through the disease phases and separate SCT sub-models are structures considered appropriate and plausible by previous committees(146, 157), they were also validated with a clinical expert (68).

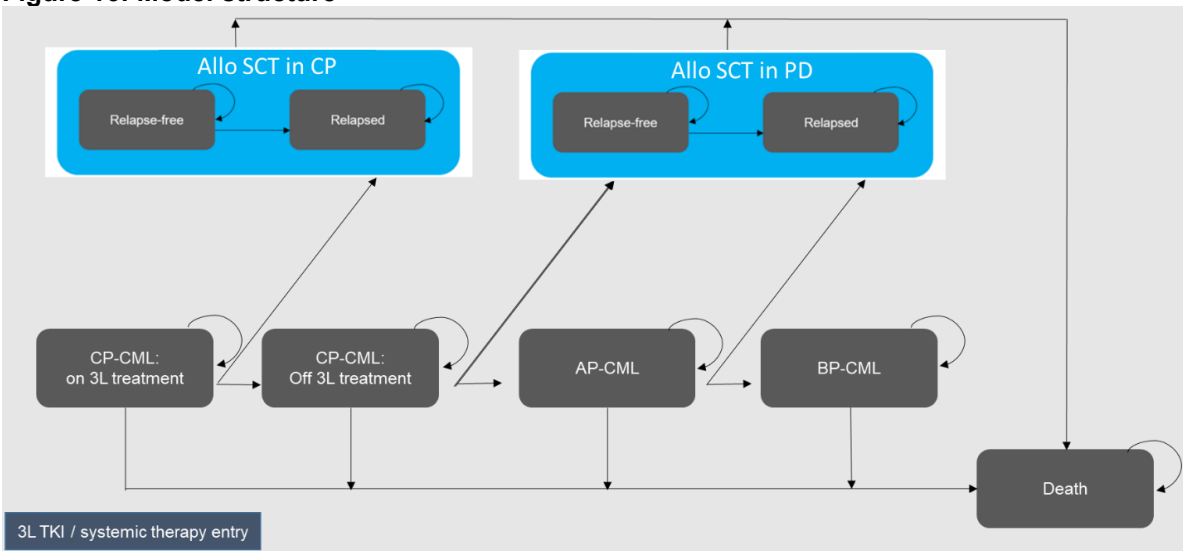
The model is implemented as a set of partitioned survival models. The 'main model' captures the trajectory of the cohort who have not undergone an allo-SCT. State occupancy is determined by a series of partitions derived ultimately from the TTD curve. State occupancy in the main model is implemented using a series of survival curves capturing discontinuation of third-line treatment, progression to AP and to BP, and death. Discontinuation of third-line treatment is derived by fitting a survival model to trial data on treatment discontinuation for asciminib and the comparators. The model assumes a fixed duration of OS following discontinuation of third-line treatment, independent of which third line-treatment was given. The model further assumes that, prior to death, patients spend a period of time in AP and then a further period of time in BP. Figure 17 illustrates the partitioning of the cohort across the five states constituting the main model.

Very few deaths or progression events were observed in ASCEMBL. This low event rate is reflected in data from HMRN, demonstrating 5-year survival above 50% from initiation of third-line treatment for patients with CML. Consequently, extrapolation of OS from the ASCEMBL trial data was unlikely to provide meaningful conclusions. Instead, mean OS of 7 years post discontinuation of third-line treatment is assumed. The approach aligns with the resubmission of bosutinib, which estimated a mean OS of 3.5 years based on data from Kantarjian 2007 (149). The ERG reanalysed these data, and concluded that they indicate a mean OS of 7 years, but the manufacturer justified the original value of 3.5 years with clinical opinion. Clinical opinion sought as part of this submission, and data from HMRN, supports a value of 7 years post discontinuation of third-line treatment (see section B.3.3.3). Mean time in the AP and BP states was assumed to be 10 months and 6 months, respectively. This assumption is the same as that applied in the bosutinib resubmission (146) and was validated with a clinical expert (68).

Patients undergoing an allo-SCT (at either the chronic or progressed stages) leave the main model and join one of the two allo-SCT sub-models. These models are also

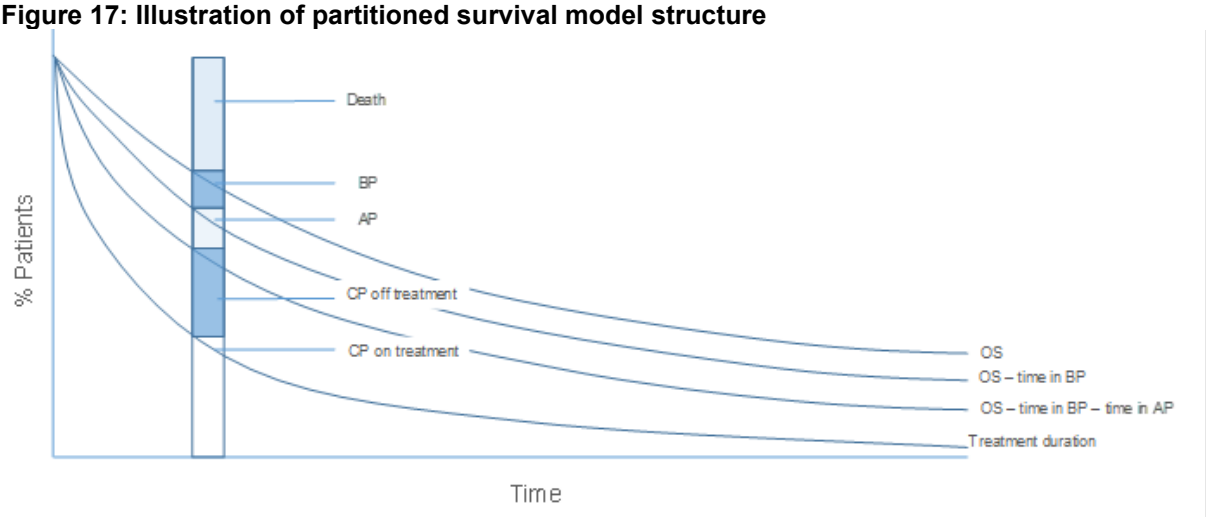
partitioned survival models. One model captures disease trajectory following allo-SCT at discontinuation of third-line treatment; the second captures disease trajectory following allo-SCT at transition to either AP or BP. The allo-SCT sub-models follow the traditional three state partitioned survival structure. However, as allo-SCT occurs in each time cycle of the model, 't0' is different for the cohorts undergoing allo-SCT in each time cycle. For this reason, it is necessary to implement the allo-SCT sub-models as a set of models with a separate model for each time cycle (analogous to the use of tunnel states in a Markov model).

Figure 16: Model structure



Abbreviations: 3L, third-line treatment; Allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast crisis phase; CP, chronic phase; CML, chronic myeloid leukaemia; PD, progressed disease; TKI: tyrosine kinase inhibitor.

Figure 17: Illustration of partitioned survival model structure



Abbreviations: AP, advanced phase; BP, blast phase; CP, chronic phase; OS, overall survival.

B.3.2.3 Features of the economic analysis

Table 56: Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	**TA451 (ponatinib)**	**TA401 (bosutinib)**	**Chosen values**	**Justification**
Cycle Length	3 months	1 month	1 month	Consistent with TA401.
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	This approach is consistent with previous models in CML and is in line with current NICE guidelines (159).
Time horizon	Lifetime	Lifetime	Lifetime	A lifetime horizon was selected to capture all differences in costs and outcomes between treatments, as per the NICE reference case (159).
Discounting	3.5%	3.5%	3.5%	In line with the NICE methods guide (159).
Population	For CP-CML the third line patients were used from the PACE trial. Fourth line was also modelled separately	The third line arm of the trial was used. A second line population was also looked at separately as this was a separate arm of the trial.	The population from ASCEMBL of third line plus.	The whole population from ASCEMBL was used. These are patients who have previously tried at least two TKI treatments. Some of the comparators only had third line data. Therefore the analysis is considered for a third line + population, with the knowledge that this may be a conservative estimate of TTD for some treatments (nilotinib and dasatinib) as TTD fourth line is likely to be lower.
Model type	Markov model	Semi-Markov model	Partitioned survival analysis	Allows parsimonious implementation of assumptions underpinning extrapolation of OS.
Extrapolation of OS	OS is estimated as a function of cytogenic response	Assumes fixed duration of survival beyond 3L therapy	Assumes fixed duration of survival beyond 3L therapy	OS data too immature to extrapolate. Surrogacy approach considered inferior on the grounds of incomparability of patient populations based on their lines of treatment.

	Previous appraisals		Current appraisal	
Factor	**TA451 (ponatinib)**	**TA401 (bosutinib)**	**Chosen values**	**Justification**
Source of utilities	• For chronic and progressed states: Szabo et al(160) applied as utility decrements to the age adjusted baseline utilities. • For SCT states: from published literature.	Values from previous appraisals (TA241 and TA251)	• For chronic and progressed states: mean values from the ASCEMBL trial applied as multipliers to the age adjusted baseline utilities. • For SCT states: from TA451 (157).	Utilities were available from the ASCEMBL trial. Scenario analysis using Szabo et al utility values were also explored.
Source of costs	• NHS reference costs • Marie curie cancer care • UK stem cell strategy oversight committee • BNF		• NHS reference costs • NHS Blood and Transplant • BNF	The sources of cost data are as per the NICE methods guide (159).

Abbreviations: 3L, third-line treatment; BNF, British National Formulary; CML, chronic myeloid leukaemia; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSS, personal social services; SCT, stem cell transplant; TA, technology appraisal.

B.3.2.4 Intervention technology and comparators

The intervention is asciminib at a dose of 40 mg administered orally twice a day. The intervention is compared with the following TKIs likely to be utilised as a third-line or later treatment for CML:

- Bosutinib administered at a dose of 500 mg orally once a day
- Ponatinib administered at a dose of 45 mg orally once a day
- Nilotinib administered at a dose of 400 mg orally twice a day
- Dasatinib administered at a dose of 100 mg orally twice a day.

The comparators included in the evaluation are aligned with the final NICE scope (16). NICE guidance exists on the following: ponatinib for previously treated chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451) (157) dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia (TA425) (161) and bosutinib for previously treated chronic myeloid leukaemia (TA401) (146). Although dasatinib and nilotinib are recommended as second-line treatments, they are also used as third-line alternatives if they have not been tried before. Hence both can be considered comparators in a subset of the population who are naïve to the relevant comparator. In practice, many patients will have been treated with nilotinib at first or second line, and would not be suitable candidates for treatment at third line. The use of ponatinib is typically restricted to patients for whom alternative TKIs are contraindicated due to the significant risk of serious cardiovascular events (162). As such it is typically used at fourth-line or fifth-line, and less commonly at third-line. According to clinical opinion, TKI use typically continues beyond fourth-line and fifth-line in patients failing to achieve a complete response, with patients reverting to previously used TKIs to achieve a partial response and delay disease progression. Data from the HMRN on third-line treatment indicates that the majority of patients are currently treated with bosutinib, dasatinib and nilotinib, with a smaller proportion treated with ponatinib or imatinib.

B.3.3 Clinical parameters and variables

The principal source of data for the analysis is the ASCEMBL clinical trial. Patient level data from ASCEMBL were used to determine the following parameters for asciminib and bosutinib:

- TTD

- HSUVs in CP on third-line treatment and after discontinuation of third-line treatment
- AE frequencies.

Expert opinion was also elicited from a clinical expert practicing in England with experience of treating patients with CML in September 2021, for resource use data and assumptions, and clinical validation of extrapolation of curves (163).

Data on TTD and AE frequencies for the remaining comparators (ponatinib, dasatinib, nilotinib) were derived from published studies. For TTD, in the absence of a connected network, an unanchored MAIC was performed (see section B.2.9) to match the characteristics of patients in the ASCEMBL trial to those reported in the relevant study for the comparator, and TTD for asciminib was re-estimated on the weighted ASCEMBL data. An exponential function was assumed for TTD for the comparators, parameterised from median TTD reported in the relevant study. Frequencies of AEs for comparators were taken directly from the most relevant studies. The availability of studies reporting outcomes for patients with CML receiving third and later lines of treatment was limited.

- Data on TTD and AEs for ponatinib were taken from the PACE trial (58) - a single arm Phase II clinical trial in patients with CML or acute lymphoblastic leukaemia (ALL) with resistance to or unacceptable side effects from dasatinib or nilotinib (with the majority being at least a third-line population), or with the T315I mutation.
- Data on TTD and AEs for nilotinib were taken from Giles et al. 2010 (114), which reported outcomes for 60 patients with CML prescribed nilotinib after failure of imatinib and dasatinib.
- Rossi et al. 2013 was considered the most appropriate source of data for TTD for dasatinib (116). Rossi et al. 2013 report outcomes for 34 Italian patients switched to dasatinib after failure of imatinib (first-line) and nilotinib (second-line). As Rossi et al. does not report AE data, these data were taken from Tan 2019 et al (115). Tan et al 2019 retrospectively evaluated the efficacy and safety of dasatinib among 48 patients with CML who were treated with dasatinib as a second- or third-line treatment (with second and third-line being distinct groups, and the AE data taken from the third-line group of 24 patients). Data on TTD are not reported in Tan et al. 2019.

The starting age and proportion of females in the model were based on the mean characteristics from ASCEMBL. Mean age and proportion of females (across both arms) was 51% (asciminib arm) and 52% (bosutinib arm) (12).

OS, PFS and TTD from ASCEMBL are shown in Figure 18. Few progression events had occurred across both treatments in the ASCEMBL trial (146).

Figure 18: ASCEMBL KM data

Abbreviations: KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival, TTD, time to treatment discontinuation

Few progression events had occurred across both treatments in the ASCEMBL trial. As previously discussed in Section B.3.2.2, assumptions were made around the mean time for post-discontinuation survival and mean time in AP and BP states. The analysis assumed no survival benefit following treatment discontinuation, independent of the third-line treatment given. Survival curves for AP, BP, and OS were determined directly from the following assumptions on mean time in those states, from which the parameter for exponential survival was generated:

- Mean time on third-line treatment directly estimated from extrapolation of TTD curves
- Mean overall survival = mean time on third-line treatment + 84 months (7 years)
- Mean time off third-line treatment, pre-progression = 68 months (84 months minus time in AP and BP of 16 months)
- Mean time in AP state = 10 months
- Mean time in BP state = 6 months

Data on event free survival (EFS) and OS following allo-SCT were taken from the publication by Jabbour et al. 2011 (164), which was used in previous submissions (146, 157) and reviewed the outcomes of imatinib-resistant CML patients (mainly third-line) who underwent SCT. This was a small study of only 16 patients in the CP and 31 in the progressed phases. However, the patient population in CP in Jabbour et al. was considered broadly representative of patients in the model receiving allo-SCT after discontinuation of third-line treatment. SCT extrapolations from Jabbour et al 2011 were validated with a clinical expert (163). Survival data were recreated by digitisation of the KM plots in the publication and application of the Guyot algorithm (151). Parametric survival models were then fitted to the recreated data to allow extrapolation of EFS and OS.

B.3.3.1 TTD

B.3.3.1.1 *TTD for asciminib and bosutinib*

Data on TTD were available up to 37 months and 34 months, for asciminib and bosutinib respectively, after treatment initiation for patients in the ASCEMBL trial. These data were relatively mature for bosutinib, but the median TTD was [redacted]

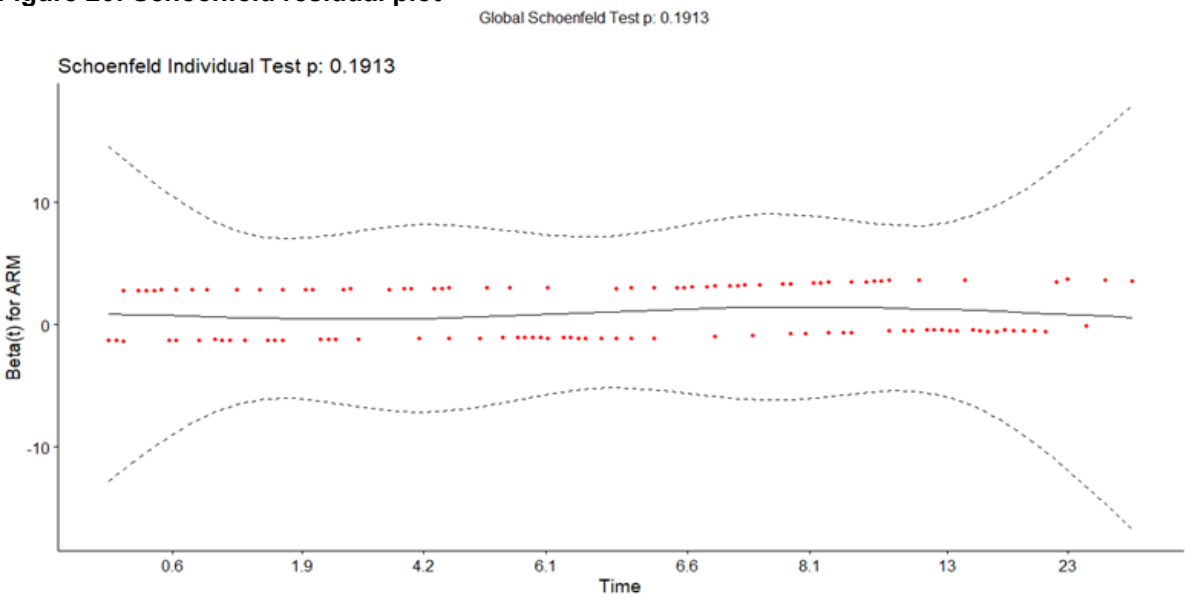
Figure 19: ASCEMBL TTD KM's with uncertainty and numbers at risk

Abbreviations: ABL, asciminib; bosu, bosutinib; TTD, time to treatment discontinuation

Parametric survival models were fitted to the TTD data for asciminib and bosutinib to allow extrapolation of TTD over the lifetime of patients. A test of the Schoenfeld

residuals (Figure 20) yielded a p-value of 0.1913, implying that the null hypothesis of proportional hazards could not be rejected. As a consequence, parametric models including a covariate representing asciminib vs bosutinib ('joint models') were deemed suitable for the prediction of TTD.

Figure 20: Schoenfeld residual plot

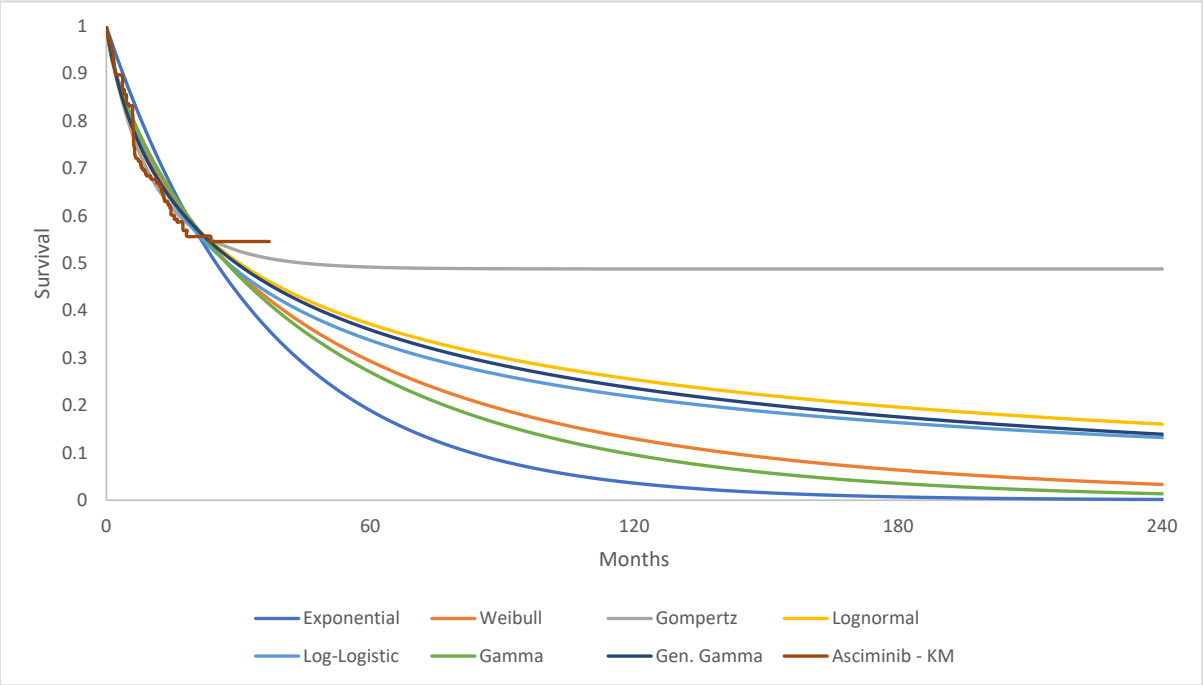


Seven commonly applied survival models were fitted to the data: exponential, Weibull, Gompertz, lognormal, loglogistic, gamma, and generalised gamma. Model selection for the comparison of asciminib and bosutinib was based on consideration of fit with the observed data and the plausibility of extrapolated values. Model fit with the observed data was judged by visual inspection and Akaike's Information Criteria (AIC), Bayesian information criterion (BIC), as well as clinical opinion.

Figure 21 and Figure 22 show the extrapolated data for each of the survival models fitted to the data for patients in the asciminib and the bosutinib arms, alongside the KM survival plots.

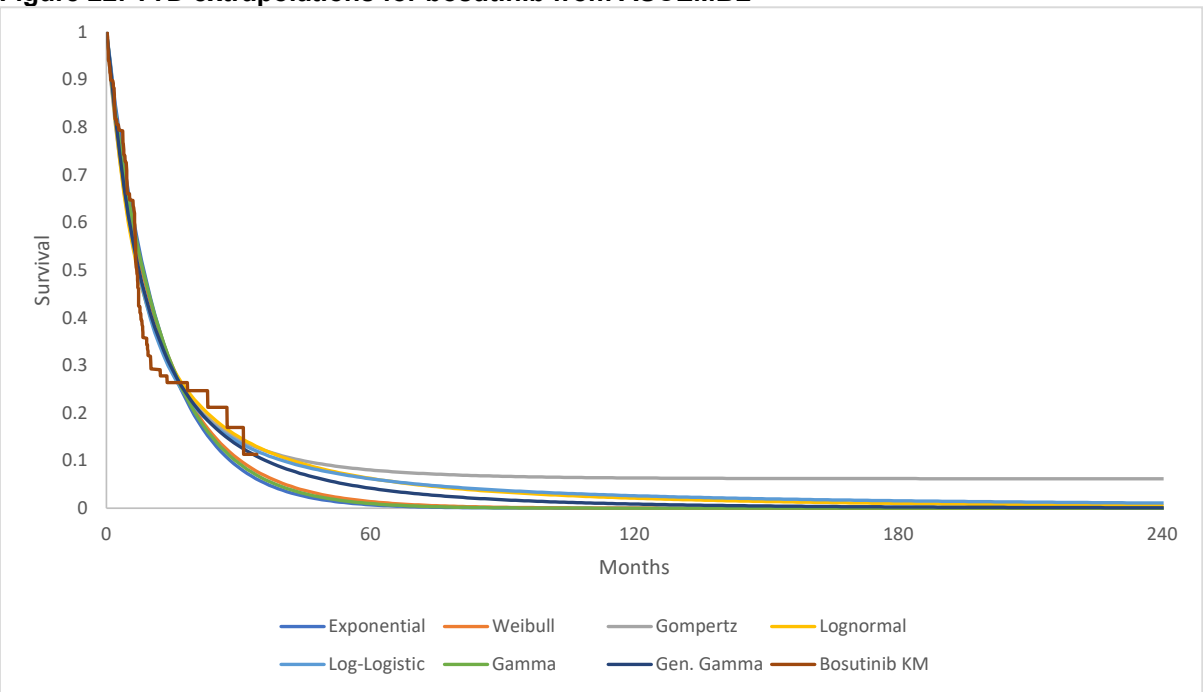
Table 57 reports the survival estimates for each distribution at 2, 5, and 10 years for asciminib and bosutinib.

Figure 21: TTD extrapolations for asciminib from ASCEMBL



Abbreviations: Gen, generalised; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 22: TTD extrapolations for bosutinib from ASCEMBL



Abbreviations: Gen, generalised; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 57: Proportion remaining on treatment for each distribution

Years	Survival						
	Asciminib						
	Exponential	Weibull	Gompertz	Lognormal	Log-Logistic	Gamma	Gen. Gamma
2	51%	54%	55%	54%	53%	54%	54%
5	19%	29%	49%	37%	34%	27%	36%
10	4%	13%	49%	25%	22%	10%	24%
	Bosutinib						
2	14%	16%	18%	19%	18%	15%	18%
5	1%	1%	8%	6%	6%	1%	4%
10	0%	0%	6%	2%	3%	0%	1%

Abbreviations: Gen, generalised.

Table 58 reports model diagnostics for each of the models fitted to the TTD from ASCEMBL.

Table 58: Model diagnostics for asciminib and bosutinib joint model from ASCEMBL

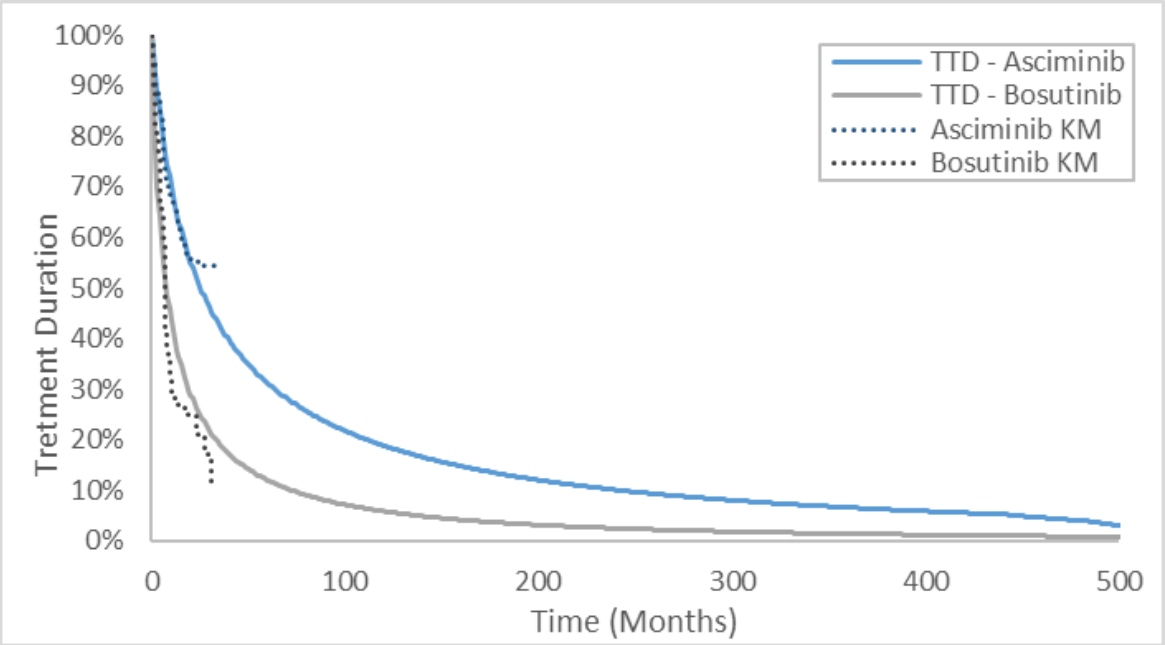
Model	AIC	Rank	BIC	Rank
Exponential	1048.122	7	1055.024	6
Weibull	1042.399	4	1052.752	3
Gompertz	1030.132	1	1040.485	1
Lognormal	1043.2	5	1053.553	4
Log-Logistic	1039.018	2	1049.371	2
Gamma	1044.092	6	1054.445	5
Gen. Gamma	1041.492	3	1055.296	7

Abbreviations: AIC, Akaike's information criteria; BIC, Bayesian information criteria; Gen, generalised.

Visual inspection and measures of model fit indicate that the Gompertz specification provides the best fit to the joint TTD data. The function is best able to match the plateau in the asciminib data beyond 20 months. However, this led to extrapolated values the clinical expert consulted considered implausibly high. Model fit, as measured by AIC and BIC, is similar for the remaining six functions. The log-normal was considered the most plausible based on clinical opinion, as it was thought around a quarter of patients would gain long term control of their disease on asciminib, and on bosutinib around 1 in 20 patients would gain long term control of their disease at 5 years.

The base case joint log-normal distributions are shown in Figure 23.

Figure 23: Base case TTD extrapolations for asciminib vs bosutinib



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

B.3.3.1.2 *TTD for other comparators (based on MAIC)*

TTD for asciminib was compared with ponatinib, nilotinib, and dasatinib using a MAIC (matched-adjusted indirect comparison) (see Section B.2.9.2.4.1). The KM curves for TTD for ponatinib, nilotinib, and dasatinib was not available, and only median treatment duration was reported in the respective trials:

- Ponatinib: 32.1 months (58)
- Nilotinib: 11 months (114)
- Dasatinib: 14 months (147)

Based on matching, weights for each patient for the asciminib arm were assigned such that summary statistics matched with those in the comparator trials.

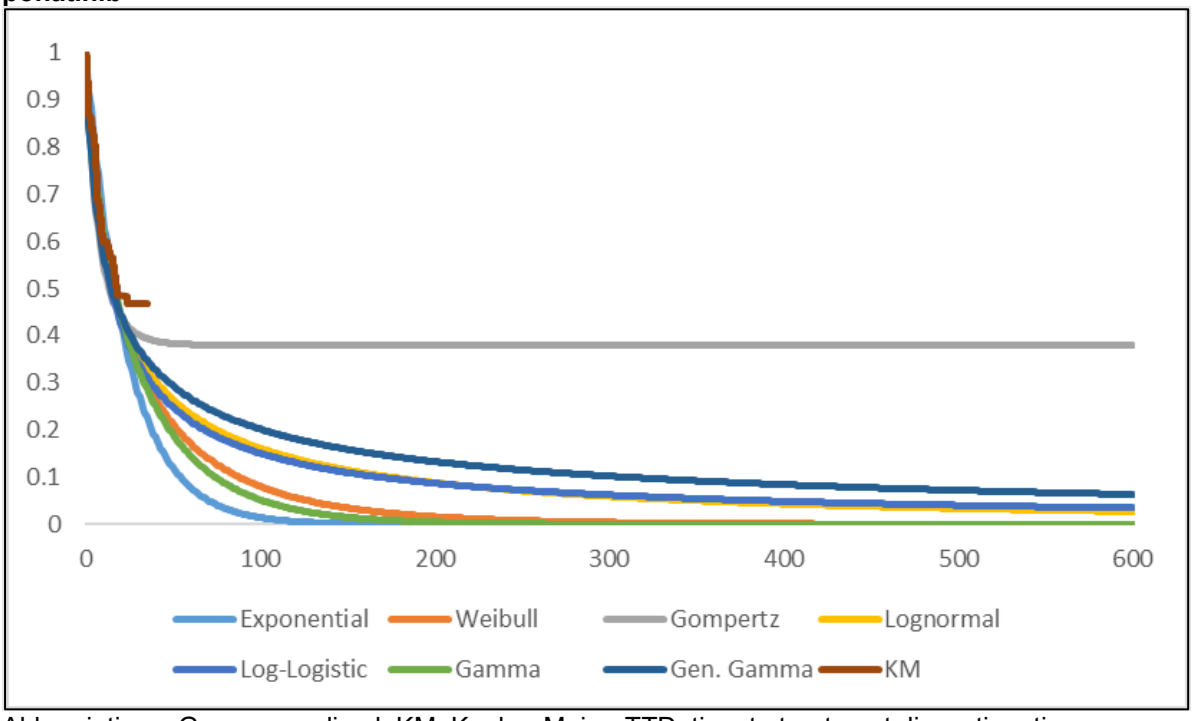
In the absence of data beyond median TTD, exponential functions were assumed for TTD of each comparator (other than bosutinib). This approach generates conservative estimates of TTD and does not require application of a HR to a survival model which may be inconsistent with a proportional hazards assumption. Scenario analysis undertaken for the comparison of asciminib with bosutinib indicates that the choice of function to extrapolate TTD does not have a marked impact on the ICER.

Visual inspection and measures of model fit both indicate that the Gompertz specification provides the best fit to the asciminib TTD data for all three comparisons. However, the exponential function was selected for the base case analysis vs each comparator to match the parameterisation of TTD for ponatinib, nilotinib and dasatinib.

B.3.3.1.2.1 Asciminib vs ponatinib

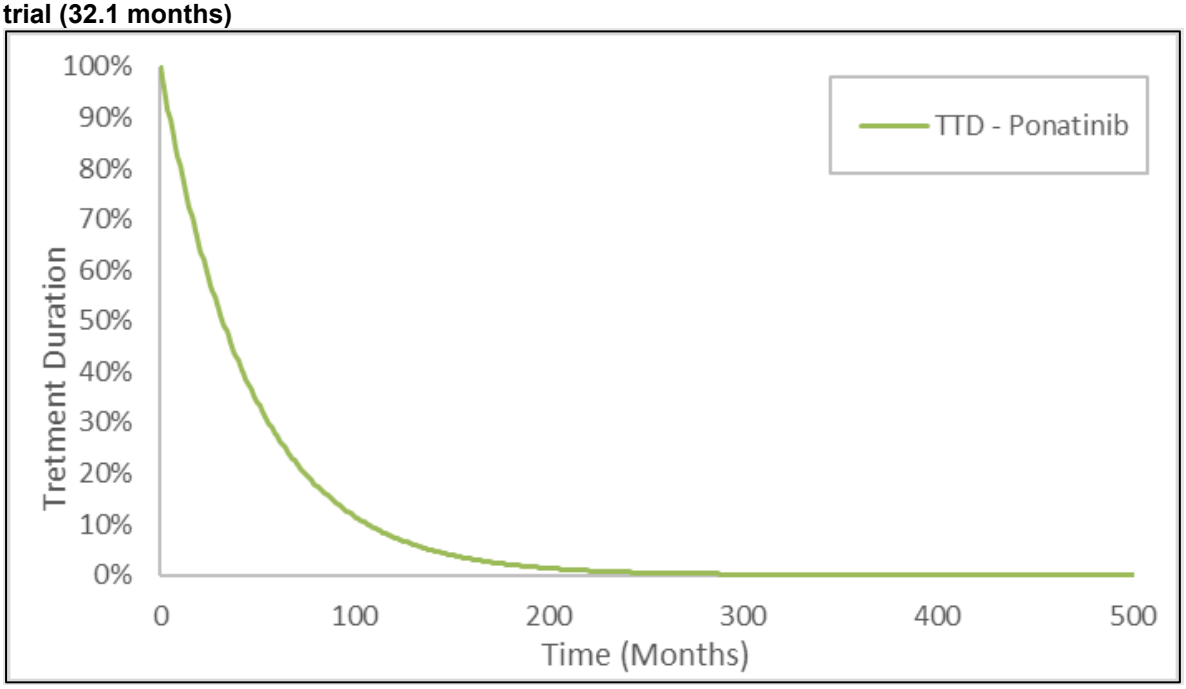
Table 59 reports AIC and BIC values for each of the models fitted to the asciminib TTD derived from the MAIC. Figure 24 shows the extrapolated data for each of the survival models fitted to the asciminib data adjusted to match ponatinib patients, alongside the adjusted asciminib KM. The exponential extrapolation parameterised from median TTD reported in the PACE trial can be seen in Figure 25.

Figure 24: TTD extrapolations for asciminib adjusted to match the patient characteristics of ponatinib



Abbreviations: Gen, generalised; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 25: Exponential model fit to meet the median treatment duration reported in the PACE trial (32.1 months)



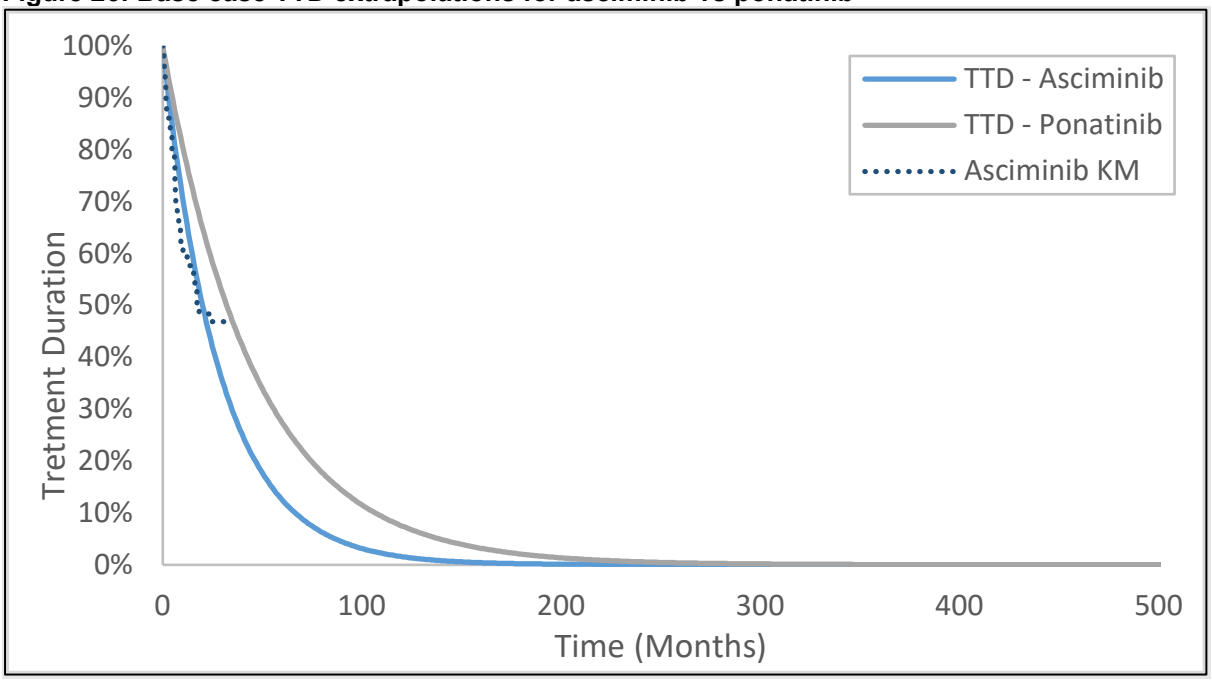
Abbreviations: TTD, time to treatment discontinuation.

Table 59: Model diagnostics for asciminib TTD after adjustment of patient data to match the PACE trial

	Asciminib			
Model	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	654.84	7	657.77	7
Weibull	642.68	5	648.54	5
Gompertz	627.83	1	633.69	1
Lognormal	633.11	2	638.97	2
Log-Logistic	635.49	4	641.34	3
Gamma	645.73	6	651.59	6
Gen. Gamma	634.01	3	642.79	4

Abbreviations: AIC, Akaike's information criteria; BIC, Bayesian information criteria; Gen, generalised; TTD, time to treatment discontinuation.

Figure 26: Base case TTD extrapolations for asciminib vs ponatinib

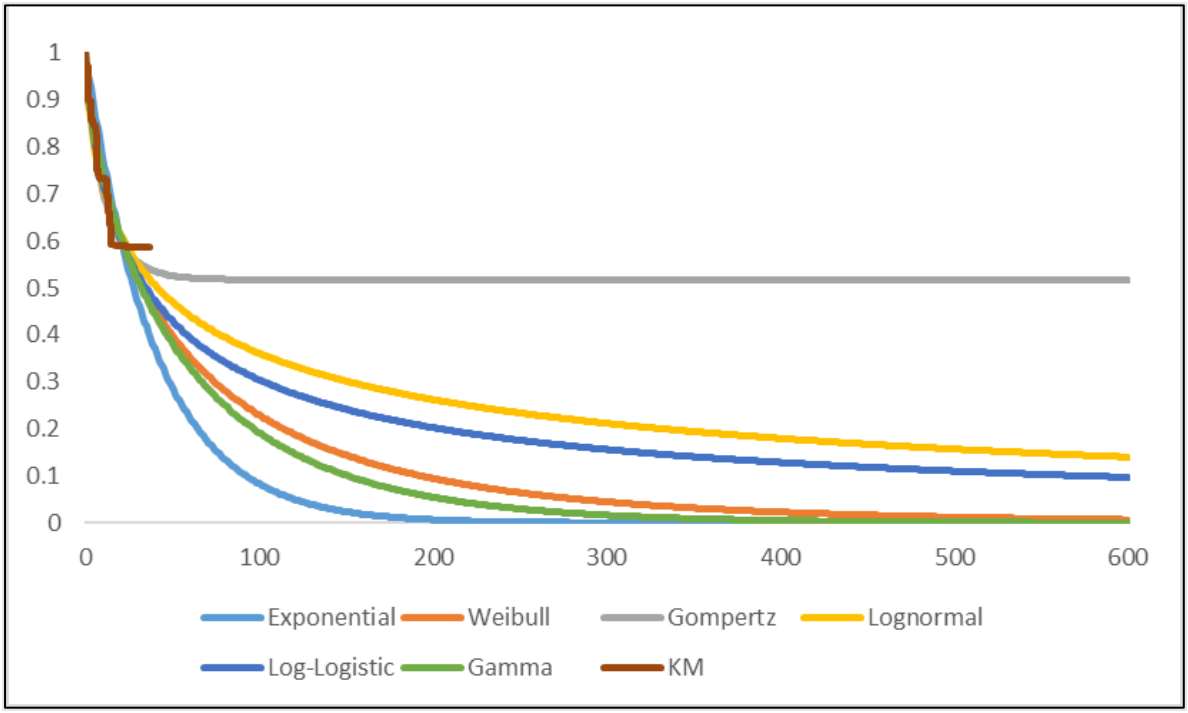


Abbreviations: TTD, time to treatment discontinuation.

B.3.3.1.2.2 Asciminib vs nilotinib

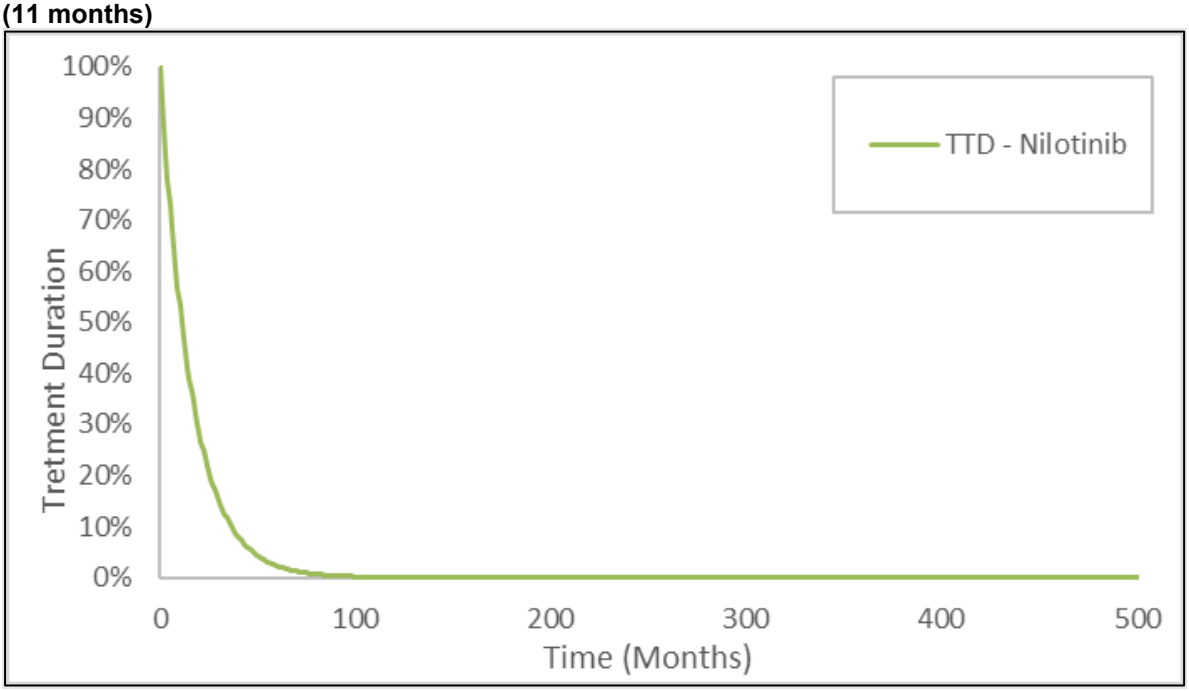
Table 60 reports AIC and BIC values for each of the models fitted to the asciminib TTD derived from the MAIC. Figure 27 shows the extrapolated data for each of the survival models fitted to the asciminib data after adjustment to match nilotinib patients, alongside the adjusted asciminib KM. An exponential function was assumed for TTD for nilotinib, parameterised from median TTD reported in Giles et al. 2011 (Figure 28).

Figure 27: TTD extrapolations for asciminib adjusted to match the patient characteristics of nilotinib



Abbreviations: Gen, generalised; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 28: Exponential model fit to meet the median treatment duration reported in Giles 2011 (11 months)



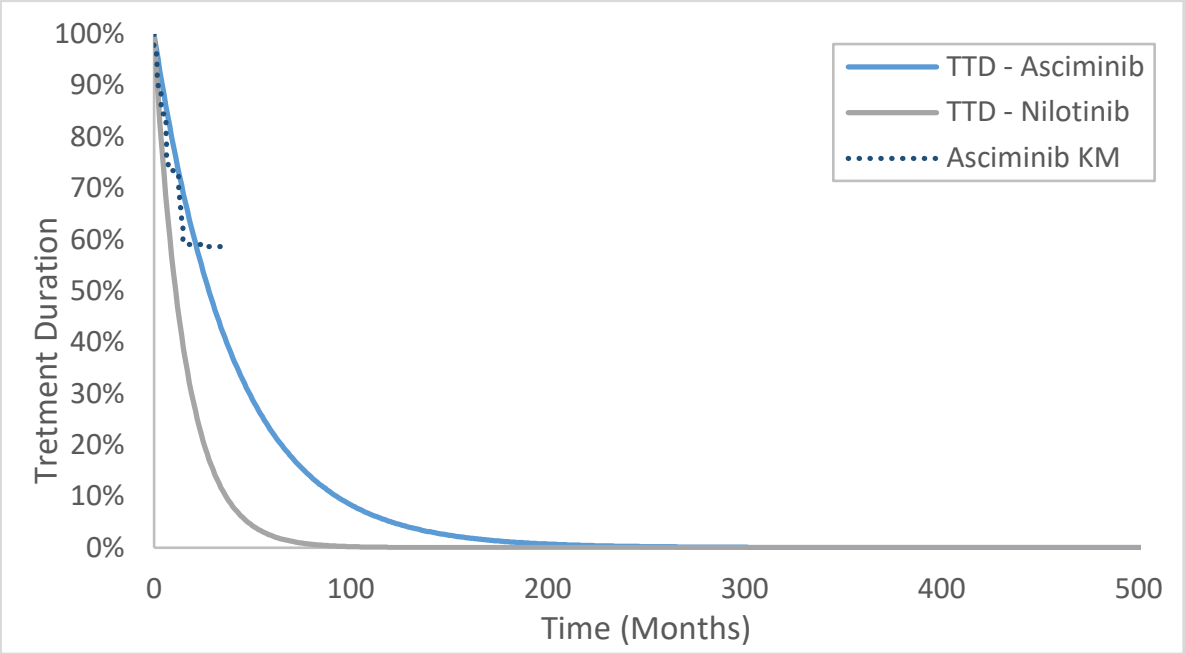
Abbreviations: TTD, time to treatment discontinuation.

Table 60: Model diagnostics for asciminib TTD adjusted to match the patient characteristics of nilotinib trial

	Asciminib			
Model	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	604.57	6	607.63	6
Weibull	593.66	3	599.77	3
Gompertz	590.27	1	596.38	1
Lognormal	596.57	5	602.68	5
Log-Logistic	592.35	2	598.46	2
Gamma	594.44	4	600.55	4
Gen. Gamma				

Blank for distributions which did not converge.
Abbreviations: AIC, Akaike's information criteria; BIC Bayesian information criteria; Gen, generalized.

Figure 29: Base case TTD extrapolations for asciminib vs nilotinib

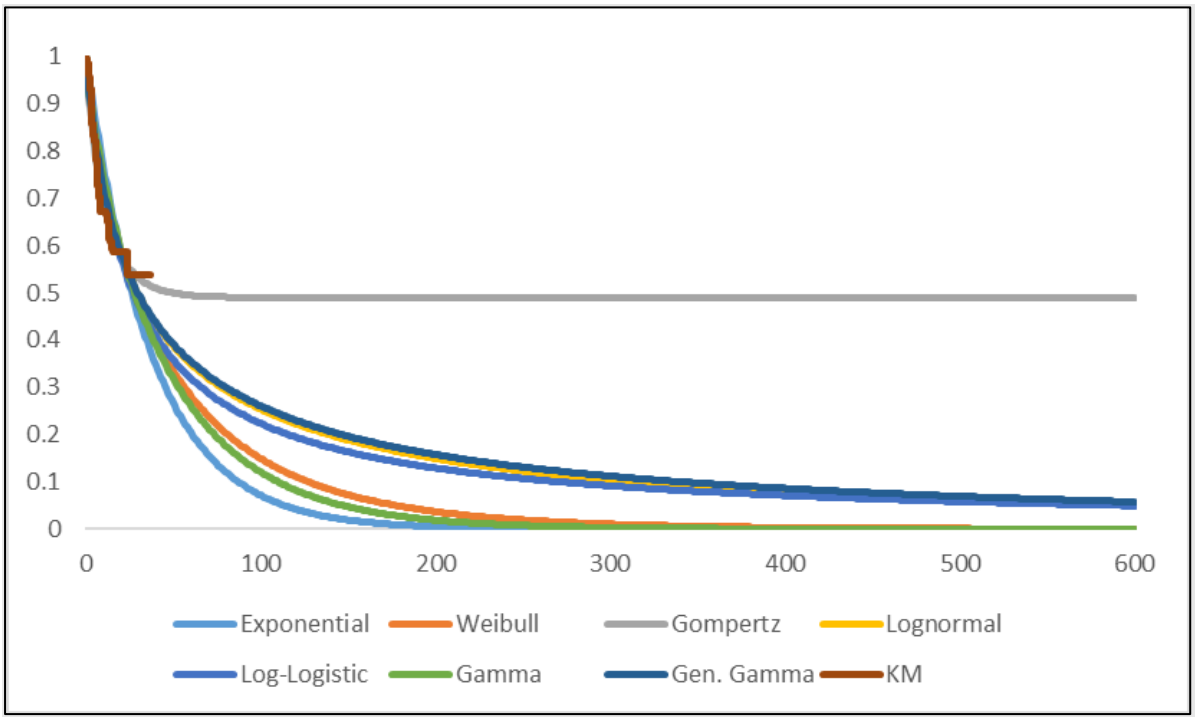


Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

B.3.3.1.2.3 Asciminib vs dasatinib

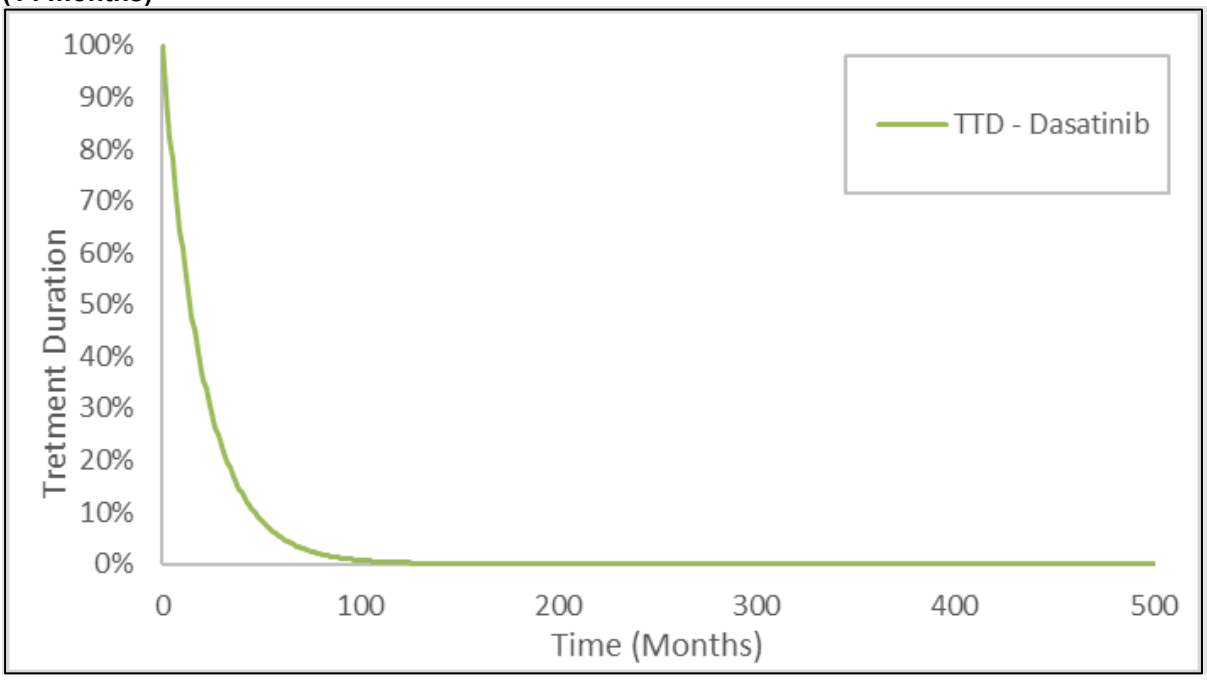
Table 61 reports AIC and BIC values for each of the models fitted to the asciminib TTD derived from the MAIC. Figure 30 shows the extrapolated data for each of the survival models fitted to the asciminib data, following adjustment to match the characteristics of patients in Rossi et al. 2013, alongside the adjusted asciminib KM. An exponential function was assumed for TTD for dasatinib, parameterised from median TTD reported in the relevant study, this can be seen in Figure 31.

Figure 30: TTD extrapolations for asciminib adjusted to match the patient characteristics of dasatinib



Abbreviations: Gen, generalised; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 31: Exponential model fit to meet the median treatment duration reported in Rossi 2013 (14 months)



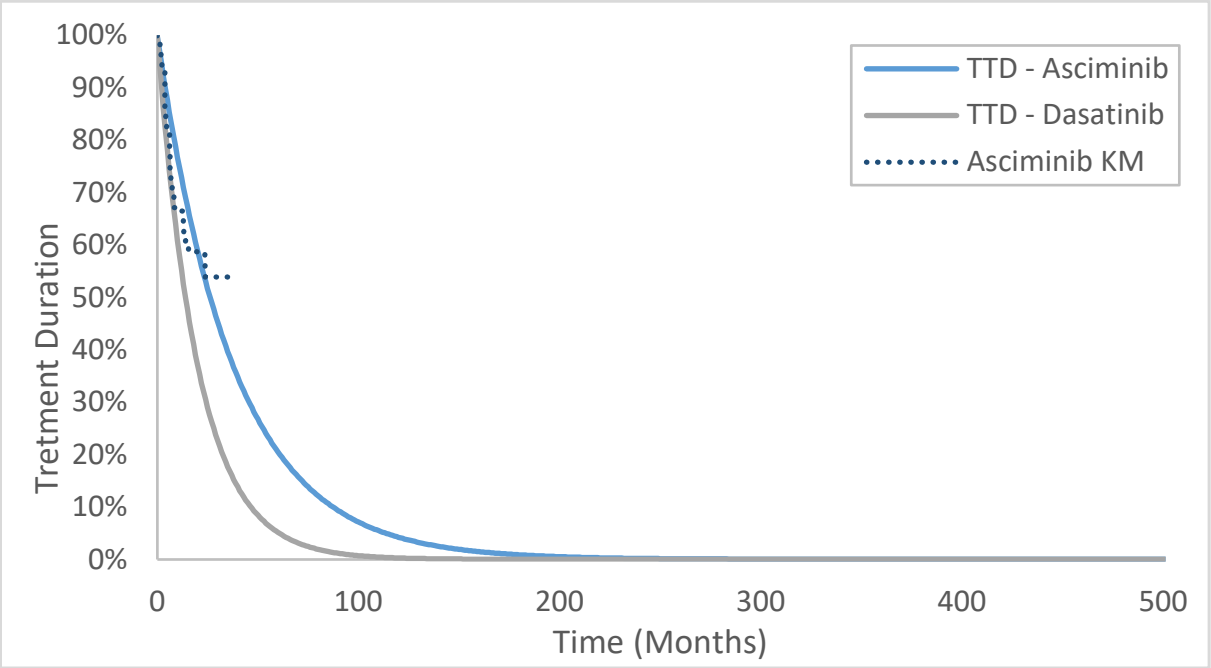
Abbreviations: TTD, time to treatment discontinuation.

Table 61: Model diagnostics for asciminib TTD adjusted to match the patient characteristics of dasatinib

	Asciminib			
Model	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	622.21	7	625.26	5
Weibull	619.61	5	625.72	6
Gompertz	606.83	1	612.95	1
Lognormal	612.23	2	618.35	2
Log-Logistic	613.9	3	620.01	3
Gamma	621.12	6	627.23	7
Gen. Gamma	614.21	4	623.38	4

Abbreviations: AIC, Akaike's information criteria; BIC Bayesian information criteria; Gen, generalised.

Figure 32: Base case TTD extrapolations for asciminib vs nilotinib



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

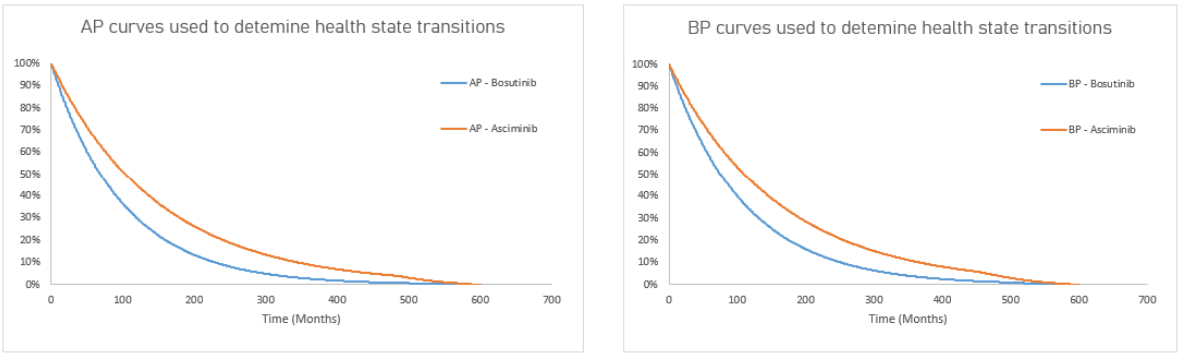
All curve extrapolations can be found in Appendix L.

B.3.3.2 Progressed disease

Progression-free survival for asciminib and bosutinib was immature from the ASCEMBL trial. As previously described in section B.3.2.2, the model assumes OS of 7 years post-discontinuation of third line treatment, with the last 6 months spent in CML-BP and the preceding 10 months spent in CML-AP. Therefore, mean PFS with respect to CML-AP is equal to overall survival minus 16 months (84 – 16 = 68 months), and mean PFS with respect to CML-BP is equal to overall survival minus 6 months (84 – 6 = 78 months). Exponential curves were fitted to derive long-term PFS curves for the intervention as well as for all the comparators. The curves were

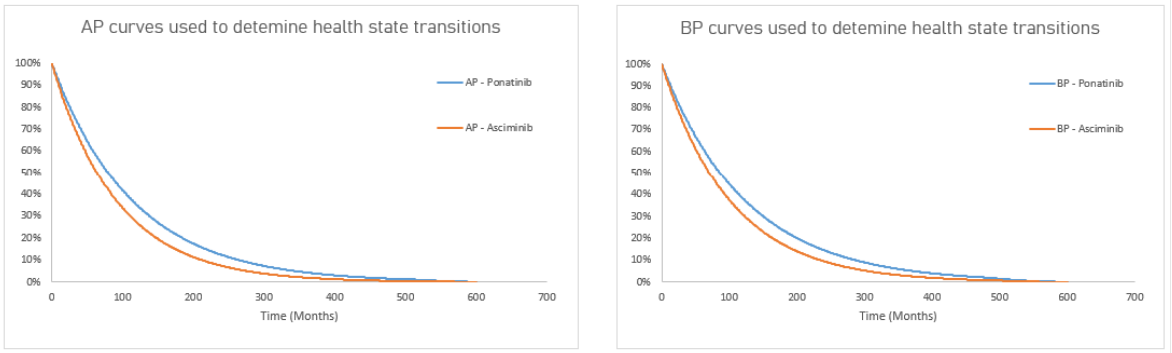
parameterised to ensure a mean PFS of 68 months with regard to progression to CML-AP, and 78 months with regard to progression to BP. The resulting curves for AP and BP for each comparison can be seen in Figure 33, Figure 34, Figure 35, and Figure 36.

Figure 33: AP and BP survival curves for asciminib vs bosutinib



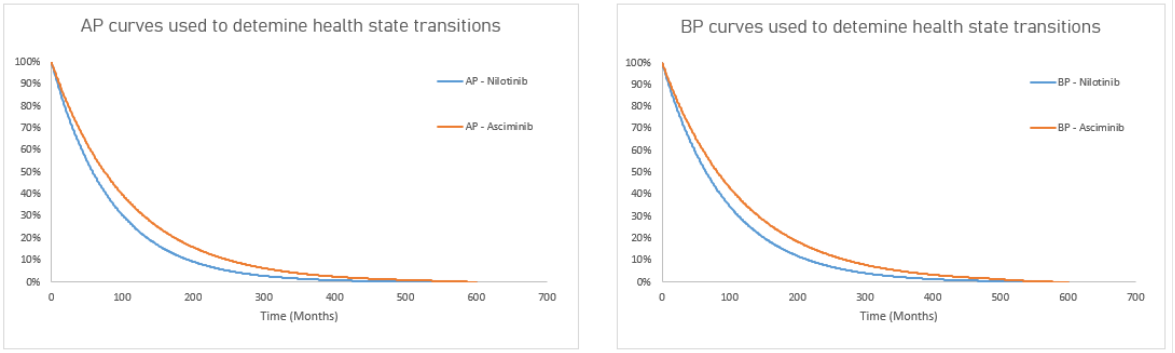
Abbreviations: AP, advanced phase; BP, blast phase.

Figure 34: AP and BP survival curves for asciminib vs ponatinib



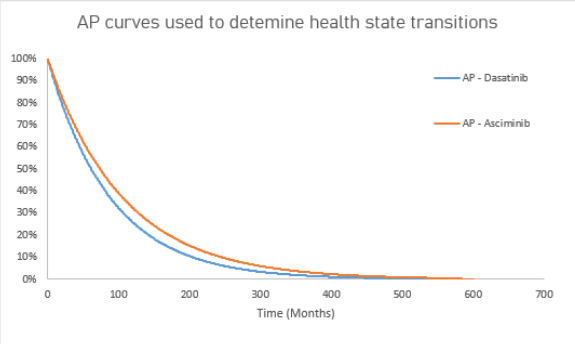
Abbreviations: AP, advanced phase; BP, blast phase.

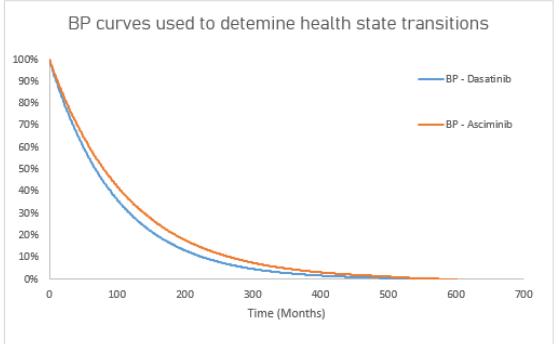
Figure 35: AP and BP survival curves for asciminib vs nilotinib



Abbreviations: AP, advanced phase; BP, blast phase.

Figure 36: AP and BP survival curves for asciminib vs dasatinib





Abbreviations: AP, advanced phase; BP, blast phase.

B.3.3.3 Overall survival

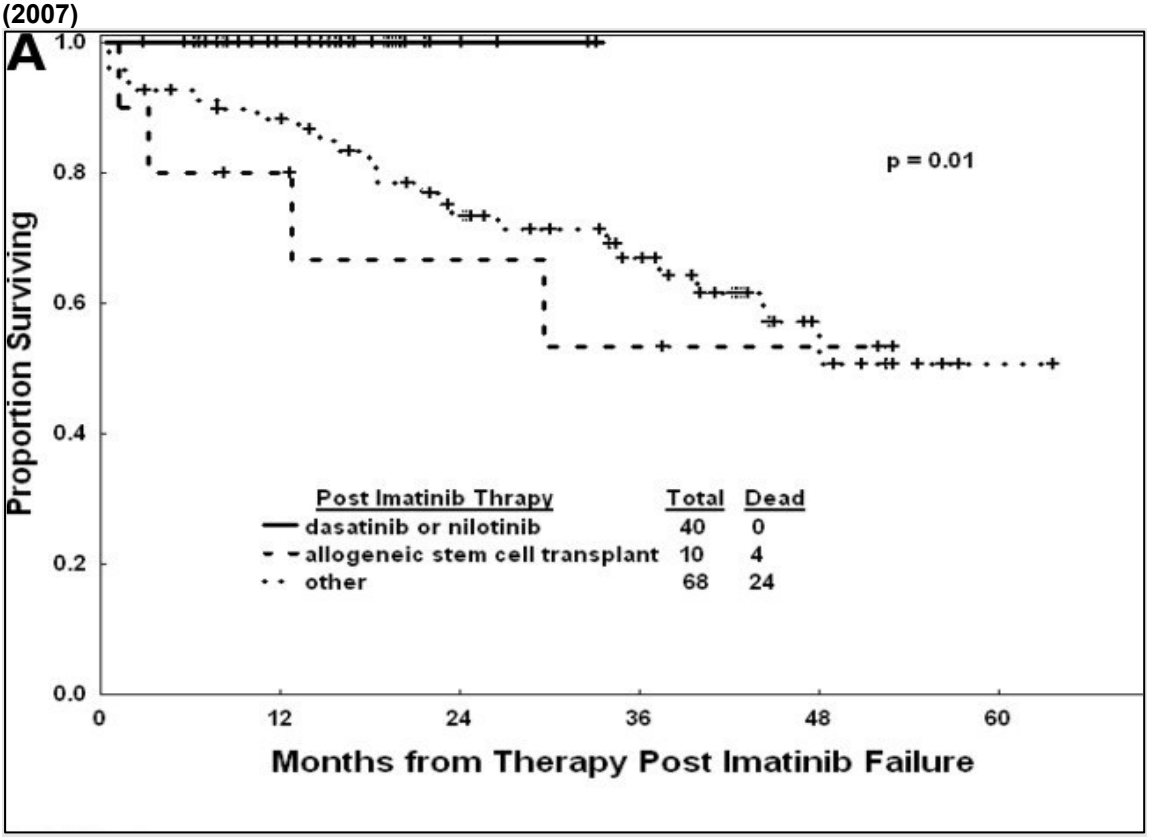
B.3.3.3.1 *All treatments*

Overall survival for asciminib and bosutinib was [redacted] from the ASCEMBL trial. TA401 (146) used Kantarjian 2007 (149) to estimate mean overall survival post-discontinuation of treatment. Kantarjian 2007 reported KM survival plots over 5 years for patients discontinuing imatinib according to subsequent therapy. Figure 37 shows the plot of OS from the publication for patients discontinuing imatinib in CP categorised by subsequent treatment. The key data are the patients categorised as 'other' who received neither SCT nor TKI treatment following imatinib discontinuation. Data reported by the authors indicates that approximately one fifth of these patients received hydroxycarbamide. The most common treatment was tipifarnib. Survival for the 'other' group is 77% at two years and 70% at three years.

TA401 fitted an exponential distribution to the KM for the 'other' group, and found the mean survival to be 3.5 years. However, this estimate appears erroneous as Figure 37 shows median survival to be at least 5 years. The ERG in TA401 also estimated mean overall survival from Kantarjian 2007 and found this mean to be 7 years. In TA401, the Committee concluded that this estimate is likely to be somewhere between 3.5 years and 7 years. Clinical expert opinion sought for this submission confirmed 7 years was more appropriate as 3.5 was likely to be too low (163). Kantarjian 2007 is also considered less relevant because of the age of the study, as well as the fact that it is a second line population, whereas the population of interest is a fourth line population.

In summary, 7 years was used in the base case as an estimate of overall survival after discontinuing third-line treatment, with 3.5 years tested in a sensitivity analysis.

Figure 37: Kaplan-Meier survival plot for patients discontinuing imatinib in CP from Kantarjian (2007)



Abbreviations: CP, chronic phase.

An exponential model was used for OS, and calibrated to ensure mean OS is mean TTD + 7 years. The exponential model assumes the mortality rate is constant over time, but requires a single parameter, which can be specified directly from the mean. Mortality in each cycle was prevented from falling below the relevant value for the general population (section B.3.3.3.2).

Figure 38 shows a comparison of:

- Overall survival from the cost-effectiveness model (for asciminib and bosutinib – the only comparison where all survival models could be fitted)
- The OS KMs from ASCEMBL
- The estimates of OS third-line from the HMRN report

Figure 38: Comparison of OS from ASCEMBL, the cost-effectiveness model using an assumption of survival post-discontinuation of third-line treatment of 7 years, and third-line OS from HMRN

Abbreviations: HMRN, Haematological Malignancy Research Network; OS, overall survival.

The OS from ASCEMBL is immature, hence the need to use alternative data for overall survival. Based on the limited data available, the HMRN is roughly in agreement with the estimated overall survival for asciminib, although HMRN data does not yet include asciminib.

B.3.3.3.2 *Life tables*

Age- and gender-specific probabilities of death were taken from published national life tables for England, using data for 2018–2020 (165). Life tables are used in the model to ensure the monthly probability of mortality never falls below that of the general population.

B.3.3.4 Allo-SCT

B.3.3.4.1 *Proportion receiving allo-SCT*

The proportion progressing from each disease phase to allo-SCT in each cycle of the model is reported in Table 62. This is different for the chronic phase and for the progressed phases of the disease (AP and BP).

The HMRN report reported a full treatment pathway for allografted patients. This was observed in [redacted] patients. It was assumed that all these patients had an SCT in the chronic phase, however only [redacted] of these patients have SCT at fourth line. [redacted] patients were reported to have gone onto a fourth line TKI. Therefore [redacted] were assumed to have an SCT at fourth line in the chronic phase ([redacted]).

There were [redacted] patients in HMRN reported as progressing to AP or BP. Of these, [redacted] underwent an SCT. At the time the data were prepared, [redacted] of the patients remained alive, [redacted] of whom had not undergone an SCT. Therefore, the estimate of [redacted] of patients undergoing SCT in AP or BP may be an underestimate. Consequently, it was assumed that [redacted] of patients would undergo SCT at transition to AP and a further [redacted] at transition to BP. Other values were tested in sensitivity analysis. Note that AP and BP were not distinguished within the HMRN data.

Clinician estimates for the proportion of patients undergoing allo-SCT in CP were similar to those from HMRN. However, the clinical expert suggested around 40–50% of patients will undergo SCT at transition to AP and a further 40-50% at transition to BP (68). It is possible these estimates did not fully consider the proportion of patients at these transition points who would be suitable candidates for allo-SCT.

Other values were tested in sensitivity analysis.

Table 62: Proportion progressing to allo-SCT

Health state	Proportion progressing to allo-SCT	Source
CP	[redacted]	HMRN report (14)
AP	[redacted]	HMRN report (14)
BP	[redacted]	HMRN report (14)

Abbreviations: allo-SCT, allogenic stem cell transplant; AP, advanced phase; BP, blast phase; CP, chronic phase.

B.3.3.4.2 *Transition calculations*

The calculations to determine the proportion in each state in each cycle in the main model, accounting for those leaving for the SCT sub-models, is explained in more detail below.

As mentioned in section B.3.2.2, patients undergoing allo-SCT are removed from the main model each cycle and move to the SCT sub-models (either the chronic phase SCT sub-model or the progressed disease SCT sub-model) (see Figure 16).

In the chronic phase, of those that discontinue treatment each cycle, [redacted] are assumed to undergo allo-SCT, and transition to the CP SCT sub-model. This means that over the course of a lifetime simulation, [redacted] of the entire cohort enter the CP SCT sub-model. This implicitly assumes there is no mortality in the CP on treatment health state.

Adjustment of state occupancy in the main model is required to account for patients leaving to undergo SCT. Therefore, occupancy in the subsequent health states (CP off treatment, AP, BP, death) is reweighted to account for the cumulative total proportion leaving for the SCT CP model at each cycle.

Transition to SCT following progression to AP or BP is parameterised in a similar fashion. In each cycle, a proportion of patients entering AP (as calculated from the relevant survival curve), leave the main model and enter the SCT PD sub-model. The proportion is [redacted]; the latter correction is made to account for the proportion of patients who already underwent allo-SCT at discontinuation of third-line treatment (Note: state occupancies are adjusted in the main model to account for patients leaving to undergo SCT; survival curves are not adjusted and hence the correction to the proportion calculated from the survival curve is required). Similarly, a proportion of patients entering BP also undergo SCT and are removed from the main model to join the SCT PD sub-model. The proportion is [redacted], a further correction being applied for patients who have already undergone SCT on entering AP. Once again, the state occupancies of the AP and BP health states have to be reweighted to adjust for those leaving the AP state for SCT, and the occupancy of the BP health state is further adjusted for patients undergoing SCT at transition to BP.

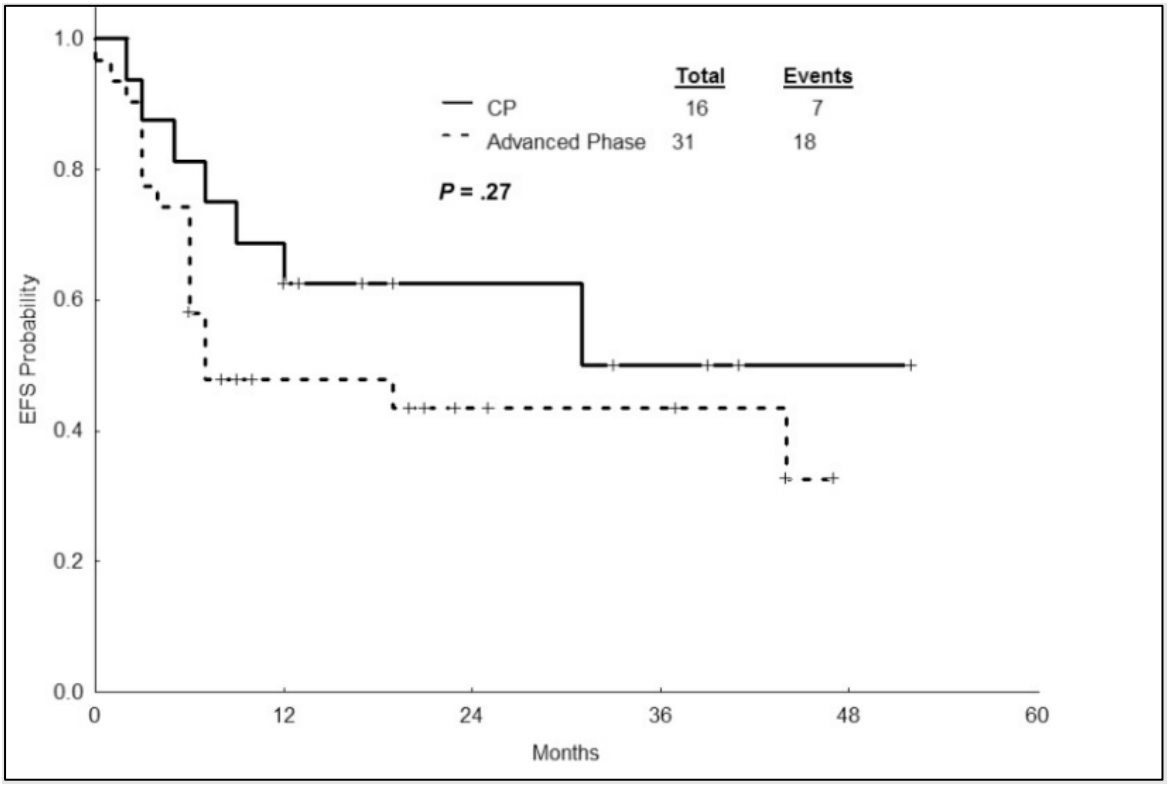
B.3.3.4.3 *Survival*

In the current model allo-SCT is considered as subsequent treatment. There are two sub-models for allo-SCT based on the phase patients were in before receiving allo-SCT – allo-SCT in CML-CP and allo-SCT in progressed disease. The two models use the same structure; transition parameters are estimated from sources reflecting the different patient populations (Jabbour 2011 was used for both the CP and progressed disease transitions) (164).

After receiving allo-SCT, patients can experience a relapse or death. Relapse free survival (RFS) curves and overall survival curves for patients who receive allo-SCT in the chronic phase and progressed disease phase were taken from Jabbour 2011 (164), a source used in prior TAs (such as TA401). The KM plots from Jabbour 2011

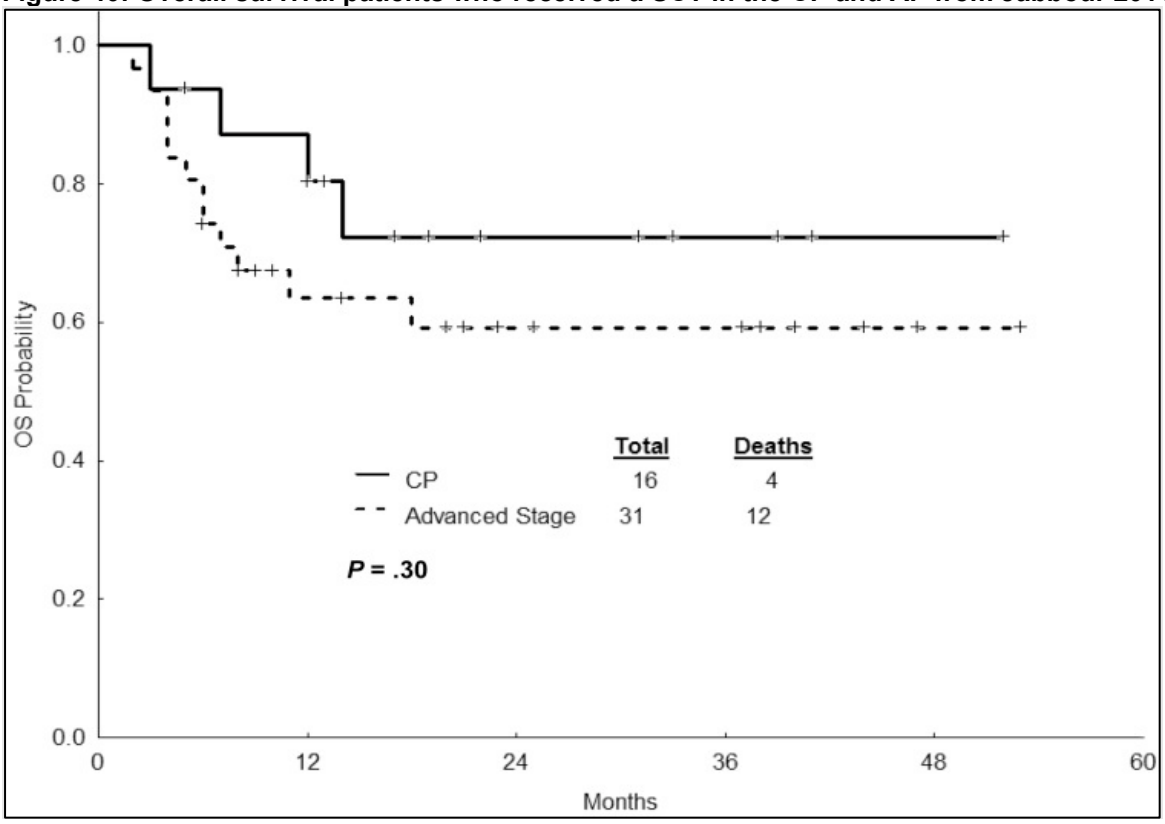
can be seen in Figure 39 and Figure 40. The curves were digitised, and the IPD was reconstructed using the method of Guyot et al (151).

Figure 39: Event free survival patients who received a SCT in the CP and AP from Jabbour 2011



Abbreviations: AP, accelerated phase; CP, chronic phase; SCT, stem cell transplantation.

Figure 40: Overall survival patients who received a SCT in the CP and AP from Jabbour 2011



Abbreviations: AP, accelerated phase; CP, chronic phase; SCT, stem cell transplantation.

A number of parametric models were fitted to RFS and OS curves for the CP and progressed disease subgroups, including seven commonly applied survival models: exponential, Weibull, Gompertz, lognormal, loglogistic, gamma and generalised gamma.

Model selection was based on consideration of fit with the observed data and the plausibility of extrapolated values, and extrapolations were also validated with a clinician. Model fit with the observed data was judged by visual inspection and measures of model fit; AIC and BIC.

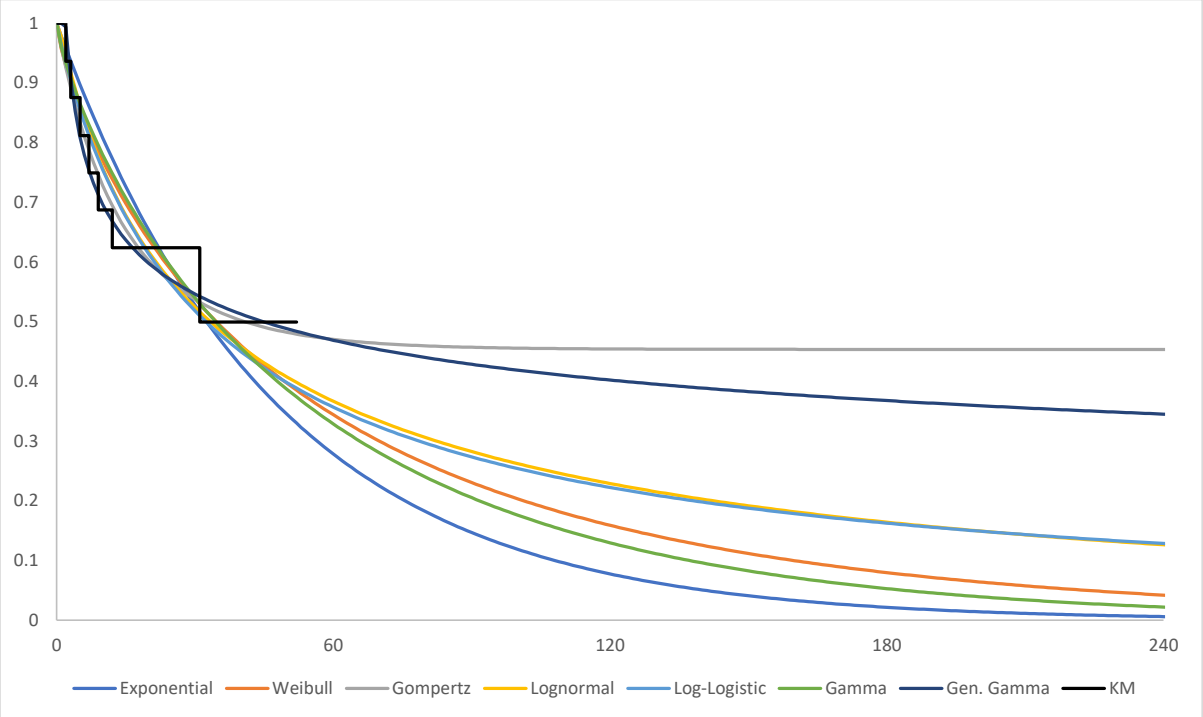
Table 63 reports AIC and BIC values for each of the models fitted to data for patients in the CP subgroup. Figure 41 and Figure 42 show the extrapolated data for each of the survival models fitted to the RFS and OS data for patients in the CP subgroup, alongside the KM survival plots, and Table 64 shows the survival estimates at various time points.

Table 63: Model diagnostics for RFS and OS in SCT from CP

	RFS				OS			
Model	**AIC**	**Rank**	**BIC**	**Rank**	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	69.88	3	70.6	2	45.86	1	46.64	1
Weibull	71.29	6	72.8	6	47.69	6	49.23	6
Gompertz	69.98	4	71.5	4	46.43	3	47.98	2
Lognormal	69.87	2	71.4	3	46.83	4	48.37	3
Log-Logistic	70.58	5	72.1	5	47.36	5	48.91	5
Gamma	71.49	7	73.0	7	47.76	7	49.31	7
Gen. Gamma	68.32	1	70.6	1	46.06	2	48.37	4

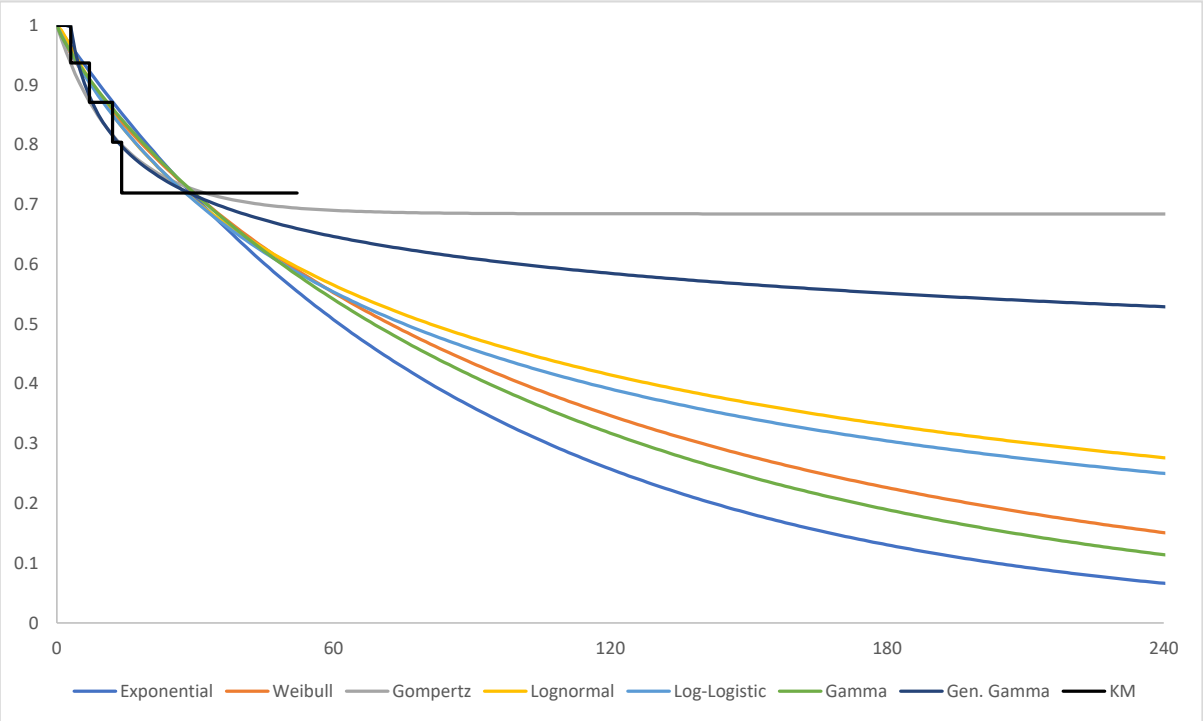
Abbreviations: AIC, Akaike's information criteria; BIC, Bayesian information criteria; CP, chronic phase; Gen, generalised;

Figure 41: Allo-SCT RFS extrapolations for CP subgroup



Abbreviations: Allo-SCT, allogeneic stem cell transplantation; CP, chronic phase; Gen, generalised; KM, Kaplan-Meier; RFS, relapse free survival.

Figure 42: Allo-SCT OS extrapolations for CP subgroup



Abbreviations: Allo-SCT, allogeneic stem cell transplantation; CP, chronic phase; Gen, generalised; KM, Kaplan-Meier; OS, overall survival.

Table 64: Survival estimates at 2, 5, and 10 years according to survival model selected

	Relapse free survival						
Years	**Exponential**	**Weibull**	**Gompertz**	**Lognormal**	**Log-Logistic**	**Gamma**	**Gen. Gamma**
2	60%	59%	57%	58%	57%	60%	57%
5	28%	34%	47%	37%	36%	33%	47%
10	8%	16%	45%	23%	22%	13%	40%
	Overall survival						
2	76%	76%	74%	75%	75%	76%	74%
5	51%	55%	69%	57%	55%	54%	65%
10	26%	35%	68%	42%	39%	32%	59%

The generalised gamma distribution had the best fit on both the AIC and BIC criteria to data on RFS for patients in the CP subgroup. Clinical opinion was that around 50% of patients would be alive and disease free at 5 years, therefore the generalised gamma distribution was used in the base case for RFS following SCT in the chronic phase.

For OS in the CP subgroup, the exponential model provided the best fit, followed by generalised gamma according to AIC, and Gompertz according to BIC. Clinical expert opinion was that the generalised gamma distribution had the best fit when

compared to long term survival estimates in the disease area (68), therefore this was used as the base case.

Distribution selection for SCT made very little difference to the results, therefore alternatives are not presented in sensitivity analysis for this submission.

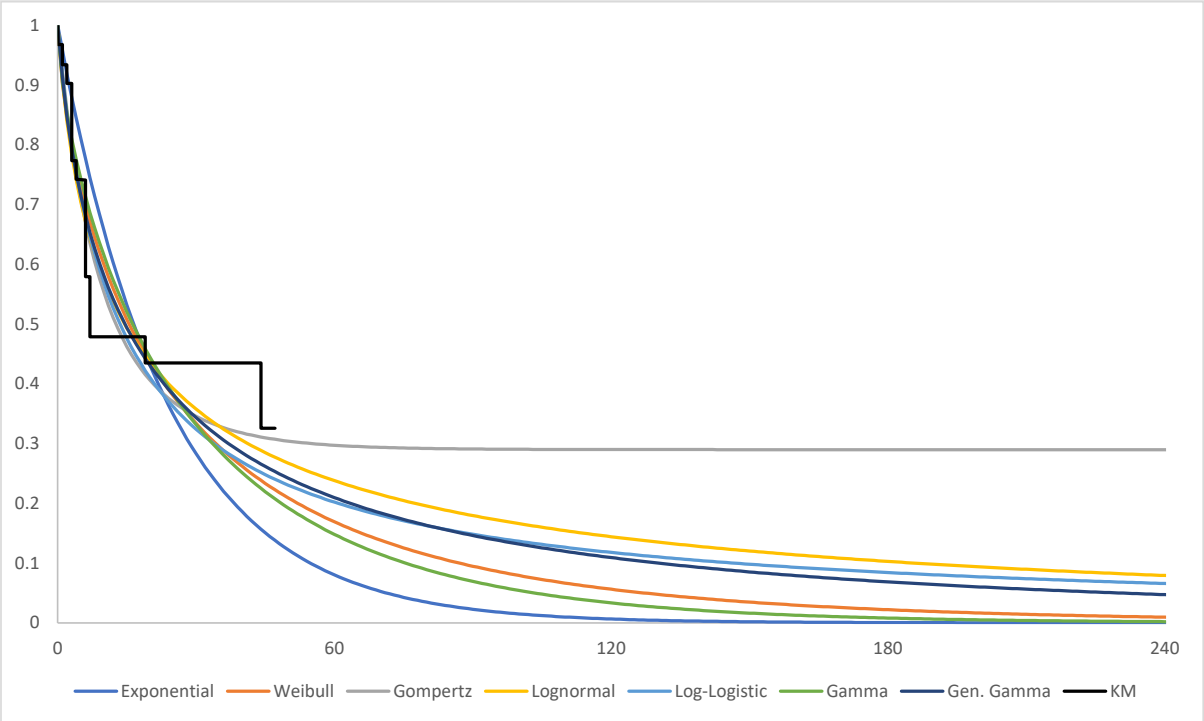
Table 65 reports model diagnostics for each of the models fitted to data for patients in the progressed disease subgroup.Figure 43 and Figure 44 show the extrapolated data for each of the survival models fitted to the RFS and OS data for patients in the progressed phase subgroup, alongside the KM survival plots, and Table 66 shows the survival estimates at various time points.

Table 65: Model diagnostics for RFS and OS in SCT from PD

	RFS				OS			
Model	**AIC**	**Rank**	**BIC**	**Rank**	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	152.08	7	153.52	5	120.06	6	121.50	5
Weibull	150.15	4	153.02	4	119.84	5	122.71	6
Gompertz	148.02	1	150.88	1	112.92	2	115.79	2
Lognormal	149.32	3	152.19	3	116.33	3	119.20	3
Log-Logistic	148.35	2	151.22	2	118.03	4	120.89	4
Gamma	150.93	5	153.80	6	120.54	7	123.40	7
Gen. Gamma	151.06	6	155.36	7	110.20	1	114.50	1

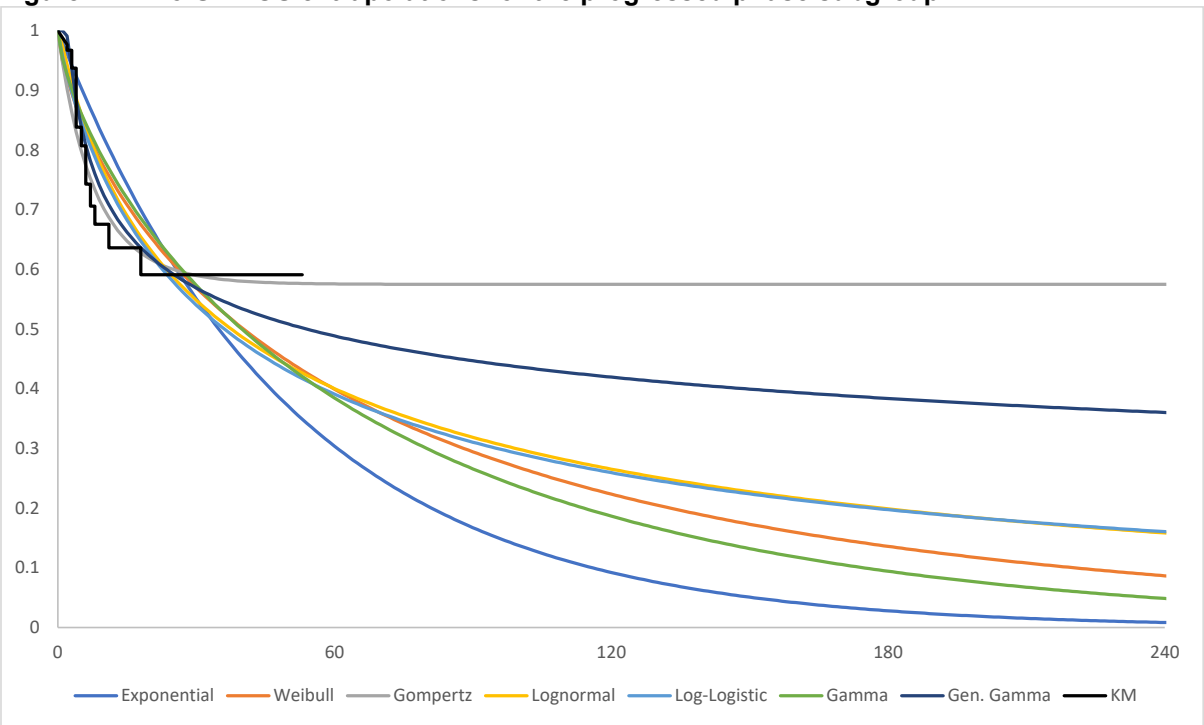
Abbreviations: AIC, Akaike's information criteria; BIC Bayesian information criteria; Gen, generalised; OS, overall survival; PD, progressed disease; RFS, relapse free survival; SCT, stem cell transplantation.

Figure 43: Allo-SCT RFS extrapolations for the progressed phase subgroup



Abbreviations: Allo-SCT, allogeneic stem cell transplantation; Gen, generalised; KM, Kaplan-Meier; RFS, relapse free survival.

Figure 44: Allo-SCT OS extrapolations for the progressed phase subgroup



Abbreviations: Allo-SCT, allogeneic stem cell transplantation; Gen, generalised; KM, Kaplan-Meier; RFS, relapse free survival.

Table 66: Survival estimates at 2, 5, and 10 years according to survival model selected

	Relapse free survival						
Years	**Exponential**	**Weibull**	**Gompertz**	**Lognormal**	**Log-Logistic**	**Gamma**	**Gen. Gamma**
2	36%	39%	38%	40%	37%	39%	39%
5	8%	17%	30%	24%	20%	15%	21%
10	1%	6%	29%	14%	12%	3%	11%
	Overall survival						
2	62%	62%	60%	60%	59%	63%	60%
5	30%	40%	58%	40%	39%	38%	49%
10	9%	22%	58%	27%	26%	19%	42%

Abbreviations: Gen, generalised.

In the progressed phase, for RFS the Gompertz distribution had the best fit on both the AIC and BIC criteria. Clinical opinion noted that most mortality would occur within the first year or two and that survival would plateau beyond that. On this basis, the lognormal curve was therefore considered most clinically plausible, as this was not as optimistic as the Gompertz distribution.

For the OS for the progressed disease subgroup, the generalised gamma had the best statistical fit. However clinical opinion considered the log-normal the most plausible, as again this had a plateau in keeping with what might be expected post SCT in clinical practice, but was more conservative than the Gompertz and generalised gamma.

Again, distribution selection for SCT (RFS or OS in either phase) made very little difference to the results, and are not presented in the sensitivity analysis.

B.3.3.5 Adverse events

Adverse events that occurred in at least 10% of patients in either arm were included from ASCEMBL, as well as any additional adverse events that occurred for the non-ASCEMBL comparators.

AE numbers were assessed during the safety period of ASCEMBL. AEs have not been extrapolated beyond the safety period and all costs and quality-adjusted life years (QALY) losses associated with AEs are assumed to occur in the first cycle of the model.

The AE inputs used in the asciminib and bosutinib arms of the model are presented in Table 67.

Table 67: Adverse events, asciminib and bosutinib

	Asciminib (%)		Bosutinib (%)	
Adverse event	**Grade 1 & 2**	**Grade 3 & 4**	**Grade 1 & 2**	**Grade 3 & 4**
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]	[redacted]	[redacted]
Muscoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Elevated bilirubin levels	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycemia	[redacted]	[redacted]	[redacted]	[redacted]

In the ponatinib arm of the model, adverse event frequencies were taken from the PACE trial and were based on grade 1&2 and 3&4 adverse events that occurred in at least 10% of patients (58).

AE frequencies for ponatinib are presented in Table 68.

Table 68: Adverse events, ponatinib

	Ponatinib	
Adverse event	**Grade 1 & 2**	**Grade 3 & 4**
Abdominal pain	35.93%	10.37%
Alanine aminotransferase increased	0.00%	0.00%
Anaemia	9.26%	10.37%
Arthralgia	30.37%	2.96%
Aspartate aminotransferase increased	0.00%	0.00%
Cough	0.00%	0.00%
Decreased appetite	0.00%	0.00%
Diarrhoea	19.26%	0.74%
Fatigue	27.78%	2.22%
Headache	39.63%	3.33%
Hypertension	22.96%	13.70%
Hypophosphataemia	0.00%	0.00%
Lipase increased	14.44%	12.59%
Nasopharyngitis	0.00%	0.00%
Nausea	28.52%	0.74%
Neutropenia	2.96%	16.67%
Neutrophil count decreased	0.00%	0.00%
Platelet count decreased	0.00%	0.00%
Rash	43.33%	3.70%
Thrombocytopenia	10.37%	35.19%
Vomiting	17.04%	1.48%
Constipation	38.89%	2.59%
Dry skin	38.89%	3.33%
Pyrexia	24.81%	1.11%
Myalgia	22.96%	1.11%
Pain in extremity	21.11%	2.96%

In the nilotinib arm of the model, adverse event frequencies were taken from Giles 2010 and were based on all reported grade 1&2 and 3&4 adverse events (114). AE frequencies for nilotinib are presented in Table 69.

Table 69: Adverse events, nilotinib

	Nilotinib	
Adverse event	**Grade 1 & 2**	**Grade 3 & 4**
Alanine aminotransferase increased	–	8%
Fatigue	10%	–
Headache	13%	–
Hypophosphataemia	–	13%
Lipase increased	–	25%
Nausea	15%	–
Neutropenia	–	23%
Platelet count decreased	28%	–
Rash	28%	–
Thrombocytopenia	–	28%
Elevated bilirubin levels	–	8%
Hypokalemia	–	5%
Hyperglycemia	–	13%
Hypermagnesemia	–	11%
Hypocalcemia	–	10%
Cardiac events	–	15.38%

In the dasatinib arm of the model, adverse event frequencies were taken from Tan 2019, as these were not reported in Rossi 2013, and were based on all reported grade 1&2 and 3&4 adverse events (115). AE frequencies for dasatinib are presented in Table 70.

Table 70: Adverse events, dasatinib

	Nilotinib	
Adverse event	**Grade 1 & 2**	**Grade 3 & 4**
Abdominal pain	29.2%	–
Diarrhoea	16.7%	–
Fatigue	45.8%	–
Headache	37.5%	–
Nausea	29.2%	–
Rash	16.7%	–
Muscoskeletal pain	29.2%	–
Pleural effusion	8.3%	–
Superficial edema	12.5%	–
Haemotological AEs	20.8%	58.3%

Abbreviations: AE, adverse events.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was assessed in ASCEMBL using the EQ-5D-5L. EQ-5D-3L utilities were generated from EQ-5D-5L responses using the crosswalk calculator presented by van Hout (2012) (139). This is in line with the NICE reference case and the NICE position statement on the use of the EQ-5D-5L (141).

Data were collected at screening, and then at each of the on-treatment visits, in line with the protocol (Week 4, 8, 12, 16, 24, 36, 48, and 96 [Section B.2.3.1.5.1]). The data here relate to the latest available cut-off of the week 48 data.

The health states of interest investigated included:

- By treatment
- Disutility relative to death
- On/off treatment
- Overall
- Pre/post progression.

Utility values by health state were estimated from a MMRM and a GLM, accounting for multiple assessments per patients, and including baseline EQ-5D value as a covariate, in the EQ-5D analysis population (patients with baseline and post-baseline EQ-5D data).

In all randomised patients ([redacted] had EQ-5D responses ([redacted] in the asciminib arm and [redacted] in the bosutinib arm. Across the [redacted] patients, in total there are [redacted] utility assessments; with [redacted] assessments at baseline and [redacted] 146 assessments post-baseline. There were [redacted] patients with both baseline and post-baseline assessments [redacted] (the EQ-5D analysis population) and a total of [redacted] post-baseline assessments were included in the modelling of utilities estimation.

Considering on/off treatment status in the EQ-5D analysis population, only a total of [redacted] had some EQ-5D assessments in the off-treatment phase; there were a total of [redacted] EQ-5D assessments in the off-treatment phase [redacted]% of the post-baseline assessments). There were [redacted] EQ-5D assessments post-progression [redacted] patients with progression). There were [redacted] patients who died, of these patients there were [redacted] EQ-5D assessments within [redacted] of death [redacted] within 28 days of death).

Analysis of data was undertaken by treatment allocation, by treatment status (on treatment or discontinued treatment), and by both treatment allocation and status. Given the low number of assessments in some health states, no health state utilities were estimated for pre/post progression and the inclusion of a disutility for death in the statistical models did not significantly impact the estimates. The use of a MMRM approach or a GLM approach for modelling utilities produced very similar results. In the models, the terms for intercept and baseline were significant, but no other fixed effects were significant (treatment arm, on/off treatment, disutility for death). Parameter estimates from MMRM models are reported in Table 72. Parameter estimates from the GLM models are reported in Table 73.

The completion of the questionnaire at the scheduled visits can be seen below in Table 71.

Table 71: Mean EQ-5D-3L tariff (after crosswalk) by visit (UK)

	Asciminib (N=157)		Bosutinib (N=76)	
Week	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
96	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation; UK, United Kingdom.

Table 72: Mean EQ-5D-3L tariff (after crosswalk): Health State Utility Estimates: Overall and by treatment (MMRM Model)

Specification	Health State	Parameter	Standard error	95% confidence interval
Treatment allocation and treatment status	On-treatment: Asciminib	[redacted]	[redacted]	[redacted]
	Off-treatment: Asciminib	[redacted]	[redacted]	[redacted]
	On-treatment: Bosutinib	[redacted]	[redacted]	[redacted]
	Off-treatment: Bosutinib	[redacted]	[redacted]	[redacted]
Treatment status	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]
Treatment allocation	Asciminib	[redacted]	[redacted]	[redacted]
	Bosutinib	[redacted]	[redacted]	[redacted]

Source: MMRM Model 1, GLM model 1
Abbreviations: MMRM, mixed measures repeated method.

Table 73: Mean EQ-5D-3L tariff (after crosswalk): Health State Utility Estimates: On/off treatment (GLM Model)

Specification	Health State	Parameter	Standard error	95% confidence interval
Treatment allocation and treatment status	On-treatment: Asciminib	[redacted]	[redacted]	[redacted]
	Off-treatment: Asciminib	[redacted]	[redacted]	[redacted]
	On-treatment: Bosutinib	[redacted]	[redacted]	[redacted]
	Off-treatment: Bosutinib	[redacted]	[redacted]	[redacted]
Treatment status	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]
Treatment allocation	Asciminib	[redacted]	[redacted]	[redacted]
	Bosutinib	[redacted]	[redacted]	[redacted]

Source: MMRM Model 2, GLM model 2
Abbreviations: GLM, generalised linear model.

Overall utility values were similar between treatment arms, and were slightly lower when off-treatment, although this should be interpreted with caution because of the

low numbers of observations in patients off treatment within the ASCEMBL trial at the latest data cut-off available.

The results of analysis with the GLM model and MMRM model were of no substantial difference. Utilities from the MMRM model were selected as this model is commonly used for analysis of repeated observations on QoL.

B.3.4.2 Mapping

EQ-5D-5L data collected within the trial were mapped to EQ-5D-3L responses to generate utility values, as described in Section B.3.4.1.

B.3.4.3 Health-related quality-of-life studies

A SLR to identify relevant HRQoL (utilities) studies was conducted. See Appendix H for full details of the methods of the SLR and the identified studies. The SLR identified 10 studies from 11 publications. An overview of the study details and results from included utility studies, together with the quality assessments, is presented in Appendix H.

B.3.4.4 Adverse events

The impact of AEs on HRQoL is captured as a one-off QALY loss in the first cycle of the model. Disutilities were sourced from the literature representing the overall impact of the AE in QALYs. These were combined with the AE frequencies from the relevant studies for each comparator (see Section B.3.3.5), to determine the QALY loss from AEs for each treatment. Where available, AE disutilities were taken directly from other TAs, or published literature. In the absence of available data, the QALY loss for an AE was assumed to be 0.05 in line with assumptions applied in TA426 (156). TA451 (ponatinib), and TA401 (bosutinib) did not directly model individual adverse event disutilities, as the former assumed the same decrement for all disutilities, and the latter assumed that adverse events were already captured through the treatment utilities.

The AE disutilities used in the model are presented in Table 74.

Table 74: AE disutilities

AE	Disutility	Source
Abdominal pain	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Alanine aminotransferase increased	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Anaemia	–0.09	Beusterien 2010 (166), Wehler 2018 (167)
Arthralgia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Aspartate aminotransferase increased	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Cough	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Decreased appetite	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Diarrhoea	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Fatigue	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Headache	–0.18	Stein 2017 (168), Wehler 2018 (167)
Hypertension	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Hypophosphatemia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Lipase increased	–0.07	Nafees 2008 (169)
Nasopharyngitis	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Nausea	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Neutropenia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Neutrophil count decreased	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Platelet count decreased	–0.02	ICER 2017,(170) Wehler 2018(167)
Rash	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Thrombocytopenia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Vomiting	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Constipation	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Dry skin	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Pyrexia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML
Myalgia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML(156)
Pain in extremity	–0.05	Nafees 2008 (169)
Pruritis	–0.09	Nafees 2008 (169)

AE	Disutility	Source
Muscoskeletal pain	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Pleural effusion	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Elevated bilirubin levels	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Hypokalaemia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Hyperglycaemia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Hypermagnesemia	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Hypocalcaemia	–0.06	Stein 2017(168), Wehler 2018 (167)
Something Cardiac events	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)
Superficial oedema	–0.09	Nafees 2008 (169)
Haematological AEs	–0.05	Assumption, consistent with TA426 NICE submission for dasatanib for CML (156)

Abbreviations: AE, adverse event; CML, chronic myeloid leukaemia; NICE, National Institute of Health and Care Excellence.

The total QALY loss for each treatment arm in the model is presented in Table 75.

Table 75: Total QALY loss

Treatment	QALY loss
Asciminib	–0.0345
Bosutinib	–0.0453
Ponatinib	–0.0722
Nilotinib	–0.0807
Dasatinib	–0.0292

Abbreviations: QALY, quality-adjusted life year.

B.3.4.5 Health-related quality-of-life data in the cost-effectiveness analysis

SLRs of economic evaluations and HRQoL studies for CML were conducted. The HRQoL SLR identified Szabo et al (160) which provided health state utility values for responding to treatment and not responding to treatment separately for CML-CP, AP, and BP. These utility values were derived for Australia, the UK, the US and Canada; UK values were selected. Another UK source was also identified from the SLR (Guest et al 2012 (171), Guest et al 2014 (172)) however these studies presented utility values by type of response (hematologic, cytogenetic, and molecular) rather than disease phase.

Data from the ASCEMBL trial was used to determine HSUVs for the CML-CP states in the model. The base case applied HSUV to the CML-CP states according to whether patients were on or off treatment (and therefore no differentiation by treatment). In sensitivity analyses, utilities in the CP health states by arm were also used (so the same value across on or off treatment but differing by arm), as well as values from ASCEMBL that varied by treatment status and by arm, and data from Szabo 2010 (with CML-CP on treatment utility coming from 'CML-CP responding to treatment' group, and utility for CML-CP off treatment coming from the 'CML-CP not responding to treatment' group in Szabo 2010). A summary of utility scenarios is presented in Table 77.

The HSUV for the AP and BP states were calculated as the mean of the respective values for patients responding to treatment and patients not responding to treatment.

The health state utility values for the SCT sub-models are taken from the NICE submission for ponatinib (TA451) (157).

Health state utility values used in the model are summarised in Table 76.

Table 76: Health state utility values used in the model

Health state	Value	95% CI	Source
CML-CP on 3L treatment	[redacted]	[redacted]	ASCEMBL trial (12)
CML-CP off 3L treatment	[redacted]	[redacted]	
CML-AP	0.66	0.61, 0.7	Szabo et al., 2016 (160).
CML-BP	0.43	0.40, 0.47	
SCT in CP – relapse free	0.71	0.57, 0.85	NICE TA 451 – Ponatinib (157).
SCT in CP – relapsed	0.59	0.47, 0.70	
SCT in PD – relapse free	0.71	0.57, 0.85	
SCT in PD – relapsed	0.59	0.47, 0.70	

Abbreviations: 3L, third-line treatment; AP, advanced phase; bp, blast phase; CI, confidence interval; CP, chronic phase; SCT, stem cell transplant

Table 77: Health state utility values tested in scenarios

Scenario	Health state	Asciminib	Comparator	Source
ASCEMBL data by arm	CML-CP on 3L treatment	[redacted]	[redacted]	ASCEMBL trial (12)
	CML-CP off 3L treatment			
ASCEMBL data by arm & treatment status	CML-CP on 3L treatment	[redacted]	[redacted]	
	CML-CP off 3L treatment	[redacted]	[redacted]	
Szabo 2010	CML-CP on 3L treatment	0.9100		Szabo et al., 2016 (160).
	CML-CP off 3L treatment	0.7300		

Abbreviations: 3L, third-line treatment; AP, advanced phase; bp, blast phase; CI, confidence interval; CP, chronic phase; SCT, stem cell transplant

B.3.4.6 General population utility

Age-specific utility multipliers are derived based on the relationship between age and utility values observed in the general population. The following relationship is presented by Ara and Brazier: (173)

$$General\ population\ EQ-5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.000033 * age^2$$

HSUVs identified in the published literature are assumed to apply to each relevant health state at the start of the model; for every year subsequent to this, the reduction in HRQoL in each cycle (based on the current age and starting age) could then be calculated and applied to the HSUVs according to disease state using an additive model. The baseline starting age of 51 and the proportion of women (51.5%) in the model was taken from the mean values for the patients in the ASCEMBL trial.

B.3.4.7 Summary of utility values for cost-effectiveness analysis

Table 78: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
CML-CP on 3L treatment	[redacted]	[redacted]	B.3.4.5	Derived from ASCEMBL (12)
CML-CP off 3L treatment	[redacted]	[redacted]	B.3.4.5	
CML-AP	0.66	0.61, 0.7	B.3.4.5	Derived from literature identified from SLR (Szabo 2010)
CML-BP	0.43	0.40, 0.47	B.3.4.5	
SCT in CP – relapse free	0.71	0.57, 0.85	B.3.4.5	Derived from TA451
SCT in CP – relapsed	0.59	0.47, 0.70	B.3.4.5	
SCT in PD – relapse free	0.71	0.57, 0.85	B.3.4.5	
SCT in PD – relapsed	0.59	0.47, 0.70	B.3.4.5	

Abbreviations: AP, advanced phase; AR, adverse reaction; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; HS, health state; PD, progressed disease; SCT, stem cell transplant; SLR, systematic literature review.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Evidence from published studies on the economic burden in patients with CML was identified and summarised using a targeted literature review. The results were predominantly US based, and have not been included as an appendix as were not utilised for this submission, but are available upon request.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 *Drug acquisition costs*

The acquisition costs for each comparator are presented in Table 80. Note costs for drugs included only as subsequent treatments are also included in Table 80. All costs were sourced from eMIT if available, or from the BNF (174). All treatments are oral and costs reflect dose information derived from the BNF. Where formulations with differing doses were available, the formulation closest to the recommended dose, but not above it, was selected.

Table 79: Drug acquisition costs

Drug	List price	mg per tablet	Tablets per pack	Cost source
Asciminib	[redacted]	40mg	60	
Bosutinib	£3,436.67	500mg	28	BNF (drug tariff price)
Ponatinib	£5,050.00	45mg	30	BNF (NHS indicative price)
Dasatinib	£2,504.96	100mg	30	BNF (drug tariff price)
Dasatinib	£2,504.96	140mg	30	BNF (drug tariff price)
Nilotinib	£2,432.85	200mg	112	BNF (drug tariff price)
Imatinib	£55.13	100mg	60	eMIT
Imatinib	£112.90	400mg	30	eMIT

Abbreviations: BNF, British National Formulary; eMIT, pharmaceutical electronic market information tool; mg, milligram.
BNF drug tariff price used where available, and NHS indicative price if not. Only imatinib available in eMIT

For some drugs, the recommended dose varies depending on the disease phase (chronic or progressed). This was the case for dasatinib, and imatinib. The costs per day for each drug and by disease phase can be seen in Table 80.

Note that a proportion of patients are assumed to receive imatinib as a fourth-line or subsequent treatment, reflecting real world data, although it is not evaluated as a treatment comparator for asciminib (in line with the final scope).

Table 80: Daily cost of drugs

Drug	Daily dose (Mg/MU) - CP	Daily dose (Mg/MU) - Progressed Disease	Daily cost – CP	Daily cost – PD
Asciminib	80.00		[redacted]	
Bosutinib	500.00		£122.74	
Ponatinib	45.00		£168.33	
Dasatinib	100.00	–	£83.50	–
Dasatinib	–	140.00	–	£83.50
Nilotinib	400.00		£43.44	
Imatinib	400.00	–	£3.76	–
Imatinib	–	600.00	–	£5.60

Abbreviations: CP, chronic phase; PD, progressed disease

No drug administration costs are assumed as all the drugs are taken orally. Drug costs are applied as monthly per model cycle.

B.3.5.1.2 *Relative dose intensity*

Relative dose intensity (RDI) is taken from the ASCEMBL trial from the 48 week data cut, after 30 days, for asciminib and bosutinib. For the other comparators the RDI is assumed to be 100%. See Table 81 for more detail.

Table 81: Relative dose intensity (RDI)

Drug	RDI	Source
Asciminib	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]
Ponatinib	100%	Assumption
Dasatinib	100%	Assumption
Nilotinib	100%	Assumption

B.3.5.1.3 *Drug monitoring costs*

Resource use associated with treatment of CML was not collected as part of the ASCEMBL trial. Typical resource use associated with monitoring patients were specified following discussion with a clinician (163). Unit costs for monitoring activities were derived from NHS reference costs(175). Table 82 reports resource use and unit costs applied per visit in the analysis for patients on third-line treatment and Table 83 reports total monitoring costs.

Following clinical advice (163), the model assumed that an outpatient visit and the associated tests were undertaken at the following timepoints after initiation of third-line treatment: 2 weeks, 4 weeks, 7 weeks, 10 weeks, 14 weeks, 18 weeks, 26 weeks, 38 weeks, 50 weeks, and every three months thereafter until discontinuation of third-line therapy.

Table 82: Monitoring costs

Item	Resource per visit (all treatments)	Unit cost	Cost source
Blood count	1	£1.81	NHS ref costs 2018/19, DAPS03 Integrated blood services
Electrolytes	1	£1.20	NHS ref costs 2018/19, DAPS04 Clinical biochemistry
Liver function	1	£3.55	NHS ref costs 2018/19, DAPS09 Other
Serum Amylase	1	£3.55	NHS ref costs 2018/19, DAPS09 Other
Renal Function	1	£1.20	NHS ref costs 2018/19, DAPS04 Clinical biochemistry
Outpatient visit	1	£173.10	NHS Ref costs, WF01A non-admitted face-to-face attendance, follow-up, medical oncology

Abbreviations: ref, reference.

Table 83: Total monitoring costs

	All treatments
Total monitoring cost	£184.41

B.3.5.1.4 *Subsequent therapies*

Clinical advice indicates that failure of a TKI usually leads to treatment with a different TKI, with patients potentially cycling through TKIs and being retreated with an earlier failed therapy if it achieved at least a partial response. Hence patients are expected to be treated with a TKI throughout their disease, and potentially with a number of different therapies. In the model, patients are assumed to commence therapy with a fourth-line TKI, either imatinib, bosutinib, ponatinib, nilotinib or dasatinib following discontinuation of third-line treatment, and to continue treatment throughout the time in CP state. The relative proportion of patients on each TKI was informed by data from HMRN (14), with modification to the proportion of patients on ponatinib following advice from the clinical expert and reflecting the relatively recent availability of ponatinib as a treatment option(68). Proportions were not varied according to the choice of third-line therapy. The proportions represent the expected distribution of therapies for patients who have progressed beyond third-line treatment (i.e. fourth-line and further). Drug acquisition costs per day were assumed to be the same regardless of whether the TKI was used in third-line or fourth-line treatment.

RDI for all fourth line therapies were assumed to be 100%. Patients are treated until progression to the AP phase.

Patients progressing to AP and BP are also treated with TKIs. In addition, and as confirmed with a clinical expert (68), FLAG-Ida (made up of fludarabine, cytarabine, filgrastim and idarubicin) is also used. The costs for this regimen can be seen in Table 84, with component costs based on the BNF (174) and eMIT (176). Doses were based on guidance from an NHS trust (177). Cost per week is based on calculating the number of doses needed per week, and taking into account the first dose will be provided using an administration cost involving a prolonged infusion (£352.24) and the subsequent doses will be given based on administration costs of a subsequent infusion (£253.77), both from NHS reference costs 2019/20 (178). The cost of 2 courses is assumed (i.e. 2 weeks) and applied to the relevant proportion of patients starting at transition to AP, and at transition to BP.

Table 84: FLAG-Ida costs

Drug	List price (£)	mg/MU per pack	Daily dose (Mg/MU)	Days dosed per cycle	Daily cost (£)	Cost for 1 week (£)
Filgrastim	52.70	0.06	0.033	7.00	52.70	4099.30
Fludarabine	99.88	50.00	53.70	5.00	199.76	
Cytarabine	7.05	2,000.00	3580.00	5.00	14.10	
Idarubicin	262.08	15.00	14.32	3.00	262.08	

Abbreviations: FLAG-IDA, fludarabine, cytarabine, filgrastim and idarubicin.

The proportion of different therapies used for patients in AP and in BP was determined from advice from a clinical expert (163). The proportions being treated in BP add to more than 100% because FLAG-Ida can be used in addition to ponatinib.

Following successful allo-SCT, clinical advice indicates that patients are not treated with TKIs beyond the first year after transplantation. Hence no treatment costs were included for successful allo-SCT (relapse free). Relapse of allo-SCT would lead to treatment, and the proportion of different therapies was estimated by a clinical expert (163). The proportion of patients on each TKI in fourth-line treatment, following disease progression, and following allo-SCT is shown in Table 85.

Table 85: Subsequent treatment assumptions across health states

Health state	Proportion						Weighted cost per day
	Nilotinib	Dasatinib	Ponatinib	Imatinib	Bosutinib	FLAG-Ida	
Chronic phase off-treatment	21%	18%	25%	5%	30%	0%	£103.64
AP	10%	30%	30%	0%	20%	10%	£104.44[1]
BP	0%	20%	80%	0%	0%	50%	£151.37[1]
Allo-SCT post relapse	25%	25%	25%	0%	25%	0%	£104.50

Abbreviations: CP, chronic phase, PD, progressed disease; SCT, stem cell transplant.
1. Note that these do not include the cost of FLAG-Ida, as this is applied within the model engines to new patients on subsequent treatments only for two courses of 7 days.

B.3.5.2 Health-state unit costs and resource use

Resource use for disease management was adapted from data utilised in TA451 (ponatinib). In TA451 the manufacturer conducted a survey of twelve leading clinicians to quantify resource use according to disease phase. Resource use in CP was further classified according to cytogenic response. These data were considered the most up-to-date and relevant data available on resource use for managing CML. The data were scrutinised by a clinical expert and changes applied following advice to reflect recent changes in clinical practice (163).

Resource use for patients on third-line treatment was based on data tabulated in TA451 for patients in CML with a complete cytogenic response (table 5-23). Resource use in the CP off treatment state was based on data tabulated in TA451 for patients in CP without a complete cytogenic response (table 5-23). Data in TA451 did not distinguish AP and BP, except for days in hospital. The relevant data were assumed to apply to patients in both AP and BP.

Detailed data on resource use following allo-SCT were unavailable. Following clinical advice, resource use was limited to an annual check-up with a haematologist following successful allo-SCT (relapse-free). This assumption on resource use reflects the management of patients over the longer term following successful allo-SCT. In the initial period following allo-SCT, clinical contact is expected to be more frequent. For patients relapsing after allo-SCT, resource use was assumed to be the same as for patients in AP.

The health state resource use per 3 months can be seen in Table 86.

The costs associated to each health care resource use can be seen in Table 87 and the total costs by health state can be seen in Table 88.

Table 86: Health state resource use

	Resource use per 3 months							
	CP - CML				Progressed disease			
	On 3L treatment	Off 3L treatment	Post allo-SCT - Relapse-free	Post allo-SCT - Relapsed	AP	BP	Post allo-SCT - Relapse-free	Post allo-SCT - Relapsed
Outpatient visits nurse led	0.29	0.38	0.00	0.51	0.51	0.51	0.00	0.51
Outpatient visits haematologist led	0.93	1.72	0.25	3.63	3.63	3.63	0.25	3.63
Hospital days	0.00	0.00	0.00	2.13	2.13	26.64	0.00	2.13
Full blood count	1.13	1.97	0.00	4.38	4.38	4.38	0.00	4.38
Blood transfusion	0.01	0.01	0.00	1.98	1.98	1.98	0.00	1.98
Bone marrow aspiration	0.03	0.30	0.00	0.30	0.30	0.30	0.00	0.30
FISH	0.22	0.56	0.00	0.13	0.13	0.13	0.00	0.13
PCR	0.79	1.31	0.00	1.68	1.68	1.68	0.00	1.68
Cytochemistry analysis	0.00	0.05	0.00	0.12	0.12	0.12	0.00	0.12
Blood film exam	0.50	1.09	0.00	2.19	2.19	2.19	0.00	2.19
Blood chemistry	1.13	1.88	0.00	3.15	3.15	3.15	0.00	3.15
Kinase domain mutation	0.00	0.00	0.00	0.5	0.5	0.5	0.00	0.5
Platelet transfusion	0.00	0.00	0.00	0.30	0.30	0.30	0.00	0.30

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; FISH, Fluorescence In-situ hybridisation; PCR, polymerase chain reaction; SCT, stem cell transplant

Table 87: Resource use costs

	Unit cost (£)	Source
Outpatient visits nurse led	173.10	NHS Reference costs 2019/20: WF01A non-admitted face-to-face attendance, follow-up, medical oncology
Outpatient visits haematologist led	171.18	NHS Reference costs 2019/20: non-admitted, consultant-led, face-to-face attendance, follow-up, clinical haematology
Hospital day	576.61	NHS Reference costs 2019/20: weighted average of SA32A to D Chronic Lymphocytic Leukaemia, including Related Disorders. Non-elective short stay
Hospice day	196.22	NHS Reference costs 2019/20: weighted mean of SD01A, Inpatient Specialist Palliative Care, 19 years and over and SD03A hospital (inpatient) specialist palliative care support, 19 years and over
Emergency department visits	174.05	NHS Reference costs 2019/20: weighted average of VB01Z, VB02Z, VB03Z,.. …VB09Z for non-admitted episodes of types 01 to 04
Full blood count	2.53	NHS Reference costs 2019/20: DAPS05 haematology
Blood transfusion	199.45	NHS Blood and transplant BC001 standard red cells plus administration costs from Stokes et al. 2018 (179, 182)
Bone marrow aspiration	563.62	NHS Reference costs 2019/20: SA33Z diagnostic bone marrow extraction (total)
FISH	120	TA529 (All Wales laboratory cost) (180)
PCR	22.70	Szczepura et al. 2006† (181)
Cytochemistry analysis	3.18	NHS Reference costs 2019/20: DAPS01 Cytology
Blood film exam	1.81	NHS Reference costs 2019/20: DAPS03 Integrated blood services
Blood chemistry	1.20	NHS Reference costs 2019/20: DAPS04 Clinical biochemistry
Kinase domain mutation	512.15	https://privatebloodtests.co.uk/products/private-blood-test-for-bcr-abl-in-blood
Platelet transfusion	286.22	NHS Blood and transplant BC0044 platelets, apheresis plus administration costs from Stokes et al. 2018 (179, 182)

Abbreviations: FISH, Fluorescence in situ hybridisation; PCR, polymerase chain reaction.

†Cost of quantitative PCR with automated extraction assuming 2nd round and 1 of batch of 5, £15.17. Price year not reported; assumed to be 2002/3 and inflated to 2019/20.

Table 88: Total health state costs per cycle

	Health state	Unit cost per month (£)
CML-CP	On 3L treatment	277.75
	Off 3L treatment	637.60
	Post allo-SCT - Relapse-free	42.80
	Post allo-SCT - Relapsed	2,916.72
Progressed disease	AP	2,916.72
	BP	17,049.44
	Post allo-SCT - Relapse-free	42.80
	Post allo-SCT - Relapsed	2,916.72

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase, PD, progressed disease; SCT, stem cell transplant

B.3.5.3 Adverse event unit costs and resource use

Costs of AEs were sourced from NHS reference costs 2019/20 (178). Table 89 and Table 90 present the unit costs of AEs and total costs of AEs by treatment, respectively.

AE costs were applied as a one-off cost in the first cycle of the model. The differences in the costs applied to each comparator in the model are driven primarily by differences in AE frequencies.

Table 89: Adverse event costs

Adverse event	Unit cost	NHS reference costs source
Abdominal pain	£649.20	FD05A and B, abdominal pain with and without interventions, total
Alanine aminotransferase increased	£1,755.63	Weighted average of GC17A to K, Non-Malignant, Hepatobiliary or Pancreatic Disorders, with or without Interventions, total
Anaemia	£1,162.71	Weighted average of SA03G and SA03H haemolytic anaemia CC0-2, CC3+, total
Arthralgia	£1059.61	Weighted average of HD26D to G, musculoskeletal signs and symptoms, total
Aspartate aminotransferase increased	£1,755.63	Weighted average of GC17A to K, Non-Malignant, Hepatobiliary or Pancreatic Disorders, with or without Interventions, total
Cough	£684.35	Weighted average of DZ19H, J, K, L, M, N, Other Respiratory Disorders with Single Intervention, total
Decreased appetite	£1,577.78	Weighted average of FD04A to E, Nutritional Disorders with or without Interventions, total
Diarrhoea	£1,446.42	Weighted average of FD10A to M, Non-Malignant Gastrointestinal Tract Disorders , total
Fatigue	£205.10	Weighted average of VB01Z, VB02Z, VB03Z, VB04Z… …VB09Z, Emergency medicine, various categories of investigation and treatment, total
Headache	£643.40	Weighted average of AA31C to E, headache, migraine or cerebrospinal fluid leak, total
Hypertension	£639.00	EB04Z hypertension
Hypophosphataemia	£1,330.00	Weighted average of KC05G to N, Fluid or Electrolyte Disorders with or without interventions, total
Lipase increased	£1,755.63	Weighted average of GC17A to K, Non-Malignant, Hepatobiliary or Pancreatic Disorders, with or without Interventions, total
Nasopharyngitis	£684.35	Weighted average of DZ19H to N, other respiratory disorders with and without interventions, total
Nausea	£205.10	Weighted average of VB01Z, VB02Z, VB03Z, VB04Z… …VB09Z, Emergency medicine, various categories of investigation and treatment, total
Neutropenia	£1,082.77	Weighted average of SA08G, H and J, other haematological or splenic disorders, total
Neutrophil count decreased	£1,082.77	Weighted average of SA08G, H and J, other haematological or splenic disorders, total
Platelet count decreased	£770.57	Weighted average of SA12G, H, J and K, thrombocytopaenia, total
Rash	£1,479.36	Weighted average of JD07A to K, skin disorders with or without interventions, total
Thrombocytopenia	£770.57	Weighted average of SA12G, H, J and K, thrombocytopaenia, total
Vomiting	£205.10	Weighted average of VB01Z, VB02Z, VB03Z, VB04Z… …VB09Z, Emergency medicine, various categories of investigation and treatment, total
Constipation	£690.87	Weighted average of FF34A to C, Major Large Intestine Procedures, 19 years and over, FF36Z, Intermediate Large Intestine Procedures, 19 years and over, total
Dry skin	£1,479.36	Weighted average of JD07A to K, skin disorders with or without interventions, total
Pyrexia	£1,002.21	NHS reference costs, weighted average of WJ07A to D, fever of unknown origin with or without interventions, total
Myalgia	£1,000.07	Weighted average of WH08A and B, unspecified pain, total

Adverse event	Unit cost	NHS reference costs source
Pain in extremity	£1,059.61	Weighted average of HD26D to G, musculoskeletal signs and symptoms, total
Pruritis	£1,479.36	Weighted average of JD07A to K, skin disorders with or without interventions, total
Muscoskeletal pain	£1,059.61	Weighted average of HD26D to G, musculoskeletal signs and symptoms, total
Pleural effusion	£1,812.64	Weighted average of DZ16H to R, pleural effusion with or without interventions, total
Elevated bilirubin levels	£1,755.63	Weighted average of GC17A to K, Non-Malignant, Hepatobiliary or Pancreatic Disorders, with or without Interventions, total
Hypokalemia	£1,330.00	Weighted average of KC05G to N, Fluid or Electrolyte Disorders with or without interventions, total
Hyperglycemia	£1,169.86	Weighted average of KB02H, J, K, Diabetes with Hyperglycaemic Disorders, total
Hypermagnesemia	£1,330.00	Weighted average of KC05G to N, Fluid or Electrolyte Disorders with or without interventions, total
Hypocalcemia	£1,330.00	Weighted average of KC05G to N, Fluid or Electrolyte Disorders with or without interventions, total
Cardiac events	£1,624.73	Weighted average of EB03A to E, Heart Failure or Shock, EB05A to C, Cardiac Arrest, EB08A to E, Syncope or Collapse, EB10A to E, Actual or Suspected Myocardial Infarction, total
Superficial edema	£589.58	Weighted average of WH10A and B, unspecified oedema, total
Haemotological adverse events	£1,082.77	Weighted average of SA08G, H and J, other haematological or splenic disorders, total

Source: NHS reference costs 2019-2020 (178).

Table 90: Adverse event costs by treatment

Treatment	AE cost
Asciminib	£613.72
Bosutinib	£1,129.81
Ponatinib	£1,153.24
Nilotinib	£2,105.35
Dasatinib	£631.25

Abbreviations: AE, adverse event.

B.3.5.4 Allo-SCT costs

Costs of an allo-SCT were taken from a costing study undertaken by NHS blood and transplant report in 2014 on unrelated donor stem cell transplantation in the UK (183). This report also formed the basis of the cost of allo-SCT in the TA451 (ponatinib) (157).

Resource use captured in the study included: transplantation unit personnel, the transplantation, and follow up costs up to 24 months. This led to a total cost of £98,178 which was inflated to 2019/2020 prices generating a cost of transplantation of £109,279.

Following advice from a clinician (163), additional costs were included for patients undergoing SCT after transition to AP or after transition to BP. It was assumed that prior to allo-SCT, patients would require a month of myeloablative therapy to stabilise their condition. For patients in BP, two months of myeloablative therapy were assumed. Each month of myeloablative therapy was costed on the basis of a 30 day inpatient stay assuming a cost of each inpatient day of £576.61 (Table 87).

B.3.5.5 Miscellaneous unit costs and resource use

A cost upon death was assigned in the model. Data from TA451 was used for the resource use associated with terminal care, based on: the number of days in hospital as an inpatient; the proportion of patients treated in hospital; the number of days in a hospice, and; the proportion treated in a hospice. These data were based on the UK clinical expert survey undertaken for TA451. The number of days and proportions for hospital and hospice were multiplied by the cost per day of being in a hospital and hospice (as reported in Table 87).

The total cost of terminal care can be seen in Table 91.

Table 91: Cost of terminal care

Resource	Input	Cost per day
Inpatient stay, days	21.5	£576.61
Patients treated in hospital, %	51.5%	
Hospice stay, days	17.4	£196.22
Patients treated in hospice, %	23.1%	
Total cost of terminal care	£7,173.20	

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 92: Summary of variables in economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline characteristics			
Mean age	51	NA	B.3.2.1
% female	0.515	NA	B.3.2.1
OS/TTD/Progression data			
Mean overall survival from discontinuation of 3L treatment – asciminib arm (years)	7.0	Not varied	B.3.2.2
Mean overall survival from discontinuation of 3L treatment – bosutinib arm(years)	7.0	Not varied	B.3.2.2
Median treatment duration – bosutinib (months)	[redacted]		
Median treatment duration – ponatinib (months)	[redacted]	[redacted]	B.3.3.1.2.1
Median treatment duration – nilotinib (months)	11	se 0.753 (Gamma distribution)	B.3.3.1.2.1
Median treatment duration – dasatinib (months)	14	se 1.029 (Gamma distribution)	B.3.3.1.2.1
Average time in AP phase (months)	10	se 1.02 (Gamma distribution)	B.3.2.2
Average time in BP phase (months)	6	se 0.61 (Gamma distribution)	B.3.2.2
SCT assumptions			
% of patients who receive SCT on discontinuation of 3L treatment	[redacted]	[redacted]	B.3.3.4.1
% of patients who receive SCT on progression to accelerated phase	[redacted]	[redacted]	B.3.3.4.1
% of patients who receive SCT on progression to blast crisis phase	[redacted]	[redacted]	B.3.3.4.1
Adverse events grade 1/2			
Asciminib - Abdominal pain	[redacted]	[redacted]	B.3.3.5
Asciminib - Alanine aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Asciminib - Anaemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Arthralgia	[redacted]	[redacted]	B.3.3.5
Asciminib - Aspartate aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Asciminib - Cough	[redacted]	[redacted]	B.3.3.5
Asciminib - Decreased appetite	[redacted]	[redacted]	B.3.3.5
Asciminib - Diarrhoea	[redacted]	[redacted]	B.3.3.5
Asciminib - Fatigue	[redacted]	[redacted]	B.3.3.5
Asciminib - Headache	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypertension	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypophosphataemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Lipase increased	[redacted]	[redacted]	B.3.3.5
Asciminib - Nasopharyngitis	[redacted]	[redacted]	B.3.3.5
Asciminib - Nausea	[redacted]	[redacted]	B.3.3.5
Asciminib - Neutropenia	[redacted]	[redacted]	B.3.3.5
Asciminib - Neutrophil count decreased	[redacted]	[redacted]	B.3.3.5
Asciminib - Platelet count decreased	[redacted]	[redacted]	B.3.3.5
Asciminib - Rash	[redacted]	[redacted]	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Asciminib - Thrombocytopenia	[redacted]	[redacted]	B.3.3.5
Asciminib - Vomiting	[redacted]	[redacted]	B.3.3.5
Asciminib - Constipation	[redacted]	[redacted]	B.3.3.5
Asciminib - Dry skin	[redacted]	[redacted]	B.3.3.5
Asciminib - Pyrexia	[redacted]	[redacted]	B.3.3.5
Asciminib - Myalgia	[redacted]	[redacted]	B.3.3.5
Asciminib - Pain in extremity	[redacted]	[redacted]	B.3.3.5
Asciminib - Pruritis	[redacted]	[redacted]	B.3.3.5
Asciminib - Muscoskeletal pain	[redacted]	[redacted]	B.3.3.5
Asciminib - Pleural effusion	[redacted]	[redacted]	B.3.3.5
Asciminib - Elevated bilirubin levels	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypokalemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Hyperglycemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypermagnesemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Abdominal pain	[redacted]	[redacted]	B.3.3.5
Bosutinib - Alanine aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Anaemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Arthralgia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Aspartate aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Cough	[redacted]	[redacted]	B.3.3.5
Bosutinib - Decreased appetite	[redacted]	[redacted]	B.3.3.5
Bosutinib - Diarrhoea	[redacted]	[redacted]	B.3.3.5
Bosutinib - Fatigue	[redacted]	[redacted]	B.3.3.5
Bosutinib - Headache	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypertension	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypophosphataemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Lipase increased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Nasopharyngitis	[redacted]	[redacted]	B.3.3.5
Bosutinib - Nausea	[redacted]	[redacted]	B.3.3.5
Bosutinib - Neutropenia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Neutrophil count decreased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Platelet count decreased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Rash	[redacted]	[redacted]	B.3.3.5
Bosutinib - Thrombocytopenia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Vomiting	[redacted]	[redacted]	B.3.3.5
Bosutinib - Constipation	[redacted]	[redacted]	B.3.3.5
Bosutinib - Dry skin	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pyrexia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Myalgia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pain in extremity	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pruritis	[redacted]	[redacted]	B.3.3.5
Bosutinib - Muscoskeletal pain	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pleural effusion	[redacted]	[redacted]	B.3.3.5
Bosutinib - Elevated bilirubin levels	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypokalemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hyperglycemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypermagnesemia	[redacted]	[redacted]	B.3.3.5
Ponatinib - Abdominal pain	35.93%	se 0.029 (Beta)	B.3.3.5
Ponatinib - Alanine aminotransferase increased	0.00%	Not varied	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Ponatinib - Anaemia	9.26%	se 0.018 (Beta)	B.3.3.5
Ponatinib - Arthralgia	30.37%	se 0.028 (Beta)	B.3.3.5
Ponatinib - Aspartate aminotransferase increased	0.00%	Not varied	B.3.3.5
Ponatinib - Cough	0.00%	Not varied	B.3.3.5
Ponatinib - Decreased appetite	0.00%	Not varied	B.3.3.5
Ponatinib - Diarrhoea	19.26%	se 0.024 (Beta)	B.3.3.5
Ponatinib - Fatigue	27.78%	se 0.027 (Beta)	B.3.3.5
Ponatinib - Headache	39.63%	se 0.03 (Beta)	B.3.3.5
Ponatinib - Hypertension	22.96%	se 0.026 (Beta)	B.3.3.5
Ponatinib - Hypophosphataemia	0.00%	Not varied	B.3.3.5
Ponatinib - Lipase increased	14.44%	se 0.021 (Beta)	B.3.3.5
Ponatinib - Nasopharyngitis	0.00%	Not varied	B.3.3.5
Ponatinib - Nausea	28.52%	se 0.027 (Beta)	B.3.3.5
Ponatinib - Neutropenia	2.96%	se 0.01 (Beta)	B.3.3.5
Ponatinib - Neutrophil count decreased	0.00%	Not varied	B.3.3.5
Ponatinib - Platelet count decreased	0.00%	Not varied	B.3.3.5
Ponatinib - Rash	43.33%	se 0.03 (Beta)	B.3.3.5
Ponatinib - Thrombocytopenia	10.37%	se 0.019 (Beta)	B.3.3.5
Ponatinib - Vomiting	17.04%	se 0.023 (Beta)	B.3.3.5
Ponatinib - Constipation	38.89%	se 0.03 (Beta)	B.3.3.5
Ponatinib - Dry skin	38.89%	se 0.03 (Beta)	B.3.3.5
Ponatinib - Pyrexia	24.81%	se 0.026 (Beta)	B.3.3.5
Ponatinib - Myalgia	22.96%	se 0.026 (Beta)	B.3.3.5
Ponatinib - Pain in extremity	21.11%	se 0.025 (Beta)	B.3.3.5
Nilotinib - Abdominal pain	0.00%	Not varied	B.3.3.5
Nilotinib - Alanine aminotransferase increased	0.00%	Not varied	B.3.3.5
Nilotinib - Anaemia	0.00%	Not varied	B.3.3.5
Nilotinib - Arthralgia	0.00%	Not varied	B.3.3.5
Nilotinib - Aspartate aminotransferase increased	0.00%	Not varied	B.3.3.5
Nilotinib - Cough	0.00%	Not varied	B.3.3.5
Nilotinib - Decreased appetite	0.00%	Not varied	B.3.3.5
Nilotinib - Diarrhoea	0.00%	Not varied	B.3.3.5
Nilotinib - Fatigue	10.00%	se 0.048 (Beta)	B.3.3.5
Nilotinib - Headache	13.00%	se 0.053 (Beta)	B.3.3.5
Nilotinib - Hypertension	0.00%	Not varied	B.3.3.5
Nilotinib - Hypophosphataemia	0.00%	Not varied	B.3.3.5
Nilotinib - Lipase increased	0.00%	Not varied	B.3.3.5
Nilotinib - Nasopharyngitis	0.00%	Not varied	B.3.3.5
Nilotinib - Nausea	15.00%	se 0.057 (Beta)	B.3.3.5
Nilotinib - Neutropenia	0.00%	Not varied	B.3.3.5
Nilotinib - Neutrophil count decreased	0.00%	Not varied	B.3.3.5
Nilotinib - Platelet count decreased	28.00%	se 0.071 (Beta)	B.3.3.5
Nilotinib - Rash	28.00%	se 0.071 (Beta)	B.3.3.5
Nilotinib - Thrombocytopenia	0.00%	Not varied	B.3.3.5
Nilotinib - Vomiting	0.00%	Not varied	B.3.3.5
Nilotinib - Constipation	0.00%	Not varied	B.3.3.5
Nilotinib - Dry skin	0.00%	Not varied	B.3.3.5
Nilotinib - Pyrexia	0.00%	Not varied	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Nilotinib - Myalgia	0.00%	Not varied	B.3.3.5
Nilotinib - Pain in extremity	0.00%	Not varied	B.3.3.5
Nilotinib - Pruritis	15.00%	Not varied	B.3.3.5
Nilotinib - Muscoskeletal pain	0.00%	Not varied	B.3.3.5
Nilotinib - Pleural effusion	0.00%	Not varied	B.3.3.5
Nilotinib - Elevated bilirubin levels	0.00%	Not varied	B.3.3.5
Nilotinib - Hypokalemia	0.00%	Not varied	B.3.3.5
Nilotinib - Hyperglycemia	0.00%	Not varied	B.3.3.5
Nilotinib - Hypermagnesemia	0.00%	Not varied	B.3.3.5
Nilotinib - Hypocalcemia	0.00%	Not varied	B.3.3.5
Nilotinib - Cardiac events	0.00%	Not varied	B.3.3.5
Dasatinib - Abdominal pain	29.20%	se 0.091 (Beta)	B.3.3.5
Dasatinib - Alanine aminotransferase increased	0.00%	Not varied	B.3.3.5
Dasatinib - Anaemia	0.00%	Not varied	B.3.3.5
Dasatinib - Arthralgia	0.00%	Not varied	B.3.3.5
Dasatinib - Aspartate aminotransferase increased	0.00%	Not varied	B.3.3.5
Dasatinib - Cough	0.00%	Not varied	B.3.3.5
Dasatinib - Decreased appetite	0.00%	Not varied	B.3.3.5
Dasatinib - Diarrhoea	16.70%	se 0.075 (Beta)	B.3.3.5
Dasatinib - Fatigue	45.80%	se 0.1 (Beta)	B.3.3.5
Dasatinib - Headache	37.50%	se 0.097 (Beta)	B.3.3.5
Dasatinib - Hypertension	0.00%	Not varied	B.3.3.5
Dasatinib - Hypophosphataemia	0.00%	Not varied	B.3.3.5
Dasatinib - Lipase increased	0.00%	Not varied	B.3.3.5
Dasatinib - Nasopharyngitis	0.00%	Not varied	B.3.3.5
Dasatinib - Nausea	29.20%	se 0.091 (Beta)	B.3.3.5
Dasatinib - Neutropenia	0.00%	Not varied	B.3.3.5
Dasatinib - Neutrophil count decreased	0.00%	Not varied	B.3.3.5
Dasatinib - Platelet count decreased	0.00%	Not varied	B.3.3.5
Dasatinib - Rash	16.70%	se 0.075 (Beta)	B.3.3.5
Dasatinib - Thrombocytopenia	0.00%	Not varied	B.3.3.5
Dasatinib - Vomiting	0.00%	Not varied	B.3.3.5
Dasatinib - Constipation	0.00%	Not varied	B.3.3.5
Dasatinib - Dry skin	0.00%	Not varied	B.3.3.5
Dasatinib - Pyrexia	0.00%	Not varied	B.3.3.5
Dasatinib - Myalgia	0.00%	Not varied	B.3.3.5
Dasatinib - Pain in extremity	0.00%	Not varied	B.3.3.5
Dasatinib - Pruritis	0.00%	Not varied	B.3.3.5
Dasatinib - Muscoskeletal pain	29.20%	se 0.091 (Beta)	B.3.3.5
Dasatinib - Pleural effusion	8.30%	se 0.055 (Beta)	B.3.3.5
Dasatinib - Elevated bilirubin levels	0.00%	Not varied	B.3.3.5
Dasatinib - Hypokalemia	0.00%	Not varied	B.3.3.5
Dasatinib - Hyperglycemia	0.00%	Not varied	B.3.3.5
Dasatinib - Hypermagnesemia	0.00%	Not varied	B.3.3.5
Dasatinib - Hypocalcemia	0.00%	Not varied	B.3.3.5
Dasatinib - Cardiac events	0.00%	Not varied	B.3.3.5
Dasatinib - Superficial edema	12.50%	se 0.066 (Beta)	B.3.3.5
Dasatinib - Haemotological Aes	20.80%	se 0.081 (Beta)	B.3.3.5
Adverse events grade 3/4			
Asciminib - Abdominal pain	[redacted]	[redacted]	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Asciminib - Alanine aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Asciminib - Anaemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Arthralgia	[redacted]	[redacted]	B.3.3.5
Asciminib - Aspartate aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Asciminib - Cough	[redacted]	[redacted]	B.3.3.5
Asciminib - Decreased appetite	[redacted]	[redacted]	B.3.3.5
Asciminib - Diarrhoea	[redacted]	[redacted]	B.3.3.5
Asciminib - Fatigue	[redacted]	[redacted]	B.3.3.5
Asciminib - Headache	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypertension	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypophosphataemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Lipase increased	[redacted]	[redacted]	B.3.3.5
Asciminib - Nasopharyngitis	[redacted]	[redacted]	B.3.3.5
Asciminib - Nausea	[redacted]	[redacted]	B.3.3.5
Asciminib - Neutropenia	[redacted]	[redacted]	B.3.3.5
Asciminib - Neutrophil count decreased	[redacted]	[redacted]	B.3.3.5
Asciminib - Platelet count decreased	[redacted]	[redacted]	B.3.3.5
Asciminib - Rash	[redacted]	[redacted]	B.3.3.5
Asciminib - Thrombocytopenia	[redacted]	[redacted]	B.3.3.5
Asciminib - Vomiting	[redacted]	[redacted]	B.3.3.5
Asciminib - Constipation	[redacted]	[redacted]	B.3.3.5
Asciminib - Dry skin	[redacted]	[redacted]	B.3.3.5
Asciminib - Pyrexia	[redacted]	[redacted]	B.3.3.5
Asciminib - Myalgia	[redacted]	[redacted]	B.3.3.5
Asciminib - Pain in extremity	[redacted]	[redacted]	B.3.3.5
Asciminib - Pruritis	[redacted]	[redacted]	B.3.3.5
Asciminib - Muscoskeletal pain	[redacted]	[redacted]	B.3.3.5
Asciminib - Pleural effusion	[redacted]	[redacted]	B.3.3.5
Asciminib - Elevated bilirubin levels	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypokalemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Hyperglycemia	[redacted]	[redacted]	B.3.3.5
Asciminib - Hypermagnesemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Abdominal pain	[redacted]	[redacted]	B.3.3.5
Bosutinib - Alanine aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Anaemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Arthralgia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Aspartate aminotransferase increased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Cough	[redacted]	[redacted]	B.3.3.5
Bosutinib - Decreased appetite	[redacted]	[redacted]	B.3.3.5
Bosutinib - Diarrhoea	[redacted]	[redacted]	B.3.3.5
Bosutinib - Fatigue	[redacted]	[redacted]	B.3.3.5
Bosutinib - Headache	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypertension	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypophosphataemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Lipase increased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Nasopharyngitis	[redacted]	[redacted]	B.3.3.5
Bosutinib - Nausea	[redacted]	[redacted]	B.3.3.5
Bosutinib - Neutropenia	[redacted]	[redacted]	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Bosutinib - Neutrophil count decreased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Platelet count decreased	[redacted]	[redacted]	B.3.3.5
Bosutinib - Rash	[redacted]	[redacted]	B.3.3.5
Bosutinib - Thrombocytopenia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Vomiting	[redacted]	[redacted]	B.3.3.5
Bosutinib - Constipation	[redacted]	[redacted]	B.3.3.5
Bosutinib - Dry skin	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pyrexia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Myalgia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pain in extremity	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pruritis	[redacted]	[redacted]	B.3.3.5
Bosutinib - Muscoskeletal pain	[redacted]	[redacted]	B.3.3.5
Bosutinib - Pleural effusion	[redacted]	[redacted]	B.3.3.5
Bosutinib - Elevated bilirubin levels	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypokalemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hyperglycemia	[redacted]	[redacted]	B.3.3.5
Bosutinib - Hypermagnesemia	[redacted]	[redacted]	B.3.3.5
Ponatinib - Abdominal pain	10.37%	se 0.019 (Beta)	B.3.3.5
Ponatinib - Alanine aminotransferase increased	0.00%	Not varied	B.3.3.5
Ponatinib - Anaemia	11.48%	se 0.019 (Beta)	B.3.3.5
Ponatinib - Arthralgia	2.96%	se 0.01 (Beta)	B.3.3.5
Ponatinib - Aspartate aminotransferase increased	0.00%	Not varied	B.3.3.5
Ponatinib - Cough	0.00%	Not varied	B.3.3.5
Ponatinib - Decreased appetite	0.00%	Not varied	B.3.3.5
Ponatinib - Diarrhoea	0.74%	se 0.005 (Beta)	B.3.3.5
Ponatinib - Fatigue	2.22%	se 0.009 (Beta)	B.3.3.5
Ponatinib - Headache	3.33%	se 0.011 (Beta)	B.3.3.5
Ponatinib - Hypertension	13.70%	se 0.021 (Beta)	B.3.3.5
Ponatinib - Hypophosphataemia	0.00%	Not varied	B.3.3.5
Ponatinib - Lipase increased	12.59%	se 0.02 (Beta)	B.3.3.5
Ponatinib - Nasopharyngitis	0.00%	Not varied	B.3.3.5
Ponatinib - Nausea	0.74%	se 0.005 (Beta)	B.3.3.5
Ponatinib - Neutropenia	11.48%	se 0.023 (Beta)	B.3.3.5
Ponatinib - Neutrophil count decreased	0.00%	Not varied	B.3.3.5
Ponatinib - Platelet count decreased	0.00%	Not varied	B.3.3.5
Ponatinib - Rash	3.70%	se 0.011 (Beta)	B.3.3.5
Ponatinib - Thrombocytopenia	35.19%	se 0.029 (Beta)	B.3.3.5
Ponatinib - Vomiting	1.48%	se 0.007 (Beta)	B.3.3.5
Ponatinib - Constipation	2.59%	se 0.01 (Beta)	B.3.3.5
Ponatinib - Dry skin	3.33%	se 0.011 (Beta)	B.3.3.5
Ponatinib - Pyrexia	1.11%	se 0.006 (Beta)	B.3.3.5
Ponatinib - Myalgia	1.11%	se 0.006 (Beta)	B.3.3.5
Ponatinib - Pain in extremity	2.96%	se 0.01 (Beta)	B.3.3.5
Nilotinib - Abdominal pain	0.00%	Not varied	B.3.3.5
Nilotinib - Alanine aminotransferase increased	8.00%	se 0.042 (Beta)	B.3.3.5
Nilotinib - Anaemia	0.00%	Not varied	B.3.3.5
Nilotinib - Arthralgia	0.00%	Not varied	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Nilotinib - Aspartate aminotransferase increased	0.00%	Not varied	B.3.3.5
Nilotinib - Cough	0.00%	Not varied	B.3.3.5
Nilotinib - Decreased appetite	0.00%	Not varied	B.3.3.5
Nilotinib - Diarrhoea	0.00%	Not varied	B.3.3.5
Nilotinib - Fatigue	0.00%	Not varied	B.3.3.5
Nilotinib - Headache	0.00%	Not varied	B.3.3.5
Nilotinib - Hypertension	0.00%	Not varied	B.3.3.5
Nilotinib - Hypophosphataemia	13.00%	se 0.053 (Beta)	B.3.3.5
Nilotinib - Lipase increased	25.00%	se 0.069 (Beta)	B.3.3.5
Nilotinib - Nasopharyngitis	0.00%	Not varied	B.3.3.5
Nilotinib - Nausea	0.00%	Not varied	B.3.3.5
Nilotinib - Neutropenia	23.00%	se 0.067 (Beta)	B.3.3.5
Nilotinib - Neutrophil count decreased	0.00%	Not varied	B.3.3.5
Nilotinib - Platelet count decreased	0.00%	Not varied	B.3.3.5
Nilotinib - Rash	0.00%	Not varied	B.3.3.5
Nilotinib - Thrombocytopenia	28.00%	se 0.071 (Beta)	B.3.3.5
Nilotinib - Vomiting	0.00%	Not varied	B.3.3.5
Nilotinib - Constipation	0.00%	Not varied	B.3.3.5
Nilotinib - Dry skin	0.00%	Not varied	B.3.3.5
Nilotinib - Pyrexia	0.00%	Not varied	B.3.3.5
Nilotinib - Myalgia	0.00%	Not varied	B.3.3.5
Nilotinib - Pain in extremity	0.00%	Not varied	B.3.3.5
Nilotinib - Pruritis	0.00%	Not varied	B.3.3.5
Nilotinib - Muscoskeletal pain	0.00%	Not varied	B.3.3.5
Nilotinib - Pleural effusion	0.00%	Not varied	B.3.3.5
Nilotinib - Elevated bilirubin levels	8.00%	se 0.042 (Beta)	B.3.3.5
Nilotinib - Hypokalemia	5.00%	se 0.035 (Beta)	B.3.3.5
Nilotinib - Hyperglycemia	13.00%	se 0.053 (Beta)	B.3.3.5
Nilotinib - Hypermagnesemia	11.00%	se 0.048 (Beta)	B.3.3.5
Nilotinib - Hypocalcemia	10.00%	se 0.048 (Beta)	B.3.3.5
Nilotinib - Cardiac events	15.38%	se 0.057 (Beta)	B.3.3.5
Dasatinib - Abdominal pain	0.00%	Not varied	B.3.3.5
Dasatinib - Alanine aminotransferase increased	0.00%	Not varied	B.3.3.5
Dasatinib - Anaemia	0.00%	Not varied	B.3.3.5
Dasatinib - Arthralgia	0.00%	Not varied	B.3.3.5
Dasatinib - Aspartate aminotransferase increased	0.00%	Not varied	B.3.3.5
Dasatinib - Cough	0.00%	Not varied	B.3.3.5
Dasatinib - Decreased appetite	0.00%	Not varied	B.3.3.5
Dasatinib - Diarrhoea	0.00%	Not varied	B.3.3.5
Dasatinib - Fatigue	0.00%	Not varied	B.3.3.5
Dasatinib - Headache	0.00%	Not varied	B.3.3.5
Dasatinib - Hypertension	0.00%	Not varied	B.3.3.5
Dasatinib - Hypophosphataemia	0.00%	Not varied	B.3.3.5
Dasatinib - Lipase increased	0.00%	Not varied	B.3.3.5
Dasatinib - Nasopharyngitis	0.00%	Not varied	B.3.3.5
Dasatinib - Nausea	0.00%	Not varied	B.3.3.5
Dasatinib - Neutropenia	0.00%	Not varied	B.3.3.5
Dasatinib - Neutrophil count decreased	0.00%	Not varied	B.3.3.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Dasatinib - Platelet count decreased	0.00%	Not varied	B.3.3.5
Dasatinib - Rash	0.00%	Not varied	B.3.3.5
Dasatinib - Thrombocytopenia	0.00%	Not varied	B.3.3.5
Dasatinib - Vomiting	0.00%	Not varied	B.3.3.5
Dasatinib - Constipation	0.00%	Not varied	B.3.3.5
Dasatinib - Dry skin	0.00%	Not varied	B.3.3.5
Dasatinib - Pyrexia	0.00%	Not varied	B.3.3.5
Dasatinib - Myalgia	0.00%	Not varied	B.3.3.5
Dasatinib - Pain in extremity	0.00%	Not varied	B.3.3.5
Dasatinib - Pruritis	0.00%	Not varied	B.3.3.5
Dasatinib - Muscoskeletal pain	0.00%	Not varied	B.3.3.5
Dasatinib - Pleural effusion	0.00%	Not varied	B.3.3.5
Dasatinib - Elevated bilirubin levels	0.00%	Not varied	B.3.3.5
Dasatinib - Hypokalemia	0.00%	Not varied	B.3.3.5
Dasatinib - Hyperglycemia	0.00%	Not varied	B.3.3.5
Dasatinib - Hypermagnesemia	0.00%	Not varied	B.3.3.5
Dasatinib - Hypocalcemia	0.00%	Not varied	B.3.3.5
Dasatinib - Cardiac events	0.00%	Not varied	B.3.3.5
Dasatinib - Superficial edema	0.00%	Not varied	B.3.3.5
Dasatinib - Haemotological AEs	58.30%	se 0.099 (Beta)	B.3.3.5
Drug costs			
Pack price - Asciminib 40mg	[redacted]	Not varied	B.3.5.1.1
Pack price – Bosutinib 500mg	£3,436.67	Not varied	B.3.5.1.1
Pack price – Ponatinib 45mg	£5,050.00	Not varied	B.3.5.1.1
Pack price – Dasatinib 100mg	£2,504.96	Not varied	B.3.5.1.1
Pack price – Dasatinib 140mg	£2,504.96	Not varied	B.3.5.1.1
Pack price – Nilotinib 200mg	£2,432.85	Not varied	B.3.5.1.1
Pack price – Imatinib 400mg	£112.90	Not varied	B.3.5.1.1
Pack price – Imatinib 100mg	£55.13	Not varied	B.3.5.1.1
RDI - asciminib	[redacted]	[redacted]	B.3.5.1.2
RDI - bosutinib	[redacted]	[redacted]	B.3.5.1.2
RDI all other treatments	100%	Not varied	B.3.5.1.2
Chronic phase subsequent treatment distribution - nilotinib	21%	se 0.022 (Dirichlet)	B.3.5.1.4
Chronic phase subsequent treatment distribution - dasatinib	18%	se 0.018 (Dirichlet)	B.3.5.1.4
Chronic phase subsequent treatment distribution - ponatinib	25%	se 0.026 (Dirichlet)	B.3.5.1.4
Chronic phase subsequent treatment distribution - imatinib	5%	se 0.006 (Dirichlet)	B.3.5.1.4
Chronic phase subsequent treatment distribution - bosutinib	30%	se 0.031 (Dirichlet)	B.3.5.1.4
Accelerated phase treatment distribution - nilotinib	10%	se 0.010 (Dirichlet)	B.3.5.1.4
Accelerated phase treatment distribution - dasatinib	30%	se 0.031 (Dirichlet)	B.3.5.1.4
Accelerated phase treatment distribution - ponatinib	30%	se 0.031 (Dirichlet)	B.3.5.1.4
Accelerated phase treatment distribution - imatinib	0%	Not varied	B.3.5.1.4
Accelerated phase treatment distribution - bosutinib	20%	se 0.020 (Dirichlet)	B.3.5.1.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Accelerated phase treatment distribution – FLAG-Ida	10%	se 0.010 (Dirichlet)	B.3.5.1.4
Blast phase treatment distribution - dasatinib	20%	1 minus proportion on ponatinb	B.3.5.1.4
Blast phase treatment distribution - ponatinib	80%	se 0.082 (Beta)	B.3.5.1.4
Blast phase treatment distribution - bosutinib	50%	se 0.051 (Beta)	B.3.5.1.4
Following SCT relapse free subsequent treatment distribution - nilotinib	25%	se 0.026 (Dirichlet)	B.3.5.1.4
Following SCT relapse free subsequent treatment distribution - dasatinib	25%	se 0.026 (Dirichlet)	B.3.5.1.4
Following SCT relapse free subsequent treatment distribution - ponatinib	25%	se 0.026 (Dirichlet)	B.3.5.1.4
Following SCT relapse free subsequent treatment distribution - imatinib	0%	Not varied	B.3.5.1.4
Following SCT relapse free subsequent treatment distribution - bosutinib	25%	se 0.026 (Dirichlet)	B.3.5.1.4
Weighted cost per day subsequent treatment – chronic phase	103.64	Composite value (components varied)	B.3.5.1.4
Weighted cost per day subsequent treatment – accelerated phase	104.44	Composite value (components varied)	B.3.5.1.4
Weighted cost per day subsequent treatment – blast phase	£151.37	Composite value (components varied)	B.3.5.1.4
Weighted cost per day subsequent treatment – following SCT relapsed	£104.50	Composite value (components varied)	B.3.5.1.4
Monitoring costs			
Drug monitoring resource use: blood count	1	Not varied	B.3.5.1.3
Drug monitoring resource use: liver function test	1	Not varied	B.3.5.1.3
Drug monitoring resource use: serum amylase test	1	Not varied	B.3.5.1.3
Drug monitoring resource use: electrolytes test	1	Not varied	B.3.5.1.3
Drug monitoring resource use: renal function test	1	Not varied	B.3.5.1.3
Drug monitoring resource use: outpatient visit	1	Not varied	B.3.5.1.3
Drug monitoring unit cost: blood count	1.81	se 0.185 (Gamma)	B.3.5.1.3
Drug monitoring unit cost: liver function test	3.55	se 0.362 (Gamma)	B.3.5.1.3
Drug monitoring unit cost: serum amylase test	3.55	se 0.362 (Gamma)	B.3.5.1.3
Drug monitoring unit cost: electrolytes test	1.20	se 0.122 (Gamma)	B.3.5.1.3
Drug monitoring unit cost: renal function test	1.20	se 0.122 (Gamma)	B.3.5.1.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Drug monitoring unit cost: outpatient visit	173.10	se 17.644 (Gamma)	B.3.5.1.3
Drug monitoring cost - total	£184.41	Composite value (components varied)	B.3.5.1.3
Health care resource use			
Resource use on 3L treatment: outpatient visit nurse led	0.29	se 0.03 (Gamma)	B.3.5.2
Resource use on 3L treatment: haematologist visit	0.93	se 0.095 (Gamma)	B.3.5.2
Resource use on 3L treatment: inpatient days	0	Not varied	B.3.5.2
Resource use on 3L treatment: full blood count	1.13	se 0.115 (Gamma)	B.3.5.2
Resource use on 3L treatment: blood transfusion	0.01	se 0.001 (Gamma)	B.3.5.2
Resource use on 3L treatment: bone marrow aspiration	0.03	se 0.003 (Gamma)	B.3.5.2
Resource use on 3L treatment: FISH	0.22	se 0.022 (Gamma)	B.3.5.2
Resource use on 3L treatment: PCR	0.79	se 0.081 (Gamma)	B.3.5.2
Resource use on 3L treatment: cytochemistry analysis	0	Not varied	B.3.5.2
Resource use on 3L treatment: blood film examination	0.5	se 0.051 (Gamma)	B.3.5.2
Resource use on 3L treatment: blood chemistry	1.13	se 0.115 (Gamma)	B.3.5.2
Resource use on 3L treatment: kinase domain mutation	0	Not varied	B.3.5.2
Resource use on 3L treatment: platelet transfusion	0	Not varied	B.3.5.2
Resource use off 3L treatment: outpatient visit nurse led	0.38	se 0.039 (Gamma)	B.3.5.2
Resource use off 3L treatment: haematologist visit	1.72	se 0.176 (Gamma)	B.3.5.2
Resource use off 3L treatment: inpatient days	0	Not varied	B.3.5.2
Resource use off 3L treatment: full blood count	1.97	se 0.201 (Gamma)	B.3.5.2
Resource use off 3L treatment: blood transfusion	0.01	se 0.001 (Gamma)	B.3.5.2
Resource use off 3L treatment: bone marrow aspiration	0.3	se 0.031 (Gamma)	B.3.5.2
Resource use off 3L treatment: FISH	0.56	se 0.057 (Gamma)	B.3.5.2
Resource use off 3L treatment: PCR	1.31	se 0.134 (Gamma)	B.3.5.2
Resource use off 3L treatment: cytochemistry analysis	0.05	se 0.005 (Gamma)	B.3.5.2
Resource use off 3L treatment: blood film examination	1.09	se 0.111 (Gamma)	B.3.5.2
Resource use off 3L treatment: blood chemistry	1.88	se 0.192 (Gamma)	B.3.5.2
Resource use off 3L treatment: kinase domain mutation	0	Not varied	B.3.5.2
Resource use off 3L treatment: platelet transfusion	0	Not varied	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Resource use post Allo-SCT, relapse free: outpatient visit nurse led	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: haematologist visit	0.25	se 0.026 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapse free: inpatient days	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: full blood count	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: blood transfusion	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: bone marrow aspiration	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: FISH	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: PCR	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: cytochemistry analysis	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: blood film examination	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: blood chemistry	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: kinase domain mutation	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapse free: platelet transfusion	0	Not varied	B.3.5.2
Resource use post Allo-SCT, relapsed: outpatient visit nurse led	0.51	se 0.052 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: haematologist visit	3.63	se 0.37 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: inpatient days	2.13	se 0.217 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: full blood count	4.38	se 0.447 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: blood transfusion	1.98	se 0.202 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: bone marrow aspiration	0.3	se 0.031 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: FISH	0.13	se 0.013 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: PCR	1.68	se 0.171 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: cytochemistry analysis	0.12	se 0.012 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: blood film examination	2.19	se 0.223 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: blood chemistry	3.15	se 0.321 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: kinase domain mutation	0.50	se 0.051 (Gamma)	B.3.5.2
Resource use post Allo-SCT, relapsed: platelet transfusion	0.30	se 0.031 (Gamma)	B.3.5.2
Resource use accelerated phase: outpatient visit nurse led	0.51	se 0.052 (Gamma)	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Resource use accelerated phase: haematologist visit	3.63	se 0.37 (Gamma)	B.3.5.2
Resource use accelerated phase: inpatient days	2.13	se 0.217 (Gamma)	B.3.5.2
Resource use accelerated phase: full blood count	4.38	se 0.447 (Gamma)	B.3.5.2
Resource use accelerated phase: blood transfusion	1.98	se 0.202 (Gamma)	B.3.5.2
Resource use accelerated phase: bone marrow aspiration	0.3	se 0.031 (Gamma)	B.3.5.2
Resource use accelerated phase: FISH	0.13	se 0.013 (Gamma)	B.3.5.2
Resource use accelerated phase: PCR	1.68	se 0.171 (Gamma)	B.3.5.2
Resource use accelerated phase: cytochemistry analysis	0.12	se 0.012 (Gamma)	B.3.5.2
Resource use accelerated phase: blood film examination	2.19	se 0.223 (Gamma)	B.3.5.2
Resource use accelerated phase: blood chemistry	3.15	se 0.321 (Gamma)	B.3.5.2
Resource use accelerated phase: kinase domain mutation	0.50	se 0.051 (Gamma)	B.3.5.2
Resource use accelerated phase: platelet transfusion	0.30	se 0.031 (Gamma)	B.3.5.2
Resource use blast phase: outpatient visit nurse led	0.51	se 0.052 (Gamma)	B.3.5.2
Resource use blast phase: haematologist visit	3.63	se 0.37 (Gamma)	B.3.5.2
Resource use blast phase: inpatient days	26.64	se 2.718 (Gamma)	B.3.5.2
Resource use blast phase: full blood count	4.38	se 0.447 (Gamma)	B.3.5.2
Resource use blast phase: blood transfusion	1.98	se 0.202 (Gamma)	B.3.5.2
Resource use blast phase: bone marrow aspiration	0.3	se 0.031 (Gamma)	B.3.5.2
Resource use blast phase: FISH	0.13	se 0.013 (Gamma)	B.3.5.2
Resource use blast phase: PCR	1.68	se 0.171 (Gamma)	B.3.5.2
Resource use blast phase: cytochemistry analysis	0.12	se 0.012 (Gamma)	B.3.5.2
Resource use blast phase: blood film examination	2.19	se 0.223 (Gamma)	B.3.5.2
Resource use blast phase: blood chemistry	3.15	se 0.321 (Gamma)	B.3.5.2
Resource use blast phase: kinase domain mutation	0.50	se 0.051 (Gamma)	B.3.5.2
Resource use blast phase: platelet transfusion	0.30	se 0.031 (Gamma)	B.3.5.2
Unit cost: outpatient visit nurse led	£173.10	se 17.664 (Gamma)	B.3.5.2
Unit cost: haematologist visit	£171.18	se 17.468 (Gamma)	B.3.5.2
Unit cost: inpatient days	£576.61	se 58.839 (Gamma)	B.3.5.2
Unit cost: full blood count	£2.53	se 0.258 (Gamma)	B.3.5.2
Unit cost: blood transfusion	£199.45	se 20.352 (Gamma)	B.3.5.2
Unit cost: bone marrow aspiration	£563.62	se 57.513 (Gamma)	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Unit cost: FISH	£120.00	se 12.245 (Gamma)	B.3.5.2
Unit cost: PCR	£22.70	se 2.316 (Gamma)	B.3.5.2
Unit cost: cytochemistry analysis	£3.18	se 0.324 (Gamma)	B.3.5.2
Unit cost: blood film examination	£1.81	se 0.185 (Gamma)	B.3.5.2
Unit cost: blood chemistry	£1.20	se 0.122 (Gamma)	B.3.5.2
Unit cost: kinase domain mutation	£512.15	se 52.261 (Gamma)	B.3.5.2
Unit cost: platelet transfusion	£286.22	se 29.207 (Gamma)	B.3.5.2
Health state cost per 3 months CP on treatment state	£277.75	Composite value (components varied)	B.3.5.2
Health state cost per 3 months CP off treatment state	£637.60	Composite value (components varied)	B.3.5.2
Health state cost per 3 months allo-SCT relapse free state	£42.80	Composite value (components varied)	B.3.5.2
Health state cost per 3 months allo-SCT relapsed state	£2916.72	Composite value (components varied)	B.3.5.2
Health state cost per 3 months AP state	£2916.72	Composite value (components varied)	B.3.5.2
Health state cost per 3 months BP state	£17049.44	Composite value (components varied)	B.3.5.2
Terminal care costs – no. of inpatient days	21.5	se 2.194 (Gamma)	B.3.5.5
Terminal care costs – % treated in hospital	51.5%	se 0.053 (Beta)	B.3.5.5
Terminal care costs – no. of hospice days	17.4	se 1.776 (Gamma)	B.3.5.5
Terminal care costs – % treated in hospice	23.1%	se 0.024 (Beta)	B.3.5.5
Total terminal care cost	£7,173.20	Composite value (components varied)	B.3.5.5
SCT cost	£109,279	se 11,151 (Gamma)	B.3.5.4
Cost of myeloablative therapy (one month)	£17,298	Composite value (components varied)	B.3.5.4
Adverse event costs (grade 3/4)			
Abdominal pain	£649.20	se 66 (Gamma)	B.3.5.3
Alanine aminotransferase increased	£1,755.63	se 179 (Gamma)	B.3.5.3
Anaemia	£1,162.71	se 119 (Gamma)	B.3.5.3
Arthralgia	£1,059.61	se 108 (Gamma)	B.3.5.3
Aspartate aminotransferase increased	£1,755.63	se 179 (Gamma)	B.3.5.3
Cough	£684.35	se 70 (Gamma)	B.3.5.3
Decreased appetite	£1,577.78	se 161 (Gamma)	B.3.5.3
Diarrhoea	£1,446.42	se 148 (Gamma)	B.3.5.3
Fatigue	£205.10	se 21 (Gamma)	B.3.5.3
Headache	£643.40	se 66 (Gamma)	B.3.5.3
Hypertension	£639.00	se 65 (Gamma)	B.3.5.3
Hypophosphataemia	£1,330.00	se 136 (Gamma)	B.3.5.3
Lipase increased	£1,755.63	se 179 (Gamma)	B.3.5.3
Nasopharyngitis	£684.35	se 70 (Gamma)	B.3.5.3
Nausea	£205.10	se 21 (Gamma)	B.3.5.3
Neutropenia	£1,082.77	se 110 (Gamma)	B.3.5.3
Neutrophil count decreased	£1,082.77	se 110 (Gamma)	B.3.5.3
Platelet count decreased	£770.57	se 79 (Gamma)	B.3.5.3
Rash	£1,479.36	se 151 (Gamma)	B.3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Thrombocytopenia	£770.57	se 79 (Gamma)	B.3.5.3
Vomiting	£205.10	se 21 (Gamma)	B.3.5.3
Constipation	£690.87	se 70 (Gamma)	B.3.5.3
Dry skin	£1,479.36	se 151 (Gamma)	B.3.5.3
Pyrexia	£1,002.21	se 102 (Gamma)	B.3.5.3
Myalgia	£1,000.07	se 102 (Gamma)	B.3.5.3
Pain in extremity	£1,059.61	se 108 (Gamma)	B.3.5.3
Pruritis	£1,479.36	se 151 (Gamma)	B.3.5.3
Muscoskeletal pain	£1,059.61	se 108 (Gamma)	B.3.5.3
Pleural effusion	£1,812.64	se 185 (Gamma)	B.3.5.3
Elevated bilirubin levels	£1,755.63	se 179 (Gamma)	B.3.5.3
Hypokalemia	£1,330.00	se 136 (Gamma)	B.3.5.3
Hyperglycemia	£1,169.86	se 119 (Gamma)	B.3.5.3
Hypermagnesemia	£1,330.00	se 136 (Gamma)	B.3.5.3
Hypocalcemia	£1,330.00	se 136 (Gamma)	B.3.5.3
Cardiac events	£1,624.73	se 166 (Gamma)	B.3.5.3
Superficial edema	£589.58	se 60 (Gamma)	B.3.5.3
Haemotological Aes	£1,082.77	se 110 (Gamma)	B.3.5.3
Total AE costs - asciminib	£613.72	Composite value (components varied)	B.3.5.3
Total AE costs - bosutinib	£1,129.81	Composite value (components varied)	B.3.5.3
Total AE costs - ponatinib	£1,153.24	Composite value (components varied)	B.3.5.3
Total AE costs - nilotinib	£2,105.35	Composite value (components varied)	B.3.5.3
Total AE costs - dasatinib	£631.25	Composite value (components varied)	B.3.5.3
Utilities			
Szabo 2010, CP-CML, on treatment	0.91	se 0.093 (Beta)	B.3.4.5
Szabo 2010, CP-CML, off treatment	0.73	se 0.074 (Beta)	B.3.4.5
ASCEMBL, HSUV, CP, on treatment	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, off treatment	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, asciminib	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, bosutinib	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, on treatment, asciminib	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, on treatment, bosutinib	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, off treatment, acsiminib	[redacted]	[redacted]	B.3.4.5
ASCEMBL, HSUV, CP, off treatment, bosutinib	[redacted]	[redacted]	B.3.4.5
HSUV in Allo-SCT, relapse free	0.71	se 0.072 (Beta)	B.3.4.5
HSUV in Allo-SCT, relapsed	0.59	se 0.06 (Beta)	B.3.4.5
HSUV in AP	0.655	se 0.067 (Beta)	B.3.4.5
HSUV in BP	0.425	se 0.043 (Beta)	B.3.4.5
Regression model from Ara and Brazier, constant	0.950857	Not varied	B.3.4.5
Regression model from Ara and Brazier, male	0.021213	Not varied	B.3.4.5
Regression model from Ara and Brazier, age	–0.00026	Not varied	B.3.4.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Regression model from Ara and Brazier, age squared	–0.00003	Not varied	B.3.4.5
Adverse event disutilities			
Abdominal pain	–0.05	se 0.005 (Gamma)	B.3.4.4
Alanine aminotransferase increased	–0.05	se 0.005 (Gamma)	B.3.4.4
Anaemia	–0.09	se 0.009 (Gamma)	B.3.4.4
Arthralgia	–0.05	se 0.005 (Gamma)	B.3.4.4
Aspartate aminotransferase increased	–0.05	se 0.005 (Gamma)	B.3.4.4
Cough	–0.05	se 0.005 (Gamma)	B.3.4.4
Decreased appetite	–0.05	se 0.005 (Gamma)	B.3.4.4
Diarrhoea	–0.05	se 0.005 (Gamma)	B.3.4.4
Fatigue	–0.05	se 0.005 (Gamma)	B.3.4.4
Headache	–0.18	se 0.018 (Gamma)	B.3.4.4
Hypertension	–0.05	se 0.005 (Gamma)	B.3.4.4
Hypophosphataemia	–0.05	se 0.005 (Gamma)	B.3.4.4
Lipase increased	–0.07	se 0.007 (Gamma)	B.3.4.4
Nasopharyngitis	–0.05	se 0.005 (Gamma)	B.3.4.4
Nausea	–0.05	se 0.005 (Gamma)	B.3.4.4
Neutropenia	–0.05	se 0.005 (Gamma)	B.3.4.4
Neutrophil count decreased	–0.05	se 0.005 (Gamma)	B.3.4.4
Platelet count decreased	–0.02	se 0.002 (Gamma)	B.3.4.4
Rash	–0.05	se 0.005 (Gamma)	B.3.4.4
Thrombocytopenia	–0.05	se 0.005 (Gamma)	B.3.4.4
Vomiting	–0.05	se 0.005 (Gamma)	B.3.4.4
Constipation	–0.05	se 0.005 (Gamma)	B.3.4.4
Dry skin	–0.05	se 0.005 (Gamma)	B.3.4.4
Pyrexia	–0.05	se 0.005 (Gamma)	B.3.4.4
Myalgia	–0.05	se 0.005 (Gamma)	B.3.4.4
Pain in extremity	–0.05	se 0.005 (Gamma)	B.3.4.4
Pruritis	–0.09	se 0.009 (Gamma)	B.3.4.4
Muscoskeletal pain	–0.05	se 0.005 (Gamma)	B.3.4.4
Pleural effusion	–0.05	se 0.005 (Gamma)	B.3.4.4
Elevated bilirubin levels	–0.05	se 0.005 (Gamma)	B.3.4.4
Hypokalemia	–0.05	se 0.005 (Gamma)	B.3.4.4
Hyperglycemia	–0.05	se 0.005 (Gamma)	B.3.4.4
Hypermagnesemia	–0.05	se 0.005 (Gamma)	B.3.4.4
Hypocalcemia	–0.06	se 0.006 (Gamma)	B.3.4.4
Cardiac events	–0.05	se 0.005 (Gamma)	B.3.4.4
Superficial edema	–0.09	se 0.009 (Gamma)	B.3.4.4
Haemotological Aes	–0.05	se 0.005 (Gamma)	B.3.4.4

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; CI, confidence interval; PD, progressed disease; SCT, stem cell transplant

B.3.6.2 Assumptions

Table 93 provides a summary of assumptions made in the model.

Table 93: Model Assumptions

Assumption	Justification
All patients have a mean survival of 7 years following treatment discontinuation	Based on clinical opinion and the approach used in TA401
All patients spend an average of 10 months in the AP health state and 6 months in the BP health state	Based on the approach used in TA401
No mortality is assumed upon transitions from states except for in BP	Simplifying assumption reflecting the structure of the model in which patients are assumed to live a mean of 7 years after discontinuation of 3L treatment
Rates of progression other than TTD of 3L treatment are assumed to be constant over time	Insufficient data to allow modelling of survival for transitions other than TTD, requiring assumptions on mean survival and application of a constant hazard rate
Time on treatment for the comparators other than bosutinib is modelled using an exponential function	Only median treatment duration was available for the these comparators
Once patients discontinue 3L treatment, 100% go on to receive 4L treatment	Assumption in line with other appraisals in this area.
Patients received the same subsequent treatments regardless of 3L treatment	Assumption in line with other appraisals in this area.
Patients with CML who receive allo-SCT are assumed to be in one of two health states: in remission or relapsed	Based on other TA's e.g. TA451
The rate of AEs is applied to the first cycle only on the assumption that such events will happen sooner rather than later, with a on-off fixed cost applied.	Common practice; in line with recent oncology models
Zero cost is applied for the treatment of grade 1 – 2 adverse events	Common practice, as these are assumed to resolve on their own.
Patients experience the same QoL in each health state beyond CP, regardless of 3L treatment	Common practice, as the utilities are dependent on the health state the patient is living in.
An age and sex specific utility decrement is applied over the time horizon	Common practice, to take account of utilities changing with age.
A one-off fixed utility decrement was applied to all grade 3-4 adverse events	This is a common approach, as adverse events are expected to only occur when the patient is on treatment.
A utility decrement of -0.05 was applied to any adverse events where event specific QoL data were not available	Assumption, taken from TA426

Abbreviations: 3L, third-line; 4L, fourth-line; AE, adverse event; allo-SCT, allogenic stem cell therapy; AP, advanced phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; QoL, quality of life; TA, technology appraisal; TTD, time to discontinuation.

B.3.6.3 Scenarios examined in sensitivity analysis

Scenarios tested are summarised in Table 94.

Table 94: Scenarios examined in sensitivity analysis

Scenario name	Base case setting	Scenario value
TTD curve distribution (for bosutinib comparison)	Joint log-normal distribution	Weibull, exponential, Gompertz, loglogistic, gamma, generalised gamma
Overall survival post-discontinuation of third line treatment	7 years	3.5 years
		5 years
Alternative utilities	Utilities from ASCEMBL by treatment status	Utilities from ASCEMBL by treatment arm
		Utilities from ASCEMBL by treatment status & arm
		Utilities from Szabo 2010
Proportion undergoing allo-SCT at discontinuation of 3L treatment	[redacted]	10%
		30%
Proportion undergoing allo-SCT at progression to AP	[redacted]	10%
		40%
Proportion undergoing allo-SCT at progression to BP	[redacted]	10%
		40%
Mean duration in AP	10 months	8 months
		12 months
Mean duration in BP	6 months	4 months
		8 months
Discounting	3.5% for costs and QALYs	0% for costs and QALYs
		5% for costs and QALYs

Abbreviations: 3L, third-line; allo-SCT, allogenic stem cell transplant; AP, advanced phase; BP, blast phase; QALY, quality-adjusted life year; TTD, time to discontinuation.

B.3.7 Base-case results

Results are presented pairwise and not incrementally because asciminib is compared to all the non-ASCEMBL comparators using a MAIC, where the asciminib TTD data is adjusted to match the population of the relevant comparator trial. As the results for the asciminib arm change in each comparison, it is not possible to undertake an incremental analysis.

Deterministic pairwise results for each comparison at list prices for all comparators (including asciminib) are presented in Table 95, Table 97, Table 99, and Table 101.

Deterministic pairwise results are also presented with an asciminib PAS price when compared to bosutinib, ponatinib, and dasatinib – with the price for these comparators remaining at list prices, as PAS discounts for bosutinib, dasatinib and ponatinib are confidential. While Novartis are the manufacturer of nilotinib and the PAS for nilotinib is known ([redacted]), therefore the with-PAS price comparison for asciminib compared to nilotinib includes the PAS prices for both treatments. (The PAS discount to the price of nilotinib was applied only in the comparison of asciminib

with nilotinib after discounting. In the comparisons of asciminib at the PAS-price with bosutinib, dasatinib and ponatinib, the list price for any subsequent treatment with nilotinib was applied. The impact of discounting subsequent costs of treatment is small.) Deterministic pairwise results with PAS discounts are presented in Table 96, Table 98, Table 100, and Table 102.

When compared with bosutinib, asciminib at list price is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] per QALY gained. At the PAS discounted price, asciminib remains marginally more expensive than bosutinib and the ICER falls to £3,192.

When compared with nilotinib at list price, asciminib at list price is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] per QALY gained. After applying PAS discounts to the price of asciminib and nilotinib the incremental costs reduce and the ICER falls to £49,584.

When compared with dasatinib, asciminib at list price is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] per QALY gained. At the PAS discounted price, asciminib remains marginally more expensive than dasatinib and the ICER falls to £3,180.

When compared with ponatinib, asciminib at list price is associated with lower costs but also lower QALYs, resulting in an ICER for asciminib compared to ponatinib of [redacted] saved per QALY lost. At the PAS discounted price, the costs associated with asciminib fall further, and the ICER for asciminib compared to ponatinib rises to £253,193 saved per QALY lost.

The submission considers the effectiveness and cost-effectiveness of asciminib in a third and later line population as aligned with the marketing authorisation, and data from the pivotal ASCEMBL trial which assessed patients at third line and beyond. The supporting economic analysis also focuses on a third and later line population. With regard to the comparators, data on TTD for ponatinib and bosutinib include patients in the fourth line setting. While data for dasatinib and nilotinib do not include patients in the fourth line setting, this is largely due to the evolution of the CML treatments over the last 10-15 years. Our approach to the modelling of OS following discontinuation of third line treatment is based on the approach recommended by the ERG in TA401 (bosutinib), in which OS is the sum of TTD plus a fixed period of

survival beyond third line treatment. Further, scenario analysis in which survival following discontinuation of third line treatment is reduced generated lower ICERs. The presented cost-effectiveness analysis could, therefore, be regarded as a conservative proxy assessment of the cost-effectiveness of asciminib.

Clinical outcomes and disaggregated results from the model can be found in Appendix J.

B.3.7.1 Asciminib vs bosutinib

Table 95: Base-case results pairwise – asciminib vs bosutinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Bosutinib	[redacted]	9.47	6.74				
Asciminib	[redacted]	11.31	8.25	[redacted]	1.84	1.51	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 96: Base-case results pairwise – asciminib vs bosutinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Bosutinib	[redacted]	9.47	6.74				
Asciminib	[redacted]	11.31	8.25	4,824	1.84	1.51	3,192

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

B.3.7.2 Asciminib vs ponatinib

Table 97: Base-case results pairwise – asciminib vs ponatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Ponatinib	[redacted]	10.14	7.27				
Asciminib	[redacted]	9.42	6.71	[redacted]	-0.95	-0.56	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 98: Base-case results pairwise – asciminib vs ponatinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Ponatinib	[redacted]	10.14	7.27				
Asciminib	[redacted]	9.42	6.71	-141,299	-0.95	-0.56	253,193

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

B.3.7.3 Asciminib vs nilotinib

Table 99: Base-case results pairwise – asciminib vs nilotinib (list prices of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Nilotinib	[redacted]	8.84	6.18				
Asciminib	[redacted]	9.90	7.11	[redacted]	1.06	0.93	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 100: Base-case results pairwise – asciminib vs nilotinib (PAS price – for asciminib and nilotinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Nilotinib	[redacted]	8.84	6.18				
Asciminib	[redacted]	9.90	7.11	46,081	1.06	0.93	49,584

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

B.3.7.4 Asciminib vs dasatinib

Table 101: Base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Dasatinib	[redacted]	9.04	6.40				
Asciminib	[redacted]	9.80	7.03	[redacted]	0.76	0.63	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 102: Base-case results pairwise – asciminib vs dasatinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Dasatinib	[redacted]	9.04	6.40				
Asciminib	[redacted]	9.80	7.03	1,995	0.76	0.63	3,180

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The convergence plots in Figure 45 and Figure 46 (vs bosutinib) show that simulations even prior to 1,000 would result in a change to outcomes of less than 0.1%.

Figure 45: Convergence plot of incremental QALYs vs bosutinib

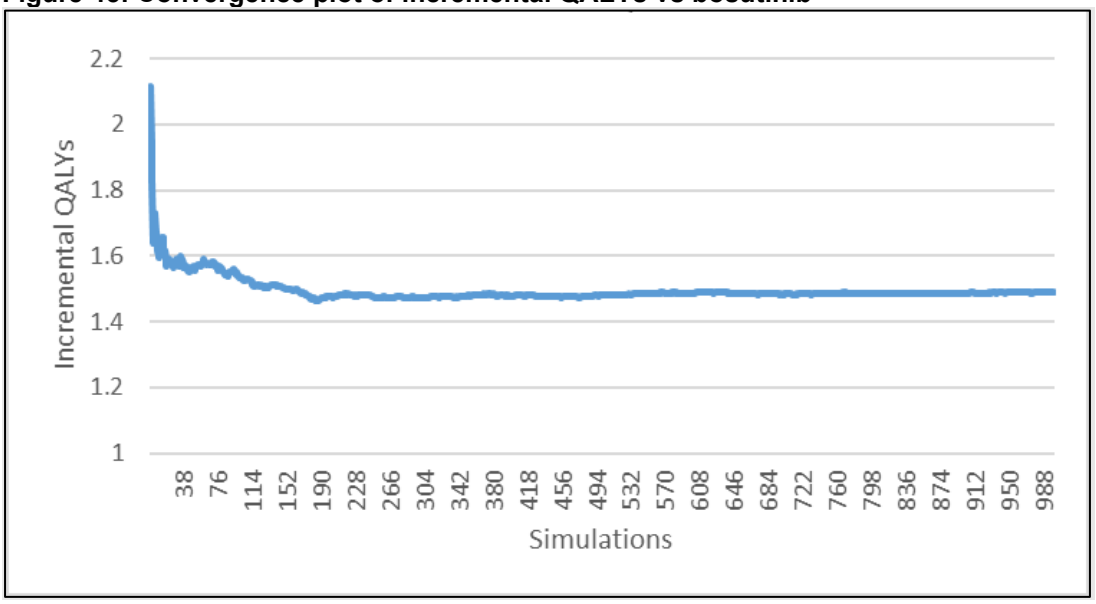
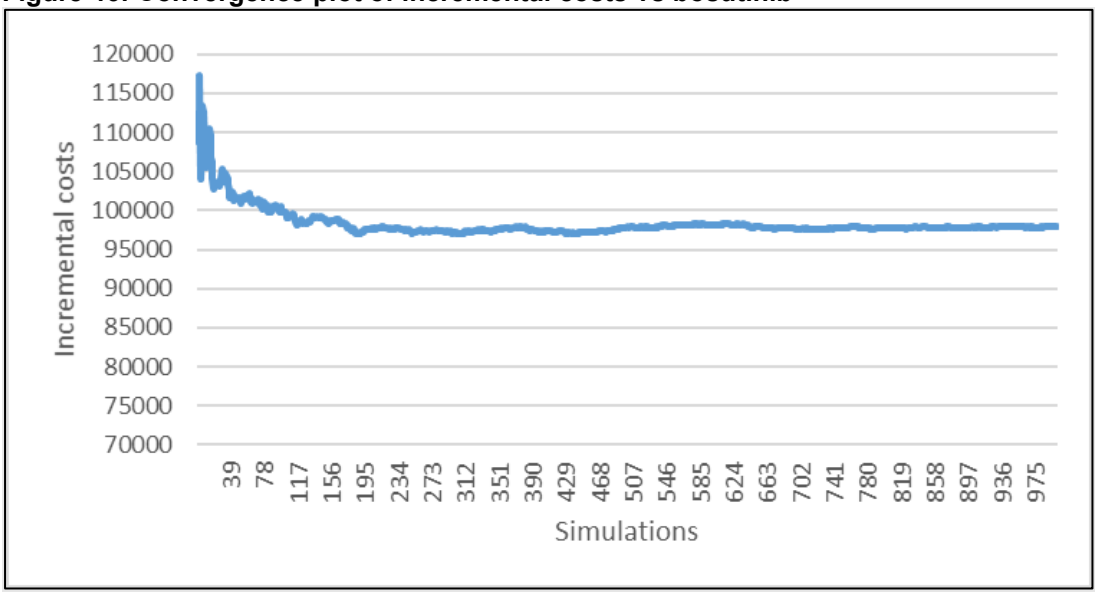


Figure 46: Convergence plot of incremental costs vs bosutinib



Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated.

Probabilistic results at list prices are presented in Table 103, Table 105, Table 107, and Table 109. Probabilistic results based on the approach to with-PAS analysis described above are presented in Table 104, Table 106, Table 108, and Table 110.

Overall, probabilistic results were very similar to deterministic results, When compared with bosutinib, asciminib at list price is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] per QALY gained. At the PAS discounted price, asciminib remains marginally more expensive than bosutinib and the ICER falls to £2,767.

When compared with ponatinib, asciminib at list price is associated with lower costs but also lower QALYs, resulting in an ICER for asciminib compared to ponatinib of [redacted] saved per QALY lost. At the PAS discounted price, the costs associated with asciminib fall further, and the ICER for asciminib compared to ponatinib rises to £261,615 saved per QALY lost.

When compared with nilotinib at list price, asciminib at list price is associated with higher costs but also higher QALYs, resulting in an ICER of £[redacted] per QALY gained. After applying PAS discounts to the price of asciminib and nilotinib the incremental costs reduce and the ICER falls to £49,001.

When compared with dasatinib, asciminib at list price is associated with higher costs but also higher QALYs, resulting in an ICER of [redacted] per QALY gained. At the PAS discounted price, asciminib remains marginally more expensive than dasatinib and the ICER falls to £3,665.

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) can be seen in Figure 47–Figure 62.

Based on list prices, asciminib had a [redacted] probability of being cost-effective compared to bosutinib at both £20,000 and £30,000 per QALY respectively. Asciminib had a [redacted] probability of being cost-effective compared to ponatinib at both £20,000 and £30,000 per QALY respectively. Asciminib had a [redacted] chance of being cost-effective

compared to nilotinib at both £20,000 and £30,000 per QALY. Asciminib had a [redacted] chance of being cost-effective compared to dasatinib at both £20,000 and £30,000 per QALY.

Based on PAS prices, asciminib had a 99% and 100% probability of being cost-effective compared to bosutinib at £20,000 and £30,000 per QALY respectively. Asciminib had a 100% probability of being cost-effective compared to ponatinib at both £20,000 and £30,000 per QALY respectively. Asciminib had a 0% and 1% chance of being cost-effective compared to nilotinib at £20,000 and £30,000 per QALY respectively. Asciminib had a 98% and 100% chance of being cost-effective compared to dasatinib at £20,000 and £30,000 per QALY respectively.

B.3.8.1.1 *Asciminib vs bosutinib*

Table 103: Base-case results pairwise – asciminib vs bosutinib (List price of all treatments)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Bosutinib	[redacted]	6.75			
Asciminib	[redacted]	8.25	[redacted]	1.50	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 104: Base-case results pairwise – asciminib vs bosutinib (PAS price of asciminib)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Bosutinib	[redacted]	6.75			
Asciminib	[redacted]	8.25	4,159	1.50	2,767

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 47: Cost-effectiveness plane – asciminib (list price) vs bosutinib

Abbreviations: QALYs, quality-adjusted life years.

Figure 48: Cost-effectiveness plane – asciminib (PAS price) vs bosutinib

Abbreviations: QALYs, quality-adjusted life years.

Figure 49: Cost-effectiveness acceptability curve - asciminib (list price) vs bosutinib

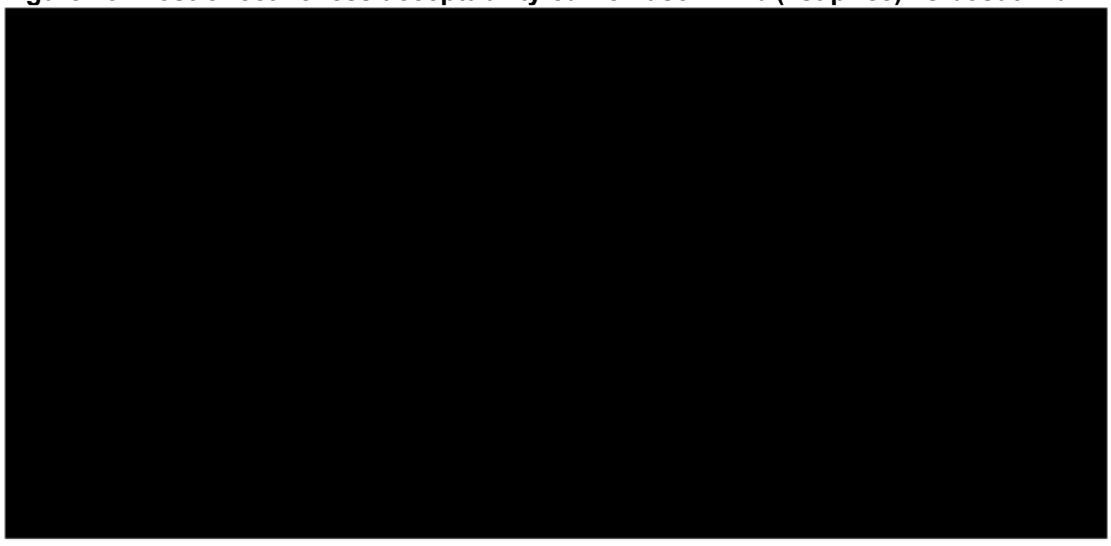
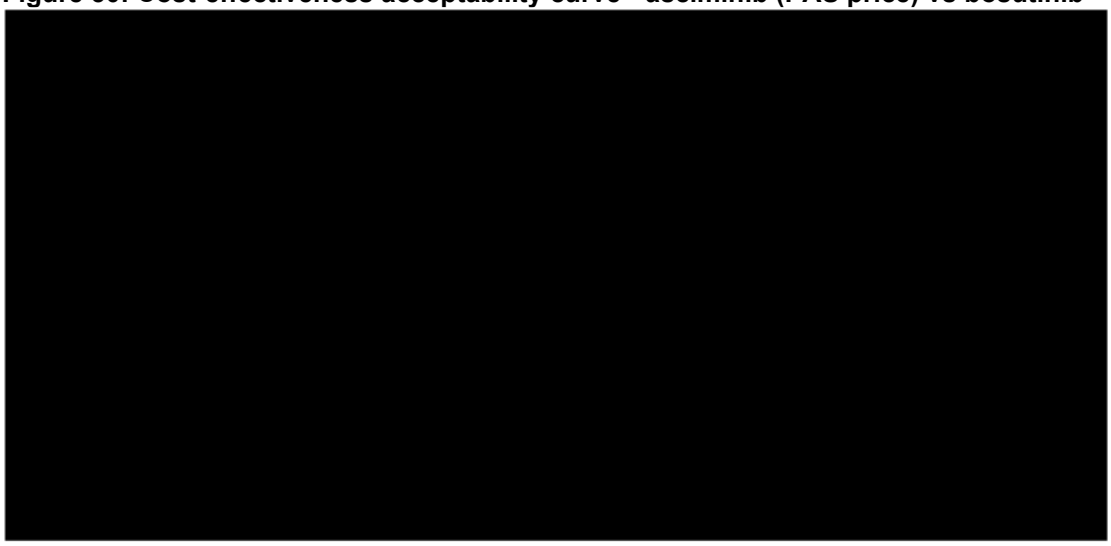


Figure 50: Cost-effectiveness acceptability curve - asciminib (PAS price) vs bosutinib



B.3.8.1.2 *Asciminib vs ponatinib*

Table 105: Base-case results pairwise – asciminib vs ponatinib (List price of all treatments)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Ponatinib	[redacted]	7.26			
Asciminib	[redacted]	6.72	[redacted]	-0.55	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 106: Base-case results pairwise – asciminib (PAS price) vs ponatinib

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Ponatinib	[redacted]	7.26			
Asciminib	[redacted]	6.72	-141,406	-0.54	261,615

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 51: Cost-effectiveness plane - asciminib (list price) vs ponatinib

Abbreviations: QALYs, quality-adjusted life years.

Figure 52: Cost-effectiveness plane - asciminib (PAS price) vs ponatinib

Abbreviations: QALYs, quality-adjusted life years.

Figure 53: Cost-effectiveness acceptability curve - asciminib (list price) vs ponatinib

Figure 54: Cost-effectiveness acceptability curve - asciminib (PAS price) vs ponatinib

B.3.8.1.3 *Asciminib vs nilotinib*

Table 107: Base-case results pairwise – asciminib vs nilotinib (list prices of all treatments)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Nilotinib	[redacted]	6.18			
Asciminib	[redacted]	7.13	[redacted]	0.95	[redacted]

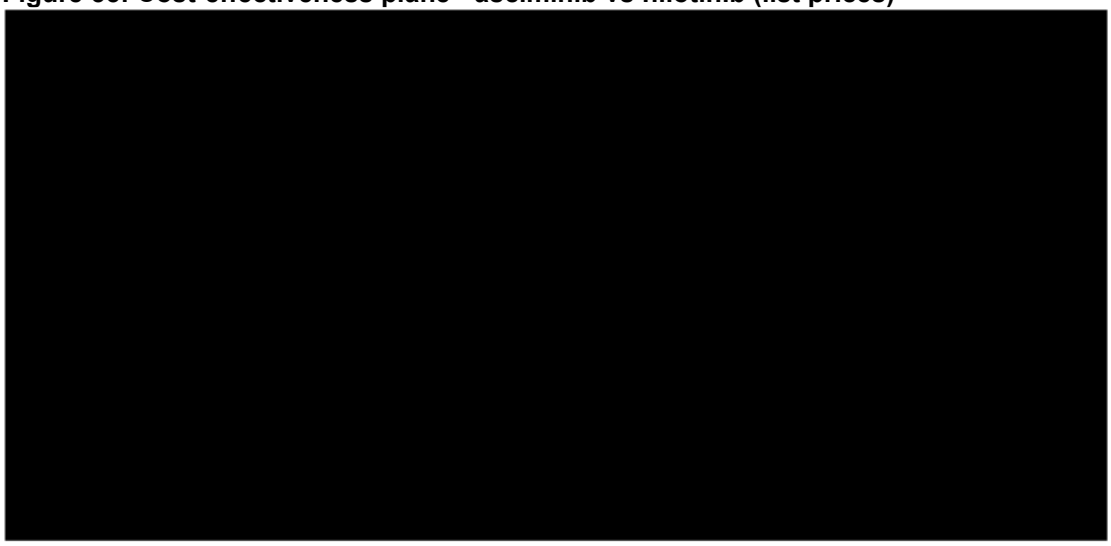
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 108: Base-case results pairwise – asciminib (PAS price) vs nilotinib (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Nilotinib	[redacted]	6.18			
Asciminib	[redacted]	7.12	46,354	0.95	49,001

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 55: Cost-effectiveness plane - asciminib vs nilotinib (list prices)



Abbreviations: QALYs, quality-adjusted life

Figure 56: Cost-effectiveness plane - asciminib (PAS price) vs nilotinib (PAS price)

Abbreviations: QALYs, quality-adjusted life years.

Figure 57: Cost-effectiveness acceptability curve - asciminib vs nilotinib (list prices)

Figure 58: Cost-effectiveness acceptability curve - asciminib (PAS price) vs nilotinib (PAS price)

B.3.8.1.4 *Asciminib vs dasatinib*

Table 109: Base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Dasatinib	[redacted]	6.40			
Asciminib	[redacted]	7.05	[redacted]	0.65	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 110: Base-case results pairwise – asciminib (PAS price) vs dasatinib

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Dasatinib	[redacted]	6.41			
Asciminib	[redacted]	7.05	2,356	0.64	3,665

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 59: Cost-effectiveness plane - asciminib (list price) vs dasatinib

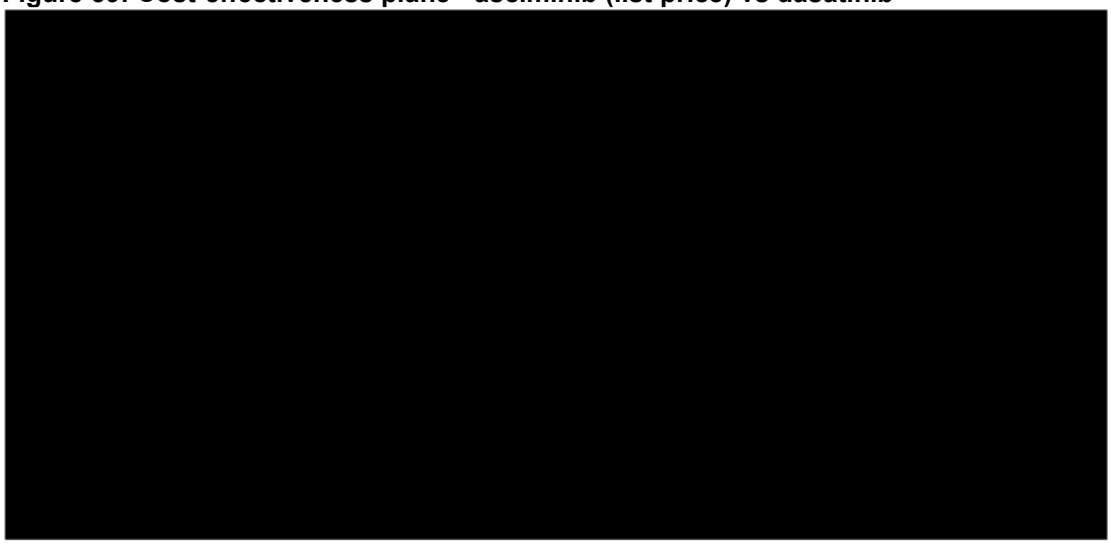
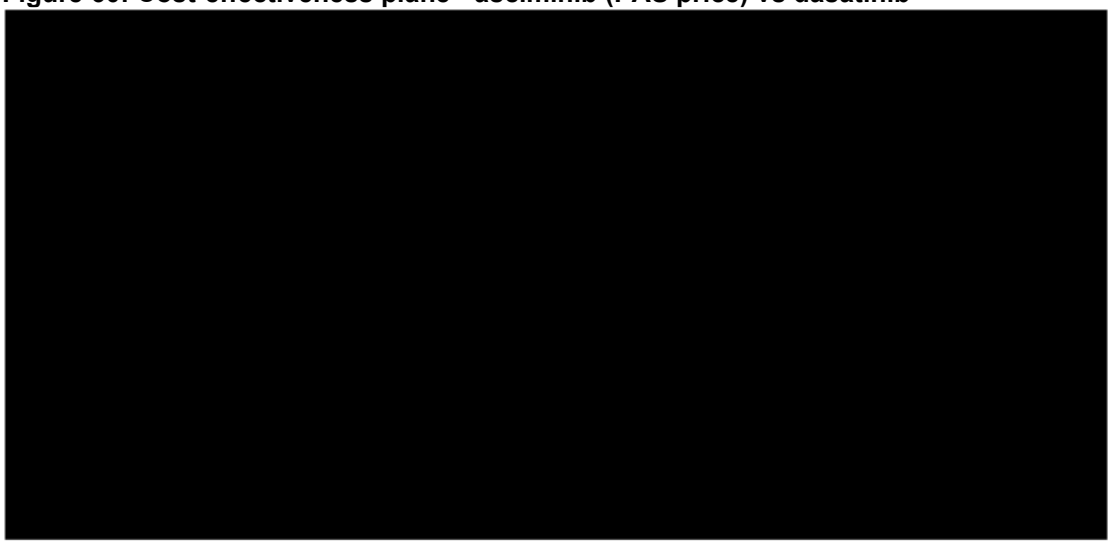


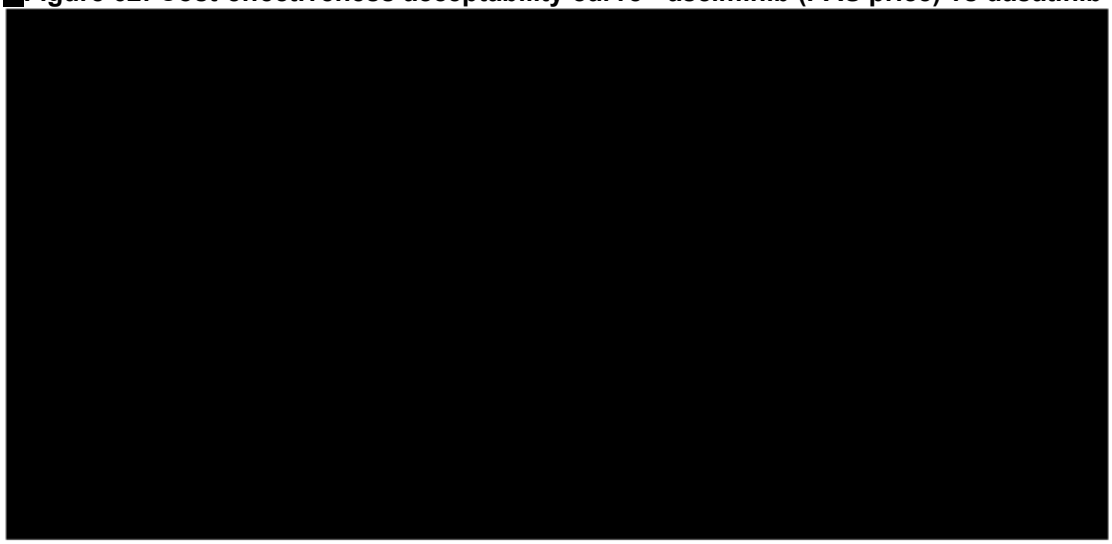
Figure 60: Cost-effectiveness plane - asciminib (PAS price) vs dasatinib



Abbreviations: QALYs, quality-adjusted life years.

Figure 61: Cost-effectiveness acceptability curve - asciminib (list price) vs dasatinib

Figure 62: Cost-effectiveness acceptability curve - asciminib (PAS price) vs dasatinib



B.3.8.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±20% where no estimates of precision were available. Analysis was undertaken using list prices for asciminib and comparators, and again after applying the PAS discount to asciminib and to nilotinib. In the analysis of list prices, the ICER was recorded at the upper and lower values, and the values for the ten parameters with the largest influence on the ICER were plotted as a tornado diagram. After application of PAS discounts, variation in some parameters led to scenarios in which asciminib dominated. Hence for these analyses, the net monetary benefit (NMB) was recorded at the upper and lower values of the parameter and a tornado diagram generated for the ten most influential parameters.

In comparisons of asciminib at list price, mean overall survival post-discontinuation of asciminib and on the comparator were the two most influential parameters in the comparison with ponatinib, dasatinib and nilotinib, and were the third and fifth most influential in the comparison with bosutinib. The HSUV whilst on third-line treatment was the most influential parameter in the comparison with bosutinib, and the third most influential in the comparisons with ponatinib, nilotinib and dasatinib. The second and fourth most influential parameters in the comparison with bosutinib were RDI for asciminib and for bosutinib respectively; RDI was influential in the comparison with ponatinib, dasatinib and nilotinib albeit less so. In the comparisons with ponatinib, nilotinib and dasatinib, the median time to treatment discontinuation for the relevant comparator was the fifth or sixth most influential parameter. In all four comparisons, parameters appearing further down the list of the most influential parameters did not exert a large influence on the ICER.

After application of the PAS discount to prices for asciminib and nilotinib, the influence of RDI and median treatment duration (for ponatinib, dasatinib and nilotinib) increased. The influence of mean overall survival on asciminib and on the comparators decreased. The relative influence of the HSUV whilst on third-line treatment remained broadly as observed in the analysis with list prices.

B.3.8.2.1 *Asciminib vs bosutinib*

Table 111: One-way sensitivity analysis - asciminib vs bosutinib (list price for both treatments)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	[redacted]	[redacted]
RDI - Asciminib (0.80, 0.95)	[redacted]	[redacted]
Mean overall survival from discontinuation of 3L treatment - Bosutinib (5.60, 8.40)	[redacted]	[redacted]
RDI – Bosutinib (0.80, 0.95)	[redacted]	[redacted]
Mean overall survival from discontinuation of 3L treatment - Asciminib (5.60, 8.40)	[redacted]	[redacted]
TTD Survival parameters - asciminib from ascembl - vs bosutinib - lognormal – scale parameter (2.58, 3.87)	[redacted]	[redacted]
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	[redacted]	[redacted]
TTD Survival parameters - asciminib from ascembl - vs bosutinib - lognormal - bosutinib dummy (-0.97, -1.45)	[redacted]	[redacted]
TTD Survival parameters - asciminib from ascembl - vs bosutinib - lognormal – shape parameter (1.41, 2.12)	[redacted]	[redacted]
SCT survival - PD - RFS - log-normal – scale parameter (2.14, 3.21)	[redacted]	[redacted]

Abbreviations: 3L, third-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; PD, progressed disease; QALY, quality-adjusted life-year; RDI, relative dose intensity; RFS, relapse-free survival; TTD, time to discontinuation.

Figure 63: Tornado diagram - asciminib vs bosutinib (list price for both treatments)

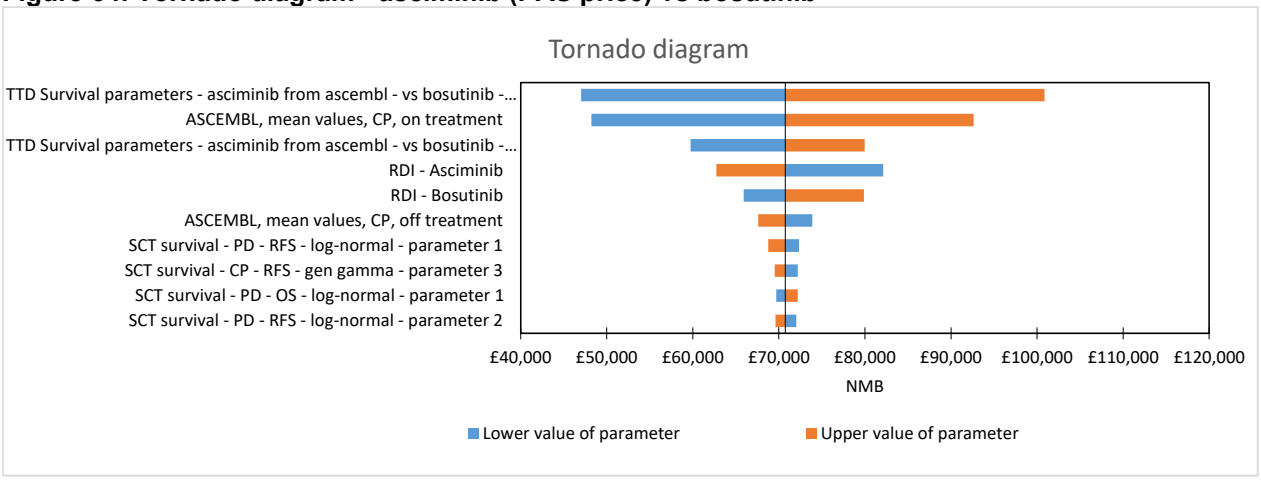
Abbreviations: 3L, third-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; PD, progressed disease; QALY, quality-adjusted life-year; PD, progressed disease; RDI, relative dose intensity; RFS, relapse-free survival; TTD, time to discontinuation.

Table 112: One-way sensitivity analysis - asciminib vs bosutinib (PAS discounted price for asciminib)

Parameter	NMB at lower value of parameter	NMB at upper value of parameter
TTD Survival parameters - asciminib from ascembl - vs bosutinib - lognormal – scale parameter (2.58, 3.87)	£47,025	£100,874
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	£48,218	£92,635
TTD Survival parameters - asciminib from ascembl - vs bosutinib - lognormal – shape parameter (1.41, 2.12)	£59,750	£79,980
RDI - Asciminib (0.80, 0.95)	£82,124	£62,731
RDI – Bosutinib (0.80, 0.95)	£65,907	£79,867
Mean overall survival from discontinuation of 3L treatment - Asciminib (5.60, 8.40)	£73,884	£67,610
SCT survival - PD - RFS - log-normal – scale parameter (2.14, 3.21)	£72,335	£68,775
SCT survival - CP - RFS - gen gamma – shape parameter (-19.34, -29.01)	£72,194	£69,516
SCT survival - PD - OS - log-normal – scale parameter (2.90, 4.35)	£69,684	£72,207
SCT survival - PD - RFS - log-normal – shape parameter (1.59, 2.39)	£72,025	£69,619

Abbreviations: 3L, third-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; QALY, quality-adjusted life-year; RDI, relative dose intensity; RFS, relapse-free survival; TTD, time to discontinuation.

Figure 64: Tornado diagram - asciminib (PAS price) vs bosutinib



Abbreviations: 3L, third-line; CP, chronic phase; NMB, net monetary benefit; OS, overall survival; PD, progressed disease; QALY, quality-adjusted life-year; RDI, relative dose intensity; RFS, relapse-free survival; TTD, time to discontinuation.

B.3.8.2.2 *Asciminib vs ponatinib*

Table 113: One-way sensitivity analysis - asciminib vs ponatinib (list price for both treatments)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Mean overall survival from discontinuation of 3L treatment - Asciminib (5.60, 8.40)	[redacted]	[redacted]
Mean overall survival from discontinuation of 3L treatment - Ponatinib (5.60, 8.40)	[redacted]	[redacted]
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	[redacted]	[redacted]
Median Treatment Duration - Ponatinib (25.68, 38.52)	[redacted]	[redacted]
TTD Survival parameters - asciminib vs ponatinib - exponential - parameter 1 (0.03, 0.04)	[redacted]	[redacted]
RDI - Ponatinib (0.80, 1.00)	[redacted]	[redacted]
RDI - Asciminib (0.80, 0.95)	[redacted]	[redacted]
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	[redacted]	[redacted]
Time horizon (30 years, 50 years)	[redacted]	[redacted]
HSUV in Allo-SCT, relapse free, from CP (0.57, 0.85)	[redacted]	[redacted]

Abbreviations: 3L, third-line; Allo-SCT, allogenic stem cell transplant; CP, chronic phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 65: 66: Tornado diagram - asciminib vs ponatinib (list price for both treatments)

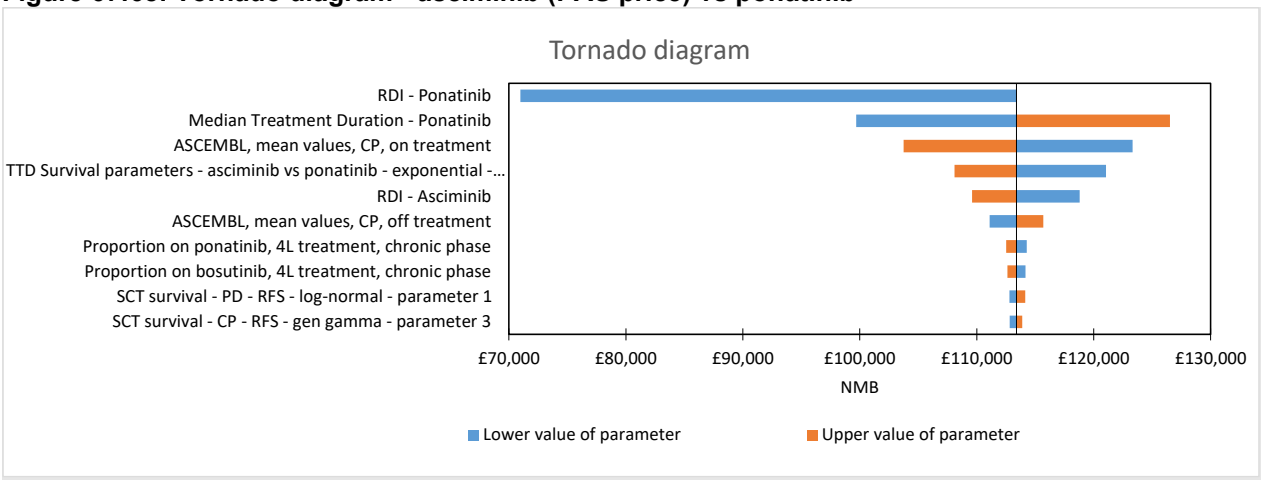
Abbreviations: 3L, third-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time to discontinuation.

Table 114: One-way sensitivity analysis - asciminib (PAS price) vs ponatinib

Parameter	NMB at lower value of parameter	NMB at upper value of parameter
RDI - Ponatinib (0.80, 1.00)	£70,987	£113,395
Median Treatment Duration - Ponatinib (25.68, 38.52)	£99,692	£126,525
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	£123,328	£103,746
TTD Survival parameters - asciminib vs ponatinib - exponential - parameter 1 (0.03, 0.04)	£121,052	£108,106
RDI - Asciminib (0.80, 0.95)	£118,796	£109,591
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	£111,098	£115,693
Proportion on imatinib, 4L treatment, chronic phase (0.20, 0.30)	£114,271	£112,520
Proportion on omacetaxine, 4L treatment, chronic phase (0.24, 0.36)	£114,169	£112,621
SCT survival - PD - RFS - log-normal - parameter 1 (2.14, 3.21)	£112,797	£114,135
SCT survival - CP - RFS - gen gamma - parameter 3 (-19.34, -29.01)	£112,812	£113,889

Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; NMB, net monetary benefit; PD, progressed disease; RDI, relative dose intensity; RFS, relapse free survival; SCT, stem cell transplant; TTD, time to discontinuation.

Figure 67:68: Tornado diagram - asciminib (PAS price) vs ponatinib



Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; NMB, net monetary benefit; NMB, net monetary benefit; RDI, relative dose intensity; SCT, stem cell transplant; TTD, time to discontinuation.

B.3.8.2.3 *Asciminib vs nilotinib*

Table 115: One-way sensitivity analysis - asciminib vs nilotinib (list price for both treatments)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Mean overall survival from discontinuation of 3L treatment - Nilotinib (5.60, 8.40)	[redacted]	[redacted]
Mean overall survival from discontinuation of 3L treatment - Asciminib (5.60, 8.40)	[redacted]	[redacted]
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	[redacted]	[redacted]
Median Treatment Duration - Nilotinib (8.80, 13.20)	[redacted]	[redacted]
TTD Survival parameters - asciminib vs nilotinib - exponential - parameter 1 (0.02, 0.03)	[redacted]	[redacted]
RDI - Asciminib (0.80, 0.95)	[redacted]	[redacted]
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	[redacted]	[redacted]
Time horizon (30 years, 50 years)	[redacted]	[redacted]
HSUV in Allo-SCT, relapse free, from CP (0.57, 0.85)	[redacted]	[redacted]
Proportion on imatinib, 4L treatment, chronic phase (0.20, 0.30)	[redacted]	[redacted]

Abbreviations: 3L, third-line; Allo-SCT, allogenic stem cell transplant; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 69: Tornado diagram - asciminib vs nilotinib (list price for both treatments)

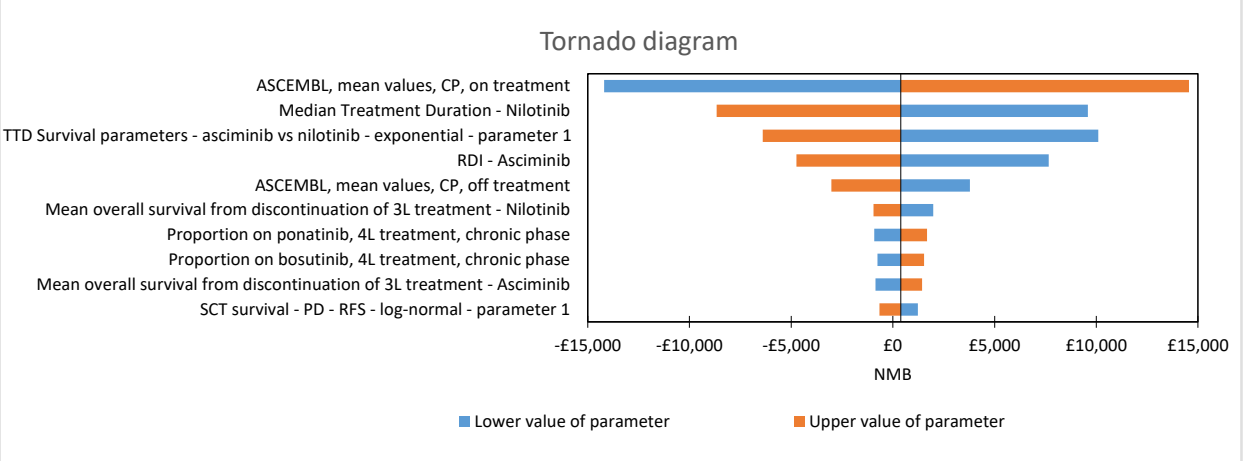
Abbreviations: 3L, third-line; 4L, fourth-line; Allo-SCT, allogenic stem cell transplant; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time to discontinuation.

Table 116: One-way sensitivity analysis - asciminib vs nilotinib (PAS price for both)

Parameter	NMB at lower value of parameter	NMB at upper value of parameter
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	-£14,192	£14,551
Median Treatment Duration - Nilotinib (8.80, 13.20)	£9,592	-£8,657
TTD Survival parameters - asciminib vs nilotinib - exponential - parameter 1 (0.02, 0.03)	£10,093	-£6,400
RDI - Asciminib (0.80, 0.95)	£7,662	-£4,739
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	£3,792	-£3,019
Mean overall survival from discontinuation of 3L treatment - Nilotinib (5.60, 8.40)	£1,989	-£948
Proportion on ponatinib, 4L treatment, chronic phase (0.20, 0.30)	-£912	£1,685
Proportion on bosutinib, 4L treatment, chronic phase (0.24, 0.36)	-£761	£1,534
Mean overall survival from discontinuation of 3L treatment - Asciminib (5.60, 8.40)	-£853	£1,440
SCT survival - PD - RFS - log-normal - parameter 1 (2.14, 3.21)	£1,234	-£658

Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; ICER, NMB, net monetary benefit; PD, progressed disease; RDI, relative dose intensity; RFS, relapse free survival; SCT, stem cell transplant; TTD, time to discontinuation.

Figure 70: Tornado diagram - asciminib vs nilotinib (PAS price for both treatments)



Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; NMB, net monetary benefit; PD, progressed disease; RDI, relative dose intensity; RFS, relapse free survival; SCT, stem cell transplant; TTD, time to discontinuation.

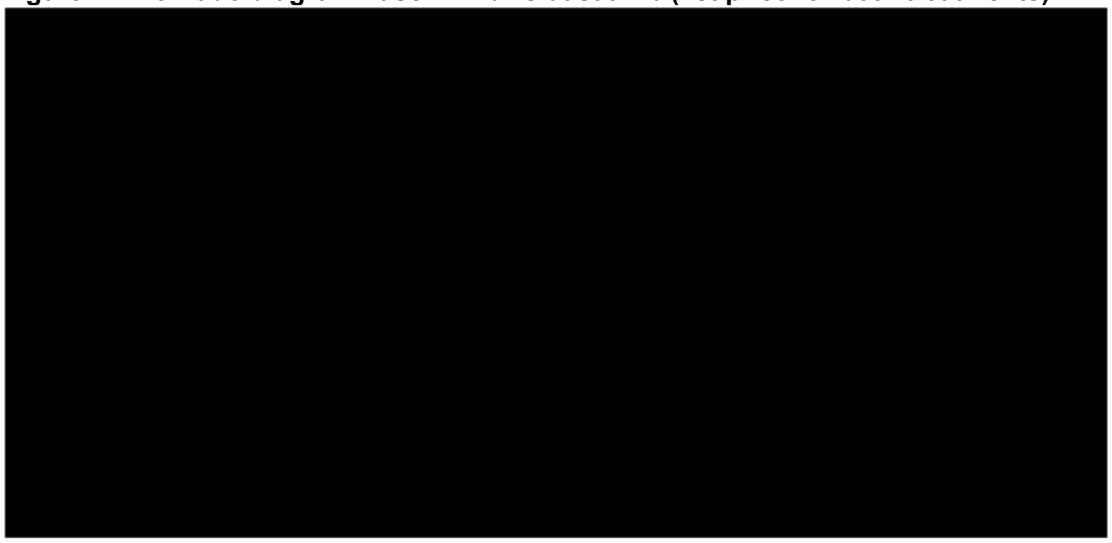
B.3.8.2.4 *Asciminib vs dasatinib*

Table 117: One-way sensitivity analysis - asciminib vs dasatinib (list price for both technologies)

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Mean overall survival from discontinuation of 3L treatment - Dasatinib (5.60, 8.40)	[redacted]	[redacted]
Mean overall survival from discontinuation of 3L treatment - Asciminib (5.60, 8.40)	[redacted]	[redacted]
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	[redacted]	[redacted]
RDI - Asciminib (0.80, 0.95)	[redacted]	[redacted]
Median Treatment Duration - Dasatinib (11.20, 16.80)	[redacted]	[redacted]
TTD Survival parameters - asciminib vs dasatinib - exponential - parameter 1 (0.02, 0.03)	[redacted]	[redacted]
RDI - Dasatinib (0.80, 1.00)	[redacted]	[redacted]
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	[redacted]	[redacted]
Proportion on ponatinib, 4L treatment, chronic phase (0.20, 0.30)	[redacted]	[redacted]
HSUV in Allo-SCT, relapse free, from CP (0.57, 0.85)	[redacted]	[redacted]

Abbreviations: 3L, third-line; 4L, fourth-line; Allo-SCT, allogenic stem cell transplant; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 71: Tornado diagram - asciminib vs dasatinib (list price for both treatments)



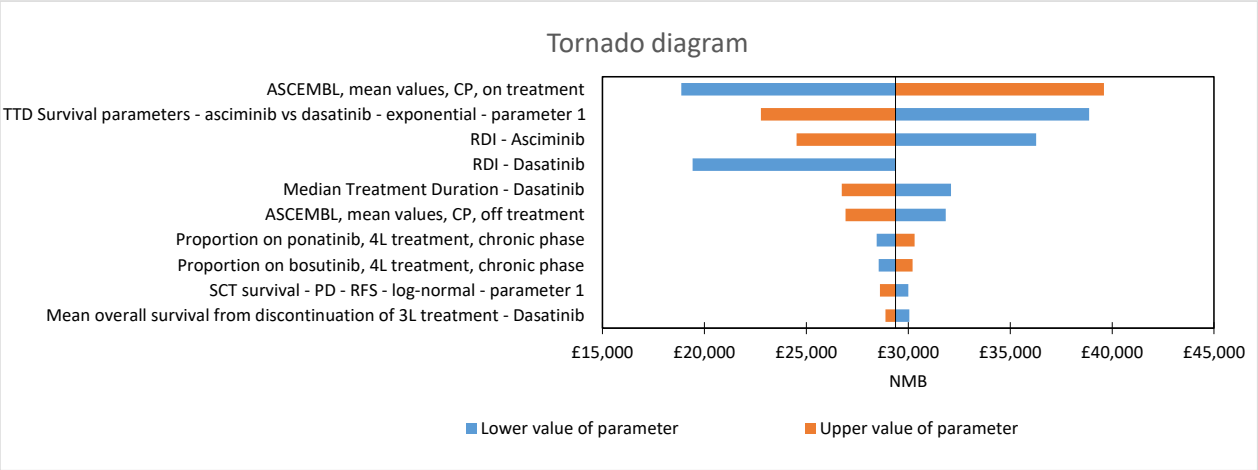
Abbreviations: 3L, third-line; 4L, fourth-line; Allo-SCT, allogenic stem cell transplant; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time to discontinuation.

Table 118: One-way sensitivity analysis - asciminib (PAS price) vs dasatinib

Parameter	NMB at lower value of parameter	NMB at upper value of parameter
ASCEMBL, mean values, CP, on treatment (0.67, 1.00)	£18,863	£39,601
TTD Survival parameters - asciminib vs dasatinib - exponential - parameter 1 (0.02, 0.03)	£38,871	£22,768
RDI - Asciminib (0.80, 0.95)	£36,277	£24,523
RDI - Dasatinib (0.80, 1.00)	£19,421	£29,381
Median Treatment Duration - Dasatinib (11.20, 16.80)	£32,095	£26,736
ASCEMBL, mean values, CP, off treatment (0.65, 0.97)	£31,834	£26,929
Proportion on ponatinib, 4L treatment, chronic phase (0.20, 0.30)	£28,447	£30,316
Proportion on bosutinib, 4L treatment, chronic phase (0.24, 0.36)	£28,555	£30,208
SCT survival - PD - RFS - log-normal - parameter 1 (2.14, 3.21)	£30,009	£28,607
Mean overall survival from discontinuation of 3L treatment - Dasatinib (5.60, 8.40)	£30,059	£28,885

Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; NMB, net monetary benefit; RDI, relative dose intensity; RFS, relapse free survival; SCT, stem cell transplant; TTD, time to discontinuation.

Figure 72: Tornado diagram - asciminib (PAS price) vs dasatinib



Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; PD, progressed disease; QALY, quality-adjusted life-year; RDI, relative dose intensity; RFS, relapse free survival; SCT, stem cell transplant; TTD, time to discontinuation.

B.3.8.3 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied. Analyses were undertaken with asciminib and comparators at list price, and again after applying a PAS discount to prices for asciminib and nilotinib.

In the analysis using list prices, ICERs reduced as the duration of overall survival after discontinuation of third-line therapy was reduced, but the impact was modest. (As ponatinib is more costly and more effective than asciminib, this change for ponatinib makes asciminib less cost-effective, but it remains cost-effective). The

impact of changing the proportions of patients undergoing allo-SCT was minimal, as was the impact of changing the duration of AP or BP. The impact of alternative assumptions on HSUV was modest; in the comparisons with dasatinib, nilotinib and bosutinib ICERs for asciminib fell when alternative HSUVs were applied and this was most marked where data were taken from Szabo et al. 2010 (160). In the comparison with ponatinib, the ICER for ponatinib increased using alternative HSUVs from the ASCEMBL data. Overall, the assumption that quality of life is dependent on treatment status but not treatment arm (base case) generates conservative results. In the comparison with bosutinib, the use of alternative model specifications for TTD had a modest impact on the ICER; ICERs fell with all of the alternative specifications apart from the Gompertz model, and there the increase was minimal. In summary, ICERs were robust to scenario analysis. Where changes were not minimal the impact was to reduce the ICER for asciminib vs all comparators from the base case.

Analysis after application of PAS discounts was generally in agreement with that based on list prices. The ICER for asciminib compared to bosutinib was more markedly influenced by the choice of model specification for TTD. However, the results again indicated that the base case lognormal specification generated conservative results. Comparisons where the asciminib PAS led to highly cost-effective results (vs bosutinib and dasatinib) were more influenced by varying parameters, as the relative impact on incremental costs was higher given the smaller over incremental cost, although results still remained below £30,000 per QALY and occasionally asciminib was dominant.

As previously mentioned, this submission considers the effectiveness and cost-effectiveness of asciminib in a third and later line population as aligned with the marketing authorisation, and data from the pivotal ASCEMBL trial which assessed patients at third line and beyond. Our approach to the modelling of OS following discontinuation of third line treatment is based on the approach recommended by the ERG in TA401 (bosutinib), in which OS is the sum of TTD plus a fixed period of survival beyond third line treatment. Scenario analysis - in which survival following discontinuation of third line treatment is reduced - demonstrate that it reduces the ICERs for asciminib vs all comparators.

B.3.8.3.1 *Asciminib vs bosutinib*

Table 119: Scenario results – asciminib vs bosutinib (list price for both treatments)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	1.51	[redacted]	[redacted]
Five years survival post 3L discontinuation	[redacted]	1.68	[redacted]	[redacted]
Three and a half years survival post 3L discontinuation	[redacted]	1.82	[redacted]	[redacted]
Discount rates zero	[redacted]	2.69	[redacted]	[redacted]
Discount rates 5%	[redacted]	1.23	[redacted]	[redacted]
Mean time in AP 12 months	[redacted]	1.52	[redacted]	[redacted]
Mean time in AP 8 months	[redacted]	1.51	[redacted]	[redacted]
Mean time in BP 8 months	[redacted]	1.52	[redacted]	[redacted]
Mean time in BP 4 months	[redacted]	1.50	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 30%	[redacted]	1.47	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 10%	[redacted]	1.53	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 40%	[redacted]	1.48	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 10%	[redacted]	1.53	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 40%	[redacted]	1.47	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 10%	[redacted]	1.53	[redacted]	[redacted]
HSUV by treatment arm	[redacted]	1.57	[redacted]	[redacted]
HSUV by treatment status & arm	[redacted]	1.62	[redacted]	[redacted]
HSUV from Szabo 2010	[redacted]	1.74	[redacted]	[redacted]
Exponential survival for TTD for asciminib & bosutinib	[redacted]	0.89	[redacted]	[redacted]
Weibull survival for TTD for asciminib & bosutinib	[redacted]	1.18	[redacted]	[redacted]
Gompertz survival for TTD for asciminib & bosutinib	[redacted]	3.17	[redacted]	[redacted]
Loglogistic survival for TTD for asciminib & bosutinib	[redacted]	1.38	[redacted]	[redacted]
Gamma survival for TTD for asciminib & bosutinib	[redacted]	1.09	[redacted]	[redacted]
Generalised Gamma survival for TTD for asciminib & bosutinib	[redacted]	1.87	[redacted]	[redacted]

Abbreviations: 3L, third-line; AP, accelerated phase; BP, blast phase; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; QALY, quality-adjusted life-year; SCT, stem cell transplant; TTD, time to discontinuation.

Table 120: Scenario results – asciminib (PAS price) vs bosutinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	£4,824	1.51	£3,192	0%
Five years survival post 3L discontinuation	£13,753	1.68	£8,186	156%
Three and a half years survival post 3L discontinuation	£21,905	1.82	£12,031	277%
Discount rates zero	£46,511	2.69	£17,313	442%
Discount rates 5%	-£3,911	1.23	Dominant	-
Mean time in AP 12 months	£4,828	1.52	£2,189	-31%
Mean time in AP 8 months	£4,829	1.51	Dominant	-
Mean time in BP 8 months	£4,050	1.52	Dominant	-
Mean time in BP 4 months	£5,608	1.50	Dominant	-
Proportion undergoing SCT at 3L discontinuation 30%	£6,234	1.47	£4,229	33%
Proportion undergoing SCT at 3L discontinuation 10%	£4,254	1.53	£2,786	-13%
Proportion undergoing SCT at start of AP 40%	£4,258	1.48	£3,205	0%
Proportion undergoing SCT at start of AP 10%	£5,107	1.53	£2,663	-17%
Proportion undergoing SCT at start of BP 40%	£3,243	1.47	£3,733	17%
Proportion undergoing SCT at start of BP 10%	£5,615	1.53	£2,925	-8%
HSUV by treatment arm	£4,824	1.57	£2,377	-26%
HSUV by treatment status & arm	£4,824	1.62	£2,880	-10%
HSUV from Szabo 2010	£4,824	1.74	£3,343	5%
Exponential survival for TTD for asciminib & bosutinib	£2,234	0.89	£2,207	-31%
Weibull survival for TTD for asciminib & bosutinib	£7,816	1.18	£3,664	15%
Gompertz survival for TTD for asciminib & bosutinib	£19,340	3.17	£3,076	-4%
Loglogistic survival for TTD for asciminib & bosutinib	£2,579	1.38	£2,982	-7%
Gamma survival for TTD for asciminib & bosutinib	£6,130	1.09	£2,778	-13%
Generalised Gamma survival for TTD for asciminib & bosutinib	£33,692	1.87	£2,519	-21%

Abbreviations: 3L, third-line; AP, accelerated phase; BP, blast phase; CP, chronic phase; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; QALY, quality-adjusted life-year; SCT, stem cell transplant; TTD, time to discontinuation.

B.3.8.3.2 *Asciminib vs ponatinib*

Table 121: Scenario results – asciminib vs ponatinib (list price for both treatments)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base–case ICER
Base-case	[redacted]	-0.56	[redacted]	[redacted]
Five years survival post 3L discontinuation	[redacted]	-0.62	[redacted]	[redacted]
Three and a half years survival post 3L discontinuation	[redacted]	-0.68	[redacted]	[redacted]
Discount rates zero	[redacted]	-0.97	[redacted]	[redacted]
Discount rates 5%	[redacted]	-0.46	[redacted]	[redacted]
Mean time in AP 12 months	[redacted]	-0.56	[redacted]	[redacted]
Mean time in AP 8 months	[redacted]	-0.56	[redacted]	[redacted]
Mean time in BP 8 months	[redacted]	-0.56	[redacted]	[redacted]
Mean time in BP 4 months	[redacted]	-0.55	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 30%	[redacted]	-0.56	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 10%	[redacted]	-0.56	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 40%	[redacted]	-0.55	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 10%	[redacted]	-0.56	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 40%	[redacted]	-0.54	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 10%	[redacted]	-0.57	[redacted]	[redacted]
HSUV by treatment arm	[redacted]	-0.44	[redacted]	[redacted]
HSUV by treatment status & arm	[redacted]	-0.46	[redacted]	[redacted]
HSUV from Szabo 2010	[redacted]	-0.67	[redacted]	[redacted]

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCT, stem cell transplant.

Table 122: Scenario results – asciminib (PAS price) vs ponatinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base–case ICER
Base-case	-£141,299	-0.56	£253,193	0%
Five years survival post 3L discontinuation	-£144,357	-0.62	£231,366	-9%
Three and a half years survival post 3L discontinuation	-£146,844	-0.68	£216,014	-15%
Discount rates zero	-£178,503	-0.97	£184,865	-27%
Discount rates 5%	-£130,876	-0.46	£285,441	13%
Mean time in AP 12 months	-£141,291	-0.56	£252,355	0%
Mean time in AP 8 months	-£141,307	-0.56	£254,033	0%
Mean time in BP 8 months	-£141,004	-0.56	£251,107	-1%
Mean time in BP 4 months	-£141,596	-0.55	£255,305	1%
Proportion undergoing SCT at 3L discontinuation 30%	-£142,601	-0.56	£255,801	1%
Proportion undergoing SCT at 3L discontinuation 10%	-£140,769	-0.56	£252,109	0%
Proportion undergoing SCT at start of AP 40%	-£141,072	-0.55	£258,547	2%
Proportion undergoing SCT at start of AP 10%	-£141,412	-0.56	£250,604	-1%
Proportion undergoing SCT at start of BP 40%	-£140,693	-0.54	£259,566	3%
Proportion undergoing SCT at start of BP 10%	-£141,602	-0.57	£250,141	-1%
HSUV by treatment arm	-£141,299	-0.44	£319,675	26%
HSUV by treatment status & arm	-£141,299	-0.46	£309,260	22%
HSUV from Szabo 2010	-£141,299	-0.67	£212,138	-16%

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCT, stem cell transplant.

B.3.8.3.3 *Asciminib vs nilotinib*

Table 123: Scenario results – asciminib vs nilotinib (list price for both treatments)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	0.93	[redacted]	[redacted]
Five years survival post 3L discontinuation	[redacted]	1.03	[redacted]	[redacted]
Three and a half years survival post 3L discontinuation	[redacted]	1.11	[redacted]	[redacted]
Discount rates zero	[redacted]	1.49	[redacted]	[redacted]
Discount rates 5%	[redacted]	0.79	[redacted]	[redacted]
Mean time in AP 12 months	[redacted]	0.93	[redacted]	[redacted]
Mean time in AP 8 months	[redacted]	0.93	[redacted]	[redacted]
Mean time in BP 8 months	[redacted]	0.93	[redacted]	[redacted]
Mean time in BP 4 months	[redacted]	0.92	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 30%	[redacted]	0.93	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 10%	[redacted]	0.93	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 40%	[redacted]	0.91	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 10%	[redacted]	0.94	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 40%	[redacted]	0.91	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 10%	[redacted]	0.94	[redacted]	[redacted]
HSUV by treatment arm	[redacted]	0.98	[redacted]	[redacted]
HSUV by treatment status & arm	[redacted]	1.04	[redacted]	[redacted]
HSUV from Szabo 2010	[redacted]	1.09	[redacted]	[redacted]

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCT, stem cell transplant.

Table 124: Scenario results – asciminib vs nilotinib (PAS discounted price for both treatments)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base–case ICER
Base-case	£46,081	0.93	£49,584	0%
Five years survival post 3L discontinuation	£50,373	1.03	£49,074	-1%
Three and a half years survival post 3L discontinuation	£53,854	1.11	£48,534	-2%
Discount rates zero	£76,131	1.49	£51,157	3%
Discount rates 5%	£39,006	0.79	£49,326	-1%
Mean time in AP 12 months	£46,063	0.93	£49,424	0%
Mean time in AP 8 months	£46,100	0.93	£49,744	0%
Mean time in BP 8 months	£45,649	0.93	£48,855	-1%
Mean time in BP 4 months	£46,516	0.92	£50,322	1%
Proportion undergoing SCT at 3L discontinuation 30%	£47,944	0.93	£51,565	4%
Proportion undergoing SCT at 3L discontinuation 10%	£45,324	0.93	£48,733	-2%
Proportion undergoing SCT at start of AP 40%	£45,748	0.91	£50,206	1%
Proportion undergoing SCT at start of AP 10%	£46,248	0.94	£49,282	-1%
Proportion undergoing SCT at start of BP 40%	£45,207	0.91	£49,903	1%
Proportion undergoing SCT at start of BP 10%	£46,519	0.94	£49,431	0%
HSUV by treatment arm	£46,081	0.98	£46,949	-5%
HSUV by treatment status & arm	£46,081	1.04	£44,444	-10%
HSUV from Szabo 2010	£46,081	1.09	£42,346	-15%

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCT, stem cell transplant.

B.3.8.3.4 *Asciminib vs dasatinib*

Table 125: Scenario results – asciminib vs dasatinib (list price for both treatments)

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	0.63	[redacted]	[redacted]
Five years survival post 3L discontinuation	[redacted]	0.70	[redacted]	[redacted]
Three and a half years survival post 3L discontinuation	[redacted]	0.76	[redacted]	[redacted]
Discount rates zero	[redacted]	1.03	[redacted]	[redacted]
Discount rates 5%	[redacted]	0.53	[redacted]	[redacted]
Mean time in AP 12 months	[redacted]	0.63	[redacted]	[redacted]
Mean time in AP 8 months	[redacted]	0.63	[redacted]	[redacted]
Mean time in BP 8 months	[redacted]	0.63	[redacted]	[redacted]
Mean time in BP 4 months	[redacted]	0.62	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 30%	[redacted]	0.63	[redacted]	[redacted]
Proportion undergoing SCT at 3L discontinuation 10%	[redacted]	0.63	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 40%	[redacted]	0.61	[redacted]	[redacted]
Proportion undergoing SCT at start of AP 10%	[redacted]	0.63	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 40%	[redacted]	0.61	[redacted]	[redacted]
Proportion undergoing SCT at start of BP 10%	[redacted]	0.64	[redacted]	[redacted]
HSUV by treatment arm	[redacted]	0.69	[redacted]	[redacted]
HSUV by treatment status & arm	[redacted]	0.73	[redacted]	[redacted]
HSUV from Szabo 2010	[redacted]	0.74	[redacted]	[redacted]

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCT, stem cell transplant.

Table 126: Scenario results – asciminib (PAS price) vs dasatinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base–case ICER
Base-case	£1,995	0.63	£3,180	0%
Five years survival post 3L discontinuation	£5,198	0.70	£7,453	134%
Three and a half years survival post 3L discontinuation	£7,799	0.76	£10,297	224%
Discount rates zero	£22,584	1.03	£21,831	587%
Discount rates 5%	-£2,573	0.53	Dominant	-
Mean time in AP 12 months	£1,987	0.63	£3,157	-1%
Mean time in AP 8 months	£2,003	0.63	£3,202	1%
Mean time in BP 8 months	£1,691	0.63	£2,678	-16%
Mean time in BP 4 months	£2,302	0.62	£3,689	16%
Proportion undergoing SCT at 3L discontinuation 30%	£3,378	0.63	£5,382	69%
Proportion undergoing SCT at 3L discontinuation 10%	£1,433	0.63	£2,283	-28%
Proportion undergoing SCT at start of AP 40%	£1,745	0.61	£2,840	-11%
Proportion undergoing SCT at start of AP 10%	£2,121	0.63	£3,344	5%
Proportion undergoing SCT at start of BP 40%	£1,350	0.61	£2,211	-30%
Proportion undergoing SCT at start of BP 10%	£2,318	0.64	£3,644	15%
HSUV by treatment arm	£1,995	0.69	£2,892	-9%
HSUV by treatment status & arm	£1,995	0.73	£2,718	-15%
HSUV from Szabo 2010	£1,995	0.74	£2,689	-15%

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SCT, stem cell transplant.

B.3.8.4 Summary of sensitivity analyses results

Results were most sensitive to variation in duration of post third-line treatment survival by treatment arm, HSUVs and RDI. Unsurprisingly, ICERs increased when it was assumed that OS post third-line treatment is higher with the comparators compared to asciminib. ICERs increased when the HSUV for patients on third-line treatment was reduced to 0.67. However, this value is notably lower than that reported in the literature by Szabo et al (2010) (160). Increasing RDI for asciminib did increase ICERs. However, the change was not substantial in the comparison with nilotinib, dasatinib or ponatinib. As might be expected, ICERs for comparisons with nilotinib, dasatinib and ponatinib were influenced by the duration of time on treatment with the respective comparator, but the impact was not substantial.

The scenario analysis demonstrated that the results were not sensitive to parameters estimated from HMRN or from clinical opinion on the proportion of patients undergoing allo-SCT and the duration of AP and BP. Analysis also showed that the ICER for asciminib compared to bosutinib was not strongly dependent on the specification of the TTD model, and further that the lognormal assumption generates conservative results. Overall, the analysis demonstrated that the base case assumptions are conservative, with alternative assumptions on survival post discontinuation of third-line treatment or on the dependence of HSUVs on treatment arm generating lower ICERs for asciminib vs all comparators.

B.3.9 Subgroup analysis

No subgroup analysis was undertaken (Appendix E).

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinical validation of the outcomes of the model was undertaken by comparing OS data from the model with long-term published overall survival of the comparators: this comparison used real-world data from HMRN, long term trial data from comparator trials, and was further supported by expert clinical opinion.

Modelled OS is broadly in line with data from HMRN (Figure 38). Data on OS for patients commencing third-line treatment in HMRN is very similar to predicted overall survival for asciminib, and slightly higher than the model prediction for bosutinib, bearing in mind that HMRN does not yet include asciminib.

Long-term estimates of OS for comparator treatments were identified, firstly by identifying long-term outcomes from the trials that were the basis of the ponatinib (TA451) and bosutinib (TA401) submissions (146, 157).

Cortes et al 2018 reports the final 5-year results of the PACE trial (58). Khoury et al 2012 reports outcomes of the third-line population from study 200 of the bosutinib submission (94). For dasatinib and nilotinib, there has been no third-line submission, and therefore a non-systematic search was undertaken to look for third-line nilotinib or dasatinib trials. Three trials were identified; Garg et al 2009, which focused on 47

patients with CML who were sequentially treated with three different TKIs (nilotinib or dasatinib after failure of two TKIs) (118); Rossi 2013 included 82 patients who were on a third-line TKI of nilotinib or dasatinib after failure of two TKIs (147); finally Ongoren 2017 investigated 21 patients who were on third-line treatment of nilotinib or dasatinib after failure of two TKIs (117). The results in comparison to the model are outlined in the below table.

Table 127: Comparison of modelled OS with long term clinical trials

	Bosutinib		Ponatinib		Nilotinib/dasatinib				
Yrs	**Model OS**	**Khoury et al 2012**	**Model OS**	**PACE**	**Model OS (das)**	**Model OS (nil)**	**Rossi et al 2013**	**Garg et al 2009**	**Ongoren et al 2017**
2	86%	84%	89%	86%	85%	85%	100%	70%	100%
5	68%	-	72%	77%	66%	65%	100%	-	80%
10				-	44%	43%	100%	-	-

Abbreviations: nil, nilotinib; das, dasatinib

The results show that simulations for bosutinib and ponatinib are producing model outcomes that are very similar to those seen in long term trials of bosutinib and ponatinib. This is reassuring as these trials have sufficient patients to interpret the survival data with confidence. OS estimates for nilotinib and dasatinib are discordant across studies, potentially reflecting the modest size of each of the studies. With regard to concordance with model predictions, observed survival is higher than predicted in two studies and lower in the third. Interpretation of this evidence is limited by the small size of each study.

B.3.11 Interpretation and conclusions of economic evidence

The cost-effectiveness analysis demonstrates the economic value of asciminib as a treatment for adult patients with Ph+ CML-CP, previously treated with two or more TKIs, compared with other available treatment options used at this point in the pathway. Base case analyses, using the PAS price for asciminib (and nilotinib), produced a probabilistic cost per QALY gained of £2,767 vs bosutinib, a cost per QALY gained of £49,001 vs nilotinib, and a cost per QALY gained of £3,665 vs dasatinib. Compared to ponatinib, asciminib produced a probabilistic cost saving per

QALY lost of £261,615 (as asciminib is in the south west quadrant compared to ponatinib [less expensive and less effective]).

The benefits of asciminib are driven by a longer time on treatment compared to bosutinib, nilotinib, and dasatinib, leading to a higher QALY gain as this delays progression and death. This led to higher costs for asciminib. Ponatinib has a longer treatment duration than asciminib leading to more QALYs. However, asciminib is substantially less costly. Ponatinib is also associated with elevated risks of cardiovascular adverse events, as a result of which it is typically used where other effective TKI treatment options have been exhausted (162).

Sensitivity analysis showed that the model was most sensitive to variation in duration of post third-line treatment survival by treatment arm, HSUVs and RDI. Scenario analyses showed the model was not sensitive to the proportions of patients undergoing allo-SCT and the duration of AP and BP. Application of alternative model specifications for TTD for asciminib and HSUV generally improved cost-effectiveness for asciminib vs all the comparators.

This is the first economic evaluation focussed on assessing the cost-effectiveness of asciminib for the treatment of adult patients with Ph+ CML-CP, previously treated with two or more TKIs. The economic evaluation reflects patients assessed in ASCEMBL, some of whom were treated at fourth or fifth line. As such, results for asciminib are likely to represent a conservative estimate of cost-effectiveness when compared to nilotinib and dasatinib in particular, which were purely third line population trials. A key assumption in the model is the overall survival following treatment discontinuation, which reflected a third-line population. It is likely this would be lower in subsequent lines of treatment. Scenario analysis in which overall survival following treatment discontinuation was reduced, generated improved cost-effectiveness of asciminib compared to nilotinib, dasatinib and bosutinib.

B.3.11.1 Strengths and limitations

The model was designed after careful consideration of the clinical and treatment pathways for patients with CML to ensure that key aspects of the disease and treatment practices were captured in the model. The model structure was developed based on a review of previous economic modelling approaches and available NICE HTA submission reports, and in consultation with a clinical expert in the CML field.

The model was designed to provide flexibility on how to estimate clinical benefits associated with asciminib. Base-case parameter values and assumptions were selected based on their clinical validity.

Strengths of the analysis include that ASCEMBL is the first head-to-head comparison of treatments in this disease area, with previous submissions all being based on single arm studies. The ASCEMBL data demonstrated a substantial improvement in time on treatment with asciminib compared to bosutinib.

Identifying the best data inputs for use in the base case was the key challenge for this analysis. The ASCEMBL trial only provided data for asciminib and bosutinib, and inputs for all other comparators had to be taken from the literature and informed using a MAIC. PFS and OS data from ASCEMBL were not mature enough to be used in the model, requiring extrapolation using TTD as a proxy measure. TTD was projected beyond the end of follow-up by fitting parametric survival distributions to data from ASCEMBL. This inevitably introduces structural uncertainty that may have a material impact on estimates of cost-effectiveness. However, sensitivity analysis indicates that the impact on ICERs is modest and the base case is likely to be conservative with regard to asciminib.

There are limitations associated with using published data for comparator treatments, such as heterogeneity in the patient populations and enrollment criteria between trials. Reporting for some key endpoints such as treatment duration was also limited, with only median values available. For ponatinib, the PACE trial provided the median treatment duration for the cohort which include T315I mutated patients (~25%) along with CML-CP patients on their third or later line of therapy. The studies included for nilotinib and dasatinib are of small sample size. For these non-ASCEMBL comparisons, only median treatment duration was available from various publications. In order to account for between study differences, ASCEMBL data on time to treatment discontinuation was adjusted to match the patient population for the comparator trial of interest where possible.

To predict PFS and OS, assumptions were made based on previous NICE submissions. It was assumed that there will not be any benefit of prior treatment following treatment discontinuation, with patients then experiencing a mean survival of 7 years, irrespective of third-line TKI received. Sensitivity analysis has shown that

shorter overall survival post-discontinuation survival (as accepted by the committee in TA401) leads to a lower ICER (vs bosutinib, nilotinib, and dasatinib), therefore the base case result could be considered conservative. Clinical validation against data from long term trials of bosutinib and ponatinib (that were the basis of those submissions and have now had more follow up time), confirm that overall survival predicted from our model are broadly in line with long term estimates, and add validity to the modelling approach for overall survival.

The results of this clinical- and cost-effectiveness analysis suggest that, for CML-CP patients who were treated with two or more TKIs, asciminib is likely to result in substantial gains in life expectancy and QALYs compared with bosutinib.

B.3.11.2 Conclusions

The ASCEMBL data demonstrated a substantial improvement in time on treatment with asciminib compared to bosutinib (median treatment duration of [redacted] months for bosutinib, and median [redacted] for asciminib with follow up of 36 months).

Under plausible assumptions of the impact of this on OS, the economic analysis indicates substantial QALY gains for patients when compared to nilotinib, dasatinib or bosutinib. Data from ASCEMBL suggests that TTD on asciminib is not as long as that observed with patients on ponatinib in the PACE trial (58). However, the safety profile in general, and cardiovascular risks in particular, render ponatinib the treatment of last choice when other TKI options have been exhausted. Asciminib offers an alternative therapy that is well tolerated and likely to defer the point at which ponatinib is the only untried TKI available.

After application of the asciminib PAS, the incremental cost of asciminib when compared to dasatinib or bosutinib is modest and the analysis indicates asciminib is cost-effective vs the list price of those treatments (with a probability of 100% at a cost-effectiveness threshold of £30,000 for both treatments). Asciminib was associated with considerable cost savings relative to ponatinib (list price); where asciminib displaces the use of ponatinib it will generate significant cost savings. The ICER for asciminib compared to nilotinib remained above conventional accepted thresholds when a PAS discount was applied to both drugs. Nilotinib is likely to remain a mainstay of treatment after failure of imatinib in first-line. However, many patients at third-line will already have tried nilotinib as it is commonly used first or

second-line, and asciminib offers an additional treatment with potential to improve OS.

In summary, asciminib is a cost-effective alternative to dasatinib, bosutinib and ponatinib and offers the potential for significant QALY gains in patients for whom nilotinib is still a viable treatment option. Asciminib is an important addition to the available treatments for CML in patients who have already progressed to third or later lines of treatment, offering improved outcomes compared with bosutinib and other TKIs. Providing access to asciminib is a cost-effective decision compared with the majority of TKIs currently used in third-line treatment and beyond.

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B.5 Appendices

All appendices are provided as separate documents:

Appendix C: Draft summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Summary of subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Compare Time to Treatment Discontinuation (TTD) and responses for Asciminib vs ponatinib, nilotinib, dasatinib and omacetaxine through MAIC for CML-CP patients who were treated with 2 or more TKIs

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Extrapolation of TTD, and OS and RFS for SCT

Appendix M: 24-week efficacy and safety evidence from the ASCEMBL trial

Appendix N: Safety data from Study X2101 and pooled analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Clarification questions

December 2021

File name	Version	Contains confidential information	Date
ID3813 Asciminib ERG Clarification letter [ACIC]	**1**	**Yes**	**06/12/2021**

Abbreviation	Definition
AE	Adverse event
AIC	Akaike's Information Criteria
Allo-SCT	Allogeneic stem cell transplant
AMCP	Academy of Managed Care Pharmacy
AP	Accelerated phase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AWMSG	All Wales Medicines Strategy Group
BD	Twice-daily
BIC	Bayesian Information Criteria
BP	Blast phase
BSBMTCT	British Society of Blood and Marrow Transplantation and Cellular Therapy
BSH	British Society of Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CCyR	Complete cytogenetic response
CEM	Cost-effectiveness model
CHR	Complete haematologic response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CP	Chronic phase
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CTAF	The California Technology Assessment Forum
DSU	Decision support unit
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EED	Economic evaluations database
EFS	Event free survival
EHA	European Hematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GELMC	Spanish CML Group
HAS	Haute Autorité de Santé
HMRN	Haematological Malignancy Research Network
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform

Abbreviation	Definition
IPD	Individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRT	Interactive response technology
IS	International Scale
ISPOR	International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting
ISSG	InterTASC Information Specialists' Sub-Group
K-M	Kaplan-Meier
LYG	Life years gained
MAIC	Matching adjusted indirect comparison
MMR	Major molecular response
MR	Molecular response
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NOS	Newcastle-Ottawa Scale
NR	No response
OS	Overall survival
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PCyR	Partial cytogenetic response
PD	Progressed disease
PFS	Progression-free survival
Ph	Philadelphia chromosome
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RFS	Relapse-free survival
RoB	Risk of bias
RR	Relative risk
SAE	Serious adverse event
SCT	Stem cell transplant
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SOHO	Society of Hematologic Oncology
TFS	Treatment-free survival
TKI	Tyrosine kinase inhibitor
TLV	The Dental and Pharmaceutical Benefits Agency
TSD	Technical support document
TTD	Time to treatment discontinuation

Abbreviation	Definition
UK	United Kingdom
WHO	World Health Organization

Section A: Clarification on effectiveness data

Background

A1. Priority question: Please elaborate on the strength of evidence for the association between intermediate outcomes (major molecular response [MMR], complete cytogenetic response [CCyR], time to treatment discontinuation [TTD]) and progression free survival (PFS) and overall survival (OS) in individuals with chronic myeloid leukaemia (CML) with a history of two or more tyrosine kinase inhibitors (TKIs).

Outcome measures of CML treatment efficacy such as overall survival (OS), event-free survival (EFS), and transformation-free survival (TFS) require long follow-up times, and this may delay the approval and availability of new treatments for patients with CML (1). CML in the chronic phase (CML-CP) has a relatively long disease course, and with high response rates achieved with available treatments, survival-based outcome measures are not practical. To address the shortcoming of using long-term outcomes, shorter-term measures of treatment efficacy, such as response rates, are widely recognised as surrogate endpoints of survival (1). Cytogenetic response as a surrogate outcome for OS has been used in prior National Institute for Health and Care Excellence (NICE) technology appraisals (TA241 and TA251) and health technology assessments (HTAs) by Rogers et al. 2012 (2), Pavey et al. 2012 (3), and Loveman et al. 2012 (4). Supporting cytogenetic response as a surrogate for OS in these aforementioned evaluations is a systematic review and meta-analysis of studies evaluating first-line treatment with imatinib, dasatinib, or nilotinib, that showed an association between complete cytogenetic response (CCyR) and major molecular response (MMR) and long-term OS (1, 5).

The systematic review by Oriana et al. 2013 (5), commissioned by the National Institute for Health Research (NIHR) following the NICE technology appraisal on dasatinib, nilotinib and imatinib (TA241), identified three cohort studies (6-8) and two randomised controlled trials (RCTs) (9-11) examining the association between these two biomarkers (cytogenetic response and molecular response) and OS in patients with CML-CP receiving first-line imatinib. These studies showed a consistent

association between CCyR and MMR and long-term (i.e. 1–7 years) OS, although this was based on observational analyses comparing responders versus non-responders (5). Based on the pooled observational association between CCyR and MMR and OS, this study's modeling showed comparable predicted mean duration of survival (21–23 years) following first-line treatment with imatinib, dasatinib, or nilotinib (5).

An additional systematic review and meta-analysis has evaluated the efficacy and safety of second-generation tyrosine kinase inhibitors (TKIs) (including bosutinib) versus imatinib (12). Although the objective was not to validate CCyR and MMR at 12 months as surrogates for OS, there was no statistically significant difference between first- and second-generation TKI groups in all-cause mortality rates at 12 months (relative risk [RR]: 0.76; 95% CI: 0.42, 1.37). This was despite a general improvement in the CCyR rate at 12 months (RR: 1.16; 95% confidence interval [CI]: 1.09, 1.23) and MMR at 12 months (RR: 1.68; 95% CI: 1.48, 1.91) in patients allocated to the second-generation TKIs arm compared with patients allocated to the imatinib arm (12).

Although systematic reviews have the advantage of collating all relevant material and help provide stronger evidence than individual studies, reviews often use aggregate data, rather than patient level data. In addition, models predicted from systematic reviews do not take into account the speed of achieving the surrogate response, its depth, or duration (13). This could induce underestimation of long-term effectiveness of certain TKIs (e.g. dasatinib and nilotinib), given that they are believed to be superior to imatinib in all these respects and considering that historical surrogate data are based on OS for patients taking imatinib. However, the extent of this bias is unquantifiable. For the same reason, the model suits only those situations in which no subsequent TKI therapy is implemented following first-line treatment. In reality this is unlikely to be the case as people would most likely go on to subsequent treatments.

Unfortunately, the published data (5-11) are based on first-line TKI therapy and whilst from a molecular biology standpoint the relative importance of CCyR very likely still holds, the absolute accuracy of the OS estimates may be different in a

third-line setting. Data are lacking on relative survival according to treatment line in patients achieving a CCyR. In other technology appraisals, it has been questioned whether evidence for surrogate endpoints could be transferred to other lines of treatment. For example in TA573 (daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma), the committee concluded that *"there may be a documented association between minimal residual disease and short-term overall survival, and that it was not unreasonable to expect some people with no residual disease to live longer. However, it concluded that the relationship between these outcomes over the long term in people with relapsed disease had not been established and could not inform the economic model"*.

Surrogate endpoints can provide early indications of treatment success, and can also identify patients who would benefit from switching therapies. For example, achieving an MMR (BCR-ABL1 ≤0.1%) predicts a CML-specific survival close to 100%, as disease progression is uncommon once this level of cytoreduction has been achieved (14). In line with this, the 2020 European LeukemiaNet (ELN) recommendations for the management of CML recommend monitoring for cytogenetic, haematologic, and molecular responses to evaluate treatment efficacy, regardless of which TKI is used (14).

Systematic literature review

A2. Priority question: Please provide a more detailed tabulation of the studies identified for inclusion in the systematic literature review (SLR) (Document B, Table 5). This should include: interventions used, with dosages and schedules; study date; sample size in all arms; where available, a summary of results for key outcomes [OS, PFS, MMR, CCyR and TTD].

An updated tabulation of the studies identified for inclusion in the clinical systematic literature review (SLR) conducted on 9th November 2020 and updated on 13th May 2021 is presented in Table 1 (15).

Table 1: Studies identified in the clinical SLR

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
ASCEMBL (16)†	≥2 prior lines of TKI; failure or intolerance to the last previous TKI therapy at screening. Prior allo-SCT: excluded, ECOG PS: 0–2; T315I mutation: excluded	Asciminib: 40 mg BD (n=157) Bosutinib: 500 mg OD (n=76)	–	• CCyR: CCyR rate at 24 weeks was 40.8% with asciminib compared with 24.2% with bosutinib • MMR: MMR rate at 24 weeks was 25.5% with asciminib compared with 132.2% with bosutinib
X2101 (17-19)	≥2 different TKIs prior to study entry and are relapsed, refractory to or intolerant of TKIs. ECOG PS: 0–2; T315I mutation: allowed	Asciminib: OD or BD (doses of 10–200 mg, median follow-up 59 weeks) (N=150)	May 2014–Sept 2017	• CCyR: 54% of patients with CML-CP with no T3151 mutation achieved CCyR, and 87% maintained CCyR • MMR: 47% of patients with CML-CP with no T3151 mutation who had failed ≥2 previous TKIs achieved MMR by 12 months, and 80% maintained MMR
Luna 2020 (20-22)	≥1 prior TKIs. ECOG PS: NR; T315I mutation: NR	Asciminib: 40 mg BD, median time on asciminib was 35 weeks (N=31)	Oct 2018–June 2020	• CCyR: probability of reaching or maintaining previous response was 61.3% • MMR: Probability of reaching or maintaining previous response was 35.5%
PACE (23-28)	Resistant or intolerant to dasatinib or nilotinib. ECOG PS: 0–2; T315I mutation: allowed	Ponatinib: 45 mg OD (N=449 [CML-CP n=270])	Sept 2010–Oct 2011	• CCyR: 54% of patients with CML-CP achieved CCyR • MMR: 40% of patients with CML-CP achieved MMR • OS and PFS: K-M–estimated OS and PFS at 5 years were 73% and 53%, respectively

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
PEARL (29)	Resistant or intolerant to 2 or 3 lines of prior TKI (or with harbouring a T315I mutation). ECOG PS: 0–2; T315I mutation: allowed	Ponatinib: 45 mg OD (CML-CP N=48)	May 2013–Jan 2014	• CCyR: At 6 months, 64.8% of ponatinib-treated patients reached at least CCyR • MMR: The cumulative incidence of MMR of ponatinib-treated patients was 66.7% and 81.8% at 6 and 18 months, respectively • OS: The probability of OS was 95.7% and 81.5% at 12 and 36 months, respectively
OPTIC (28, 30-34)	Have received ≥2 prior TKI therapies and have demonstrated resistance to treatment or have documented history of presence of T315I mutation after receiving any number of prior TKI. ECOG PS: 0–2; T315I mutation: allowed	Ponatinib: 45 mg, 30 mg, or 15 mg OD (N=283)	Aug 2015–May 2019	• OS: the survival probability at 36 months was 89% (45 mg group and 30 mg group), and 92% (15 mg group) • PFS: the survival probability at 36 months was 73% (45 mg group), 66% (30 mg group), and 92% (15 mg group)
Cortes 2012 (35)	Relapsed or refractory CP-CML. ECOG PS: 0–2; T315I mutation: NR	Ponatinib: 2–60 mg OD (N=81 [CML-CP n=43])	June 2008–Oct 2011	• CCyR: 63% of patients with CML-CP had a CCyR • MMR: 44% of patients with CML-CP had a MMR

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
Tojo 2017 (36)	Previously treated with and resistant, or intolerant to either dasatinib or nilotinib ECOG PS: 0–2; T315I mutation: NR	Ponatinib: 45 mg OD (N=35)	Aug 2012–Sept 2013	• CCyR: 59% of patients with CML-CP achieved CCyR • MMR: 35% of patients with CML-CP achieved MMR • OS and PFS: For patients with CML-CP, median OS and PFS were not reached
Khan 2017 (37)	Failure to first- or second-line TKIs. ECOG PS: NR; T315I mutation: NR	Bosutinib: (n=13) Ponatinib: (n=22) Dasatinib: (n=64) Nilotinib: (n=67) Imatinib: (n=19)	–	• OS: Third-generation ponatinib was associated with significantly better OS compared with imatinib (HR, 0.248; 95% CI: 0.067, 0.917; p=0.037)
Swaminathan 2018 (38)	Only patients who received ponatinib as a second or subsequent line of therapy of CML were included. ECOG PS: NR; T315I mutation: NR	Ponatinib: (N=80)	2009–2018	• CCyR: CCyR was achieved by 100% of patients receiving ponatinib at second-line; 67% at third-line; 50% at fourth-line; and 58% at fifth-or higher line • MMR: MMR was achieved by 44% of patients receiving ponatinib at second-line; 38% at third-line; 12% at fourth-line; and 29% at fifth or later line

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
OITI (39)	≥1 prior lines of TKI. ECOG PS: NR; T315I mutation: NR	Ponatinib: 45 mg OD (N=56)	–	• CCyR: At Month 6, 88.6% of patients with CML-CP achieved a CCyR • MMR: At Month 6, 37.5% of patients with CML-CP achieved a MMR • OS: Estimated PFS rates for patients with CML-CP at Months 12 and 24 were 96.2% and 93.1%, respectively • PFS: Estimated PFS rates for patients with CML-CP at Months 12 and 24 were 86.6% and 83.7%, respectively
Chan 2020 (40)	≥1 prior lines of TKI. ECOG PS: NR; T315I mutation: allowed	Ponatinib: 39.65 mg (N=78 [CML-CP n=51])	Jan 2011–Dec 2017	• CCyR: 69.6% of patients with CML-CP achieved CCyR • MMR: 58.7% of patients with CML-CP achieved MMR • OS: OS at 5 years for CML-CP was estimated at 72.1% with allo-SCT and at 79.7% without allo-SCT
Sasaki 2020 (41)	≥2 prior lines of TKI. ECOG PS: NR; T315I mutation: NR	Bosutinib: (n=13) Ponatinib: (n=15) Dasatinib: (n=22) Nilotinib: (n=63) Imatinib: (n=15)	Mar 2005–Nov 2015	• MMR: Among 154 evaluable patients, 9% achieved MMR
Khoury 2012 (42-49)	Resistant to or intolerant of - Imatinib, AND - Dasatinib and/or nilotinib. ECOG PS: 0–1; T315I mutation: allowed	Bosutinib: (N=403)	–	• CCyR: after ≥10years, 49.6% achieved a CCyR • MMR: after ≥10years, 42.1% achieved a MMR • OS: after ≥10years, OS was 72%
BYOND (50-59)	Previously treated with ≥1 TKIs (imatinib, dasatinib and/or nilotinib) Excluded:	Bosutinib: (N=163 [Ph+ CML-CP n=156])	Nov 2014–Sept 2017	• CCyR: Cumulative CCyR rate by 1-year was 80.6% in patients with Ph+ CML-CP • MMR: The cumulative MMR rate by 1-year was 70.5% in patients with Ph+ CML-CP

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
	- Prior treatment with bosutinib - Prior treatment with ponatinib. ECOG PS: NR; T315I mutation: excluded			• OS: The 1- and 2-year K-M OS rates were 98.0% and 96.0%, respectively, for patients with Ph+ CP CML
Garcia-Gutierrez 2019 (60)	Prior experience with all of the following: - Imatinib, AND - Dasatinib, AND - Nilotinib. ECOG PS: NR; T315I mutation: allowed	Bosutinib: 500 mg/day (N=62)	Nov 2011–Jan 2016	• CCyR: 65% of patients achieved CCyR • MMR: 41% of achieved MMR • PFS: Median PFS was not reached
Tiribelli 2018 (61)	≥1 prior lines of TKI. ECOG PS: NR; T315I mutation: NR	Bosutinib: 290 mg/day (mean) (N=20)	–	• CCyR: 20% of patients achieved CCyR • MMR: 20% of patients achieved MMR
Takahashi 2017 (62, 63)	≥1 prior lines of TKI. ECOG PS: 0–1; T315I mutation: NR	Bosutinib: 400–600 mg/day, then 500 mg/day (N=63)	Dec 2007–Aug 2012	• CCyR: 65% of patients achieved a CCyR • MMR: In the CP second line cohort, MMR was achieved or maintained by 53% of patients. In the CP third-line cohort, MMR was achieved or maintained by 40% of patients • OS: At week 96, OS rate was 98% in CP second-line, and 100% in the CP third-line cohorts • PFS: At week 96, PFS rate was 91% in CP second-line, and 88% in the CP third-line cohorts
Cortes 2019 (64)	≥1 prior lines of TKI; ECOG PS: NR; T315I mutation: NR	Bosutinib: 500 mg (N=70 [CML-CP n=68])	2006–2018	• CCyR: 1.5% of patients achieved CCyR • MMR: 7% of patients achieved MMR • OS: 60 month OS rate was 96%

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
Giles 2010 (65)	Resistance to/intolerance of imatinib, failure to respond to dasatinib. ECOG PS: NR; T315I mutation: allowed	Nilotinib: 400 mg/day (N=60)	–	• CCyR: 24% of patients achieved CCyR • PFS: Estimated PFS at 18-months was 59%
Tan 2019 (66)	Failure of imatinib, AND failure of nilotinib. ECOG PS: NR; T315I mutation: excluded	Dasatinib: (N=48)	July 2008–Mar 2016	• CCyR: 72.7% patients achieved MMR using dasatinib at second-line, and 46.2% at third-line • MMR: 45.8% patients achieved MMR using dasatinib at second-line, and 20.8% at third-line
Rossi 2013 (67)	Failed imatinib, AND failed dasatinib or nilotinib. ECOG PS: NR; T315I mutation: allowed	Dasatinib: 70 mg BD (n=20), 50 mg BD or 100 mg OD (n=28) Nilotinib: 400 mg BD (n= 34)	–	• CCyR: Overall, 17.1% of patients achieved CCyR • MMR: Overall, 15.9% of patients achieved MMR • OS: The 30-month probability of OS was 98.5%
Ibrahim 2010‡ (68)	Failed imatinib, AND failed dasatinib or nilotinib. ECOG PS: NR; T315I mutation: excluded	Dasatinib: (n=20) Nilotinib: (n=6)	Mar 2005–Jan 2008	• CCyR: Overall, 34.6% of patients achieved CCyR • MMR: Overall, 19.2% of patients achieved MMR • OS: The 30-month probability of OS was 46.7%
Ongoren 2017 (69)	2 prior lines of TKI; ECOG PS: NR; T315I mutation: NR	Imatinib: 400 mg/day (n=209) Dasatinib: (second-line n=45, third-line n=6) Nilotinib: (second-line n=20, third-line n=15)	1999–2013	• CCyR: CCyR was achieved in 5.3% of evaluable second-line patients (n=19), and 4.8% of third-line patients (n=21) • MMR: MMR was achieved in 47.4% of evaluable second-line patients (n=19), and 47.6% of third-line patients (n=21)

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
Garg 2009 (70)	2 prior lines of TKI; ECOG PS: NR; T315I mutation: NR	Dasatinib: 140 mg OD (n=9), 100 mg OD (n=3), 50 mg OD (n=1), 70 mg BD (n=15), 50 mg BD (n=5), 120 mg BD (n=1) Nilotinib: 800 mg OD (n=2), 400 mg OD (n=1), 400 mg BD (n=11)	Sept 2004–July 2008	• CCyR: Overall, 24% of patients with CML-CP achieved a CCyR • MMR: Overall, 20% of patients with CML-CP achieved a MMR • OS: Overall, Median OS was 20 months
Ribeiro 2015 (71)	2 prior lines of TKI; ECOG PS: NR; T315I mutation: NR	Dasatinib: 100–140 mg/day (n=9) Nilotinib: 400–800 mg/day (n=16)	July 2008–Dec 2014	• CCyR: Overall, 13% of patients a CCyR • MMR: Overall, 24% of patients achieved a MMR • OS: 5-year OS in patients with CML-CP was 86% • PFS: 5-year PFS in patients with CML-CP was 54%
Garcia-Gutierrez 2012 (72)	2 prior lines of TKI; ECOG PS: NR; T315I mutation: NR	Dasatinib: NR Nilotinib: NR	–	• CCyR: Cumulative incidence of CCyR was 18% and 50% for resistant and intolerant patients, respectively • OS: OS was 72% and 88% for resistant and intolerant patients, respectively
CML-203 (73-75)	Resistance to/intolerance of ≥2 TKIs Prior SCT was allowed; ECOG PS: 0–2; T315I mutation: allowed	Omacetaxine: 1.25 mg/m^2 administered subcutaneously BD for up to 14 consecutive days every 28 days (CML-CP n=81)	–	• CCyR: 8% of patients achieved CCyR • OS: Median OS was 40.3 months • PFS: Median PFS was 9.6 months

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
Jiang 2019 (76)	≥1 prior lines of TKI; ECOG PS: NR; T315I mutation: allowed	Olverembatinib: 1–60 mg every other day (N=101 [CML-CP n=87)	Oct 2016–May 2019	• CCyR: 60.5% of patients with CML-CP achieved a CCyR • MMR: 37.2% of patients with CML-CP achieved a MMR
Turkina 2018 (77)	Resistance to ≥1 2nd generation BCR-ABL inhibitor (dasatinib or nilotinib or bosutinib), OR intolerance of approved BCR-ABL inhibitors, OR presence of T315I mutation irrespective of treatment history. ECOG PS: 0–2; T315I mutation: allowed	PF-114: 50 mg (n=3), 100 mg (n=3), 200 mg (n=9), 300 mg (n=11), 400 mg (n=12), 500 mg (n=3), 600 mg (n=6), 730 mg (n=4)	–	• MMR: 11% of patients completing ≥13 cycles achieved a MMR
Lee 2014 (78)	0–3 prior TKIs; ECOG PS: NR; T315I mutation: NR	Allo-SCT: (N=97)	May 2001–Sept 2012	• OS: At 4 years, OS was 82.9% in patients with CML-CP
Devos 2021 (79)	≥1 prior lines of TKI; ECOG PS: NR; T315I mutation: allowed	Ponatinib: 45, 30, or 15 mg/day (CML N=33)	Mar 2016–Mar 2019	• CCyR: 6% of patients with CML achieved CCyR • MMR: 58% of patients with CML achieved a MMR • OS: Estimated OS for patients with CML was 85.3% over 3 years • PFS: Estimated PFS for patients with CML was 81.6%
Gugliotta 2020 (80)	0–3 prior TKI; ECOG PS: NR; T315I mutation: allowed	Ponatinib: (n=40) Dasatinib: (n=21) Nilotinib: (n=7) Bosutinib: (n=3)	–	• OS: Overall, estimated 4-year OS was 93.7% • PFS: Overall, estimated 4-tear PFS was 92.5%
Chitanava 2021 (81)	2 prior TKIs; ECOG PS: NR; T315I mutation: allowed	Bosutinib: (n=9) Ponatinib: (n=3)	2019	• CCyR: CCyR was achieved in 16% of patients • MMR: MMR was achieved in 6% of patients

Study	CML patient population	Intervention/dose/ sample size	Study dates	Summary of key results (OS, PFS, MMR, CCyR, TTD)
		Dasatinib: (n=43) Nilotinib: (n=18)		• OS: Estimated 1-year, 3-year, and 5-year OS were 95%, 81%, and 65%, respectively
Latagliata 2021 (82)	≥2 prior TKIs; ECOG PS: 0–1; T315I mutation: NR	Bosutinib: 500 mg/day (n=25), 400 mg/day (n=7), 300 mg/day (n=33), 200 mg/day (n=34), 100 mg/day (n=2)	–	• CCyR: 77% of patients achieved or maintained CCyR • MMR: MMR was achieved by 47.2% of patients • OS: The 3-year OS was 86.4%
TOPASE (83)	1–5 prior TKIs; ECOG PS: NR; T315I mutation: allowed	Ponatinib: 15 mg/day, 30 mg/day, or 45 mg/day (N=110 [CML-CP n=97])	Feb 2018–Dec 2020	• MMR: MMR was achieved in 51% of patients

†The ASCEMBL trial is currently ongoing (a 96-week analysis is planned, and data are expected in Quarter 2 2022).
Abbreviations: Allo-SCT, allogenic stem cell transplant; BD, twice daily; CCyR, complete cytogenetic response; CI, confidence interval; CML, chronic myeloid leukaemia; CP, chronic phase; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MMR, major molecular response; NR, not reported; OD, once-daily; OS, overall survival; PFS, progression-free survival; Ph, Philadelphia chromosome; PS, performance status; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation.

A3. Please provide a justification for risk of bias decisions (i.e. high/low/unclear) made for each risk of bias domain in Appendix D, Table 13. Please also comment on the potential direction and magnitude of bias associated with study design limitations of randomised trials and observational studies included in the SLR.

The quality of RCTs was evaluated using the Cochrane's Collaboration risk of bias (RoB) tool (Appendix D, Table 13) as described in the Cochrane handbook (84). For each domain, the reviewing authors' decisions on the risk of bias (i.e. high/low/unclear) was in accordance with guidelines provided by Cochrane. The non-randomised studies were evaluated for risk of bias using the Newcastle-Ottawa Scale (NOS) and scored as per the guidance and templates provided on the NOS website (85).

All included studies were systematically evaluated for any potential risk of bias, however there is a possibility that some level of bias may not be identified due to limited details on the study design in the publication. Furthermore, the subjective nature of this exercise can also impact the identification of the exact magnitude of bias and its potential effect on the results.

Among the two randomised studies included, the OPTIC trial was an open label study which may have a substantial impact on the total risk of bias (28, 30-34). However, the outcomes assessed in the OPTIC trial were not subjective and may not be influenced by patients' knowledge of the assigned treatment. Considering the subjectiveness of this assumption, the risk of selection and performance bias were marked as "unclear risk" instead of "low risk" or "high risk". Among the non-randomised studies, the majority were designed as single-cohort studies which have an inherent risk of bias related to the selection cohort and comparability. These limitations can affect any comparative analyses unless these are factored into the analysis with suitable assumptions and variables.

ASCEMBL study

A4. The ASCEMBL clinical study report (CSR) states that bosutinib was selected as the comparator "because, in contrast to dasatinib and nilotinib, it was specifically evaluated in patients who were resistant or intolerant to ≥2 prior TKIs."(86) Please

clarify the meaning of this justification, and where applicable, provide any other reason why dasatinib and nilotinib were not chosen.

At the time of designing the Phase III RCT of asciminib (ASCEMBL, NCT03106779) (86), dasatinib and nilotinib had been evaluated at second-line only. Dasatinib and nilotinib studies were uncontrolled, single arm studies, and only enrolled patients previously treated with first-line imatinib (65). The Company sought to evaluate the efficacy and safety of asciminib in patients with Philadelphia chromosome positive (Ph+) CML-CP previously treated with two or more TKIs. Given that the benefit/risk of nilotinib and dasatinib had not been investigated in the third-line and later patient population, the Company did not consider nilotinib and/or dasatinib to be appropriate comparators for asciminib.

In the registration study for bosutinib (Study 200-WW, NCT00261846) (45), the study population included patients in the third-line and later treatment setting after failure on first-line imatinib and subsequent treatment with dasatinib and/or nilotinib. The study included a total of 118 patients in the third or later line treatment setting (42). The efficacy and safety of bosutinib was demonstrated and approved in the patient population of relevance to asciminib at the time of designing the ASCEMBL trial. Hence, bosutinib was selected as the single suitable comparator for asciminib.

Of note, the ASCEMBL trial is the first head-to-head comparison of third and later line TKI treatment treatments in this disease area. Furthermore, the choice of comparator was subject to consultation and agreement with the European Medicines Agency (EMA) and Food and Drug Administration (FDA) prior to conducting the pivotal Phase III ASCEMBL study.

A5. Please discuss how generalisable the ASCEMBL trial population and design are to the UK under the expected license indication. Do you expect that the results of ASCEMBL may differ from what would be expected in clinical practice? If so, please comment on the direction, magnitude and possible sources of bias.

The clinical evidence supporting asciminib is highly relevant to the decision problem as the ASCEMBL trial is in line with the anticipated marketing authorisation (87), the final scope issued by NICE (16), and representative of the population who would be treated in United Kingdom (UK) clinical practice.

The ASCEMBL trial recruited patients from 87 sites across 27 countries, five of which were in the UK (three in England, one in Wales, and one in Scotland) (86). Baseline demographics and disease characteristics are available for the [redacted] new adult patients with CML from Yorkshire and the Humber & Yorkshire Coast Cancer Networks between 1st September 2004 and 31st August 2019 to evaluate the generalisability of the ASCEMBL trial population (Haematological Malignancy Research Network [HMRN]) (88). The median age of patients enrolled in the ASCEMBL trial was 52.0 years, compared with [redacted] years for patients receiving third-line TKI therapy in the HMRN. Furthermore, the vast majority of patients in both the ASCEMBL trial and real-world HMRN study had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 or 1 (99.1% in ASCEMBL and [redacted] in the HMRN studies, respectively [excluding those with missing/unknown ECOG scores]) (86, 88).

Eligibility criteria in the ASCEMBL trial did not permit the inclusion of patients with severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol. Thus, caution should be taken with respect to generalising study findings to UK patients with certain comorbidities. That notwithstanding, there were few exclusion criteria, with 233 of the 319 patients assessed for eligibility enrolled in the ASCEML trial (screening failures: n=81, patient decision: n=4, lost to follow-up: n=1). In addition, 91.1% and 94.7% of patients in the asciminib and bosutinib treatment arms, respectively, had at least one medical condition (86).

Prior treatments received by patients upon ASCEMBL trial entry were reflective of clinical practice in England, with >93% of patients having received ≥2 prior TKIs routinely used in England: dasatinib, imatinib, nilotinib, and ponatinib (86). The ASCEMBL trial compared asciminib with a comparator reflective of third-line and later clinical practice in England (bosutinib).

The outcomes assessed in the ASCEMBL trial are relevant to UK clinical practice. The primary endpoint in ASCEMBL was MMR at 24 weeks while on study treatment

without meeting any treatment failure criteria[a] (assessed by central laboratory). The primary study outcome corresponds with the ELN 2020 treatment recommendations for CML, which state that molecular response must be assessed according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts (by quantitative polymerase chain reaction whenever possible). Secondary endpoints included cytogenetic response outcomes, and the ELN highlights that cytogenetic outcomes are also useful for measuring response to treatment (in addition to molecular response). As previously mentioned in A1, CML-CP has a relatively long disease course, and with high response rates achieved with available treatments, survival-based outcome measures are not practical. To address the shortcomings of using long-term outcomes, shorter-term measures of treatment efficacy such as response rates are widely recognised as surrogate endpoints of survival (1).

A6. Priority question: The evidence review group (ERG) notes a large number of imbalances in participant characteristics between trial arms at baseline (Document B, Tables 12, 13, and 16), notably in sex, ethnicity, time since initial diagnosis of CML, prior TKIs received, number of previous TKIs, number of prior lines of TKI treatment, and reasons for discontinuation of prior TKI.

The ERG understands that some of these imbalances (sex, reason for discontinuation from last TKI, number of prior lines of therapy) were discussed and their impact on the primary efficacy analysis was explored using regression analyses and subgroup analyses.(86) Could the company please provide the following:

[a] Treatment failure was based on adapted ELN criteria for failure of second-line treatment: No CHR or >95% Ph+ metaphases at 3 months after randomisation or thereafter; BCR-ABL1 ratio >10% IS and/or >65% Ph+ metaphases at 6 months after randomisation or thereafter; BCR-ABL1 ratio >10% IS and/or >35% Ph+ metaphases at 12 months after randomisation or thereafter; Loss of CHR, CCyR or PCyR at any time after randomisation; Detection of new BCR-ABL1 mutations that potentially cause resistance to study treatment at any time after randomisation; Confirmed loss of MMR in two consecutive tests; New clonal chromosome abnormalities in Ph+ cells: clonal chromosome abnormalities (CCA)/Ph+: at any time after randomisation; Discontinuation from randomised treatment for any reason.

i. A detailed description of the randomisation procedure used in ASCEMBL.

The randomisation was stratified to ensure that the study population was balanced between treatment arms with respect to cytogenetic response status at screening as follows (89):

- Major cytogenetic response (complete or partial)
- No major cytogenetic response (minor, minimal or none)

The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A patient randomisation list was produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomisation numbers (89). These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study treatments (89).

Prior to dosing, all patients who fulfilled all inclusion/exclusion criteria were randomised via IRT to one of the treatment arms (89). The investigator or his/her delegate called or logged on to the IRT and confirmed that the patient fulfilled all the inclusion/exclusion criteria. The IRT assigned a randomisation number to the patient, which was used to link the patient to a treatment arm and specified a unique medication number for the first package of study treatment to be dispensed to the patient. The randomisation number was not communicated to the caller (89).

ii. An additional column in Tables 12, 13, 14 and 16 presenting results of statistical significance test for differences between treatment arms.

Please see Table 2 to Table 5. The p-values provided are nominal. No multiplicity adjustments were made, and therefore statistical interpretation should be made with caution.

Table 2: Demographic summary (FAS) – Document B, Section B.2.3.1.6, Table 12 (p43)

Variable	Asciminib N=157	Bosutinib N=76	All subjects N=233	P-value
Age (years), n (%)				
N	157	76	233	0.9702†
Mean (SD)	51.0 (13.48)	51.0 (13.95)	51.0 (13.61)	
Median	52.0	52.0	52.0	
Min-Max	24-83	19-77	19-83	
Age (years), n (%)				
18–<65 years	128 (81.5)	61 (80.3)	189 (81.1)	0.9727‡
65–<75 years	25 (15.9)	13 (17.1)	38 (16.3)	
≥75 years	4 (2.5)	2 (2.6)	6 (2.6)	
18–<65 years	128 (81.5)	61 (80.3)	189 (81.1)	0.8170‡
≥65 years	29 (18.5)	15 (19.7)	44 (18.9)	
Sex, n (%)				
Male	75 (47.8)	45 (59.2)	120 (51.5)	0.1014‡
Female	82 (52.2)	31 (40.8)	113 (48.5)	
Race, n (%)				
White	118 (75.2)	56 (73.7)	174 (74.7)	0.2787‡
Asian	22 (14.0)	11 (14.5)	33 (14.2)	
Black Or African American	8 (5.1)	2 (2.6)	10 (4.3)	
American Indian or Alaska Native	1 (0.6)		1 (0.4)	
Other	5 (3.2)	7 (9.2)	12 (5.2)	
Unknown	3 (1.9)		3 (1.3)	
Ethnicity, n (%)				
Hispanic or Latino	15 (9.6)	17 (22.4)	32 (13.7)	0.0531‡
Not Hispanic or Latino	102 (65.0)	43 (56.6)	145 (62.2)	
Not Reported	23 (14.6)	11 (14.5)	34 (14.6)	
Unknown	17 (10.8)	5 (6.6)	22 (9.4)	
Weight (kg)				
n	153	76	229	0.4926†
Mean (SD)	78.7 (17.73)	76.9 (20.82)	78.1 (18.79)	
Median	78.1	75.0	76.3	
Min-Max	46-184	42-194	42-194	
Height (cm)				
n	152	76	228	0.5810†
Mean (SD)	168.2 (10.65)	167.4 (10.13)	167.9 (10.46)	
Median	168.0	167.0	168.0	
Min-Max	141-195	148-191	141-195	

Variable	Asciminib N=157	Bosutinib N=76	All subjects N=233	P-value
Body mass index (kg/m^2)				
n	152	76	228	0.6641†
Mean (SD)	27.9 (6.52)	27.4 (7.16)	27.7 (6.73)	
Median	26.9	25.8	26.3	
Min-Max	18-74	18-68	18-74	
ECOG performance status, n (%)				
0	126 (80.3)	62 (81.6)	188 (80.7)	0.6885‡
1	28 (17.8)	14 (18.4)	42 (18.0)	
2	2 (1.3)	0	2 (0.9)	
Missing	1 (0.6)	0	1 (0.4)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; SD, standard deviation.
†P-values are obtained from analysis of variance F-test; ‡p-values are obtained from Chi-square test.

Table 3: Disease history (FAS) – Document B, Section B.2.3.1.7, Table 13 (p44)

Variable	Asciminib N=157	Bosutinib N=76	All subjects N=233	P-value
Time since initial diagnosis of CML (years)				
N	156	76	232	0.3185†
Mean (SD)	6.2 (5.76)	7.0 (5.63)	6.5 (5.72)	
Median	3.9	5.1	4.2	
Q1-Q3	1.9-8.9	2.4-11.7	2.0-10.4	
Min-Max	1-28	1-21	1-28	
Historical mutation response, n (%)				
No	109 (69.9)	54 (71.1)	163 (70.3)	0.9585‡
Yes	20 (12.8)	10 (13.2)	30 (12.9)	
Unknown	27 (17.3)	12 (15.8)	39 (16.9)	
Any extramedullary involvement, n (%)				
No	148 (94.9)	72 (94.7)	220 (94.8)	0.9653‡
Yes	8 (5.1)	4 (5.3)	12 (5.2)	

Abbreviations: CML, chronic myeloid leukaemia; FAS, full analysis set; SD, standard deviation.
†P-values are obtained from analysis of variance F-test; ‡p-values are obtained from Chi-square test.

Table 4: Bone marrow aspirate analysis at baseline (FAS) – Document B, Section B.2.3.1.7.1, Table 14 (p45)

Variable	Asciminib N=157	Bosutinib N=76	P-value
Blasts (%) in BM			
n	139	69	0.2296†
Mean (SD)	1.42 (1.698)	1.76 (2.192)	
Median	1.00	1.00	
Q1-Q3	0.2-2.0	0.5-2.0	
Min-Max	0.0-11.0	0.0-14.8	
Blasts (%) in BM category, n (%)			
=0%	34 (21.7)	9 (11.8)	0.2590‡
>0–<5%	97 (61.8)	56 (73.7)	
≥5–<15%	8 (5.1)	4 (5.3)	
≥15%	0	0	
Missing	18 (11.5)	7 (9.2)	
Promyelocytes (%) in BM			
N	134	68	0.1970†
Mean (SD)	3.55 (4.175)	2.81 (2.989)	
Median	2.00	2.00	
Q1-Q3	0.6–5.1	0.3–4.0	
Min-Max	0.0–26.0	0.0–11.0	
Blasts + promyelocytes (%) in BM (derived)			
N	140	71	0.5198†
Mean (SD)	4.81 (4.556)	4.40 (3.932)	
Median	4.00	3.00	
Q1-Q3	1.4-7.2	1.0-6.0	
Min-Max	0.0-29.0	0.0-16.8	

Abbreviations: BM, bone marrow; FAS, full analysis set; SD, standard deviation.
†P-values are obtained from analysis of variance F-test; ‡p-values are obtained from Chi-square test.

Table 5: Prior antineoplastic therapy (FAS) – Document B, Section B.2.3.1.8, Table 16 (p47)

Variable	Asciminib N=157	Bosutinib N=76	All subjects N=233	P-value
Prior TKIs, n (%)				
Imatinib	130 (82.8)	63 (82.9)	193 (82.8)	0.9913†
Nilotinib	104 (66.2)	56 (73.7)	160 (68.7)	
Dasatinib	131 (83.4)	65 (85.5)	196 (84.1)	
Ponatinib	23 (14.6)	18 (23.7)	41 (17.6)	
Radotinib	4 (2.5)	2 (2.6)	6 (2.6)	
Other	5 (3.2)	4 (5.3)	9 (3.9)	
Number of prior TKIs, n (%)				
2	89 (56.7)	33 (43.4)	122 (52.4)	0.3914†
3	53 (33.8)	33 (43.4)	86 (36.9)	
4	14 (8.9)	7 (9.2)	21 (9.0)	
≥5	1 (0.6)	3 (3.9)	4 (1.7)	
Number of lines of prior TKI therapy, n (%)				
2	82 (52.2)	30 (39.5)	112 (48.1)	0.7243†
3	44 (28.0)	29 (38.2)	73 (31.3)	
4	24 (15.3)	10 (13.2)	34 (14.6)	
≥5	7 (4.5)	7 (9.2)	14 (6.0)	

Abbreviations: FAS, full analysis set; TKI, tyrosine kinase inhibitor.
†P-values are obtained from Chi-square test.

iii. A discussion on why these imbalances might have occurred.

As Table 2–Table 5 demonstrate, there were no significant differences observed between the two treatment populations.

iv. A discussion on whether and how these imbalances might lead to bias in outcomes and results, including the potential direction and magnitude of any bias for efficacy and safety outcomes.

As Table 2–Table 5 demonstrate, there were no significant differences observed between the two treatment populations. Therefore, the Company believe that this will not lead to any bias in the outcomes and results.

v. Where possible, results of regression analyses (logistic or other, as appropriate), accounting for all baseline imbalances, including sex, ethnicity, time since initial diagnosis of CML, prior TKIs received, number of previous TKIs, number of prior lines of TKI treatment, and reasons for discontinuation of prior TKI.

Adjustment for differences in baseline characteristics with regression analysis was not undertaken.

A7. Please clarify which methods were used, if any, to conceal allocation to the asciminib and bosutinib arms.

The ASCEMBL trial was not blinded and methods were not used to conceal allocation to asciminib or bosutinib treatment arms for the following reasons:

- Asciminib and bosutinib have different methods of administration (bosutinib needs to be taken with food, whereas asciminib is taken fasted).
- Double dummy treatments make blinding difficult and carry inherent risks of dosing errors and reduced patient compliance.
- The characteristic adverse event (AE) profile of bosutinib (frequent gastrointestinal AEs of diarrhoea and vomiting (90)) further precludes effective blinding.

A8. Please discuss whether the lack of blinding in the ASCEMBL trial and the possibility to switch to asciminib following bosutinib treatment failure may have introduced bias for the efficacy (including MMR and TTD) and safety results of the study. Please discuss the magnitude and direction of any possible bias by outcome, including for MMR, TTD, and safety outcomes.

Randomisation and use of objective efficacy endpoints (specifically, primary and key secondary endpoints assessed by central lab determined BCR-ABL1 levels) mitigate the risks of an open label study design.

For the purpose of the primary and secondary endpoint analyses, patients meeting the ELN failure criteria while receiving study treatment (either before or by the time of conducting the analysis and irrespective of treatment arm) were considered non-responders for the specific time point and for any subsequent time point (89, 91). Failure criteria were not subjective but based on ELN haematological values at 3 months, or BCR-ABL1 transcripts levels (and/or Ph+) at 6 and 12 months (this excludes patients who were deemed intolerant from being able to switch) (91). The switch to asciminib in case of bosutinib treatment failure is not expected to introduce bias as those patients were regarded as non-responders irrespective of treatment switch and the disease burden would not improve without further treatment (89). There was no option to switch patients failing on the asciminib treatment arm, as

those patients could be offered approved therapies outside of the context of the study (89). The efficacy data collected after the switch from patients switching to asciminib following bosutinib failure were analysed separately as exploratory endpoints and were not included for primary and secondary study endpoints (89).

Haematological Malignancy Research Network (HMRN) cohort

A9. Priority question: Where possible, please provide the following additional data from the HMRN study for bosutinib, dasatinib, nilotinib and ponatinib:

i. **Proportion who discontinued treatment at 6 months, 1, 2 and 5 years (with 95% CIs).**

Please see Table 6 and Table 7.

ii. **Proportion with MMR at 6 months, 1, 2 and 5 years (with 95% CIs).**

Please see Table 8 and Table 9.

iii. **OS and PFS proportions at 6 months, 1 and 2 years (with 95% CIs).**

Please see Table 10–Table 13.

Please provide these data for each TKI separately; in CML individuals at both 3rd line and 4th line of TKI therapy, separately; and when excluding the T315I mutation.

Table 6: Treatment discontinuation (TTD) for third-line treatment by regimen

	Total n, (%)	Discontinuation		6 months % (95% CI)	1-year, % (95% CI)	2-year, % (95% CI)	5-year, % (95% CI)
		No n, (%)	Yes n, (%)				
Including patients with the T315I mutation							
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients with the T315I mutation							
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network.

Table 7: Treatment discontinuation for fourth-line treatment by regimen

	Total n, (%)	Discontinuation		6 months %, (95% CI)	1-year, % (95% CI)	2-year, % (95% CI)	5-year, % (95% CI)
		No	Yes				
Including patients with the T315I mutation							
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients with the T315I mutation							
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network.

Table 8: Response to third-line TKI therapy

	Total	MMR (95% CI)					Median Duration of response (95%CI) days	Loss of response	Median duration of response till loss, days (95% CI)
		Yes	6 months	12 months	2 years	5 years			
Including patients with the T315I mutation									
Total	[redacted]								
Imatinib	[redacted]								
Nilotinib	[redacted]								
Dasatinib	[redacted]								
Bosutinib	[redacted]								
Ponatinib	[redacted]								
Excluding patients with the T315I mutation									
Total	[redacted]								
Imatinib	[redacted]								
Nilotinib	[redacted]								
Dasatinib	[redacted]								
Bosutinib	[redacted]								
Ponatinib	[redacted]								

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, Confidence Intervals; HMRN, Haematological Malignancy Research Network; MMR, major molecular response; NR, not reached.

Table 9: Response to fourth-line TKI

	Total	Proportion who had reached an MMR (95% CI)					Median duration of response, days (95%CI)
		Yes	6 months	1-year	2 years	5 years	
Including patients with the T315I mutation							
Total	[redacted]						
Imatinib	[redacted]						
Nilotinib	[redacted]						
Dasatinib	[redacted]						
Bosutinib	[redacted]						
Ponatinib	[redacted]						
Excluding patients with the T315I mutation							
Total	[redacted]						
Imatinib	[redacted]						
Nilotinib	[redacted]						
Dasatinib	[redacted]						
Bosutinib	[redacted]						
Ponatinib	[redacted]						

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, Confidence Intervals; HMRN, Haematological Malignancy Research Network; MMR, major molecular response; NR, not reached.

Table 10: Overall survival from start of third-line treatment by regimen

	Total	Vital status		6-month OS, % (95% CI)	1-year OS, % (95% CI)	2-year OS, % (95% CI)
		Alive	Dead			
Including patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network.

Table 11: Overall survival from start of fourth-line treatment by regimen

	Total	Vital status		6 months OS, % (95% CI)	1-year OS, % (95% CI)	2-year OS, % (95% CI)
		Alive	Dead			
Including patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients with the T315I mutation:						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network.

Table 12: Progression-free survival from start of third-line treatment by regimen

	Total	PFS		6-month PFS, % (95% CI)	1-year PFS, % (95% CI)	2-year PFS, % (95% CI)
		Yes	No			
Including patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network; PFS, progression-free survival.

Table 13: Progression-free survival from start of fourth-line treatment by regimen

	Total	PFS		6-month PFS, % (95% CI)	1-year PFS, % (95% CI)	2-year PFS, % (95% CI)
		Yes	No			
Including patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding patients with the T315I mutation						
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file, adapted from HMRN (88).
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network; PFS, progression-free survival.

Other asciminib evidence

A10. The publications by Luna et al. 2020 were not considered relevant to this submission due to its geography (Spain) and most patients receiving ≥3 prior TKI therapies before initiating asciminib.(20-22) Please provide further justification for the exclusion of Luna from the submission, including:

i. A discussion on the location and applicability of the study population to the UK (including further details on the number of individuals with 2, 3, 4 and ≥5 prior TKIs).

The study detailed in Luna et al. 2020 and 2021, and Garcia-Gutierrez et al. 2021 retrospectively collected data from 31 patients with BCR-ABL1-positive CML treated with asciminib (median dose 40 mg twice-daily [BD]) between October 2018 and June 2020 in 25 institutions from the Spanish CML Group (GELMC) (20-22). Study patients did not have alternative effective treatments and were not eligible for clinical trials, and hence patients received asciminib as part of a compassionate access programme.

The majority of patients in the study were classified as intolerant to previous TKIs, and considered to be at risk of suffering side effects from TKI therapy. Patients were also older at the time of data collection than those enrolled in the ASCEMBL trial (median age of 69 years in the compassionate access programme vs 52 years in ASCEMBL). In the ASCEMBL trial, 52.2% and 39.5% of patients received asciminib and bosutinib at third-line, respectively (86). In the compassionate access programme, 90% (n=28) of patients had received three or more prior TKIs; however, no further detail is provided and it is therefore not known how comparable treatment histories are between the two study populations (20-22). Given that it is a compassionate access programme, it is assumed that patients generally had more severe disease and were more heavily treated than patients in the ASCEMBL trial (20-22, 86).

Based on the patient population studied (older with no commercially available treatment options), its geography (Spain), and treatment history (90% of patients had received ≥3 prior TKIs), the Company does not consider this study to be applicable

to the UK patient population (20-22). In addition, the protocol and results for the compassionate access programme for asciminib in Spain are based on two abstracts (20, 21) and one letter to the editor of Blood Cancer journal (22). Consequently, there are limited resources available to the Company to present detailed findings.

ii. A tabulated summary of results (including MMR, serious adverse events and grade 3 adverse events) overall and by line of therapy (LOT).

Efficacy and safety results for the compassionate access programme are available from Luna et al. 2020 and 2021 and Garcia-Gutierrez et al. 2021.

- Luna et al. 2020: Abstract (20)
- Luna et al. 2021: Abstract (21)
- Garcia-Gutierrez et al. 2021: Letter to the editor of Blood Cancer journal (22)

The three identified publications do not present results of the compassionate access programme with asciminib by line of therapy (20-22). A summary of efficacy and safety results are presented in Table 14 and Table 15, respectively.

Table 14: Efficacy response to asciminib

	Resistant (n=9)	Intolerant (n=19)	Total (N=29)
CHR, n (%)	9 (100)	19 (100)	29 (100)
CCyR, n (%)	3 (33)	16 (84)	19 (66)
MMR, n (%)	1 (11)	11 (58)	12 (41)
MR4.5, n (%)	0 (0)	4 (21)	4 (14)

Source: Garcia-Gutierrez et al. 2021 (22).
Abbreviations: CCyR, complete cytogenetic response; CHR, complete haematological response; MMR, major molecular response; MR, molecular response.

Table 15: Summary of adverse events

	Asciminib Any AE (N=31)†	Asciminib Grade 1 or 2 AE (N=31)†	Asciminib Grade 3 or 4 AE (N=31)†	Termination due to AE (N=31)†
Fatigue	4	3	1	0
Joint pain	3	3	0	0
Diarrhoea	0	0	0	0
Nausea	3	3	0	0
Appetite loss	1	1	0	0
Rash	1	1	0	0
Mucositis	0	0	0	0
Oedema	0	0	0	0
Hypertension	1	0	1	0
Ischemic event	0	0	0	0
Pleural/pericardial effusion	2	1	1	0
Pneumonitis	0	0	0	0
Pulmonary hypertension	0	0	0	0
Elevated ALT/AST	0	0	0	0
Elevated cholestatic liver enzymes	1	0	1	0
Pancreatitis	0	0	0	0
Anaemia	4	4	0	0
Thrombocytopenia	10	8	3	0
Neutropenia	3	2	2	0

Source: Luna et al. 2020 (20).
†Luna et al. 2020 does not explicitly state n numbers in their table of results, but we assumed that these are reflective of the total patient population enrolled (N=31).
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transferase.

iii. Justification for the exclusion of this study from the pooled safety analysis of asciminib (Appendix N).

As stated in response to A10i, study patients did not have alternative effective treatments and were not eligible for clinical trials, and hence patients received asciminib as part of a compassionate access programme. The majority of patients in the study were classified as intolerant to previous TKIs, and considered to be at risk of suffering side effects from TKI therapy. Based on the patient population studied (older with no commercially available treatment options), its geography (Spain), treatment history (90% of patients had received ≥3 prior TKIs), and higher risk of AEs, the Company excluded this study from the pooled safety analysis (20-22).

iv. Where appropriate, inclusion of this study to the pooled safety analysis of asciminib.

As stated in response A10i and A10iii, based on the patient population studied (older with no commercially available treatment options), its geography (Spain), treatment history (90% of patients had received ≥3 prior TKIs), and higher risk of AEs, the Company does not see it appropriate to include the compassionate access programme study in the pooled safety analysis (19-21).

Indirect treatment comparison

Commentary: The ERG has substantial concerns with the validity and completeness of the matching adjusted indirect comparison (MAIC) as it is reported. The MAIC in the submission provides adjusted results from ASCEMBL, but not the required relative estimates for comparisons to other interventions in other studies. The MAIC should also be attempted for all outcomes in the NICE scope.

A11. Appendix I, section 3.1 provides some justification for excluding from the MAIC 19 of the 23 studies that were included in the SLR. Please provide a complete justification, study by study, for why these studies were excluded from the MAIC, considering the study and participant characteristics presented in the table requested under question A2.

Studies excluded from the MAIC and justification for doing so are summarised in Table 16.

Table 16: Excluded studies

Study	Reason for exclusion	Notes
Khoury 2012	Single arm bosutinib studies excluded because bosutinib was compared with asciminib directly in the ASCEMBL trial.	–
BYOND		–
Takahashi 2017 (NCT00811070)		–
Tiribelli 2018		–
Garcia-Gutierrez 2019		–
Garg 2009	Recruited populations where <80% of patients matched the target population and did not report baseline characteristics for the target population, separately.	US study. 48 CML patients (any phase) receiving dasatinib or nilotinib after failure of 2 prior TKIs. Outcomes were reported for the 25 patients who matched the target population (pooled treatment groups).
Ribeiro 2015		Study from Brazil. 25 CML patients (any phase) who had been previously treated with imatinib and a second TKI. For the third-line treatment, patients switched to dasatinib (n=9) or nilotinib (n=16). Outcomes were reported for the 18 patients who matched the target population (pooled treatment group).
Lee 2014		Korean study. 97 patients with CP-CML underwent allo-SCT. Select outcomes were reported for the 15 patients who matched the target population; however, none of the reported outcomes was of interest for the analysis.
CML-202		A Phase II trial of omacetaxine among CP-CML patients who harboured the resistance-associated T315I mutation (such patients were excluded in ASCEMBL). Although this trial was included in the SLR for the purpose of completeness, its population did not meet the study eligibility criteria of the current analysis and was therefore excluded from the analysis.
Ongoren 2017	Excluded because they did not report outcomes for >20 participants in the target population.	A study of 21 patients with CP-CML who received dasatinib or nilotinib as a third-line treatment in Turkey. Survival curves were reported for 20 patients matching the target population (pooled treatment group).
Tojo 2017 (NCT01667133)		A Phase I/II single-arm trial of ponatinib among Japanese patients with CML, resistant/intolerant to dasatinib or nilotinib. Outcomes were reported for the entire population (94% had received ≥2 TKIs).

Study	Reason for exclusion	Notes
Swaminathan 2018	Did not report patient characteristics for interventions of interest.	A retrospective chart review of patients with CP-CML who received ponatinib as a second or subsequent line of therapy in the US. Of note, this study was only published as a conference abstract.
Khan 2017		A retrospective chart review of US patients with CP-CML with failure of first- or second-line TKIs who went on to receive third-line TKIs. Results were reported for 185 patients who matched the target population. Patient characteristics were only reported for the pooled intervention group (i.e. bosutinib, dasatinib, imatinib, nilotinib, and ponatinib, received by 7%, 35%, 10%, 36%, and 12% of patients, respectively). Since the efficacy of these treatments in the target population is likely not similar to one another, such a pooled intervention group is not a comparator of interest for the analysis. Of note, this study was only published as a conference abstract.
Garcia-Gutierrez 2012		A registry-based retrospective study of third-line TKIs among 31 Spanish patients with CML who stopped second-generation TKIs as second-line treatment. Interventions were not explicitly mentioned in this study. Of note, this study was only published as a conference abstract.
X2101 (NCT02081378)	Excluded because they were Phase I trials.	An international phase I dose-finding trial of asciminib among 141 patients with CP-CML who had received ≥2 prior lines of TKI with disease progression or unacceptable toxicity or those harbouring the T315I mutation with ≥1 prior lines of TKI prior to trial entry.
Cortes 2012 (NCT00660920)		A Phase I dose-escalation trial of ponatinib (various doses) among 43 American patients with Ph+ CML (any phase) who had relapsed or were resistant to standard care or for which no standard care was available or acceptable.
Ibrahim 2010	Excluded because TTD (time to treatment discontinuation) data were not available.	A prospective study in which CML-CP patients who had failed first-line imatinib and then failed either nilotinib or dasatinib as their second line of treatment were analysed.
Tan 2019		A retrospective study in which CML-CP patients who had failed either imatinib alone or both imatinib and nilotinib were analysed.
PEARL		A multicentre, nonrandomised, observational retrospective study examined the safety and efficacy of ponatinib in adult CML patients resistant or intolerant to at least two prior TKI or harbouring T315I mutation in France.

Abbreviations: CML, chronic myeloid leukaemia; CP, chronic phase; Ph, Philadelphia chromosome; SCT, stem cell transplant; SLR, systemic literature review; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation; US, United States of America.

A12. Whilst the ERG understands that death and disease progression within 5 years are relatively rare in CML, please ensure that all survival data are reported for all studies included in the MAIC.

Wherever possible, this should include, for both OS and PFS: median survival; Kaplan-Meier (K-M) estimates of proportions surviving at 6 months, 1 year, 2 years, 5 years (as per Document B, table 28); and corresponding K-M curves.

Requested data are presented where possible in Table 22 and Table 23 (A19).

A13. Please ensure that, if reported, duration of MMR is extracted and presented for all studies included in the indirect treatment comparison. Wherever possible, please report data as requested in A12 (as per Document B, table 28)

Duration of MMR is presented where possible in Table 20 (A15).

A14. Please provide further details on the assessment of overlap between ASCEMBL and comparator studies, including distribution of propensity scores before and after weighting for each comparison, and standardised mean differences by covariate between treatment arms before and after weighting.

The implementation of the MAICs closely followed the methodology described in the NICE decision support unit (DSU) technical support document (TSD) 18. Weights for patients in the asciminib arm of the ASCEMBL trial were estimated directly using the method of moments to match the aggregate patient characteristics with the target trial. Propensity scores were not estimated. For each of the MAICs undertaken (for nilotinib, dasatinib and ponatinib), the distributions of the resulting weights are provided in the MAIC report (appendix I). Convergence problems prevented inclusion of all relevant covariates in the estimation of weights for the MAICs. Covariate selection was prioritised following clinical opinion to rank covariates with respect to importance. The distribution of all covariates and the standardised mean difference before and after weighting to the PACE (23), Giles et al. 2010 (65), and Rossi et al. 2013 (67) is reported in Table 17, Table 18, Table 18 and Table 19.

Table 17: Distribution of covariates and standardised mean differences before after matching to PACE (ponatinib)

Characteristic	Value from PACE	Value from ASCEMBL before weighting	Value from ASCEMBL after weighting	SMD before weighting	SMD after weighting
No. of patients/ESS	270	133	74	–	–
Race - white	81%	75%	74%	14%	17%
Sex – male	53%	48%	44%	10%	19%
Median age	60	52	54		
ECOG status zero	70%	79%	76%	-21%	-13%
No mutation	51%	86%	83%	-80%	-73%
PCyR at baseline	20%	19%	20%	2%	0%
Nilotinib/dasatinib resistant	80%	68%	80%	27%	0%
Nilotinib/dasatinib intolerant only	14%	42%	14%	-65%	0%
Prior TKI = 2	34%	56%	34%	-47%	0%

Abbreviations: ESS, estimated sample size; ECOG. Eastern Cooperative Oncology Group; PCyR, partial cytogenetic response; SMD, standardized mean difference; TKI, tyrosine kinase inhibitor.

Table 18: Distribution of covariates and standardised mean differences before after matching to Giles et al. 2010 (nilotinib)

Characteristic	Value from Giles 2010	Value from ASCEMBL before weighting	Value from ASCEMBL after weighting	SMD before weighting	SMD after weighting
No. of patients/ESS	39	157	48	–	–
Median age	62	52	53	–	–
ECOG status zero	64%	80%	77%	-36%	-29%
No mutation	33%	87%	95%	-132%	-169%
Imatinib resistant	85%	54%	32%	72%	128%
Imatinib intolerant	15%	54%	74%	-90%	-148%
MCyR at baseline	21%	28%	21%	-16%	0%
Dasatinib resistant	31%	45%	31%	-29%	0%
Dasatinib intolerant	67%	35%	67%	68%	0%
Prior TKI = 2	100%	52%	100%	136%	0%

Abbreviations: ESS, estimated sample size; ECOG. Eastern Cooperative Oncology Group; MCyR, major cytogenetic response; SMD, standardized mean difference; TKI, tyrosine kinase inhibitor.

Table 19: Distribution of covariates and standardised mean differences before after matching to Rossi et al. 2013 (dasatinib)

Characteristic	Value from Rossi 2013	Value from ASCEMBL before weighting	Value from ASCEMBL after weighting	SMD before weighting	SMD after weighting
No. of patients/ESS	34	157	61	–	–
Sex – male	27%	52%	53%	-53%	-55%
Median age	60	52	46	–	–
No mutation	50%	87%	79%	-87%	-64%
Imatinib resistant	94%	54%	42%	102%	134%
Imatinib intolerant	6%	54%	39%	-123%	-86%
Nilotinib intolerant	50%	23%	12%	58%	90%
Nilotinib resistance	59%	38%	59%	43%	0%
Prior TKI = 2	100%	43%	100%	163%	0%

Abbreviations: ESS, estimated sample size; ECOG. Eastern Cooperative Oncology Group; SMD, standardized mean difference; TKI, tyrosine kinase inhibitor.

A15. Priority question: Please tabulate a naïve, unadjusted comparison for ASCEMBL and all comparator studies included in the MAIC for the following outcomes:

i. **PFS (median survival and proportion surviving at 1 and 2 years)**

ii. **MMR**

iii. **duration of MMR**

iv. **TTD**

v. **Adverse events (including Grade 3 and above, and serious adverse events)**

Outcomes requested are presented where possible in Table 20. K-M curves for time to treatment discontinuation (TTD) were not available for any comparator: only median treatment duration was available.

Table 20: Summary of included studies

	ASCEMBL (86)	PACE (23)	Giles 2010 (65)	Rossi 2013 (67)
PFS				
Median survival	NA	NA	NA	NA
1-year survival, % (95% CI)	NA	80	NA	NA
5-year survival, % (95% CI)	NA	53 (45, 60)	NA	NA
MMR				
MMR (6 months), % (95% CI)	27.4	19 (15, 26)	NA	15.9
MMR (12 months), % (95% CI)	NA	NA	NA	NA
Duration of MMR	NA	NA	NA	NA
TTD				
Median (months) (95% CI)	16.6	32.1 (0.1, 73.0)	11 (<1.0, 29.2)	1
AE				
Nonhematologic AEs any grade, n (%)				
Abdominal pain	9 (5.8)	125 (46)	NA	NA
Rash	12 (7.7)	127 (47)	(28)	NA
Constipation	NA	112 (41)	NA	NA
Headache	29 (18.6)	116 (43)	(13)	NA
Dry skin	7 (4.5)	114 (42)	NA	NA
Fatigue	21 (13.5)	81 (30)	(10)	NA
Hypertension	19 (12.2)	99 (37)	NA	NA
Pyrexia	6 (3.8)	70 (26)	NA	NA
Arthralgia	19 (12.2)	90 (33)	NA	NA
Nausea	18 (11.5)	79 (29)	(15)	NA
Diarrhoea	18 (11.5)	54 (20)	NA	NA
Increased lipase	8 (5.1)	73 (27)	NA	NA
Vomiting	11 (7.1)	50 (19)	NA	NA
Myalgia	8 (5.1)	65 (24)	NA	NA
Pain in extremity	13 (8.3)	65 (24)	NA	NA
Pruritus	8 (5.1)	NA	(15)	NA
Asthenia	9 (5.8)	NA	NA	NA
Epistaxis	NA	NA	NA	NA
Injection site erythema	NA	NA	NA	NA
Peripheral oedema	9 (5.8)	NA	NA	NA
Nonhematologic AEs grade 3/4, n (%)				
Abdominal pain	0	28 (10)	NA	NA
Rash	0	10 (4)	NA	NA
Constipation	NA	7 (3)	NA	NA
Headache	3 (1.9)	9 (3)	NA	NA
Dry skin	0	9 (3)	NA	NA
Fatigue	1 (0.6)	6 (2)	NA	NA
Hypertension	9 (5.8)	37 (14)	NA	NA
Pyrexia	2 (1.3)	3 (1)	NA	NA
Arthralgia	0	8 (3)	NA	NA
Nausea	1 (0.6)	2 (<1)	NA	NA
Diarrhoea	0	2 (<1)	NA	NA

	ASCEMBL (86)	PACE (23)	Giles 2010 (65)	Rossi 2013 (67)
Increased lipase	6 (3.8)	34 (13)	NA	NA
Vomiting	2 (1.3)	4 (1)	NA	NA
Myalgia	0	3 (1)	NA	NA
Pain in extremity	1 (0.6)	8 (3)	NA	NA
Pruritus	0	NA	NA	NA
Asthenia	0	NA	NA	NA
Epistaxis	NA	NA	NA	NA
Injection site erythema	NA	NA	NA	NA
Peripheral oedema	0	NA	NA	NA
Hematologic TEAEs, any grade, n (%)				
Thrombocytopenia	36 (23.1)	123 (46)	NA	NA
Neutropenia	30 (19.2)	53 (20)	NA	NA
Anaemia	15 (9.6)	53 (20)	NA	NA
Leukopenia	NA	NA	NA	NA
Pancytopenia	NA	NA	NA	NA
Febrile neutropenia	NA	NA	NA	NA
Hematologic TEAEs, grade 3/4, n (%)				
Thrombocytopenia	28 (17.9)	95 (35)	(28)	NA
Neutropenia	24 (15.4)	45 (17)	(23)	NA
Anaemia	2 (1.3)	28 (10)	NA	NA
Leukopenia	NA	NA	NA	NA
Pancytopenia	NA	NA	NA	NA
Febrile neutropenia	NA	NA	NA	NA
SAEs, %				
Pancreatitis	NA	7	NA	NA
Atrial fibrillation	0	6	NA	NA
Pneumonia	1 (0.6)	6	NA	NA
Angina pectoris	NA	5	NA	NA
Pyrexia	2 (1.3)	NA	NA	NA
Urinary tract infection	2 (1.3)	NA	NA	NA
Non-cardiac chest pain	1 (0.6)	NA	NA	NA
Thrombocytopenia	1 (0.6)	NA	NA	NA
COVID-19	1 (0.6)	NA	NA	NA
Cardiac arrest	1 (0.6)	NA	NA	NA
Cardiac failure	1 (0.6)	NA	NA	NA
Febrile neutropenia	1 (0.6)	NA	NA	NA
Headache	1 (0.6)	NA	NA	NA
Ischaemic stroke	1 (0.6)	NA	NA	NA
Platelet count decreased	1 (0.6)	NA	NA	NA
Vomiting	1 (0.6)	NA	NA	NA
Depression	1 (0.6)	NA	NA	NA
Myocardial ischaemia	1 (0.6)	NA	NA	NA
Postoperative wound infection	1 (0.6)	NA	NA	NA
Rash	0	NA	NA	NA

	ASCEMBL (86)	PACE (23)	Giles 2010 (65)	Rossi 2013 (67)
Pleural effusion	0	NA	NA	NA
Cardiac failure congestive	0	NA	NA	NA
Acute kidney injury	0	NA	NA	NA

Abbreviations: AE, adverse event; MMR, major molecular response; NA, not available; NR, not reached; PFS, progression-free survival; SAE, serious adverse event; TTD, time to treatment discontinuation.

A16. Priority question: Where possible, please perform a full MAIC, tabulating adjusted results from ASCEMBL compared to results from other studies, for each comparison, for the outcomes listed in question A15.

A full description of the MAIC of TTD was included in the original submission (Appendix I).

A MAIC has been undertaken to compare MMR for asciminib in comparison with ponatinib, nilotinib and dasatinib. Data on MMR for ponatinib were taken from the same source as that providing data on TTD (PACE trial) (23). Data on MMR for dasatinib and nilotinib were not available in the clinical studies selected to estimate TTD. The most suitable source of data for this outcome was considered to be Ibrahim 2010 (68). The study reports outcomes including MMR, CCyr and PCyr for 26 patients who received either nilotinib or dasatinib in third-line therapy. Table 21 provides the results of MAIC of MMR at 6 months with ponatinib (data from PACE) and nilotinib/dasatinib (data from Ibrahim 2010) (68), along with unadjusted data from ASCEMBL for asciminib compared to bosutinib.

Table 21: MMR at 6 months from MAIC

Drug	Asciminib vs bosutinib		Asciminib vs ponatinib		Asciminib vs dasatinib/nilotinib	
	Asciminib	Bosutinib	Asciminib	Ponatinib	Asciminib	Dasatinib/ nilotinib
MMR	28.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data on PFS were very limited as illustrated in Table 20. As these data are not used in either the base case cumulative survival approach in the CEM, or in the surrogate response approach undertaken in scenario analysis (see question B2), further analysis of the limited data on PFS was not considered a priority.

Due to time constraints, MAIC of time to MMR, and time to AEs, have not been undertaken.

A17. Where possible, please present results of regression analyses to illustrate the impact of covariates on TTD estimates in the MAIC analyses.

Regression analysis of the impact of covariates on TTD in the ASCEMBL data was not undertaken following weighting in the MAIC analyses.

A18. Please explain why the HMRN audit data was not included in the MAIC.

Data on TTD were taken from sources considered to provide the best available data for each of the comparators. Data for all four comparators in a third-line setting for patients without the T315I mutation are available in HMRN. However, for each comparator we considered the available published data to be superior. We discuss each in turn below:

- Bosutinib: data are available in the relevant population for [redacted] patients in HMRN. The ASCEMBL trial provided data for a larger number of patients, and the data emanate from a randomised study in comparison with asciminib (86). Consequently, the ASCEMBL data were considered superior to HMRN data.
- Ponatinib: data are available in the relevant population for only [redacted] patients in HMRN. In contrast, the PACE trial included 270 patients of whom 203 were at third line or later, and 67 had the T315I mutation. Whilst the inclusion of patients with the T315I mutation is a limitation of the data from PACE with regard to estimation of TTD for the economic analysis, consideration of sample size greatly favoured the selection of the PACE trial (23).
- Nilotinib: data are available in the relevant population for [redacted] patients in HMRN. Giles et al. 2010 reported on 39 patients receiving nilotinib after failure of imatinib and dasatinib (65). Giles was preferred for the following reasons:
    - The sample size is modestly larger than that of HMRN.

    - The Company considered the data on outcomes, such as progression and TTD, was likely to be more accurate in a clinical study than in a registry.

- Dasatinib: data are available in the relevant population for [redacted] patients in HMRN. Rossi et al. report data on 34 patients receiving dasatinib as third-line treatment (67). Patients in Rossi were monitored according to ELN recommendations (92). There was no meaningful difference in sample size between the two sources. The data in Rossi were considered marginally superior with regard to accuracy of determination of event times.

In summary, we considered the clinical studies we selected to be superior to the data in HMRN, because of reasons of sample size (albeit the difference was marginal in the case of dasatinib and nilotinib), but also patient selection criteria likely to be more robust in a clinical trial.

A19. Please present tables comparing the results of ASCEMBL against the results of the HMRN audit study for bosutinib, dasatinib, nilotinib and ponatinib to inform an indirect naïve comparison, in the same fashion as for question A15. Where available, please present the results by line of TKI therapy (3rd and 4th line), and excluding patients with a T315I mutation.

Outcomes in Table 22 and Table 23 are for those without the mutation.

Table 22: Third-line outcomes from ASCEMBL vs HMRN vs published studies

TKI	PFS Median (years)	1-year PFS, % (CI)	2-year PFS, % (CI)	OS Median (years)	1 year OS, % (CI)	2-year OS, % (CI)	TTD Median months (CI)	MMR (6 months) % (CI)	MMR (12 months), % (CI)	Median duration of response, days (CI)
Asciminib										
Asciminib (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib										
Bosutinib (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib										
Dasatinib (Rossi 2013)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib										
Nilotinib (Giles 2010)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TKI	PFS Median (years)	1-year PFS, % (CI)	2-year PFS, % (CI)	OS Median (years)	1 year OS, % (CI)	2-year OS, % (CI)	TTD Median months (CI)	MMR (6 months) % (CI)	MMR (12 months), % (CI)	Median duration of response, days (CI)
Ponatinib										
Ponatinib (PACE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†3 patients (5.6%) lost their response, KM proportion maintaining response at 24 weeks was 95.4% (95% CI: 82.8, 98.8); ‡data reported for patients receiving dasatinib and nilotinib, timepoint not specified.

Abbreviations: CI, confidence interval (95%); HMRN, haematological malignancy research network; MMR, major molecular response; NR, not reached; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

Table 23: Fourth-line outcomes from ASCEMBL vs HMRN

TKI	PFS Median (years)	1-year PFS, % (CI)	2-year PFS, % (CI)	OS Median (years)	1 year survival, % (CI)	2-year survival, % (CI)	TTD Median months (CI)	MMR (6 months), N (%)	Median duration of response, days (CI)
Asciminib (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†3 patients (5.6%) lost their response, KM proportion maintaining response at 24 weeks was 95.4% (95% CI: 82.8, 98.8)
Abbreviations: CI, confidence interval; HMRN, haematological malignancy research network; MMR, major molecular response; NR, not reached; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

A20. Where feasible, please provide full MAICs using the HMRN data as for question A16. Where a MAIC is not conducted, please justify why not.

Interpretation of the data in HMRN by treatment line is limited by the low numbers of patients on individual therapies and the resulting wide confidence intervals (see A19). Notably, median TTD for dasatinib patients at fourth line is considerably longer than that for patients at third line, which is most likely a manifestation of the small numbers of patients available for analysis. For this reason, the Company does not believe a comparison of data from ASCEMBL with that from HMRN after undertaking a MAIC will be meaningful.

A21. Please discuss and compare the efficacy and safety results of studies included in the MAIC with results from the HMRN audit study.

Safety data are not available in the HMRN registry.

Efficacy data from HMRN and comparable data from the studies included in the MAIC have been included as part of Table 22 for A19. Data on dasatinib from the HMRN show a [redacted] TTD and a [redacted] proportion of patients achieving a MMR at 12 months compared with the ASCEMBL trial (data on MMR for Rossi include patients on dasatinib and nilotinib). The data on nilotinib from HMRN also show a higher TTD compared to data in Giles 2010. However, data from HMRN on TTD in second-line nilotinib therapy indicate a median TTD of [redacted] months. Second-line data from HMRN is based on a larger sample size and it seems likely that TTD in third-line treatment will be similar or shorter. The discrepancy probably reflects the small patient numbers upon which the analysis at third line is based.

The data on bosutinib in the HMRN indicate a [redacted] TTD and a [redacted] MMR at 6 months compared with data from the ASCEMBL trial. In contrast, data from the PACE trial indicate improved progression-free survival (PFS), OS, TTD and MMR at 6 months when compared with data from HMRN. These comparisons need to be subject to the caveat that the data in HMRN are based on a small number of patients. In general, HMRN data report [redacted] TTD and MMR at 6 months when compared with data from clinical studies informing the analysis. Comparisons between bosutinib for patients in HMRN and in the ASCEMBL trial suggest that

estimates from HMRN may be more [redacted] than those derived from clinical studies.

Section B: Clarification on cost-effectiveness data

Model structure and clinical effectiveness

B1. Priority Question: The economic analysis uses cumulative survival approach previously used in TA 401.(93)

i. Please comment on the assumptions implied by this approach, commenting on the strengths and weaknesses of this approach.

Prior to the development of the first TKI, CML typically progressed from the chronic phase to the rapidly fatal blast phase (BP) in 3–5 years (94). Life expectancy has been transformed since the introduction of TKIs, with 8-year survival increasing from 6% before 1975 to 87% since 2001 (95). The dramatic change in prognosis has been achieved through induction of remission with TKIs, which effectively halt the progression of the disease in patients maintaining a response to treatment. For many patients, first-line treatment with imatinib is sufficient to prevent progression of the disease, but for some patients, resistance or intolerance necessitates second-line and subsequent treatment.

The cumulative survival approach assumes that progression to the accelerated phase of the CML is delayed in patients achieving a response to treatment, and that the duration of that response is approximated by the duration of treatment. There is ample evidence that response to treatment is associated with a delay in progression of the disease, at least in patients treated with first-line TKIs, where achievement of a complete cytogenic response is associated with five year survival in excess of 95% (5). Data are limited in a third-line setting; however, evidence from the HMRN registry indicates a five-year survival of 59% for patients commencing third-line TKI treatment. Evidence from clinicians and from the HMRN suggests that TKI therapy is changed when a loss of response is observed, and that therapies used in an earlier line may be repeated in patients who lose response to initial treatment; data from HMRN reports treatment with up to 10 lines of TKI therapy.

Hence the assumptions that achieving a response to treatment delays the progression of the disease, and that treatment is changed following loss of response, are supported by the available evidence and clinical opinion.

The cumulative survival approach further assumes a simple relationship between the duration of response to treatment, and hence the time on therapy, and progression to advanced phases of the disease. The strengths of this approach to estimating overall survival lie in its simplicity, clinical plausibility and independence from data generated in predominantly first line populations that are unlikely to be representative of the subgroup of patients commencing third-line therapy. The approach is more in keeping with a traditional partitioned survival approach, in assuming no impact of treatment on duration of post-progression survival. This is a widely accepted approach in oncology modelling.

The cumulative survival approach has limitations relevant to all methods relying on a surrogate measure of outcome. The approach assumes that prolongation of third line therapy does not lead to reduced duration of subsequent therapies or more rapid progression of the disease after progression to the accelerated phase. The robustness of the approach rests on the plausibility of the assumption that progression of the disease can be delayed indefinitely, provided patients achieve a response to treatment. Whilst data are limited in a third-line population, this assumption reflects the data on OS, and the strong link between OS and response to treatment.

The data used to estimate the duration of survival post-discontinuation of treatment was based on the same source as used in the bosutinib appraisal (TA401), Kantarjian 2007 (96), with the ERG calculating an estimate of mean OS of 7 years. The value was scrutinized and validated by a leading clinician. This source was a population of post-imatinib patients, and therefore second line. Whilst survival is expected to decrease for patients at third and fourth line compared to those at second line, the therapeutic options available to patients have increased since the publication of Kantarjian (2007) (96), and this is likely to have increased survival. Indeed, the data from HMRN for patients at fourth line, whilst limited in size,

suggests an overall mean survival of 7 years may be conservative. Alternative durations of post-discontinuation survival have been tested in sensitivity analysis and led to improvements in cost-effectiveness.

Other limitations of the cumulative survival approach are that post-TTD OS is not assumed to be influenced by the level of response to treatment, dose intensity, or reason for discontinuation. While this is a simplified assumption, all surrogacy approaches have limitations. A systematic review by Oriana et al 2013 on the relationship between response and OS noted that systematic reviews do not take into account the speed of achieving the surrogate response, its depth, or duration (5). Hence, surrogacy approaches based on systematic review of the available data linking response to OS are subject to these limitations. In addition, historical data on surrogacy is mainly based on imatinib, which is believed to be inferior to other TKIs.

In summary, whilst the cumulative survival approach has limitations, there are limitations to all surrogacy approaches. The cumulative survival approach has the benefit of being simpler, clinically validated, and in keeping with typical oncology modelling.

ii. An important assumption of the cumulative survival approach is that it implies that post-discontinuation survival is not influenced by previous treatment. Please comment on the plausibility of this assumption?

There is ample evidence to indicate that successful suppression of the disease can lead to large extensions in survival (97). Indeed, the advent of TKIs has for some patients turned a fatal disease into one that does not lead to premature mortality (98). Resistance or intolerance to TKIs can develop in some patients, and it is this subgroup who are at risk of progression to blast crisis and premature mortality. Hence, whilst CML cannot be cured by TKIs, it can be controlled and progression stalled.

The model assumes that the progression of the disease is stalled whilst response to treatment is sufficient for physicians to recommend continuation of therapy. This assumption is supported, at least in the data for treatment at earlier lines, in which survival for patients achieving a good response is close to normal life expectancy

(99). The model also assumes that extension of time on third line therapy, following a response to treatment, does not shorten the time from initiation of fourth-line therapy to progression of the disease and death. There are little direct data to verify or refute this latter assumption. However, the data from HMRN for patients commencing fourth-line therapy indicate a survival of 59% at five years. This compares favourably with earlier data from Kantarjian (2007) (96) for patients commencing second line therapy. The data would indicate that the introduction of second and third generation TKIs have extended survival to the extent that patients commencing fourth line treatment can now expect to live longer than those commencing second-line treatment prior to the introduction of second generation TKIs. This observation would support the basic premise of the model that extending response to third line therapy generates a corresponding extension in OS. We cannot be certain that extensions to time on treatment with third-line therapy do not foreshorten the subsequent time before progression of the disease. However, the available evidence would indicate that any foreshortening is likely to be small.

iii. In Table 46 (pg. 99) of the submission it is noted that two deaths were assessed as being possibly or probably related to asciminib treatment and one to bosutinib. Clarify how this has been considered in the modelling.

Two patients (1.3%) in the asciminib treatment group and one patient (1.3%) in the bosutinib treatment group had serious adverse events (SAEs) with fatal outcomes. The causes of death were embolism arterial and ischemic stroke in the asciminib treatment group and were not considered possibly or probably related to treatment with asciminib. The cause of death in the bosutinib treatment group was septic shock and was considered to be treatment-related (100, 101) (Table 24).

Table 24: Overview of AEs (Safety set) – Document B, Section B.2.10.1.2.1, Table 46 (p99)

Category	Asciminib 40 mg BD (N=156)		Bosutinib 500 mg OD (N=76)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
AEs	142 (91.0)	85 (54.5)	74 (97.4)	51 (67.1)
Treatment-related	103 (66.0)	50 (32.1)	68 (89.5)	40 (52.6)
SAEs	24 (15.4)	19 (12.2)	18 (23.7)	16 (21.1)
Treatment-related	5 (3.2)	4 (2.6)	9 (11.8)	7 (9.2)
Fatal SAEs	2 (1.3)	2 (1.3)	1 (1.3)	1 (1.3)
Treatment-related	0	0	1 (1.3)	1 (1.3)
AEs leading to discontinuation	11 (7.1)	10 (6.4)	19 (25.0)	14 (18.4)
Treatment-related	8 (5.1)	7 (4.5)	16 (21.1)	11 (14.5)
AEs leading to dose adjustment/interruption	63 (40.4)	–	46 (60.5)	–
AEs requiring additional therapy	NR (67.9)	–	NR (89.5)	–

Abbreviations: AE, adverse event; BD, twice daily; NR, not reported; OD, once-daily; SAE, serious adverse event.

The cost-effectiveness model (CEM) is not informed by mortality data from the ASCEMBL trial. As is common in trials in this patient population, the data are immature. The model applies an assumption that disease mortality arises from progression to blast crisis and models this progression. The assumption of no disease specific mortality in the chronic phase was applied in the previous assessment of ponatinib for CML (TA451). In addition, a floor on mortality rates at the relevant values for the general population of the same age is applied. Inclusion of deaths observed within trial follow-up in addition to modelling disease progression to blast crisis and death risks double counting the mortality impact of CML. It has also been clarified above that there was only one treatment-related death and this was in the bosutinib arm, therefore not including this could also be considered conservative towards asciminib.

B2. Priority Question: the company submission outlines several limitations of surrogate based modelling approach. A surrogate modelling approach, however, has several advantages over a cumulative modelling approach. Further, this approach has been accepted in several previous TA most recently TA 451.(102) Please further justify the decision not use a surrogate modelling approach making specific reference to any differences between TA 451(102) and the current appraisal.

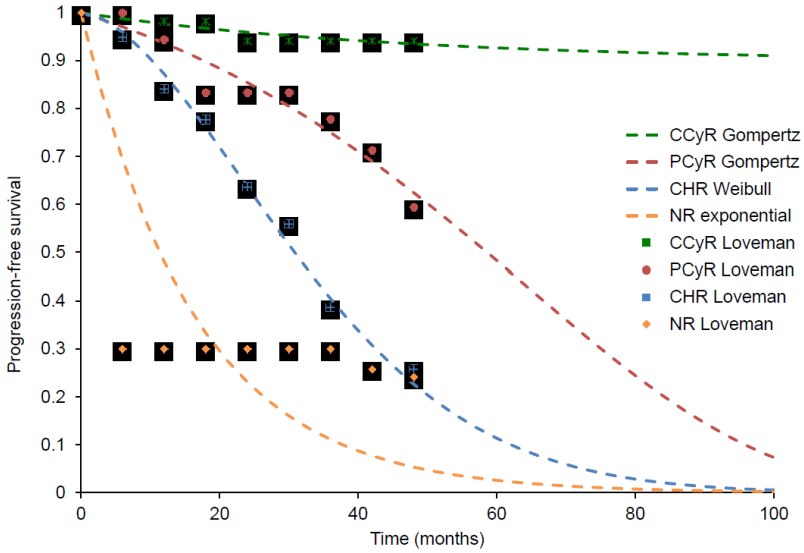
i. Please consider revising the economic analysis to reflect a surrogate modelling approach.

The submitted approach to modelling the health gains from treatment of CML with TKIs (the cumulative survival approach) is transparent and robust, and aligns with the traditional approach to economic analysis of oncology drugs whilst reflecting the disease course in patients with CML treated with TKIs. Importantly, unlike the approach adopted by the manufacturer in TA451 (ponatinib), this approach is not dependent on extrapolation methods from surrogate outcomes collected in first line populations. Specifically, it is unclear that evidence linking CCyR to OS generated in a first-line population (as used by the manufacturer in TA451) is valid to apply in a third line population. The current model structure represents a simpler approach, supported by clinical opinion, and is also in keeping with typical partitioned survival modelling in oncology which assume no post-progression survival gain from treatment.

We accept however that our approach, which relies on using time on third-line treatment as a proxy measure of OS, is accompanied with uncertainty. In order to address this uncertainty, a version of the model is provided which includes a surrogate modelling approach based on the approach used in TA451 (ponatinib). In TA451, the manufacturer reported data from the BMS-034 trial on disease progression as a function of response to treatment at 12 months. The response categories considered were CCyR, partial cytogenetic response (PCyR), complete haematologic response (CHR) and no response (NR). Figure 1 illustrates the PFS curves reported in TA451 by response status.

Figure 1: PFS as a function of response to treatment as reported in TA451 (ponatinib)

Figure 5-7. Comparison of the BMS-034 study data and the fitted parametric functions



CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, non-response; PCyR, partial cytogenetic response.

The data in Figure 1 were digitised and pseudo-patient-level data constructed using the method presented by Guyot et al (103). Parametric survival models of PFS were estimated for each response category. The same survival distributions for each response outcome were selected as per TA451 (reported in Figure 1).

The four response survival curves were weighted by the proportion of patients achieving each response category. Response data were taken from ASCEMBL, supplemented from other sources where required response data were not reported.

- Data from ASCEMBL report CCyR as an outcome. Individual patient data (IPD) data were available from ASCEMBL that also reported PCyR. These data were used for the comparison with bosutinib for these two response outcomes.

For comparisons other than bosutinib, MAICs were undertaken to derive CCyR for asciminib vs each of ponatinib, nilotinib, and dasatinib. MAICs were also used to derive PCyR for the asciminib arm versus each of ponatinib, nilotinib, and dasatinib. Data on ponatinib for the MAIC was taken from the PACE study (23). Data for nilotinib and dasatinib for the MAIC were taken from Ibrahim 2010 (68).

- The ponatinib submission (TA451) reports the proportions for the four categories of response for ponatinib (based on the unadjusted data from Tables 5–7 of TA451), and bosutinib (Tables 5–8 in TA451). The relative proportion that achieved PCyR, CHR, and no response (NR) for patients not achieving a CCyR were calculated for ponatinib and bosutinib. The relative proportions were then averaged to determine estimates of the likely proportion of PCyR, CHR, and NR in patients not achieving a CCyR. These relative proportions were used to estimate the proportion of PCyR, CHR, and NR for dasatinib and nilotinib in those patients failing to achieve a CCyR. For ponatinib, the distribution across PCyR, CHR, and NR was taken from the distribution of the ponatinib arm. For bosutinib, the distribution across CHR and NR was taken from the distribution of the bosutinib arm.

- Data on CCyR and PCyR were available for asciminib, but not the proportion of patients achieving CHR or NR. These data were estimated in an analogous fashion to the manner described above using the averaged value for the ponatinib and bosutinib data from TA451 to estimate proportions of CHR and NR relative to CCyR. This was used to derive the proportion with CHR and NR for asciminib compared with the other TKIs.

The resulting response rates for each treatment and by each response category are summarised in Table 25. In addition, Table 25 includes MMR at 24 weeks, the primary efficiency endpoint in ASCEMBL. Note that this is not used as part of the surrogacy scenario, but is presented for completeness. Molecular response is a strong predictor of disease outcomes. It is assessed according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts (14, 104, 105). BCR-ABL1 transcript levels ≤0.1% are defined as a major molecular response (MMR) (MR3) and BCR-ABL1 transcript levels ≤0.01%[b] and ≤0.0032%[c] are defined as a deep molecular response (MR) (MR4 and MR4.5, respectively). A CCyR is defined by the absence of Ph+ metaphases or <1% BCR-ABL1 nuclei out of ≥200

[b] Or BCR–ABL not detectable with ≤10,000 ABL or 24 000 β-glucuronidase [GUS] transcripts.
[c] Or BCR–ABL not detectable with ≤32,000 ABL or 77,000 GUS transcripts.

cells (104). These data are included to illustrate the consistency with the data on PCyR and CCyR; they are not utilised to estimate outcomes for patients in the economic model.

Table 25: Response rates

	CCyR	PCyR	CHR	NR	MMR
Asciminib versus bosutinib					
Asciminib	45.63%	9.71%	26.05%	18.61%	28.2%
Bosutinib	33.87%	8.06%	32.58%	25.48%	14.5%
Asciminib vs ponatinib					
Asciminib	41.86%	9.87%	28.15%	20.12%	29.04%
Ponatinib	43.26%	10.01%	28.37%	18.36%	18.7%
Asciminib vs nilotinib					
Asciminib	62.63%	3.05%	20.02%	14.30%	26.9%
Nilotinib	30.90%	9.89%	34.53%	24.67%	20.8%
Asciminib vs dasatinib					
Asciminib	62.63%	3.05%	20.02%	14.30%	26.9%
Dasatinib	30.90%	9.89%	34.53%	24.67%	20.8%

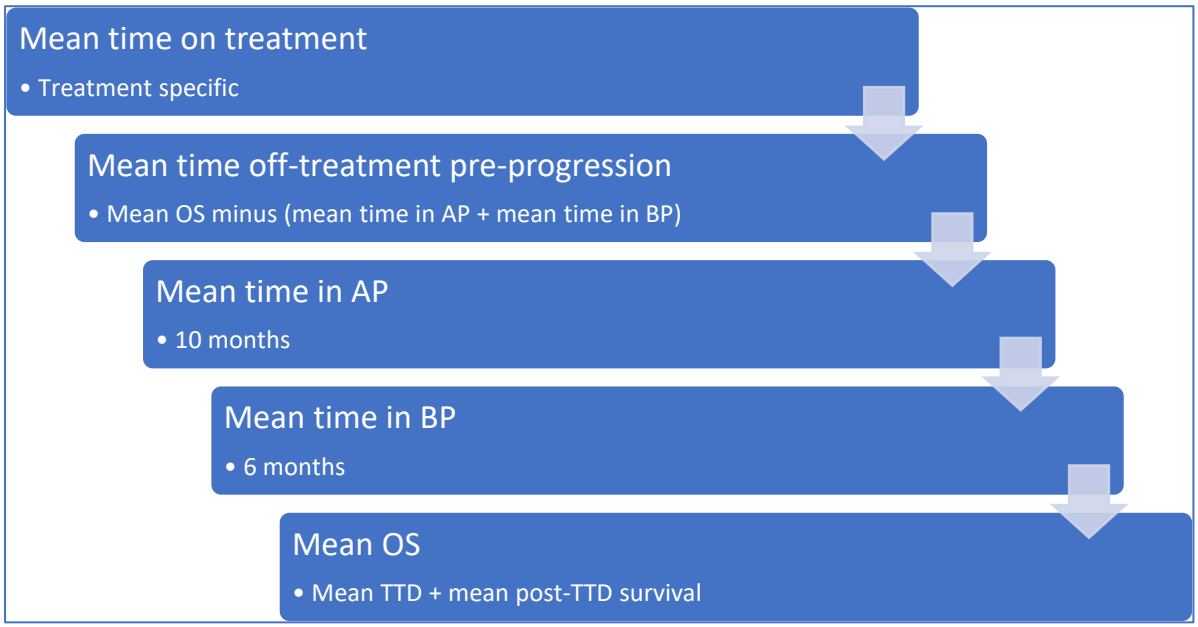
Abbreviations: CCyR, complete cytogenetic response, CHR, complete haematological response; PCyR, partial cytogenetic response; NR, not reported.

Limitations of the response data include that these are derived from different sources that may have used different definitions of response. The studies also vary according to their size. However, the MMR data consistently demonstrate improved outcomes at 6 months for asciminib compared with each of the remaining TKIs, including ponatinib.

Separate curves for progression to blast crisis and OS for the four response categories (CCyr, PCyr, CHR and NR) were generated from each of the modelled curves for progression to accelerated phase (AP). The generated curves for progression to BP and for OS were assumed to follow an exponential distribution with rates chosen to ensure that the respective curves for transition to blast crisis and OS generated a mean time to event which was 10 months and 16 months after the respective mean (over 600 model cycles) for progression to AP. For each type of transition, the data on the proportions of patients achieving CCyR, PCyr, CHR, and NR were used to weight the curves modelled for each response group and construct

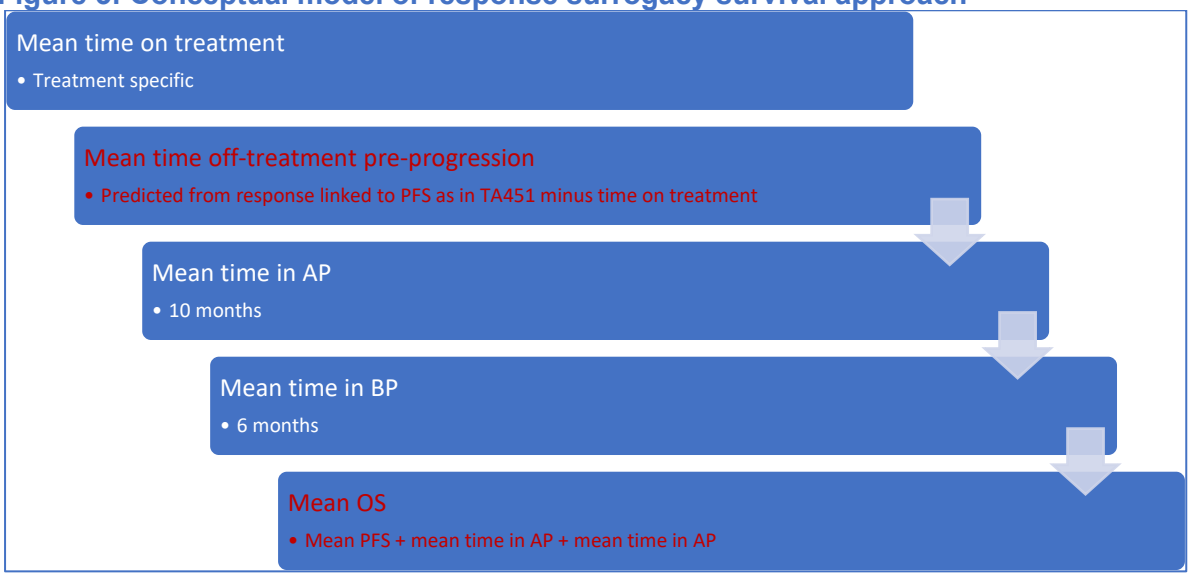
an overall curve reflecting the distribution of patients across the response categories. Hence a curve for progression to AP, a curve for progression to BP and a curve for OS was constructed from the respective four curves for patients differing by response to treatment. Conceptual diagrams representing the modelling approach with the cumulative survival approach and the response surrogacy approach are presented in Figure 2 and Figure 3.

Figure 2: Conceptual model of cumulative survival approach



Abbreviations: AP, accelerated phase; BP, blast phase; OS, overall survival; TTD, time to treatment discontinuation.

Figure 3: Conceptual model of response surrogacy survival approach



Abbreviations: AP, accelerated phase; BP, blast phase; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

The key difference between the two approaches is that disease progression is no longer influenced by the time on treatment in the surrogate response approach. As discussed in the answers to A1 and B1, both are alternatives that have limitations as are based on surrogacy assumptions. The response based surrogacy is based on data from a first line population. The extent to which these data can be generalised to a third-line population is unclear, as concern has been raised in appraisals that have used a surrogate approach to survival in other disease areas (for example in TA573 [daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma]). The cumulative survival approach is simpler, has been validated with clinicians as an approach that has clinical validity, and is in keeping with typical oncology partitioned survival modelling assumptions.

Table 26 compares the results of the scenario analysis based on the surrogate PFS approach, with the base-case analysis (in which progression is linked to time on third-line treatment) at list prices, and Table 27 with the patient access scheme (PAS) price for asciminib.

Table 26: Revised base-case results pairwise – asciminib vs bosutinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach (revised base case)							
Asciminib	[redacted]	10.48	7.79				
Bosutinib	[redacted]	8.72	6.30	[redacted]	1.76	1.49	[redacted]
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	10.51	7.74				
Bosutinib	[redacted]	9.20	6.59	[redacted]	1.31	1.15	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 27: Revised base-case results pairwise – asciminib vs bosutinib (asciminib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach (revised base case)							
Asciminib	[redacted]	10.48	7.79				
Bosutinib	[redacted]	8.72	6.30	3,959	1.76	1.49	2,654
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	10.51	7.74				
Bosutinib	[redacted]	9.20	6.59	-13,198	1.31	1.15	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Application of the surrogate approach generates a reduction in both the incremental cost and quality-adjusted life years (QALYs) associated with treatment. The overall impact on the incremental cost-effectiveness ratio (ICER) is modest.

Table 28 to Table 30 below show the breakdown of results versus bosutinib (at list price), with the surrogate PFS approach versus the cumulative survival approach. Bold formatting denotes the drivers of the main differences.

Table 28 Summary of QALY gain by health state

Health state	QALYs: Asciminib	QALYs: Bosutinib	Increment	Absolute increment	% absolute increment
Cumulative survival approach					
Pre-progression (on treatment)	3.76	1.61	2.15	2.15	77%
Pre-progression (off treatment)	3.41	3.89	-0.48	0.48	17%
Post progression	0.62	0.80	-0.18	0.18	6%
Total	7.79	6.30	1.49	2.81	100%
TA451 PFS surrogacy method					
Pre-progression (on treatment)	3.78	1.62	2.16	2.16	68%
Pre-progression (off treatment)	3.32	4.19	**-0.87**†	0.87	28%
Post progression	0.64	0.78	-0.14	0.14	4%
Total	7.74	6.59	1.15	3.17	100%

†Bold denotes drivers in main differences.
Abbreviations PFS, progression-free survival; QALY, quality adjusted life year.

Table 29 Summary of costs by health state

Health state	Costs: Asciminib	Costs: Bosutinib	Increment	Absolute increment	% absolute increment
Cumulative survival approach					
Pre-progression (on treatment)	[redacted]	83,352	[redacted]	[redacted]	78%
Pre-progression (off treatment)	[redacted]	154,389	[redacted]	[redacted]	7%
Post progression	[redacted]	44,525	[redacted]	[redacted]	5%
Allo-SCT	[redacted]	66,612	[redacted]	[redacted]	9%
terminal care costs	[redacted]	5,021	[redacted]	[redacted]	0%
Total	451,151	353,899	97,252	170,883	100%
TA451 PFS surrogacy method					
Pre-progression (on treatment)	[redacted]	83,616	[redacted]	[redacted]	71%
Pre-progression (off treatment)	[redacted]	175,753	[redacted]	[redacted]	18%
Post progression	[redacted]	32,035	[redacted]	[redacted]	4%
Allo-SCT	[redacted]	72,953	[redacted]	[redacted]	7%
terminal care costs	[redacted]	4,904	[redacted]	[redacted]	0%
Total	449,847	369,261	80,586	189,297	100%

†Bold denotes drivers in main differences.
Abbreviations: Allo-SCT, allogeneic stem cell transplant; PFS, progression-free survival.

Table 30 Summary of costs by resource use category

Health state	Costs: Asciminib	Costs: Bosutinib	Increment	Absolute increment	% absolute increment
Cumulative survival approach					
Drug costs	[redacted]	276,857	[redacted]	[redacted]	92%
Resource use costs	[redacted]	39,241	[redacted]	[redacted]	1%
AE costs	[redacted]	1,130	[redacted]	[redacted]	0%
SCT costs	[redacted]	31,651	[redacted]	[redacted]	6%
EOL costs	[redacted]	5,021	[redacted]	[redacted]	0%
Total	451,151	353,899	97,252	115,499	100%
TA451 PFS surrogacy method					
Drug costs	[redacted]	290,583	[redacted]	[redacted]	92%
Resource use costs	[redacted]	37,600	[redacted]	[redacted]	1%
AE costs	[redacted]	1,130	[redacted]	[redacted]	1%
SCT costs	[redacted]	35,045	[redacted]	[redacted]	6%
EOL costs	[redacted]	4,904	[redacted]	[redacted]	0%
Total	449,847	369,261	80,586	96,577	100%

†Bold denotes drivers in main differences; ‡Drug costs include subsequent treatment drug costs.
Abbreviations: AE, adverse event; EOL, end-of-life; SCT, stem cell therapy.

The selection of the lognormal curve for TTD was based on clinical opinion. This function generates a larger proportion of patients remaining on treatment compared to other more conservative choices, notably an exponential function. The exponential function was used for TTD in the comparison with dasatinib, nilotinib and bosutinib. When the exponential function is applied to TTD the incremental QALY and life years gained (LYG) generated for asciminib are lower than the corresponding gains generated using the surrogate survival method (Table 31).

In summary, use of the surrogate survival method generates QALY gains and LYG gains for asciminib compared to bosutinib which are larger than the gains generated from the cumulative survival method using an exponential function for TTD and smaller than the gains when a lognormal function is used for TTD. Incremental costs are similarly impacted, and the overall impact on the ICER is modest.

Table 31: Revised base-case results pairwise – asciminib vs bosutinib (list price of all treatments) – using exponential TTD distributions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	8.88	6.48	–	–	–	–
Bosutinib	[redacted]	7.99	5.67	[redacted]	0.89	0.80	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 32: Revised base-case results pairwise – asciminib vs bosutinib (list price of all treatments) using surrogate PFS approach as TA451 - using exponential TTD distributions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	10.41	7.58	–	–	–	–
Bosutinib	[redacted]	9.16	6.51	[redacted]	1.25	1.07	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Asciminib vs ponatinib, nilotinib, and dasatinib

Results versus the other comparator TKIs demonstrate improved cost-effectiveness with the ponatinib surrogacy approach, reflecting the conservative projection of survival gains using the cumulative survival method combined with an exponential model for TTD. The ICER for ponatinib compared to asciminib, which indicates asciminib is the cost-effective option, rises further when using the surrogate survival method. Compared to nilotinib and dasatinib, asciminib is more expensive. However, the response rates are improved, and hence there is more time spent on treatment and progression free (both on third-line treatment and subsequently), which leads to increased survival and QALYs gained.

Vs ponatinib

Table 33: Revised base-case results pairwise – asciminib vs ponatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach							
Asciminib	[redacted]	8.62	6.25	–	–	–	–
Ponatinib	[redacted]	9.24	6.76	[redacted]	-0.62	-0.51	[redacted]
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	10.02	7.26	–	–	–	–
Ponatinib	[redacted]	10.20	7.42	[redacted]	-0.18	-0.16	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 34: Revised base-case results pairwise – asciminib vs ponatinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach							
Asciminib	[redacted]	8.62	6.25				
Ponatinib	[redacted]	9.24	6.76	-138,189	-0.62	-0.51	271,410
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	10.02	7.26				
Ponatinib	[redacted]	10.20	7.42	-121,504	-0.18	-0.16	748,333

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Vs nilotinib

Table 35: Revised base-case results pairwise – asciminib vs nilotinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach							
Asciminib	[redacted]	9.03	6.61	–	–	–	–
Nilotinib	[redacted]	8.13	5.76	[redacted]	0.90	0.85	[redacted]
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	12.02	8.83	–	–	–	–
Nilotinib	[redacted]	8.91	6.30	[redacted]	3.11	2.53	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 36: Revised base-case results pairwise – asciminib vs nilotinib (PAS price of asciminib and nilotinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach							
Asciminib	[redacted]	9.03	6.61				
Nilotinib	[redacted]	8.13	5.76	42,559	0.90	0.85	50,167
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	12.02	8.83				
Nilotinib	[redacted]	8.91	6.30	122,601	3.11	2.53	48,395

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Vs dasatinib

Table 37: Revised base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach							
Asciminib	[redacted]	8.94	6.54	–	–	–	–
Dasatinib	[redacted]	8.30	5.97	[redacted]	0.65	0.57	[redacted]
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	12.01	8.82	–	–	–	–
Dasatinib	[redacted]	8.92	6.38	[redacted]	3.10	2.44	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 38: Revised base-case results pairwise – asciminib vs dasatinib (PAS price for asciminib))

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Using base case cumulative survival approach							
Asciminib	[redacted]	8.94	6.54				
Dasatinib	[redacted]	8.30	5.97	331	0.65	0.57	582
Using surrogate PFS approach as TA451							
Asciminib	[redacted]	12.01	8.82				
Dasatinib	[redacted]	8.92	6.38	92,124	3.10	2.44	37,740

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

In summary, this scenario has explored modelling a surrogate approach to survival, based on the relationship between response and progression free survival, as was used in TA451. Results have shown that the methods provide similar outcomes, with the cumulative survival method generating conservative estimates of health gains in the majority of comparisons presented. The results using the surrogate survival approach support the results from the cumulative survival approach. Both approaches require assumptions and use of external data. However, application of either approach generates similar QALY gains and similar ICERs, lending credibility to the results of the original submission.

B3. Priority Question: Please comment on whether all patients are expected to discontinue treatment in the future or whether there is a proportion of patients who will remain on treatment for their entire lifetime as implied by the company base-case.

Most patients with CML will remain on treatment for the duration of their disease until progression, and most will continue to receive treatment with TKIs in the AP and the BP (this is evidenced in Figure 67 of the HMRN report) (88). Assumptions on subsequent treatment, informed by data in HMRN, were discussed with a clinical expert in CML who suggested some changes reflecting a degree of historical bias in the data from HMRN (106). There is clinical evidence to support the discontinuation of TKI treatment in some patients achieving CCyR, with recommencement of therapy if required (107). However, evidence on the efficacy of discontinuation relates primarily to patients on first- and second-line therapy (108); it seems unlikely that patients who are already receiving their third-line treatment would be considered suitable candidates for discontinuation of treatment. The modelled base case reflects current clinical practice in which patients will continue to be treated with a TKI until progression, and beyond progression.

B4. Priority Question: The ERG notes that the company have capped OS curve hazards at general population mortality. The ERG considers this entirely appropriate but also considers that such a cap should be applied to all survival curves used in the model not just OS. Please modify the economic model so that a mortality cap is applied to all survival curves used in the model (TTD, SCT relapse, etc.)

Each of the survival curves in the model are capped by the OS curve, which is itself capped to ensure a floor at the general population mortality. Survival curves are further capped to ensure TTD cannot exceed progression to AP, and progression to AP cannot exceed progression to BP. The caps are implemented in rows G, H and I (for asciminib) and rows K, L and M (for the comparator) in the worksheet 'Survival' of the CEM.

B5. Priority Question: In the comparisons with nilotinib, ponatinib and dasatinib an exponential distribution is used to model TTD. Please comment on the plausibility of this assumption (given its sizable impact on total QALYs and costs) and how this may affect the relative cost-effectiveness of asciminib given the company's preference for using a lognormal distribution in the comparison with bosutinib.

K-M data were unavailable on the TTD for nilotinib, dasatinib and ponatinib. TTD was parameterised from the available data on median TTD. These single datums only allowed estimation of a single parameter exponential function. Whilst the exponential models do not generate implausible extrapolations, they may be conservative in failing to capture the long treatment durations in some patients who respond particularly well to third-line therapy. Whilst we acknowledge this is a limitation of the respective comparisons, we highlight the scenario analysis undertaken for our comparison with bosutinib in which alternative survival models for TTD were implemented. This analysis indicated that the selection of exponential survival models for TTD in the place of lognormal models for asciminib and bosutinib had minimal impact on the ICER at the list price (or with PAS price) for asciminib. Choice of TTD survival model does have a sizeable impact on both costs and QALYs. However, selection of the same model for both treatment and comparator

(as recommended in NICE TSD14 (109)) minimises the impact of any potential bias from misspecification of the TTD function on incremental costs and QALYs.

B6. Priority Question: Please clarify why a half-cycle correction was not implemented? If feasible, please adapt the model to include a half-cycle correction.

A half-cycle correction was not implemented in the original model as the time cycle of one month was considered short enough not to warrant a half-cycle correction. We have now adapted the model to include a half-cycle correction, and this is included as part of the revised base case – please see Appendix A.

B7. Please comment on the differences in the literature estimates of TTD used to inform the economic model, and the observed HMRN TTD values for those receiving third line treatment. Please provide justification for why the economic model does not consider all of the relevant data and relies solely on the literature estimates.

Table 39 summarises a comparison of median TTD from HMRN and published literature cited in the model. There are differences between data in HMRN and the clinical studies, with HMRN generally – but not exclusively – reporting [redacted] TTD. The differences may reflect the generally observed disparities in trial and registry populations in which healthier patients tend to be eligible for trials and may be treated more aggressively (110-112). Trial patients are also expected to undergo more frequent monitoring. Such monitoring may lead to quicker diagnoses of loss of treatment response and subsequently earlier initiation of the next therapy line. Furthermore, clinical practice in the UK may reflect a reduced tendency to switch therapies due to fewer approved treatment options at fourth-line and later compared with patients enrolled in an international clinical study, who may be eligible to join another clinical trial following trial drug discontinuation. Certainly, the treatment options at fourth-line were more limited in early years of the HMRN data (2004–2019). In summary, there are a number of reasons why TTD might be systematically different in the HMRN registry compared with clinical trial data.

The economic analysis utilised evidence from the HMRN where appropriate. However, no data on TTD with asciminib were available from the HMRN. Given that data on TTD for asciminib is drawn from a clinical trial, comparisons with observational data on TTD for other TKIs would be confounded for the reasons highlighted above. Consequently, data on comparator TKIs were taken from clinical studies in the appropriate third-line population. It is also important to note that the HMRN registry data was based on small numbers, particularly for some treatments such as ponatinib, which has only been used relatively recently; this is reflected in the relatively wide confidence intervals on estimates of TTD. Overall, the published literature provided data from larger patient samples and with reduced risk of bias compared with HMRN data. For these reasons, comparison of TTD with data from clinical studies was considered to be more robust.

Table 39: TTD comparison from HMRN and published literature†

Drug	Median TTD (years)	
	Literature	HMRN (95% CI)
Dasatinib	1.2	[redacted]
Nilotinib	0.9	[redacted]
Bosutinib	0.5	[redacted]
Ponatinib	2.7	[redacted]

Sources: Dasatinib, Rossi 2013; Nilotinib, Giles 2010; Bosutinib, ASCEMBL trial; Ponatinib, Cortes 2018.
†Data from HMRN based on those who discontinued at third line by drug, excluding the T315I mutation
Abbreviations: CI, confidence interval; HMRN, Haematological Malignancy Research Network; NR, not reached; TTD, time to treatment discontinuation.

B8. Priority Question: The current economic analysis presents only pairwise analysis between each of the identified comparators. This is principally justified on the grounds that data limitations prevent a fully incremental analysis from being undertaken.

i. Please comment on the relevance of an incremental analysis given NICE guidance associated with bosutinib and ponatinib; this outlines that these should only be used when nilotinib and dasatinib are not clinical indicated.

The Company's economic analysis is in alignment with the scope, in providing comparisons with nilotinib, dasatinib, bosutinib and ponatinib.

Availability of data precluded a fully incremental analysis, as data were lacking to undertake a network meta-analysis (NMA) of TTD, and instead, a matching adjusted indirect comparison (MAIC) was undertaken to compare asciminib with ponatinib, dasatinib, and nilotinib. The implementation of a MAIC with each TKI comparator generated three different MAIC weighted datasets from the asciminib arm of the ASCEMBL trial, to match the characteristics of the ASCEMBL arm to each comparator trial. This precluded direct comparison of asciminib with ponatinib, bosutinib, and ponatinib in a single analysis.

Each of the comparator TKIs is currently used at third-line and represents a potential therapeutic option for patients with CML-CP in the UK. Hence, each is considered a relevant comparator to asciminib. Ideally, a fully incremental analysis would have been undertaken to compare all four TKIs with asciminib, notwithstanding the observation that for individual patients, choice of TKI is likely to be restricted to therapies clinically indicated and not previously tried.

ii. Please justify why bosutinib is not considered as part of fully incremental analysis in the comparisons with ponatinib, nilotinib and dasatinib. The ERG is unaware of any methodological reason why this could not have been implemented.

Please implement a fully incremental analysis including bosutinib in each comparison.

As mentioned in the response to the previous question, a MAIC was undertaken whereby the asciminib arm of the ASCEMBL trial was used to match the characteristics of the asciminib population to the trial of each comparator (ponatinib, nilotinib, and dasatinib), thereby pairwise comparisons were necessary. It would be necessary to weight the data from the bosutinib arm to include bosutinib in each of the MAICs with nilotinib, dasatinib and ponatinib.

The unweighted analysis was considered the most informative analysis with regard to the ICER for asciminib compared to bosutinib. Patients were randomised in a 2:1 ratio to asciminib and bosutinib in ASCEMBL, and hence the patient data available for comparison in a MAIC is more limited for bosutinib compared to asciminib.

Data from ASCEMBL for bosutinib indicate that mean TTD is inferior compared with each of the other TKIs. This is likely to remain the case after weighting in a MAIC. As such, inclusion of bosutinib in each of the MAICs would generate costs and outcomes ranked lower than asciminib and the other three TKIs. Consequently, inclusion of bosutinib would not change the deterministic ICER for asciminib. For the comparisons with nilotinib and dasatinib, the ICER for asciminib would be generated from the incremental costs and QALYs when compared with the respective TKIs. Finally, the ICER for ponatinib would be generated from the incremental costs and QALYs for ponatinib when compared to asciminib. Consequently, the additional inclusion of MAIC weighted data from the bosutinib arm of ASCEMBL is unlikely to change the ICERs for asciminib in comparison with the other TKIs, as bosutinib would represent an inferior comparator to asciminib or any of the other three comparators because it has a shorter treatment duration than any of the other comparators. It is important to also note, that if bosutinib were included as part of the other pairwise comparisons, this would require an exponential TTD distribution for consistency with the comparators within that analysis.

B9. Priority question: The PACE trial(23) provides up-to-date data on PFS and OS for patients with advanced CML. This data could be used to inform assumptions about post-progression survival and could also be used to validate the predictions made by the model.

i. Please fit parametric survival curves to relevant KM data for PFS and OS reported in Cortes (2018).(23)

ii. Please update the economic analysis to include a scenario using PFS and OS estimates from Cortes (2018)(23) to model post-progression survival.

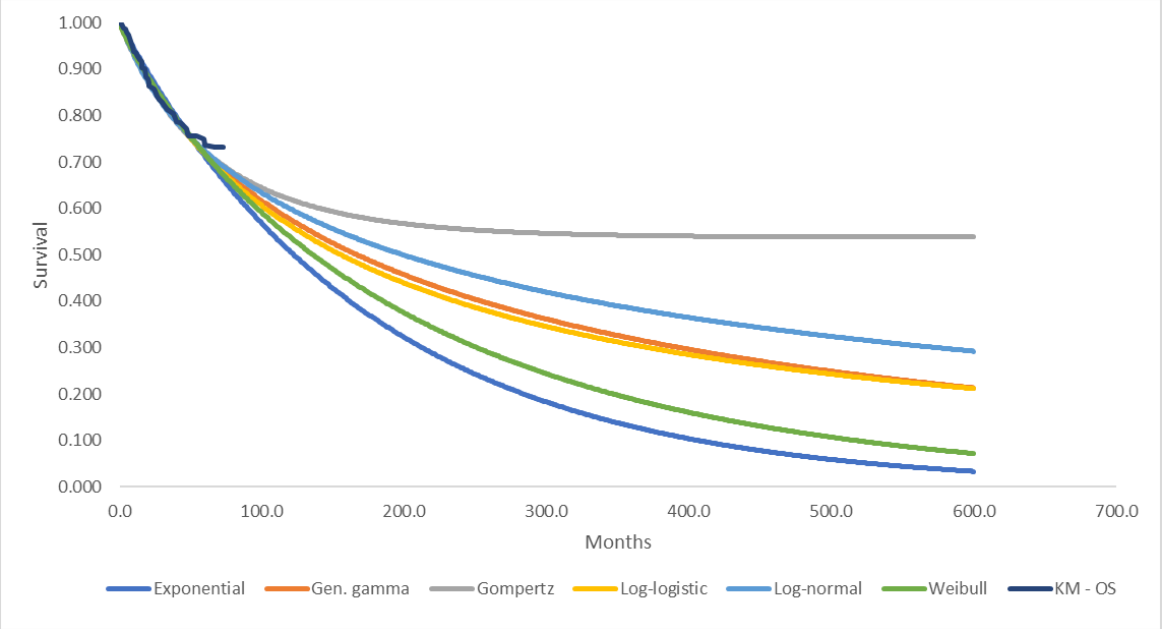
iii. Please validate PFS and OS predictions made in the company base-case using the predicted PFS and OS curves from Cortes (2018).(23)

It should be noted that disease progression was defined broadly in the PACE study*: 'Progression from CP was defined as death, development of AP or BP, loss of complete hematologic response (in absence of cytogenetic response), loss of MCyR, or increasing white blood cell count without complete hematologic response'* (23).

Such a broad definition is likely to have reduced PFS and inflated the estimates of time in progressed disease. In the economic model, progression is considered to be development of AP or BP. In the ASCEMBL trial, PFS was defined as the time from the date of randomisation to the earliest occurrence of documented disease progression to AP/BC or the date of death from any cause (including progressions and deaths observed during the survival follow-up period) before the cut-off date (86). Analysis of PFS from the PACE trial and comparison with estimates from the economic model are subject to this limitation.

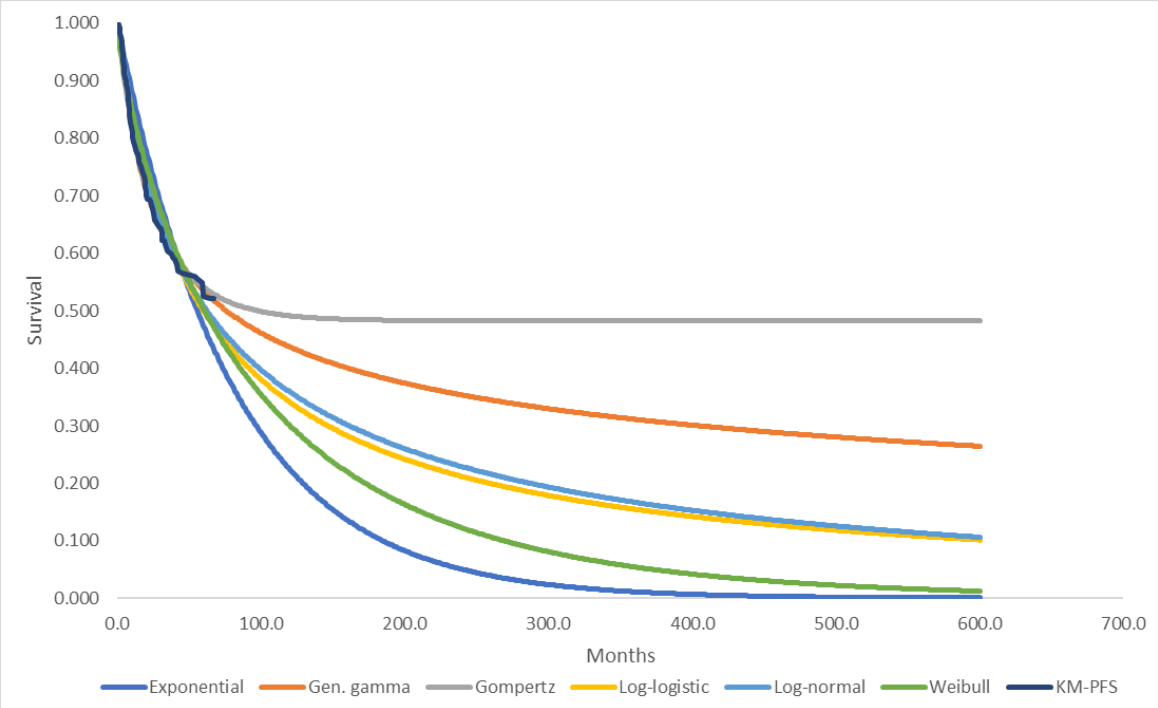
The data from the PACE trial for OS and PFS was digitised and pseudo patient level event data estimated using the Guyot algorithm (103). Survival models were fitted to the data for PFS and OS. Data for all patients rather than the subgroup without T315I mutation were digitised as this matched the population providing data on TTD for ponatinib.

Figure 4: PACE OS extrapolations



Source: PACE (23).

Figure 5: PACE PFS extrapolations



Source: PACE (23).

Table 40: Model diagnostics for PFS and OS from PACE trial

	PFS				OS			
Model	**AIC**	**Rank**	**BIC**	**Rank**	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	608.37	6	611.96	6	411.42	2	414.97	1
Weibull	603.66	5	610.83	5	412.58	5	419.66	5
Gompertz	589.72	3	596.90	3	410.86	1	417.94	2
Lognormal	589.03	2	596.20	2	411.92	4	419.00	4
Log-Logistic	596.74	4	603.91	4	411.61	3	418.70	3
Gen. Gamma	583.05	1	593.81	1	413.35	6	423.98	6

Source: PACE (23).
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression-free survival.

Curve selection was based primarily on the plausibility of extrapolations. For this reason, Gompertz models were excluded. The remaining functions were considered clinically plausible to model PFS and mortality, assuming that the mortality rate was capped at population values. The lognormal function for OS was paired with the generalized gamma for PFS to represent an optimistic prediction of disease progression and disease related mortality. The generalized gamma for OS was paired with the lognormal function for PFS to represent a pessimistic prediction of disease progression and disease related mortality. Exponential functions for PFS and OS were chosen as a worst case scenario with regard to disease progression.

A simple three state partition model was constructed to estimate duration in progression free and progressed disease health states. The time cycle was 1 month and the model was run for 600 cycles. Patients entered the model at age 51 and mortality was capped at the minimum of the value derived from the model of OS and the population life table value. The PFS curve was constrained to lie above the OS curve. For each of the three scenarios (optimistic, pessimistic and worst case), survival functions for PFS and OS derived from the PACE data were used to estimate mean duration in the progression free and progressed disease states (Table 41).

Table 41: Mean duration of PFS, progressed disease, and OS predicted from PACE

Scenario	Mean duration progression free (months)	Mean duration in progressed disease (months)	Overall survival (months)
Optimistic	191	46	237
Pessimistic	147	74	221
Worst case	81	86	167

The worst-case scenario generates a life expectancy of 14 years from commencement of third-line therapy. This is higher than that predicted using either the cumulative survival or the response surrogacy approach for patients commencing third-line treatment with ponatinib. Other scenarios generate higher life expectancy. Notably, in the worst-case scenario, time with progressed disease exceeded time progression free. Whilst this is plausible for many cancers in a third-line population, it is not consistent with the clinical picture for CML as evidenced in the HMRN report. Hence the results from the worst case scenario appear implausible with regard to split between time progression free and time in progressed disease.

The mean duration of progressed disease varies from 46 months in the optimistic scenario to 86 months in the worst-case scenario. The impact of all-cause mortality on survival is acting to curtail time in progressed disease in the more optimistic scenarios compared with the worst-case scenario.

The economic analysis assumed a total of 16 months with progressed disease in the base case, with 10 months in AP and 6 months in BP. A scenario was modelled in which total time with progressed disease was increased to 46 months (optimistic scenario) and 74 months (pessimistic scenario). Please note a version of the model has been provided with functionality for this scenario, and a separate excel file shows the calculations undertaken for the simple partition model to derive the mean post-progression time required for the scenario. This time was split between the AP and the BP states in the ratio 10:6 to align with the ratio applied in the base case analysis. The duration of OS was unchanged, so that additional time in progressed disease was at the expense of time progression free. The results of the scenario analysis are shown in (**Asciminib versus comparators (all treatments at list prices)**

Table 42–Table 45).

Asciminib versus comparators (all treatments at list prices)

Table 42: Base-case results pairwise – asciminib vs bosutinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	10.48	7.79	–	–	–	–
Bosutinib	[redacted]	8.72	6.30	[redacted]	1.76	1.49	[redacted]
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	10.37	7.49	–	–	–	–
Bosutinib	[redacted]	8.58	5.92	[redacted]	1.79	1.57	[redacted]
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	10.22	7.15	–	–	–	–
Bosutinib	[redacted]	8.40	5.50	[redacted]	1.82	1.65	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 43: Base-case results pairwise – asciminib vs ponatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.62	6.25	–	–	–	–
Ponatinib	[redacted]	9.24	6.76	[redacted]	-0.62	-0.51	[redacted]
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	8.48	5.86	–	–	–	–
Ponatinib	[redacted]	9.11	6.40	[redacted]	-0.63	-0.54	[redacted]
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	8.31	5.45	–	–	–	–
Ponatinib	[redacted]	8.96	6.02	[redacted]	-0.65	-0.57	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 44: Base-case results pairwise – asciminib vs nilotinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	9.03	6.61	–	–	–	–
Nilotinib	[redacted]	8.13	5.76	[redacted]	0.90	0.85	[redacted]
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	8.89	6.24	–	–	–	–
Nilotinib	[redacted]	7.98	5.36	[redacted]	0.91	0.89	[redacted]
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	8.74	5.85	–	–	–	–
Nilotinib	[redacted]	7.81	4.93	[redacted]	0.93	0.93	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 45: Base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.94	6.54	–	–	–	–
Dasatinib	[redacted]	8.30	5.97	[redacted]	0.65	0.57	[redacted]
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	8.81	6.17	–	–	–	–
Dasatinib	[redacted]	8.15	5.57	[redacted]	0.66	0.60	[redacted]
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	8.65	5.77	–	–	–	–
Dasatinib	[redacted]	7.98	5.14	[redacted]	0.67	0.63	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Asciminib versus comparators (PAS price of asciminib)

Table 46: Base-case results pairwise – asciminib vs bosutinib (asciminib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	10.48	7.79				
Bosutinib	[redacted]	8.72	6.30	3,959	1.76	1.49	2,654
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	10.37	7.49				
Bosutinib	[redacted]	8.58	5.92	-628	1.79	1.57	Dominant
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	10.22	7.15				
Bosutinib	[redacted]	8.40	5.50	-1,566	1.82	1.65	Dominant

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 47: Base-case results pairwise – asciminib vs ponatinib (asciminib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.62	6.25				
Ponatinib	[redacted]	9.24	6.76	-138,189	-0.62	-0.51	271,410
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	8.48	5.86				
Ponatinib	[redacted]	9.11	6.40	-136,424	-0.63	-0.54	254,314
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	8.31	5.45				
Ponatinib	[redacted]	8.96	6.02	-135,224	-0.65	-0.57	238,758

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 48: Base-case results pairwise – asciminib vs nilotinib (PAS price – for asciminib and nilotinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	9.03	6.61				
Nilotinib	[redacted]	8.13	5.76	42,559	0.90	0.85	50,167
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	8.89	6.24				
Nilotinib	[redacted]	7.98	5.36	40,124	0.91	0.89	45,280
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	8.74	5.85				
Nilotinib	[redacted]	7.81	4.92	38,602	0.93	0.93	41,512

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 49: Base-case results pairwise – asciminib vs dasatinib (asciminib PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.94	6.54				
Dasatinib	[redacted]	8.30	5.97	331	0.65	0.57	582
Outcomes following assuming a total of 46 months with progressed disease							
Asciminib	[redacted]	8.81	6.17				
Dasatinib	[redacted]	8.15	5.57	-1,369	0.66	0.60	Dominant
Outcomes following assuming a total of 74 months with progressed disease							
Asciminib	[redacted]	8.65	5.77				
Dasatinib	[redacted]	7.98	5.14	-2,423	0.67	0.63	Dominant

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The impact of extending time in the progressed disease state was to modestly increase the incremental QALY gains and to reduce the ICERs for asciminib when compared to bosutinib, nilotinib and dasatinib. In the comparison with ponatinib, the incremental QALY gain for ponatinib increased modestly, and the ICER for ponatinib compared to asciminib reduced. Overall, the impact on ICERs of modelling a much larger duration with progressed disease was modest, and in most cases the ICER for asciminib fell slightly.

Comparison with observed data from PACE are likely to provide a clearer indication of validity of the model predictions compared with extrapolations based on survival modelling of the digitized K-M survival plots, given that five year results from the PACE trial are published. Data on OS and PFS from the PACE trial (23) were compared with predictions for ponatinib from the model using both the cumulative survival approach and the surrogate response approach (Table 50). In order to calculate PFS from the model, patients who had undergone SCT were considered progression-free if they had not relapsed.

Table 50: Validation of model outcomes using PACE 5 year data

Outcome	PACE trial	Model using cumulative survival method	Model using surrogate response method
OS (5 years)	73%	70%	64%
PFS (5 years)	53%	53%	48%

Abbreviations: OS, overall survival; PFS, progression-free survival.

Both modelling approaches underpredict survival compared to the published data at five years (23). The cumulative survival approach compares favourably on this measure with the surrogate response approach, and the predicted value for OS at five years is not far below the observed value in the PACE trial (23). The comparison with the results from PACE would suggest that the assumption in the cumulative survival approach that mean survival is 84 months following discontinuation of third-line therapy is conservative, and the true value may be higher. The data would also suggest that the use of data from the BMS-034 trial to estimate PFS as a function of response at 12 months underpredicts PFS.(4) This finding may reflect the age of the BMS study and the more limited availability of subsequent therapies at the time it was undertaken. It should be noted that it is relatively easy to adjust the cumulative

survival approach to consider different durations of survival post discontinuation of third-line therapy. Adjustment of the surrogate response method to reflect the expansion of TKI therapy would require replacement of the BMS-034 data with a suitable recent study.

The cumulative survival method predicts a value for PFS at five years which is the same as that observed in the PACE trial. The surrogate response method underestimates PFS. As noted earlier in the response to this question, the PACE trial used a very broad definition of progression, which limits comparability (23).

Allo-SCT

B10. Priority Question: Please comment on how you expect asciminib will impact on the need for SCT.

The data from ASCEMBL trial indicated an improved response to treatment when compared with bosutinib. Data on TTD indicate an improved duration of response to third-line therapy with asciminib when compared to dasatinib, nilotinib and bosutinib. This would be expected to reduce the number of patients undergoing SCT after having exhausted the available TKI options for controlling their disease, as the likelihood of being a candidate for SCT also decreases with age, as confirmed with a clinical expert (106).

B11. Priority Question: The model assumes a constant probability of receiving SCT following discontinuation of treatment, and transition to accelerated phase (AP) and blast phase (BP). This means that in the asciminib arm of the model (bosutinib comparison) 20.85% of patients receive SCT over the age of 65 and 14.83% over the age of 75. Advice provided to the ERG suggests that is inconsistent with clinical practice. Please provide a version of the model in which accounts for the decreasing likelihood patients will be fit enough to receive SCT as they age.

The original model did not consider the impact of age on the likelihood of receiving a SCT. Obtaining data to quantify the impact is likely to be very challenging. Consequently, our original submission did not consider the impact of age on SCT,

but instead varied the overall likelihood of SCT at each stage in disease progression and showed the impact of variation to be small. Such analysis did not consider the impact that extended time on third-line treatment might have in reducing the proportions of patients undergoing SCT as a result of age. An adjustment to the model has now been included as part of the revised base case, whereby the proportion of patients undergoing SCT is a function of patient age (Appendix A).

The adjustment provides for a simple linear tapering of the likelihood of SCT with age, with user specified values for the starting age of the taper and the absolute reduction in the probability of SCT per year of age. Values for the start age (age 50 years) and the absolute reduction per year of age (7.5%) were selected to match the observed numbers of patients undergoing SCT with those predicted by the model for a cohort of 140 patients per year. These parameter values generate between 35 and 41 people undergoing SCT for each yearly cohort according to the TKI comparator selected. This is more in line with the estimates reported by the ERG in question B15.

B12. Priority Question: Niederwieser (2021)(113) does not find any difference in SCT outcomes received in chronic phase (CP) compared with AP but does note a difference in outcomes between CP and the BP. Please comment on the modelled assumption that AP and BP outcomes following SCT are equivalent and the assumption that outcomes in CP and AP differ.

Please provide scenario analysis in which outcomes for following SCT in CP and AP are the same.

The original model included two SCT submodels (SCT_CP) and (SCT_PD) reflecting the available data on outcomes following SCT published in Jabbour (2011) (114). Patients undergoing SCT prior to progression entered the SCT_CP submodel; patients undergoing SCT at progression to AP or progressed disease (PD) enter the SCT_PD submodel. This structure reflected the available data on outcomes after SCT in Jabbour at the time of the model construction.

A scenario has been added into the model to allow selection of either the SCT_CP or SCT-PD submodel as the destination for patients undergoing SCT at progression to

the accelerated phase. The results for this scenario, in which patients undergoing SCT at progression to AP enter the SCT-CP submodel, are shown in Asciminib versus **comparators (all treatments at list prices)**

Table 51 to Table 58, compared with the revised base case result for each comparison, at list and PAS prices.

Asciminib versus comparators (all treatments at list prices)

Table 51: Base-case results pairwise – asciminib vs bosutinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	10.48	7.79	–	–	–	–
Bosutinib	[redacted]	8.72	6.30	[redacted]	1.76	1.49	[redacted]
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	10.82	8.00	–	–	–	–
Bosutinib	[redacted]	9.16	6.57	[redacted]	1.66	1.43	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 52: Base-case results pairwise – asciminib vs ponatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.62	6.25	–	–	–	–
Ponatinib	[redacted]	9.24	6.76	[redacted]	-0.62	-0.51	[redacted]
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	9.06	6.52	–	–	–	–
Ponatinib	[redacted]	9.65	7.00	[redacted]	-0.58	-0.49	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 53: Base-case results pairwise – asciminib vs nilotinib (list prices of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	9.03	6.61	–	–	–	–
Nilotinib	[redacted]	8.13	5.76	[redacted]	0.90	0.85	[redacted]
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	9.45	6.86	–	–	–	–
Nilotinib	[redacted]	8.61	6.05	[redacted]	0.84	0.81	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 54: Base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.94	6.54	–	–	–	–
Dasatinib	[redacted]	8.30	5.97	[redacted]	0.65	0.57	[redacted]
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	9.37	6.79	–	–	–	–
Dasatinib	[redacted]	8.76	6.25	[redacted]	0.61	0.54	[redacted]

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Asciminib versus comparators (PAS price)

Table 55: Base-case results pairwise – asciminib vs bosutinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	10.48	7.79	–	–	–	–
Bosutinib	[redacted]	8.72	6.30	3,959	1.76	1.49	2,654
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	10.82	8.00	–	–	–	–
Bosutinib	[redacted]	9.16	6.57	1,519	1.66	1.43	1,062

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 56: Base-case results pairwise – asciminib vs ponatinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.62	6.25	–	–	–	–
Ponatinib	[redacted]	9.24	6.76	-138,189	-0.62	-0.51	271,410
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	9.06	6.52	–	–	–	–
Ponatinib	[redacted]	9.65	7.00	-137,254	-0.58	-0.49	282,513

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 57: Base-case results pairwise – asciminib vs nilotinib (PAS price – for asciminib and nilotinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	9.03	6.61	–	–	–	–
Nilotinib	[redacted]	8.13	5.76	42,559	0.90	0.85	50,167
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	9.45	6.86	–	–	–	–
Nilotinib	[redacted]	8.61	6.05	41,120	0.84	0.81	50,632

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 58: Base-case results pairwise – asciminib vs dasatinib (PAS price of asciminib)

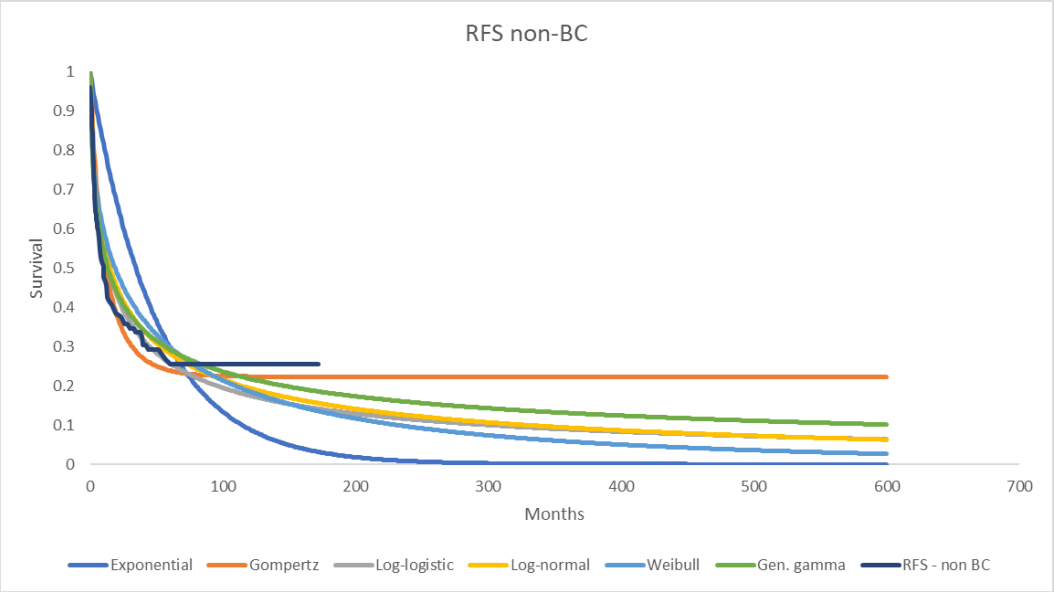
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.94	6.54	–	–	–	–
Dasatinib	[redacted]	8.30	5.97	331	0.65	0.57	582
Outcomes following rerouting patients to SCT_CP submodel at progression to AP							
Asciminib	[redacted]	9.37	6.79	–	–	–	–
Dasatinib	[redacted]	8.76	6.25	-705	0.61	0.54	Dominant

Abbreviations: AP, advanced phase; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B13. Priority Question: The model currently uses Jabbour (2011)(114) to predict outcomes following SCT. This study is, however, relatively old and contains few patients. The Niederwieser (2021)(113) is arguably a better alternative source of data to inform post SCT outcomes as it reports outcomes for a greater number of patients and is a more recent study. Please provide survival analysis using the Niederwieser (2021)(113) study to model post-SCT outcomes.

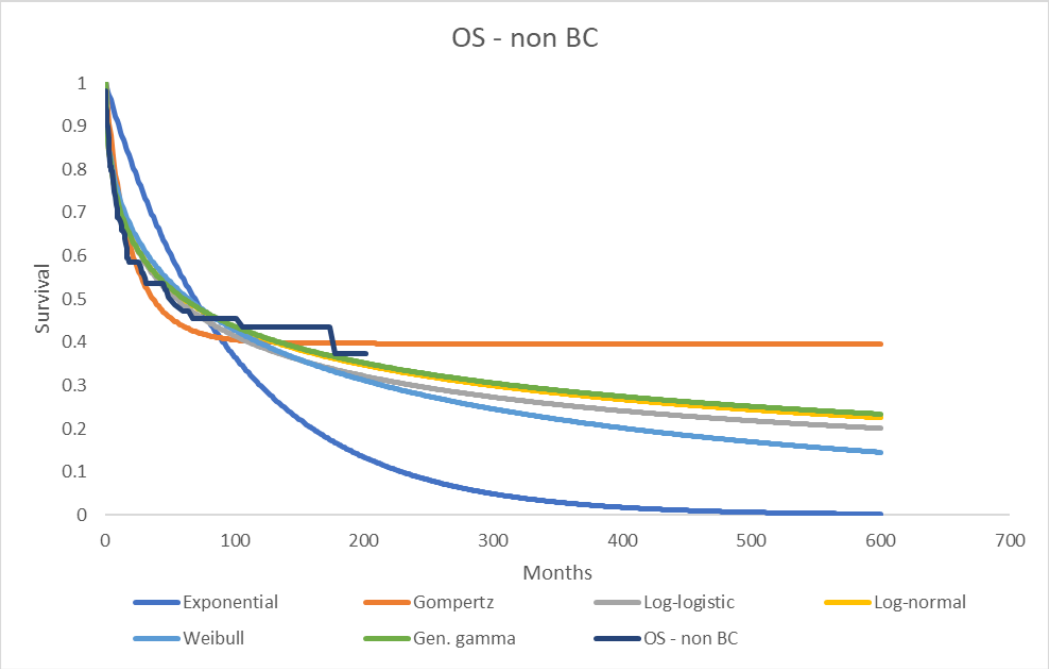
A scenario has been undertaken which allows the use of the data on relapse free survival and overall survival from Niederwieser. These data were digitised and the constituent event data estimated using the Guyot algorithm (103). Survival models were fitted to the data for relapse free survival and for overall survival for both the blast crisis and non-blast crisis groups. Distributions were chosen on the basis of goodness of fit statistics, and visual fit to the KM plots. The distributions for OS and relapse-free survival (RFS) for the blast crisis and non-blast crisis data can be seen in Figure 6 to Figure 9, and the goodness of fit statistics reported in Table 59 and Table 60.

Figure 6: Extrapolations fitted to RFS non BC curve from Niederwieser 2021



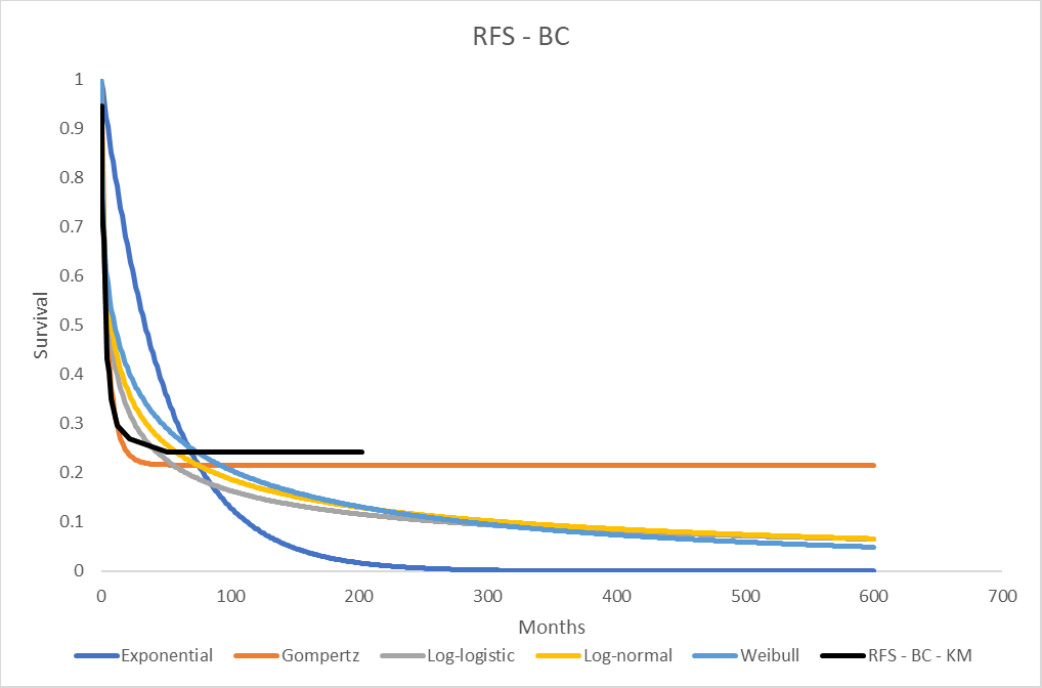
Source: Niederwieser et al. 2021 (113).
Abbreviations: BC, blast crisis; RFS, relapse-free survival.

Figure 7: Extrapolations fitted to OS non BC curve from Niederwieser 2021



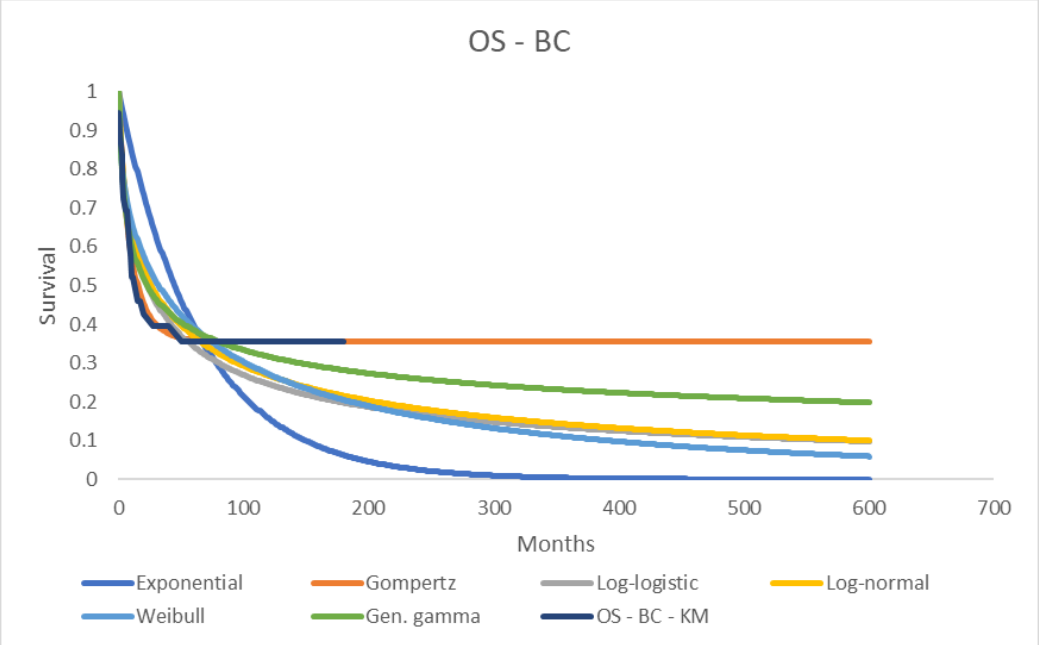
Source: Niederwieser et al. 2021 (113).
Abbreviations: BC, blast crisis; OS, overall survival.

Figure 8: Extrapolations fitted to RFS BC curve from Niederwieser 2021



Note the gen gamma distribution did not converge.
Source: Niederwieser et al. 2021 (113).
Abbreviations: BC, blast crisis; RFS, relapse-free survival.

Figure 9: Extrapolations fitted to OS BC curve from Niederwieser 2021



Source: Niederwieser et al. 2021 (113).
Abbreviations:2021 (113).
Abbreviations: BC, blast crisis; RFS, relapse-free survival.

Table 59: Model diagnostics for RFS and OS in SCT from non-BC (Niederwieser 2021)

	RFS				OS			
Model	**AIC**	**Rank**	**BIC**	**Rank**	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	498.15	6	500.77	6	417.85	6	420.54	6
Weibull	415.50	5	420.73	5	355.41	4	360.80	4
Gompertz	400.63	4	405.86	3	357.64	5	363.02	5
Lognormal	399.70	2	404.93	1	349.77	1	355.15	1
Log-Logistic	400.42	3	405.65	2	350.42	2	355.80	2
Gen. Gamma	398.71	1	406.56	4	351.73	3	359.80	3

Source: Niederwieser et al. 2021 (113).
Abbreviations: BC, blast crisis.

Table 60: Model diagnostics for RFS and OS in SCT from BC (Niederweiser 2021)

	RFS				OS			
Model	**AIC**	**Rank**	**BIC**	**Rank**	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	240.56	5	242.17	5	156.61	6	158.19	6
Weibull	171.81	4	175.03	4	134.74	5	137.91	5
Gompertz	154.88	1	158.10	1	119.86	1	123.03	1
Lognormal	162.24	2	165.46	2	128.72	3	131.89	3
Log-Logistic	162.94	3	166.16	3	129.84	4	133.01	4
Gen. Gamma	-	-	-	-	126.83	2	131.58	2

Source: Niederwieser et al. 2021 (113).
Abbreviations: BC, blast crisis.
Note the generalised gamma distribution did not converge

Visually, there are broadly three groups of curves, with the gompertz functions rapidly reaching a plateau for both OS and RFS, and likely to be an implausibly high estimate of survival. Exponential functions generate the lowest survival for all curves, with the remaining functions falling in between.

For non-blast crisis OS, the log-normal distribution has the best fit on both Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC), and this curve was selected. For the non-blast crisis RFS curve, the log-normal, gen, gamma and log-logistic distributions are the best fitting candidates, and generate similar extrapolations. The log-normal was chosen as this is ranked first for BIC and second for AIC.

For the blast crisis, the gompertz function is the best fitting for both RFS and OS on both AIC and BIC, but generates long term survival that was considered to be implausibly high. The log-normal was selected for both RFS and OS. For RFS it is the second best fitting function according to measures of model fit. For OS, it is slightly inferior to the generalised gamma on measures of model fit, but was considered to generate more plausible long term survival in this group of patients.

Two scenarios were undertaken in answer to this question:

1) The blast crisis curves for OS and RFS were applied to both those having an SCT in the AP and those having an SCT in the BP.

2) Based on the scenario presented for B12, the patients undergoing SCT at progression to AP enter the SCT-CP sub-model (based on the non-blast crisis curves), and only those having an SCT from the BP state enter the SCT-PD sub-model (based on the curves from Niederwieser for the blast crisis patients). Results comparing the revised base case, and the two scenarios mentioned above, are reported in Asciminib versus **comparators (all treatments at list prices)**

Table 61 to Table 64 for list prices of all treatments, and Table 65 to Table 68 for PAS price of asciminib (and PAS price of nilotinib for the comparison with nilotinib).

Results show that using Niederwieser 2021 has led to improvement in the ICERs for all comparisons except ponatinib, where the ICER has slightly decreased. Asciminib remains cost-effective compared to ponatinib as the costs saved per QALY loss are still considerably higher than the £20,000 threshold. The results reflect the slightly lower survival rates predicted by Niederwieser (113), a change which disfavours comparators with a shorter time on third-line treatment (and correspondingly more patients undergoing SCT).

Asciminib versus comparators (all treatments at list prices)

Table 61: Base-case results pairwise – asciminib vs bosutinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	10.48	7.79	–	–	–	–
Bosutinib	[redacted]	8.72	6.30	[redacted]	1.76	1.49	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	10.14	7.57				
Bosutinib	[redacted]	8.29	6.02	[redacted]	1.85	1.56	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	10.30	7.65				
Bosutinib	[redacted]	8.49	6.12	[redacted]	1.81	1.53	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Table 62: Base-case results pairwise – asciminib vs ponatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.62	6.25	–	–	–	–
Ponatinib	[redacted]	9.24	6.76	[redacted]	-0.62	-0.51	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	8.21	5.98				
Ponatinib	[redacted]	8.89	6.53	[redacted]	-0.68	-0.55	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	8.41	6.09				
Ponatinib	[redacted]	9.07	6.63	[redacted]	-0.66	-0.54	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Table 63: Base-case results pairwise – asciminib vs nilotinib (list prices of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	9.03	6.61	–	–	–	–
Nilotinib	[redacted]	8.13	5.76	[redacted]	0.90	0.85	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	8.66	6.37				
Nilotinib	[redacted]	7.67	5.46	[redacted]	0.99	0.91	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	8.85	6.47				
Nilotinib	[redacted]	7.89	5.57	[redacted]	0.96	0.90	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Table 64: Base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.94	6.54	–	–	–	–
Dasatinib	[redacted]	8.30	5.97	[redacted]	0.65	0.57	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	8.57	6.29				
Dasatinib	[redacted]	7.86	5.68	[redacted]	0.71	0.61	[redacted]
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	8.76	6.39				
Dasatinib	[redacted]	8.07	5.79	[redacted]	0.69	0.60	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Asciminib versus comparators (PAS price)

Table 65: Base-case results pairwise – asciminib vs bosutinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	10.48	7.79	–	–	–	–
Bosutinib	[redacted]	8.72	6.30	3,959	1.76	1.49	2,654
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	10.14	7.57				
Bosutinib	[redacted]	8.29	6.02	3,287	1.85	1.56	2,111
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	10.30	7.65				
Bosutinib	[redacted]	8.49	6.12	-237	1.81	1.53	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Table 66: Base-case results pairwise – asciminib vs ponatinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.62	6.25	–	–	–	–
Ponatinib	[redacted]	9.24	6.76	-138,189	-0.62	-0.51	271,410
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	8.21	5.98				
Ponatinib	[redacted]	8.89	6.53	-137,652	-0.68	-0.55	251,041
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	8.41	6.09				
Ponatinib	[redacted]	9.07	6.63	-136,302	-0.66	-0.54	252,865

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Table 67: Base-case results pairwise – asciminib vs nilotinib (PAS price – for asciminib and nilotinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	9.03	6.61	–	–	–	–
Nilotinib	[redacted]	8.13	5.76	42,559	0.90	0.85	50,167
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	8.66	6.37				
Nilotinib	[redacted]	7.67	5.46	41,742	0.99	0.91	45,870
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	8.85	6.47				
Nilotinib	[redacted]	7.89	5.57	39,677	0.96	0.90	44,303

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

Table 68: Base-case results pairwise – asciminib vs dasatinib (PAS price of asciminib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Revised base-case (after error correction, half cycle correction and inclusion of age taper for SCT)							
Asciminib	[redacted]	8.94	6.54	–	–	–	–
Dasatinib	[redacted]	8.30	5.97	331	0.65	0.57	582
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 1)							
Asciminib	[redacted]	8.57	6.29				
Dasatinib	[redacted]	7.86	5.68	-274	0.71	0.61	Dominant
Outcomes using Niederwieser 2021 for SCT outcomes (scenario 2)							
Asciminib	[redacted]	8.76	6.39				
Dasatinib	[redacted]	8.07	5.79	-1,771	0.69	0.60	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT, stem cell transplant.

B14. Please provide relevant information on the number of patients receiving SCT following discontinuation of treatment (asciminib or bosutinib) in the ASCEMBL trial.

In total, [redacted] patients received SCT following discontinuation; [redacted] in the asciminib arm [redacted] and [redacted] in the bosutinib arm [redacted] (115).

B15. The model assumes 55.8% of patients go onto receive an allo-SCT. Based on the incidence of eligible population provided in the model (140 individuals) this would estimate approximately 78 patients receive an allo-SCT. However, data from the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT; https://bsbmtct.org/activity/2020/) (116) shows on average over the last 5 years, 43 patients received allo-SCT annually. This number represents total transplant activity in CML, not just those in the 3rd line setting. Please can you comment on the differences in the assumed population receiving allo-SCT and the numbers reported in the BSBMTCT.

The original model assumed that 46.64% go on to have allo-SCT. The actual value is lower than the simple sum of the proportions undergoing allo-SCT at the different stages of the model (post-discontinuation [15.8%], upon progression to AP [20%] and upon progression to BP [20%]) because removal of patients undergoing SCT from the main model at each stage reduces the size of the remaining cohort eligible for SCT at subsequent stages.

We agree that the numbers receiving allo-SCT in the model are likely to be high, and have implemented a reduction (or tapering) of the proportion receiving SCT as a function of patient age, as part of the revised base case (see question B.11 for a detailed explanation and results in Appendix A). The inclusion of the taper leads to the changes in the overall proportion receiving allo-SCT as outlined in Table 69.

Table 69: Proportion of patients undergoing SCT before and after implementing a reduced likelihood of SCT with patient age

	Proportion receiving SCT (before annual tapering of proportion receiving SCT)	Proportion receiving SCT (after annual tapering of proportion receiving SCT)
Asciminib vs bosutinib		
Asciminib	46.64%	22.11%
Bosutinib	46.64%	27.87%
Asciminib vs ponatinib		
Asciminib	46.64%	27.75%
Ponatinib	46.64%	25.01%
Asciminib vs nilotinib		
Asciminib	46.64%	26.28%
Nilotinib	46.64%	29.24%
Asciminib vs dasatinib		
Asciminib	46.64%	26.28%
Dasatinib	46.64%	29.24%

Abbreviations: SCT, stem cell transplant.

Prior to the model change, the proportion of patients receiving SCT is the same across all comparisons, as the impact of extending time on third-line TKI treatment is simply to delay progression to the stages at which patients are eligible for SCT. Following the introduction of a reducing likelihood of SCT as a function of age, the proportion having SCT varies across comparators. Prolonged duration of time on third-line treatment now increases the age distribution at the subsequent stages of the disease at which patients are candidates for SCT, and hence reduces the absolute proportion of patients undergoing SCT. Hence there are fewer SCTs with asciminib compared with bosutinib, dasatinib, and nilotinib.

Taking the range of the comparator arm proportions on SCT (25.01% to 29.24%) means there would be approximately 35–41 patients receiving allo-SCT as predicted by the model. This is more in line with the figures presented in the BSBMTCT (116), after taking into account that not all SCTs would be at third line and subsequent points in the disease progression.

Resource use

B16. Priority Question: The model assumes that all patients will move to a subsequent treatment. Please comment on the clinical plausibility of this assumption.

i. **Please provide data from ASCEMBL on the proportion of patients receiving subsequent treatment following a) discontinuation of asciminib, b) discontinuation of bosutinib.**

The proportion of patients receiving subsequent treatment following discontinuation of asciminib was 43 out of 67 patients that discontinued (64.2%), and following discontinuation of bosutinib was 35 out of 58 (60.3%).

ii. **Please provide details of the subsequent treatment received following a) discontinuation of asciminib, b) discontinuation of bosutinib.**

This information was not captured in the follow-up period for patients.

B17. Priority question: The model currently uses HRMN data supplemented with clinician insight to inform the distribution of subsequent treatments received.

i. **Please provide details of the data used to inform these assumptions and describe the adjustments made in light of clinical advice received.**

The model bases the proportions of subsequent treatments on data taken from the HMRN after adjustment following consultation with a clinical expert (Professor Mead) (106) (Table 70). Data from HMRN reflect treatment patterns from inception of the registry in 2003. For much of the period of data collection, newer TKIs were not available. In light of that fact, we followed advice from Professor Mead to increase the proportion for ponatinib to 25% and to reduce the proportions for other TKIs proportionately, each (106).

Table 70: Subsequent treatment proportions adjusted and unadjusted from HMRN

Treatment	Proportion from HMRN (%)	Adjusted proportions (%)
Imatinib	6.3	5.4
Dasatinib	20.8	17.8
Nilotinib	25	21.4
Bosutinib	35.4	30.3
Ponatinib	12.5	25

ii. Please clarify why it is assumed that treatments used post discontinuation of treatment are independent of treatment received.

Clinical opinion from Professor Mead indicates that patients refractory to treatment tend to cycle though different TKI treatments with the aim of achieving at least partial control of their disease (106). This is supported by evidence from HMRN indicating that multiple therapy lines in some patients, with reintroduction of TKIs tried at earlier stages of treatment and continuation of TKI therapy to the point of progression to blast crisis and beyond. For this reason, the economic model assumes continued treatment with TKI therapy throughout the chronic phase. The distribution of treatments reflects the likely proportions of each TKI as patients' disease progresses and they cycle through multiple treatments. It reflects the likelihood that previously used TKI therapy will be tried again in some patients. Given that previous use of a TKI is not a bar to further use at a subsequent point in a patient's treatment pathway we elected to apply the same proportion of TKI treatments in subsequent therapy to all patients regardless of third-line treatment.

iii. Please present additional scenario analysis using the data reported in the HMRN data set Figures 1 to update assumptions about the mix of treatments received post-discontinuation of treatment. Where appropriate please adjust to account for recent updates to the pathway.

The data reported in the HMRN dataset (Figure 1 in the HMRN report) have been used to inform the base case estimate of the mix of treatments received post-discontinuation of third-line treatment (88). Table 2 of the report summarises the data in Figure 1, and the data informing the economic model originated from the fourth-line column of that table. These data were adjusted to account for updates to the pathway as advised by Professor Mead and described in response to Part ii of this question. As described in B17i, adjustments were made to the data based on clinical

expert advice (106). Therefore, the data the ERG refer to is already part of the base case.

B18. Clinical advice provided to the ERG suggests that, while it is unlikely for all, the savings associated with reduced dose intensity could be recouped in CML. Please provide versions of the model that allow the impact on the ICER of being unable to recoup savings based on reduced dose intensity.

If there were no savings associated with reduced dose intensity, this would imply a relative dose intensity of 100%. This can be changed easily within the model in the 'Costs_Drug' sheet. Results of the impact of 100% relative dose intensity for asciminib and bosutinib on each pairwise comparison are presented below in Table 71–Table 78, for each comparison, and at list and PAS prices.

Asciminib versus comparators (list price of all treatments)

Table 71: Base-case results pairwise – asciminib vs bosutinib (list price) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	10.48	7.79				
Bosutinib	[redacted]	8.72	6.30	[redacted]	1.76	1.49	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 72: Base-case results pairwise – asciminib vs ponatinib (list price) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	8.62	6.25				
Ponatinib	[redacted]	9.24	6.76	[redacted]	-0.62	-0.51	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 73: Base-case results pairwise – asciminib vs nilotinib (list price) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	9.03	6.61				
Nilotinib	[redacted]	8.13	5.76	[redacted]	0.90	0.85	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 74: Base-case results pairwise – asciminib vs dasatinib (list price) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	8.94	6.54				
Dasatinib	[redacted]	8.30	5.97	[redacted]	0.65	0.57	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Asciminib vs comparators (PAS price)

Table 75: Base-case results pairwise – asciminib vs bosutinib (PAS price for asciminib) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	10.48	7.79				
Bosutinib	[redacted]	8.72	6.30	4,823	1.76	1.49	3,233

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 76: Base-case results pairwise – asciminib vs ponatinib (PAS price for asciminib) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	8.62	6.25				
Ponatinib	[redacted]	9.24	6.76	-131,433	-0.62	-0.51	258,141

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 77: Base-case results pairwise – asciminib vs nilotinib (PAS price for asciminib and nilotinib) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	9.03	6.61				
Nilotinib	[redacted]	8.13	5.76	51,705	0.90	0.85	60,948

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 78: Base-case results pairwise – asciminib vs dasatinib (PAS price for asciminib) – RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Asciminib	[redacted]	8.94	6.54				
Dasatinib	[redacted]	8.30	5.97	8,994	0.65	0.57	15,792

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Section C: Textual clarification and additional points

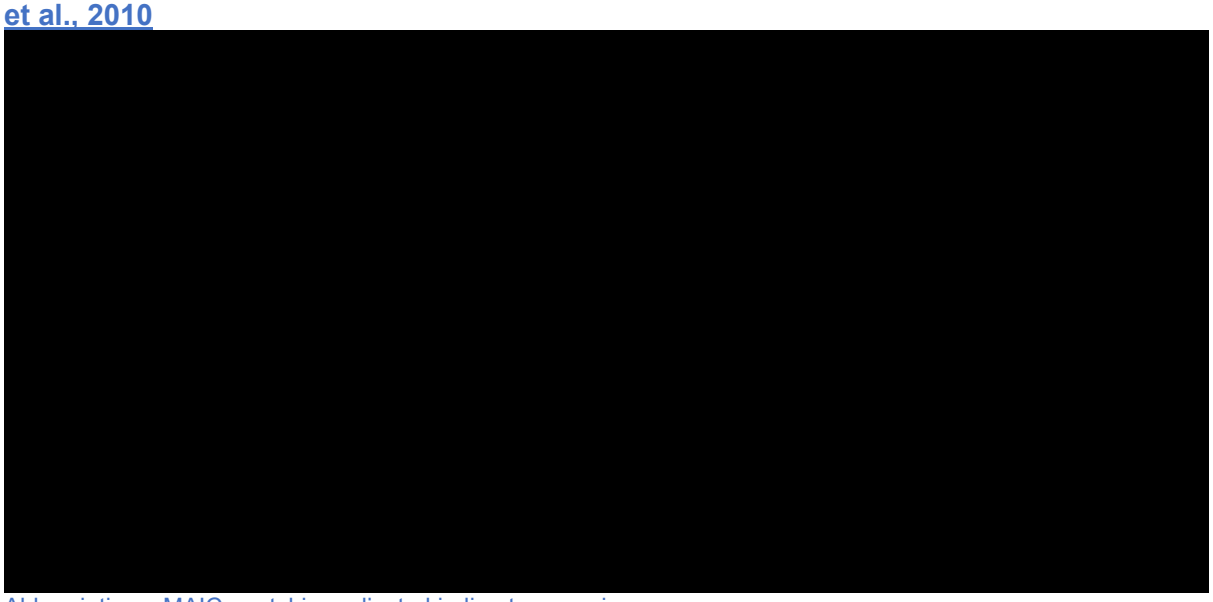
C1. Please provide a legend for X and Y axis and an explanation for Appendix I, Figures 7, 9, 11, 13 reporting the distribution of weights assigned to ASCEMBL participants after MAIC.

The respective figures below (Figure 10–Figure 13) display histograms of the weights applied in the MAICs. The x-axis on the left is the raw number of patients and refers to the height of each bar. The x-axis on the right is the proportion of the patients in the analysis and refers to the points joined by the orange lines (cumulative proportion of the cohort). The y-axis reports the MAIC weight range for each of the bins plotted in the histogram.

Figure 10: Appendix I, Figure 7 - Weights assigned to ASCEMBL patients after MAIC with PACE

Abbreviations: MAIC, matching adjusted indirect comparison.

Figure 11: Appendix I, Figure 9 - Weights assigned to ASCEMBL after MAIC with Giles et al., 2010



Abbreviations: MAIC, matching adjusted indirect comparison.

Figure 12: Appendix I, Figure 11 - Weights assigned to ASCEMBL patients after MAIC with Rossi et al.,

Abbreviations: MAIC, matching adjusted indirect comparison.

Figure 13: Appendix I, Figure 13 - Weights assigned to ASCEMBL patients after MAIC with CML-203 study

Abbreviations: MAIC, matching adjusted indirect comparison.

C2. ASCEMBL CSR, Section 14, 'Tables, figures and listings referred to but not included in the text' is blank. Please can the company provide this section.

An updated ASCEMBL clinical study report (CSR) with the inclusion of Section 14 has been provided separately.

C3. Document B, Table 16, and corresponding ASCEMBL CSR Table 10-9 report 'number of prior TKIs' and 'number of lines of prior TKI therapy' as separate variables. Please clarify the difference between these variables.

In the ASCEMBL study, a new line of therapy was considered each time a change in TKI occurred. Thus, if a TKI was repeated for further treatment after failure of an alternative TKI, it was counted separately with respect to the 'number of prior TKIs'. However, the repeated TKI was counted only once when considering the 'number of lines of prior TKI therapy'.

For example, if a patient had previously received nilotinib, dasatinib, and then nilotinib again prior to enrolling in the ASCEMBL trial, the patient was considered to have received two prior TKIs (number of prior TKIs) and three lines of prior therapy (number of lines of prior TKI therapy).

Searches

C4. Please provide the search strategies used to search the Northern Light Database and search terms used to search the conferences listed in section C1.2.2, page 8 of Appendix D.

The Northern Lights Database was searched on 9 November 2020 for conference abstracts listed during the period of 2010–2020 Week 42. The tables below list the search strategies used for searching conference abstracts from the European Society for Medical Oncology (ESMO) (Table 79), American Society of Clinical Oncology (ASCO) (Table 80), American Society of Hematology (ASH) (Table 81), European Hematology Association (EHA) (Table 82) and International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting (ISPOR) (Table 83). Abstracts from Academy of Managed Care Pharmacy (AMCP) and Society of Hematologic Oncology (SOHO) were hand searched among submissions made under “CML”, “leukemia” and related categories in the archived records available on the conference websites.

During the SLR update, hand searching of conference abstracts was conducted from November 2020 to June 2021. The recent abstracts that were available on conference websites were from AMCP 2021 (April), ASCO 2021 (June), EHA 2021 (June), ISPOR 2021 (May) and ISPOR-EU 2020 (November). Abstracts of ASH 2020 (December) were already covered in the database search and were not hand searched during the SLR update.

Table 79. Search strategy for European Society of Medical Oncology (ESMO) conference abstracts in Northern Lights Database

No.	Examples	Terms	Hits
1	Population terms	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	1,352
2		(chronic myel$ adj3 leuk?emia$1).mp.	3,887
3		cml.mp.	4,326
4		leuk?emia$1.mp.	46,666
5		3 and 4	3,161
6		((philadelphia or ph1 or BCR-ABL) adj3 myel$ adj3 leuk?emia$1).mp.	55
7		1 or 2 or 5 or 6	4,942
8	Intervention terms as	(asciminib or abl001 or "abl 001" or abl001aaa or abl001nx).mp.	19

No.	Examples	Terms	Hits
9	keywords if not explodable	(nilotinib or tasigna or amn107 or amn 107).mp.	986
10		exp Dasatinib/	2,862
11		(dasatinib or sprycel or bms354825 or bms 354825 or bms 35482503 or "bms354825 03").mp.	2,862
12		exp Imatinib Mesylate/	-
13		(imatinib or gleevec or glivec or sti571 or sti 571 or st 1571 or st1571 or st1 571).mp.	3,088
14		(bosutinib or SKI-606 or SKI 606 or bosulif or PF-05208763 or PF-5208763).mp.	190
15		(ponatinib or Iclusig or AP24534 or AP-24534).mp.	359
16		(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea or biosupressin or droxia or hydab or hydroxy carbamide or hydroxy urea or litalir or mylocel or hydroxyurea or neodrea or nsc 32065 or onco-carbide or oncocarbide or oxycarbamide or oxyurea or siklos or xromi).mp.	2,735
17		(Omacetaxine mepesuccinate or Synribo or homoharringtonine or homoharringtonin or HHT).mp.	431
18		(HSCT or SCT).mp.	10,646
19		Hematopoietic Stem Cell Transplantation.mp.	4,635
20		(stem adj2 cell adj2 transplant*).mp.	16,055
21		(best adj2 support*).mp.	625
22		BSC.mp.	457
23		(olverembatinib or HQP-1351 or HQP1351 or APG-1351 or APG1351 or D-824 or D824 or GZD-824 or GZD824).mp.	5
24		8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	29,289
25	Term for conference restriction	EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY.cf.	15,406
26	Intersection population, intervention and conference terms	7 and 24 and 25	16
27	Term for year restriction	limit 26 to yr="2017 -Current"	4

Table 80: Search strategy for American Society of Clinical Oncology (ASCO) conference abstracts in Northern Lights Database

No.	Examples	Terms	Hits
1	Population terms	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	1,352
2		(chronic myel$ adj3 leuk?emia$1).mp.	3,887
3		cml.mp.	4,326
4		leuk?emia$1.mp.	46,666
5		3 and 4	3,161
6		((philadelphia or ph1 or BCR-ABL) adj3 myel$ adj3 leuk?emia$1).mp.	55
7		1 or 2 or 5 or 6	4,942
8	Intervention terms as keywords if not explodable	(asciminib or abl001 or "abl 001" or abl001aaa or abl001nx).mp.	19
9		(nilotinib or tasigna or amn107 or amn 107).mp.	986
10		exp Dasatinib/	2,862
11		(dasatinib or sprycel or bms354825 or bms 354825 or bms 35482503 or "bms354825 03").mp.	2,862
12		exp Imatinib Mesylate/	-
13		(imatinib or gleevec or glivec or sti571 or sti 571 or st 1571 or st1571 or st1 571).mp.	3,088
14		(bosutinib or SKI-606 or SKI 606 or bosulif or PF-05208763 or PF-5208763).mp.	190
15		(ponatinib or Iclusig or AP24534 or AP-24534).mp.	359
16		(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea or biosupressin or droxia or hydab or hydroxy carbamide or hydroxy urea or litalir or mylocel or hydroxyurea or neodrea or nsc 32065 or onco-carbide or oncocarbide or oxycarbamide or oxyurea or siklos or xromi).mp.	2,735
17		(Omacetaxine mepesuccinate or Synribo or homoharringtonine or homoharringtonin or HHT).mp.	431
18		(HSCT or SCT).mp.	10,646
19		Hematopoietic Stem Cell Transplantation.mp.	4,635
20		(stem adj2 cell adj2 transplant*).mp.	16,055
21		(best adj2 support*).mp.	625
22		BSC.mp.	457
23		(olverembatinib or HQP-1351 or HQP1351 or APG-1351 or APG1351 or D-824 or D824 or GZD-824 or GZD824).mp.	5

No.	Examples	Terms	Hits
24		8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	29,289
25	Term for conference restriction	American Society of Clinical Oncology.cf.	59,353
26	Intersection population, intervention and conference terms	7 and 24 and 25	162
27	Term for year restriction	limit 26 to yr="2017 -Current"	30

Table 81: Search strategy for American Society of Hematology (ASH) conference abstracts in Northern Lights Database

No.	Examples	Terms	Hits
1	Population terms	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	1,352
2		(chronic myel$ adj3 leuk?emia$1).mp.	3,887
3		cml.mp.	4,326
4		leuk?emia$1.mp.	46,666
5		3 and 4	3,161
6		((philadelphia or ph1 or BCR-ABL) adj3 myel$ adj3 leuk?emia$1).mp.	55
7		1 or 2 or 5 or 6	4,942
8	Intervention terms as keywords if not explodable	(asciminib or abl001 or "abl 001" or abl001aaa or abl001nx).mp.	19
9		(nilotinib or tasigna or amn107 or amn 107).mp.	986
10		exp Dasatinib/	2,862
11		(dasatinib or sprycel or bms354825 or bms 354825 or bms 35482503 or "bms354825 03").mp.	2,862
12		exp Imatinib Mesylate/	-
13		(imatinib or gleevec or glivec or sti571 or sti 571 or st 1571 or st1571 or st1 571).mp.	3,088
14		(bosutinib or SKI-606 or SKI 606 or bosulif or PF-05208763 or PF-5208763).mp.	190
15		(ponatinib or Iclusig or AP24534 or AP-24534).mp.	359
16		(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea or biosupressin or droxia or hydab or hydroxy carbamide or hydroxy urea or litalir or mylocel or hydroxyurea or neodrea or nsc 32065 or onco-carbide or oncocarbide or oxycarbamide or oxyurea or siklos or xromi).mp.	2,735
17		(Omacetaxine mepesuccinate or Synribo or homoharringtonine or homoharringtonin or HHT).mp.	431

No.	Examples	Terms	Hits
18		(HSCT or SCT).mp.	10,646
19		Hematopoietic Stem Cell Transplantation.mp.	4,635
20		(stem adj2 cell adj2 transplant*).mp.	16,055
21		(best adj2 support*).mp.	625
22		BSC.mp.	457
23		(olverembatinib or HQP-1351 or HQP1351 or APG-1351 or APG1351 or D-824 or D824 or GZD-824 or GZD824).mp.	5
24		8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	29,289
25	Term for conference restriction	American Society of Hematology.cf.	50,853
26	Intersection population, intervention and conference terms	7 and 24 and 25	1,232
27	Term for year restriction	limit 26 to yr="2017 -Current"	270

Table 82: Search strategy for European Hematology Association (EHA) conference abstracts in Northern Lights Database

No.	Examples	Terms	Hits
1	Population terms	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	1,352
2		(chronic myel$ adj3 leuk?emia$1).mp.	3,887
3		cml.mp.	4,326
4		leuk?emia$1.mp.	46,666
5		3 and 4	3,161
6		((philadelphia or ph1 or BCR-ABL) adj3 myel$ adj3 leuk?emia$1).mp.	55
7		1 or 2 or 5 or 6	4,942
8	Intervention terms as keywords if not explodable	(asciminib or abl001 or "abl 001" or abl001aaa or abl001nx).mp.	19
9		(nilotinib or tasigna or amn107 or amn 107).mp.	986
10		exp Dasatinib/	2,862
11		(dasatinib or sprycel or bms354825 or bms 354825 or bms 35482503 or "bms354825 03").mp.	2,862
12		exp Imatinib Mesylate/	-
13		(imatinib or gleevec or glivec or sti571 or sti 571 or st 1571 or st1571 or st1 571).mp.	3,088
14		(bosutinib or SKI-606 or SKI 606 or bosulif or PF-05208763 or PF-5208763).mp.	190
15		(ponatinib or Iclusig or AP24534 or AP-24534).mp.	359
16		(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea or biosupressin or droxia or hydab or hydroxy carbamide or hydroxy urea or litalir or mylocel or hydroxyurea or neodrea or nsc 32065 or onco-carbide or oncocarbide or oxycarbamide or oxyurea or siklos or xromi).mp.	735
17		(Omacetaxine mepesuccinate or Synribo or homoharringtonine or homoharringtonin or HHT).mp.	431
18		(HSCT or SCT).mp.	10,646
19		Hematopoietic Stem Cell Transplantation.mp.	4,635
20		(stem adj2 cell adj2 transplant*).mp.	16,055
21		(best adj2 support*).mp.	625
22		BSC.mp.	457
23		(olverembatinib or HQP-1351 or HQP1351 or APG-1351 or APG1351 or D-824 or D824 or GZD-824 or GZD824).mp.	5

No.	Examples	Terms	Hits
24		8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	29,289
25	Term for conference restriction	European Hematology Association.cf.	21,167
26	Intersection population, intervention and conference terms	7 and 24 and 25	824
27	Term for year restriction	limit 26 to yr="2017 -Current"	122

Table 83: Search strategy for International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting (ISPOR) conference abstracts in Northern Lights Database

No.	Examples	Terms	Hits
1	Population terms	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/	1,352
2		(chronic myel$ adj3 leuk?emia$1).mp.	3,887
3		cml.mp.	4,326
4		leuk?emia$1.mp.	46,666
5		3 and 4	3,161
6		((philadelphia or ph1 or BCR-ABL) adj3 myel$ adj3 leuk?emia$1).mp.	55
7		1 or 2 or 5 or 6	4,942
8	Intervention terms as keywords if not explodable	(asciminib or abl001 or "abl 001" or abl001aaa or abl001nx).mp.	19
9		(nilotinib or tasigna or amn107 or amn 107).mp.	986
10		exp Dasatinib/	2,862
11		(dasatinib or sprycel or bms354825 or bms 354825 or bms 35482503 or "bms354825 03").mp.	2,862
12		exp Imatinib Mesylate/	-
13		(imatinib or gleevec or glivec or sti571 or sti 571 or st 1571 or st1571 or st1 571).mp.	3,088
14		(bosutinib or SKI-606 or SKI 606 or bosulif or PF-05208763 or PF-5208763).mp.	190
15		(ponatinib or Iclusig or AP24534 or AP-24534).mp.	359
16		(hydroxycarbamide or hydroxycarbamide or hydrea or hydrine or neofrea or oxyurea or biosupressin or droxia or hydab or hydroxy carbamide or hydroxy urea or litalir or mylocel or hydroxyurea or neodrea or nsc 32065 or onco-carbide or oncocarbide or oxycarbamide or oxyurea or siklos or xromi).mp.	2,735

No.	Examples	Terms	Hits
17		(Omacetaxine mepesuccinate or Synribo or homoharringtonine or homoharringtonin or HHT).mp.	431
18		(HSCT or SCT).mp.	10,646
19		Hematopoietic Stem Cell Transplantation.mp.	4,635
20		(stem adj2 cell adj2 transplant*).mp.	16,055
21		(best adj2 support*).mp.	625
22		BSC.mp.	457
23		(olverembatinib or HQP-1351 or HQP1351 or APG-1351 or APG1351 or D-824 or D824 or GZD-824 or GZD824).mp.	5
24		8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	29,289
25	Term for conference restriction	(International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting).cf.	14,972
26	Intersection population, intervention and conference terms	7 and 24 and 25	36
27	Term for year restriction	limit 26 to yr="2017 -Current"	8

C5. Please clarify if the HTA database via Centre for Reviews and Dissemination (CRD) databases https://www.crd.york.ac.uk/crdweb/ and the International HTA database via INAHTA https://database.inahta.org/ were searched for economic evaluations.

Both NHSEED and HTA database via CRD databases https://www.crd.york.ac.uk/crdweb/ were searched while International HTA database via INAHTA https://database.inahta.org/ was not searched. Apart from these databases, the following HTA websites were hand-searched:

- UK:
  - National Institute for Health and Clinical Excellence (NICE)
  - Scottish Medicines Consortium (SMC)
  - All Wales Medicines Strategy Group (AWMSG)
- US

    - The California Technology Assessment Forum (CTAF)
    - Institute for Clinical and Economic Review (ICER)
- France: Haute Autorité de Santé (HAS)
- Sweden: The Dental and Pharmaceutical Benefits Agency (TLV)
- Germany: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)
- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)
- Australia: Pharmaceutical Benefits Advisory Committee (PBAC)

C6. Please provide a description of the methods or search strategies used to hand-search the conferences listed in G1.2.2, page 3, Appendix G. In addition, outline any limits applied such as date or language limits.

Conferences covered in the database search (ASCO, ASH, EHA, ESMO, ISPOR) were not searched separately; however, manual searches were conducted on remaining conference websites (AMCP, British Society of Haematology [BSH], European Society for Blood and Marrow Transplantation [EBMT], SOHO) through the following keywords:

- “CML”
- “Chronic myeloid leukaemia”
- “Chronic leukaemia and other myeloproliferative disorders section”
- “Myeloproliferative neoplasm”

Conference abstracts published from 2018 to May 2021 were included.

C7. Please clarify if any further supplementary search methods were used to identify further studies e.g. reference checking of included studies or relevant reviews, searches of HTA agency websites.

Appendix D

Systematic and literature reviews identified through database searches were utilised for bibliography searching for identification of relevant studies. This ensured that comprehensive evidence was included in the current SLR.

Additionally, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/search/en/) was searched (using the condition search term “chronic myeloid leukemia” and intervention search term “asciminib or nilotinib or imatinib or dasatinib or bosutinib or ponatinib or radotinib or olverembatinib or HQP1351 or PF-114 or hydoxycarbamide or omacetaxine or allo-SCT or best supportive care”) to identify any ongoing or completed Phase II or Phase III clinical trials that met the inclusion criteria, but did not have the results published or publicly available.

Appendix G

For economic evaluations, the following HTA websites were hand searched to identify additional studies:

- UK:
  - National Institute for Health and Clinical Excellence (NICE)
  - Scottish Medicines Consortium (SMC)
  - All Wales Medicines Strategy Group (AWMSG)
- US
  - The California Technology Assessment Forum (CTAF)
  - Institute for Clinical and Economic Review (ICER)
- France: Haute Autorité de Santé (HAS)
- Sweden: The Dental and Pharmaceutical Benefits Agency (TLV)

- Germany: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)
- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)
- Australia: Pharmaceutical Benefits Advisory Committee (PBAC)

C8. Please clarify and provide references for study design search filters as follows:

i. Any used in the searches of MEDLINE and Embase to limit to (a) RCTs and (b) observational studies.

The search filters were adapted from those suggested in the Cochrane Handbook for Systematic Reviews of Interventions, as well as the standard search filters provided by Scottish Intercollegiate Guidelines Network (SIGN) and InterTASC Information Specialists' Sub-Group (ISSG).

- Lefebvre et al. 2011 (117)
- SIGN search filters for RCTs and observational studies (118)
- ISSG Search filters for RCTs (119)
- Glanville et al. 2019 (120)
- ISSG Search filters for non-RCTs (121)

ii. That used to limit to economic evaluations (lines #6 - line #32, in table 1, page 2, Appendix G)

Standard search filters after adaptations were used to limit the search hits for economic evaluations.

- SIGN search filters for economic evaluations (118)
- ISSG search filters for economic evaluations (122)
- McKinlay et al. 2006 (123)

iii. That used to limit to health-related quality of life studies (lines #6 - line #38 in table 1, page 2, Appendix H)

Standard search filters after adaptations were used to limit the search hits for health-related quality of life studies.

- ISSG search filters for health-related quality of life (124)

C9. There is a mismatch between the number of studies identified in table 1, page 2, Appendix G (showing 1381 hits) and table 2, page 3, Appendix G (showing x85 hits) and those reported in Figure 2, page 8, Appendix G which reports that 1492 records were retrieved in total from the searches of MEDLINE, Embase and National Health Service (NHS) economic evaluations database (EED). Please check and correct as necessary.

An updated search strategy is provided in Table 84 and in Appendix G (provided separately).

Table 84: Search strategy for EMBASE, MEDLINE, MEDLINE In-Process

No.	Query	Hits 2020	Hits 2021
#1	'chronic myeloid leukemia'/syn	51,875	54171
#2	'chronic myelogenous leukemia':ab,ti OR 'chronic myelogenous leukaemia':ab,ti OR 'chronic myeloid leukaemia':ab,ti OR 'chronic myeloid leukemia':ab,ti OR 'cml':ab,ti OR 'cml-cp':ab,ti	41,439	43448
#3	'chronic myel*' NEAR/3 leuk?emia	5,175	5401
#4	(philadelphia OR ph1 OR 'bcr-abl') NEAR/3 myel* NEAR/3 leuk?emia?	3	3
#5	#1 OR #2 OR #3 OR #4	58,570	61283
#6	'economics'/de OR 'economic aspect'/de OR 'health economics'/de	380,768	391539
#7	'cost'/de OR 'health care cost'/de	246,626	258406
#8	'drug cost'/de	76,755	79677
#9	'hospital cost'/de	21,222	22501
#10	'socioeconomics'/de	144,805	152566
#11	'cost benefit analysis'/de	83,589	86815
#12	'cost effectiveness analysis'/de	149,772	159023
#13	'cost of illness'/de	18,909	19765
#14	'cost control'/de	67,720	70515
#15	'cost minimization analysis'/de	3,464	3628
#16	'pharmacoeconomics'/de	7,291	7570

No.	Query	Hits 2020	Hits 2021
#17	'fee'/exp	41,614	42839
#18	'budget'/exp	28,737	30445
#19	'economic evaluation'/exp	302,732	318550
#20	'hospital finance'/de	2,693	2737
#21	'financial management'/de	115,624	118616
#22	'health care financing'/de	13,214	13459
#23	'low cost' OR 'high cost'	82,466	94051
#24	health*care NEXT/1 cost*	20,065	22776
#25	'health care' NEXT/1 cost*	196,053	207040
#26	fiscal OR funding OR financial OR finance	328,758	358363
#27	(cost NEXT/1 estimate*) OR 'cost variable' OR (unit NEXT/1 cost*)	7,717	8325
#28	economic*:ab,ti OR pharmacoeconomic*:ab,ti	341,490	377324
#29	price*:ab,ti OR pricing:ab,ti	57,017	62023
#30	(health*care NEXT/1 (utilisation OR utilization)) OR ('health care' NEXT/1 (utilisation OR utilization))	75,012	82319
#31	(resource NEXT/1 (utilisation OR utilization OR use)) OR ((cost* NEAR/3 (treat* OR therap*)):ab,ti)	87,520	96286
#32	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	1,540,612	1655449
#33	#5 AND #32	1,953	2090
#34	#33 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	15	16
#35	#33 NOT #34	1,938	2074
#36	#33 NOT #34 AND [2010-2020]/py	1,407	-
#37	#33 NOT #34 AND [10-5-2020]/sd NOT [26-5-2021]/sd	-	160

References

1. National Institute for Health and Care Excellence. TA451 Ponatinib committee papers. Available at: https://www.nice.org.uk/guidance/ta451/documents/committee-papers (last accessed 24th Nov 2021).
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Appendix A – revised base case

1. In the process of answering the ERG's questions, a calculation error was identified within the model. This related to cells that were summing the survival in sheet 'Survival', with only up to row 555 being summed whereas this should have been up to row 609. Cells affected were:
    - T3, W3, Z3, AC3, AE3, AI3, AL3, AO3, AR3, AW3, AZ3, BB3, BE3, BH3, and BJ3.
2. Half cycle correction was also suggested in question B6, this has been implemented and is also part of the revised based case.
3. Question B.11 refers to providing a version of the model which accounts for the decreasing likelihood patients will be fit enough to receive SCT as they age. This has also been added as part of the revised base case.

Results of correcting the error, adding in half-cycle correction, and adding in a tapering of SCT by age, are shown iteratively in Table 85 to Table 88 for list price results, and in tables Table 89 to Table 92 where the asciminib PAS price is used (and nilotinib PAS price when versus nilotinib). The changes are implemented iteratively and cumulatively, so that results after addition of the half cycle correction also include the model error correction, and the results after inclusion of the age taper for the probability of undergoing SCT include the error correction and the half cycle correction. The revised base -case incorporates both these changes. The ICERs compared to nilotinib and dasatinib are not impacted by the error correction.

Any additional analyses undertaken in response to the ERG questions, is in comparison to the revised base case result.

Asciminib versus comparators (list price of all treatments)

Table 85: Base-case results pairwise – asciminib vs bosutinib (list price of all treatments)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	9.47	6.74				
	Bosutinib	[redacted]	11.31	8.25	[redacted]	1.84	1.51	[redacted]
Error correction	Asciminib	[redacted]	11.37	8.29	[redacted]			
	Bosutinib	[redacted]	9.49	6.75	[redacted]	1.88	1.54	[redacted]
Error correction and half-cycle correction	Asciminib	[redacted]	11.34	8.27	[redacted]			
	Bosutinib	[redacted]	9.46	6.72	[redacted]	1.88	1.55	[redacted]
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	10.48	7.79	[redacted]			
	Bosutinib	[redacted]	8.72	6.30	[redacted]	1.76	1.49	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 86: Base-case results pairwise – asciminib vs ponatinib (list price of all treatments)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	10.14	7.27				
	Ponatinib	[redacted]	9.42	6.71	[redacted]	-0.95	-0.56	[redacted]
Error correction	Asciminib	[redacted]	9.42	6.71				
	Ponatinib	[redacted]	10.14	7.27	[redacted]	-0.72	-0.56	[redacted]
Error correction and half-cycle correction	Asciminib	[redacted]	9.39	6.69				
	Ponatinib	[redacted]	10.11	7.25	[redacted]	-0.72	-0.56	[redacted]
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	8.62	6.25				
	Ponatinib	[redacted]	9.24	6.76	[redacted]	-0.62	-0.51	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 87: Base-case results pairwise – asciminib vs nilotinib (list prices of all treatments)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	8.84	6.18				
	Nilotinib	[redacted]	9.90	7.11	[redacted]	1.06	0.93	[redacted]
Error correction	Asciminib	[redacted]	9.90	7.11				
	Nilotinib	[redacted]	8.84	6.18	[redacted]	1.06	0.93	[redacted]
Error correction and half-cycle correction	Asciminib	[redacted]	9.87	7.09				
	Nilotinib	[redacted]	8.81	6.15	[redacted]	1.06	0.93	[redacted]
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	9.03	6.61				
	Nilotinib	[redacted]	8.13	5.76	[redacted]	0.90	0.85	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 88: Base-case results pairwise – asciminib vs dasatinib (list price of all treatments)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	9.04	6.40				
	Dasatinib	[redacted]	9.80	7.03	[redacted]	0.76	0.63	[redacted]
Error correction	Asciminib	[redacted]	9.80	7.03				
	Dasatinib	[redacted]	9.04	6.40	[redacted]	0.76	0.63	[redacted]
Error correction and half-cycle correction	Asciminib	[redacted]	9.77	7.01				
	Dasatinib	[redacted]	9.01	6.38	[redacted]	0.76	0.63	[redacted]
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	8.94	6.54				
	Dasatinib	[redacted]	8.30	5.97	[redacted]	0.65	0.57	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Asciminib versus comparators (PAS price)

Table 89: Base-case results pairwise – asciminib vs bosutinib (PAS price of asciminib)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	9.47	6.74				
	Bosutinib	[redacted]	11.31	8.25	4,824	1.84	1.51	3,192
Error correction	Asciminib	[redacted]	11.37	8.29				
	Bosutinib	[redacted]	9.49	6.75	6,450	1.88	1.54	4,175
Error correction and half-cycle correction	Asciminib	[redacted]	11.34	8.27				
	Bosutinib	[redacted]	9.46	6.72	7,070	1.88	1.55	4,569
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	10.48	7.79				
	Bosutinib	[redacted]	8.72	6.30	3,959	1.76	1.49	2,654

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 90: Base-case results pairwise – asciminib vs ponatinib (PAS price of asciminib)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	10.14	7.27				
	Ponatinib	[redacted]	9.42	6.71	-141,299	-0.95	-0.56	253,193
Error correction	Asciminib	[redacted]	9.42	6.71				
	Ponatinib	[redacted]	10.14	7.27	-141,299	-0.72	-0.56	253,191
Error correction and half-cycle correction	Asciminib	[redacted]	9.39	6.69				
	Ponatinib	[redacted]	10.11	7.25	-139,963	-0.72	-0.56	250,341
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	8.62	6.25				
	Ponatinib	[redacted]	9.24	6.76	-138,189	-0.62	-0.51	271,410

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 91: Base-case results pairwise – asciminib vs nilotinib (PAS price – for asciminib and nilotinib)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	8.84	6.18				
	Nilotinib	[redacted]	9.90	7.11	46,081	1.06	0.93	49,584
Error correction	Asciminib	[redacted]	9.90	7.11				
	Nilotinib	[redacted]	8.84	6.18	46,082	1.06	0.93	49,584
Error correction and half-cycle correction	Asciminib	[redacted]	9.87	7.09				
	Nilotinib	[redacted]	8.81	6.15	45,203	1.06	0.93	48,561
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	9.03	6.61				
	Nilotinib	[redacted]	8.13	5.76	42,559	0.90	0.85	50,167

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 92: Base-case results pairwise – asciminib vs dasatinib (PAS price of asciminib)

Result versions	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Submitted base-case	Asciminib	[redacted]	9.04	6.40				
	Dasatinib	[redacted]	9.80	7.03	1,995	0.76	0.63	3,180
Error correction	Asciminib	[redacted]	9.80	7.03				
	Dasatinib	[redacted]	9.04	6.40	1,995	0.76	0.63	3,180
Error correction and half-cycle correction	Asciminib	[redacted]	9.77	7.01				
	Dasatinib	[redacted]	9.01	6.38	2,262	0.76	0.63	3,598
Error correction, half cycle correction and reduced SCT probability with age (REVISED BASE-CASE)	Asciminib	[redacted]	8.94	6.54				
	Dasatinib	[redacted]	8.30	5.97	331	0.65	0.57	582

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Chronic Myeloid Leukaemia Support Group (CMLSg)
3. Job title or position	Trustee and CML Patient
4a. Brief description of the organisation (including who funds it). How many members does it have?	The CMLSg is the only UK registered charity (Reg No 1114037) with a sole focus on Chronic Myeloid Leukaemia (CML). It is patient lead with all of its Trustees being CML patients. Because of the rarity of CML, CMLSg operates primarily, but not exclusively, online. Our objective is to offer support, information and advocacy to patients and those that care for them so that they can, after treatment, resume a life as close as possible to that lived before diagnosis. Our website analytics currently shows the average number of visits to the website over the period 2019-2021 to be around 150,000 per annum. It should of course be remembered that the website's reach is global. Our annual accounts, audited when required, are available via the Charity Commission website.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Directly from patients involved in our support group as well as from the available published data from clinical studies.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CML patients understand their condition to be a rare cancer, and one that is not well understood by the public, whose perception of leukaemia does not discriminate between types. Public perception is highly negative, and associates CML, as a leukaemia, with much shortened lifespan following diagnosis. Indeed, this is usually the initial perception that patients have of CML at diagnosis. At that point, patients experience the fear and concern associated with a cancer diagnosis, and in particular a leukaemia diagnosis. This has a substantial negative effect. After their initial fears subside, patients come to understand that treatment has been revolutionised by TKIs. A disease which only 20 years ago was life threatening and largely fatal can now, for most patients,

	be successfully managed with TKI therapy. Once an appropriate and functioning TKI therapy is found for a given patient, that individual is able to live a normal, productive and fulfilling life. Whatever treatment route they follow, patients' focus is on achieving three things: 1. Survival – avoiding disease progression, which is associated with a poor prognosis 2. Avoiding the necessity to consider a stem cell transplant with all its risks 3. Therapy with as few side effects as possible (and/or which are easily managed), in order that patients can return their lives to as close to normality as possible A significant majority of patients respond well to imatinib. Side effects, of which there are several, tend to be relatively minor for the majority, and/or can be relatively easily managed. Other patients may have significant or impossible to manage side effects, making them intolerant of imatinib. A further group of patients may not respond to imatinib at all or sufficiently well, or may lose response, thereby being "resistant" to it. For these patients, treatment with other TKIs is an option, in particular 2nd generation TKIs such as dasatinib, nilotinib and bosutinib. As with imatinib, each of these can have side effects of varying degrees of significance and seriousness. Patients who do not respond to dasatinib or nilotinib, or experience significant side effects (or indeed are considered to be at risk of serious side effects from these), can be treated with further TKIs, bosutinib and ponatinib. Again these have side effects and risks; they are generally more easily manageable in the case of bosutinib. Patients very quickly understand that stem cell transplants, which can potentially be curative, are (a) only possible for a minority of patients and (b) highly risky, with a very significant risk of mortality and/or long term issues with graft versus host disease. A stem cell transplant is viewed by patients as an option of absolute last resort. As will be apparent, the number of patients who need to go on second, third and subsequent TKI therapies decreases towards a small minority. However, while small in number, this minority of patients has the greatest clinical need since their experience of post diagnosis treatment is not just one of failure but of successive failure. These patients are well aware, from their visits to specialist clinics (which is where they will be seen once they have tried multiple TKIs), of their increasingly compromised clinical situation. They are also acutely aware of the contrast between their own situation and that of the majority

	of CML patients, who will have secured an optimal response to treatment with one or other of the existing TKIs. As such, this group of patients views itself as a minority within a minority, since CML is a minority (rare) disease. Feelings of panic, fear, anxiety and stress dominate their emotional life, with the same applying for those who care for them.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers welcome the availability of highly effective treatments for their condition. They also recognise and appreciate the quality of clinical care, especially in specialist centres (which is where patients on third line treatment – if not before – are generally seen). Having several treatment options, especially for patients with difficult to treat disease or who may be intolerant to one or more TKIs, is hugely reassuring. With several TKIs available to patients, an increasing proportion has been able to return to normal life without the fear of disease progression or the need to consider a stem cell transplant. Most are able to be treated with a TKI which is both effective and, crucial for what can be life-long therapy, has either minimal or manageable side effects. However, as indicated above, there remains a significant minority of patients for whom more options are needed and accordingly, further TKIs which provide effective and tolerable therapy for those patients are enthusiastically welcomed. In summary, patients view existing therapies broadly as follows: 1. Imatinib: effective for and tolerated by most patients; however, a significant minority will become intolerant of or resistant to it, requiring a second line TKI. 2. Nilotinib: effective for many patients but for some, there is a risk of serious irreversible cardio vascular side effects. 3. Dasatinib: effective for many patients but associated with side effects such as pleural effusion 4. Bosutinib: potential third line treatment; associated with diarrhoea as a side effect although this can be managed in most patients. 5. Ponatinib: regarded as a life line for patients with the rare T315i mutation and an effective option for third line treatment; associated with potentially serious cardio vascular side effects in some patients although at lower doses this risk might be reduced.

	6. Stem cell transplant: option of last resort; associated with limited availability of suitable HLA matched donors and significant risks of mortality or morbidity.
8. Is there an unmet need for patients with this condition?	As indicated above, there is a minority of patients for whom all existing TKIs prove to be either ineffective or not tolerated. These patients are at serious risk of disease progression and a stem cell transplant is, if they are eligible and can identify a suitable well matched donor, the only option.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Asciminb has a novel mode of action which makes it quite different from a patient's perspective: it provides the potential for a TKI which has a mode of action which will work for them when existing TKIs do not. For patients who have disease which has proven hard to treat with existing TKIs, this is a very welcome addition to their options, which may have been exhausted or all but exhausted.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	If administration were to be twice daily (with fasting), experience with nilotinib has presented compliance issues for some patients. However, for the group of patients who have few therapeutic options, such a dosing regimen is unlikely to be viewed as a disadvantage.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	A substantial sub-population of patients with the T315i mutation (approximately 20% of those with mutations) are resistant to all currently available TKIs except ponatinib. Vascular adverse events associated with pontatinib are of concern and an alternative treatment option would be welcome. Approximately 25% of patients experience unacceptable side effects from initial TKI therapy and those receiving 2nd and 3rd generation TKIs are at risk of vascular and pulmonary adverse events. It is our understanding from the conclusions of published results of phase I and II/III studies that asciminib works well against mutations (including T315i) because it inhibits BCR/ABL by binding to a different domain than all other available TKIs. According to studies there seems to be an improvement in tolerability of asciminib compared to other TKIs. For those patients who do not respond to one or other of the 2nd generation TKIs there is a reduction in options for successful control of their disease. Asciminib may be of help to these sub-sets of the patient population, in both chronic and accelerated phases.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	For the subset of patients who remain resistant to, or intolerant of, currently available TKIs the risk of disease progression to blast phase is high. A small number of such patients may be eligible a for stem cell transplant, should they be fit enough to withstand the risks of this procedure and have an identified a well matched donor. However, for those who are not eligible, longer term survival remains doubtful. The development of asciminib presents a credible alternative for this group with an increased chance of achieving/maintaining major cytogenic responses and progression free survival.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Clinical priorities. The clinical priorities for patients are: survival/to avoid disease progression; to avoid the need to consider a stem cell transplant with its associated very substantial risks (even if available to a patient); and to find a TKI therapy which is both effective and, crucially for what could be life-long therapy, well tolerated.
- Patient population. The patient population for whom asciminb will be an option comprises a minority of what is already a very small patient population. This minority is acutely aware both of their compromised clinical situation and the contrast with the position that other CML patients are in. This minority have a greatly heightened sense of concern at their position.
- Innovation. Asciminb, with a novel mode of action, presents the possibility of a new and effective TKI therapy for patients for whom existing TKIs are either ineffective, or not sufficiently effective, or to which they are intolerant.
- Enabling personalised medicine. Multiple TKI options are greatly welcomed by patients. They have revolutionised the outlook for CML patients, allowing a large majority to avoid disease progression and the risks of stem cell transplants. In addition and importantly, they provide patients and clinicians with options that enable patients, with side effect management where necessary, to return their lives to what is, essentially, normality.
- Quality of Life. Asciminb, as another daily, self-administered, oral, home based TKI treatment allows the possibility for patients to live well, with a normal lifespan and, eventually, with only sporadic engagement with the health care profession.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	• **Incyte:** £30,000 core funding • **Novartis:** £1,887.95 (£292.95 ASH video and £1,595 honorarium) • **Pfizer:** £10,000 support services

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was gathered through Leukaemia Care's patient survey, 'Living with Leukaemia' (2017), which included responses from 374 CML patients. Data and quotes were also gathered from a recent survey, conducted for the purpose of this submission, on patients' opinions on treatment options in CML and asciminib. The survey had 63 respondents. Additional information was gathered by analysing patient stories, one-to-one discussions with patients, including those who had experience of asciminib and from our patient panellists.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**<u>Patient experience</u>** There are 830 new cases of chronic myeloid leukaemia (CML) in the UK every year, which is more than 2 every day. CML incidence rates are highest in older people, each year nearly a quarter (23%) of all new CML cases are in people aged 75 and over. There are around 230 CML deaths in the UK every year. A diagnosis of CML impacts a patient's life in many ways. Physically patients often experience many symptoms and side-effects of treatment, e.g., fatigue, which alter their ability to lead the same life as before their diagnosis. According to our living with leukaemia survey 24% of CML patients experience pain regularly and 8% experience pain constantly. One patient told us *"I have constant bone pain, muscle*

	cramps and fatigue and still need extra treatment for chronic migraines. Another patient said "*the day-to-day reality of living with leukaemia can be tough. I have learned to listen to my body. I know what I can and can't do... sometimes I get it wrong, and I can end up totally exhausted/sick. I have had to learn to live with continuous aches and pains.... I can go through periods of exhaustion for weeks, where I just have to take things easy. Sometimes the muscle pain can be quite severe".* Living with CML can be debilitating, which leads to reduced quality of life for many patients. One aspect of life affected by a CML diagnosis is work. The patient from the first of quotes above mentioned that due to the side effects they experience, they are *"still unable to work".* In our survey 33% of CML patients who were in work or education said they had to stop altogether after their diagnosis, and 27% said they had to reduce their hours. Therefore, the majority of CML patients surveyed (60%) experienced a negative impact on their ability to work following a diagnosis, which also has a negative financial impact on patients and their families. Additionally, when we asked CML patients about the long-term impact their diagnosis had on their ability to work, the majority (56%) said the impact on their work or education was permanent, and 25% were currently unsure. From diagnosis itself to the financial strain and worry that comes from not being able to work to missing out on family time due to physical symptoms, the psychological impact of living with CML is notable. In our living with leukaemia survey, 43% of CML patients said they have felt depressed or anxious more often since their diagnosis, and 4% said they feel constantly depressed or anxious since their diagnosis. With regards to treatment, we know that not all TKI's work for every patient, as some will not respond optimally or become intolerant to the treatment. There is additional stress and worry of treatment failing and patients can always be wondering about what treatment will be next. Furthermore, whilst treatable, CML is incurable and to know this is something patients will have to struggle with for their whole life. Those with CML also have an increased risk of infection. Accordingly, they must be careful not to be in crowded spaces where the risk of infection is increased and to limit activities which could cause cuts and scratches. One patient says, *"my capability to heal from everyday cuts and scratches has been impacted...It takes weeks/months for a simple scratch to heal".*

	Some of those with CML, such as those whose disease is less well controlled, are at higher risk of severe illness should they contract COVID-19. Many have had to continue to shield or take extra precautions. Even now as restrictions have lifted, patients often tell us they do not feel safe mixing with others. But this is isolating and further impacts patient's mental health, especially the longer it goes on. We've heard directly from patients who feel forgotten about. **<u>Carer's experience</u>** A CML diagnosis can have a ripple effect on family members and friends of the patient. At our most recent patient advisory panel meeting CML patients mentioned how they are unaware of where family can go to receive support. In addition, one patient described the challenging impacts their diagnosis has on their family from their secondary stress and worry to missing out on family activities. *"My CML diagnosis has negatively impacted my wife and family in a couple of ways. The first and most significant, is the stress and worry they experience while watching me suffer the side effects from my treatment. This stress is subtle but builds up over time and while I can stay positive and upbeat, they don't have that luxury. The second, is that I can't always join them on family outings or if I do, I restrict what we can do based on how I feel".*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	During our most recent survey on treatment options in CML, when asked if they think CML treatments are sufficient, 66.7% of CML patients responded either no or not sure. While some patients might find a TKI drug that works well for them for a period of time, not all TKI's will work for all patients, so some patients could run out of treatment options if multiple TKIs fail to give them an optimal response and/or they are not able to tolerate the side effects. Many CML patients we spoke to in our survey have tried at least 2 TKI treatments, with some having taken 4 or 5. Some patients have even had to go back onto previous TKIs they were intolerant to as the side-effects were comparatively better than other TKIs, but they are still impactful enough to affect the patients' quality of life negatively, e.g., they are unable to work. This suggests there is not always a TKI for everyone at present and

	indicates this patient might have essentially run out of treatment options that strike the balance between being tolerable and effective. Patients also often report the various and sometimes severe side effects of the different treatments available. In our most recent survey one patient mentioned "*I've always changed [treatments] due to not being able to cope with side effects"*. One patient described the side-effects they experienced as including *"potential blood clots, severe gastric side effects, high bone pain levels, severe exhaustion, loss of hair, eye bleeds"*. Other symptoms patients told us about include pleural effusions, pulmonary hypertension, fatigue, nausea and reduced kidney function. Some patients even reported allergic reactions to some of the available drugs. Patients tell us this all understandably has a strong negative impact on their quality of life.
8. Is there an unmet need for patients with this condition?	As previously mentioned, different TKIs work for different people and for some people, who have already experienced intolerance and/or sub-optimal responses to 4 or 5 TKIs, they no longer have hope that they can find a treatment that works or doesn't have a significant negative impact on their day-to-day life, their physical and mental health, and their quality of life. As a result, there is a strong unmet need in this population. For some patients who experience side effects on particular drugs, they can only tolerate them for just a few days before needing another option. *"I get very sick going onto the medications and struggle to tolerate for the first few weeks. Dasatinib I keep mostly well but do get regular infections that put me in hospital. Imatinib did what it needed to but gave me a poor quality of life. Bousatinib gave me extreme sickness and diarrhoea and* ***I only managed a few days****."* This highlights how common it is for patients to struggle with the TKIs available and how quickly some options can be ruled out, reducing the total amount of options available and diminishing hope for patients. Furthermore, for the patient who has tried all TKI's and is still unable to work whilst on the TKI with the least side-effects comparatively due to intolerance, more treatment options need to be provided. The more options there are for treatment, the more likely patients are to find at least one drug which strikes the balance between effectiveness and being manageable i.e., having few and/or minor side effects.

	Adherence to treatments for chronic conditions is a common issue and this applies to CML, with estimates of 1/3 of patients not adhering to their treatment schedule. This is unsurprising, given the impact of side effects on patients, yet non-adherence brings costs to the patient, in terms of efficacy of treatment, as well as costs to the healthcare system. Jabbour et al. (2012) emphasised the need for individualised treatments as a result, meaning there is a need for a wider range of treatments to enable this. Finally, when we asked about patient's unmet needs in the CML setting in our survey for this question, several patients mentioned the lack of a cure. CML is treatable but not yet curable and for as long as we are unable to provide patients with a cure, we at least need to offer as many different treatment options as possible with the aim to further prolong and improve the quality of life for CML patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Asciminib is very effective for some patients. Several patients told us asciminib helped them to achieve MMR (major molecular response) very quickly. One said *"abl001 boosted my response to mmr 4.5 in 12 weeks"* and another said, *"I had a great response to asciminib and achieved MMR very quickly".* Achieving an MMR predicts a CML-specific survival close to 100% as disease progression is uncommon once this has been achieved (Hochhaus A, Baccarani M, Silver RT, et al., 2020). The asciminib drug technology works differently to all other comparators. All other TKIs bind at the ATP binding site, whereas asciminib binds to the myristoyl binding site. This mechanism is therefore innovative to the CML treatment setting and consequently has great potential to give patients who perhaps haven't responded well or tolerated other TKIs more options. When analysed alongside the comparator bosutinib in the ASCEMBL trial, asciminib was shown to have fewer grade 3 adverse side effects that could lead to treatment discontinuation. In addition, asciminib produced more MMR responses than bosutinib. This new mode of action means asciminib is a very specific BCR-ABL inhibitor and shows real potential to improve treatment in this setting. One patient who had taken asciminib describes how this positively impacted her experience of treatment: *"Happy that since 2019 got some improvements to Renal (kidney damage), more tolerable side effects. Better impact on my Lipid and Diabetic unlike Nilotinib and less skin allergies".*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with any other TKIs in this setting, the potential side effects are a disadvantage. From the patients who have had asciminib that we spoke to, they describe side effects as including gout, exhaustion, muscle aches and pains, weight gain, cramps, inflammatory arthritis and anxiety. When referring to the side effects of asciminib one patient said, *"initially the side effects were the same as with Imatinib, but as time has gone on, I have had more severe and new ones"*. Due to this they went on to say that *"although I am extremely thankful to it [asciminib] for getting me to MMR, I am now getting a little tired of it all"*. However, patients told us in our most recent survey that their top 2 priorities for CML patients of a treatment are that it improves/lengthens survival and brings about a remission/response. Tolerable side effects ranked 4 out of 7. As a result, for patients the disadvantages of asciminib (side effects) do not outweigh the advantages (effective at bringing about MMR and prolonging life).
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who have not responded optimally and/or are intolerant to other TKIs could all benefit from asciminib.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/a
Other issues	
13. Are there any other issues that you would like the committee to consider?	N/a
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- CML is mentally and physically difficult to live with and can greatly affect the quality of life of CML patients and those in their support network.
- Patients report the many and sometimes severe side effects from existing TKIs, meaning they can sometimes go through 4 or 5 TKIs and have run out of options that strike the balance between effectiveness and being tolerable.

- Asciminib targets a different binding site than all other TKIs. This new technology is innovative and has the potential to work in those for whom the other TKIs have given a sub-optimal response.
- Asciminib also has fewer grade 3 side effects than comparator bosutinib, according to the ASCEMBL trial.
- As other TKIs can have sub-optimal effectiveness for some people, side effects are common, and there is currently no cure for CML, we at least need to be able to offer as many treatment options as possible to prolong the lives of patients.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**RCPath (Royal College of Pathologists)** **BSH (British Society of Haematology)**
3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**We are a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	**No**

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aims of treatment of CML are to stop progression to a more aggressive acute phase of leukaemia and to control chronic myeloid leukaemia, such that patients have normal life expectancy with very low or absent levels of disease detectable. After initially preventing progression, therapy should allow for maintenance of quality of life (QoL). Subsequently deep molecular responses can be gained to ensure no loss of response, and finally allow for a more tolerable potential for treatment free remission (TFR), but this option is only available for intolerant (and not resistant) patients.
7. What do you consider a clinically significant treatment response? (For example, a	Our experts would consider a clinically significant treatment response (at a minimum) to be achievement of complete cytogenetic response (CCyR) by one year on therapy. This means that on bone marrow

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	cytogenetics 0/20 cells assessed carry the Philadelphia chromosome. Achievement of CCyR in CML has been associated with better survival outcomes. Achievement of a major molecular response (MMR) is termed an optimal response, as per the recommendations and definition of several guidelines (British Society of Haematology [BSH] 2020; European LeukaemiaNet [ELN] 2020. MMR is a standardised low number of BCR-ABL transcripts defined as < 0.1% on the International Scale (IS). This is thought to be a 'safe haven' where the chance of progression and loss of response is extremely low. The next goal is to also induce deep molecular response (DMR) defined as <0.01% , which if sustained would allow patients to stop therapy. This would not be appropriate in any patient with resistance, but in patients who are intolerant to therapy, who are finally treated with a tolerable TKI, this is a definite possibility.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, we have five tyrosine kinase inhibitors (TKIs) currently available to treat chronic myeloid leukaemia. They are all inhibitors of the ATP binding site of BCR-ABL, and hence patients on these drugs are at risk of resistance from the same mutations or compound mutations. Asciminib is allosteric inhibitor of BCR-ABL, termed a STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor so binds to a different part of the BCR-ABL molecule. Therefore, the resistance profile is different. In addition, the toxicity profile for asciminib is different to other BCR-ABL TKIs and may be favourable in terms of cardiovascular toxicity (compared to nilotinib and ponatinib) or pleural effusion (compared to dasatinib). Many patients have already cycled through the five approved TKIs, but have failed treated, either through resistance or intolerance. Therefore, there is a need for an alternative, well tolerated therapy. In further detail: **resistance to previous treatment**- patients can be resistant with or without a BCR-ABL kinase domain mutation (KDM). Asciminib bypasses KDM including the T315I mutation to which only ponatinib is effective. Ponatinib, a third-generation agent is significantly associated with arterial occlusive events (AOE), mainly heart attack, stroke, and peripheral arterial disease, which can occur up to 30% of patients. Asciminib does not have this specific side-effect of cardio-vascular (CV) adverse events (AE), so it will be of tremendous benefit to patients. It will also by-pass all other KDM to which the other second-generation (2G)TKI may or may not be sensitive to (nilotinib, dasatinib and bosutinib) . The CML specialist opinion is that 2G-TKI all have equivalent efficacy, although no head- to -head trials between the 2G-TKIs have been undertaken. Asciminib has shown greater potency and tolerability in a clinical trial against bosutinib (ASCEMBL trial) in the > second line treatment setting. This offers a fantastic opportunity for patients who are resistant to 2 previous TKIs. Next: **tolerability;** patients QoL on asciminib has been

	remarkably improved. Patients have managed to come off supportive care treatments required for other 2G-TKIs such as Erythropoietin and G-SCF support (given sub-cutaneously) for anaemia and neutropenia. In particular, overwhelming fatigue on other TKIs does not seem to be present, with negligible cardio-pulmonary toxicity on asciminib. The unmet need continues to be a tolerable potent agent against CML, and asciminib appears to fulfil these requirements.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	It is expected that asciminib would be used in third on later lines of therapy for CML patients with resistance or intolerance to existing TKIs. Currently, in the third line setting patients would receive one of the existing approved TKIs (imatinib, nilotinib, dasatinib, bosutinib, ponatinib). The choice dependent on prior toxicities, known BCR-ABL kinase domain mutations, and previous sequence of TKIs. Chronic myeloid leukaemia is currently treated with tyrosine kinase inhibitors (TKIs) in the NHS. Until April 2012 Imatinib was the only 1st line NICE approved drug available, but Nilotinib, a 2G-TKI, was also approved by NICE for 1st line use in April 2012. Since then, first line dasatinib, a 2G-TKI with an alternative side-effect profile has also been approved. The 2G-TKIs are more effective in inducing more rapid and deep responses, but also are less well tolerated. Approximately 75- 80% of patients respond satisfactorily to Imatinib /Nilotinib/Dasatinib 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 10 years of first line imatinib therapy, only around 50% of patients remain on imatinib for the reasons mentioned. Side effects on dasatinib include irreversible Pulmonary arterial hypertension, and pleural effusions, for which the biggest risk is age > 60 years. Side-effects on nilotinib include diabetes and AOE as mentioned before. Patients who are refractory or intolerant of their 1st line treatment (imatinib, nilotinib or dasatinib) are eligible to receive bosutinib (for imatinib failure, if nilotinib or dasatinib are not indicated), and alternative 2G-TKI,

	where the other TKIs are not indicated. Side-effects on bosutinib include an increase in liver function tests, and diarrhoea. Following failure of imatinib for resistance, the chance of any 2G-TKI inducing a complete cytogenetic response (CCyR) is 50%. After failure of a second line 2G-TKI in this setting for resistance, the chance of any alternative 2G-TKI inducing a CCyR is 10-30%. The chance of ponatinib working in this setting third line is more than 50%. The choice of TKI >second line for resistance is guided by a KDM, patients' base-line co-morbidities and the side-effect profile of the individual TKI. Ponatinib is the only TKI available for the t315I KDM, but the occurrence of this mutation is very low (5%). The majority of resistant patients do not have a KDM and resistance mechanisms are bcr-abl independent. In more detail, other TKIs have a spectrum of mutations that they cover – imatinib and nilotinib usually share activity, dasatinib is resistant to F317L for e.g. and bosutinib to V299L for e.g. Only ponatinib covers the T315I mutation thus farm the other TKIs are resistant to the T315I mutation. The choice of next TKI for resistance depends on the sensitivity of the KD mutation – asciminib covers all KD mutations, including T315I due to its mode of action. Finally, TFR is the next goal of chronic myeloid leukaemia therapy and is tyrosine kinase inhibitor (TKI) independent; patient suffer from withdrawal syndrome in 30% of cases, and it is very unlikely that this will occur on asciminib, due to asciminib's mode of action, with no common off - target activity.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, within the UK, we follow the European LeukemiaNet and British Society for Haematology Guidelines. Most Health Boards have developed their own clinical management guideline based on these national and international guidelines. ELN Guideline: Hochhaus et al, Leukemia 2020;34:966-84. BSH Guideline: Smith et al, British Journal of Haematology 2020;191:171-93.
• Is the pathway of care well defined? Does it vary or are there differences of opinion	The pathway of care is well defined, but once patients reach the third line setting for TKI, there may be differences in opinion between clinicians as to which is the most appropriate TKI for an individual patient.

between professionals across the NHS? (Please state if your experience is from outside England.)	For some patients, allogeneic stem cell transplantation may also be considered an appropriate treatment, especially if patients have already demonstrated resistance to 2 or more second generation TKIs.
• What impact would the technology have on the current pathway of care?	A recent clinical trial ASCEMBL (Cortes et al, Blood 2021; Aug18:blood2020009984), has recently demonstrated the superiority of asciminib to bosutinib in the third line setting. Therefore, if approved, it is likely that asciminib would be used quite extensively in the third line setting for treatment of CML. It is also likely to be used in later lines of therapy. Asciminib wouldn't change the care pathway but would be available as an alternative in the third-line setting.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, asciminib would be integrated into the existing care pathway for CML. It has already been used in a few patients, either as part of the ASCEMBL clinical trial, or in the Novartis asciminib compassionate use programme, where patients with chronic phase CML could access asciminib if they had failed all available, approved TKIs. Asciminib would be used in the exact same way as any other TKI. It is predicted that patients will require a) less input from primary care to manage CV risk factors b) have less concomitant medication to manage CV risk (aspirin, statins, anti-hypertensives) c) have further investigations such Doppler US scan, echocardiography d) attend haematology out-patients far less often as they will not require as much intervention for management of other TKI toxicity, as asciminib is very well tolerated.
• How does healthcare resource use differ between the technology and current care?	The only difference will be the cost of asciminib as compared to existing, approved TKIs. The costs of monitoring and staff resources will be the same.
• In what clinical setting should the technology be used? (For example,	Asciminib should be used in secondary care – haematology clinics, and specialist myeloid clinics. It is not appropriate for use in primary care.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant investment. Space in pharmacy to store drug. Training of pharmacy staff in dispensing, and training of clinicians in prescribing, side effects, etc. The technology will be straightforward to use once it becomes available since it is a simple tablet medication, taken as an out-patient. There are no required concomitant medications or other clinical requirements. Any side-effects of therapy are similar to any other available TKI, however, it is likely that the AE profile is less, making it an easier treatment to use. Monitoring of treatment response is the same as for the other well established tyrosine kinase inhibitors.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Asciminib has shown superiority to bosutinib in the third line setting (Cortes et al, Blood 2021; Aug18:blood2020009984). Our experts would therefore anticipate these benefits seen in the ASCEMBL clinical trial would translate into improved responses and better quality of life in the real world.
• Do you expect the technology to increase length of life more than current care?	Yes, although this question can only be answered with increased follow- up of patients. As stated before , patients survival is more affected than co-morbidities and in parallel toxicity of existing TKI therapy. As asciminib does not seem to aggravate co-morbidities, and appears well tolerated in patents with CV and renal disease, it will allow for less treatment interruption leading to increased remission, and less adverse event which would invariably affect the length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. The side effect profile of asciminib is better than some of the existing TKIs. It does not seem to have the risk of arterial thrombotic events associated with ponatinib and nilotinib, the side effect of diarrhoea seen with most patients starting bosutinib, or the risk of developing a pleural effusion seen with patients on dasatinib (Smith et al, British Journal of Haematology 2020;191:171-93). Overall, it has a favourable safety profile, which may improve HR-QoL for patients experiencing toxicities as compared to existing approved TKIs.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is limited data for the use of asciminib in patients with advanced phase CML (AP and BP). The drug may be less effective in these patients. A higher dose of asciminib may be required for patients with a T315I BCR-ABL kinase domain mutation. This needs to be assessed in ongoing clinical trials. In the main, once patients fail 2 or more TKIs, they are destined to stay on long-term TKI therapy. With age, co-morbidities increase, so asciminib will benefit the future of younger CML patients. Separately, 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 a potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an alternative TKI that would not manifest itself on asciminib would benefit considerably with regards to future morbidity and medical intervention. Other TKIs have a spectrum of mutations that they cover – imatinib and nilotinib usually share activity, dasatinib is resistant to F317L for e.g. and bosutinib to V299L for e.g. Only ponatinib covers the T315I mutation thus far- the other TKIs are resistant to the T315I mutation. The choice of next TKI for resistance depends on the sensitivity of the KD mutation – asciminib covers all KD mutations, including T315I due to its mode of action, and tolerability. Our experts believe that no data exists for the use of asciminib in children.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Asciminib will be the same to use as existing approved TKIs in current care. There are no practical implications for use. It has a twice daily dosing strategy comparable to the approved TKI nilotinib. Monitoring would be the same as for existing approved TKIs.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The decision to start or stop therapy will be based on BCR-ABL RT-qPCR results. A patient considered to have TKI treatment failure according to ELN criteria would be considered for treatment with asciminib in the third or later line setting. The patient would be expected to achieve milestone improvements in BCR-ABL levels as dictated by the ELN 2020 guideline in order to continue on asciminib. In the ELN treatment guideline (Hochhaus et al, Leukemia 2020;34:966-84), in the third line setting, failure to achieve/maintain a BCR-ABL level of <1% would be considered treatment failure. Patients developing side effects which are considered intolerable would also stop treatment with asciminib and an alternative would be sought from existing TKIs, not previously used in the patient. There would be no additional testing for asciminib as compared to existing TKIs.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are	No

unlikely to be included in the quality-adjusted life year (QALY) calculation?	As previously mentioned however, the QoL of life in CML patients is likely to improve on asciminib, and due to tolerability a greater response is likely to be achieved, and allogeneic transplantation avoided.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Our experts believe that this is an important drug, which has demonstrated superiority in a randomised phase 3 clinical trial against an existing accepted third line therapy. The drug works in a slightly different way and appears to have a favourable safety profile compared to existing second and third generation TKIs currently used in this setting. As asciminib works in a different way to other TKIs, it is innovative – asciminib can overcome kinase domain mutations (KDM), and has less organ toxicity, which has been also detailed in response et the other questions this far. It is likely that there will be less surgical, neurological and cardiological intervention in comparison to ponatinib, the third generation TKI.
• Is the technology a 'step-change' in the management of the condition?	Potentially yes, as it is a 'first in class' drug.

• Does the use of the technology address any particular unmet need of the patient population?	Yes, it provides a new therapy for those patients that have failed all existing TKIs, either through resistance or intolerance. Thus, has the potential to improve survival and quality of life in these patients with poor prognosis CML. As mentioned earlier, the approval of this technology would allow more tolerable and effective treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an alternative TKI that would not manifest itself on asciminib would benefit considerably with regards to future morbidity and medical intervention.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Asciminib has a side effect profile like other TKIs. Most side effects are grade 1 and grade 2, manageable with dose reductions or interruptions to improve side effects and quality of life. The commonest grade 3/4 adverse event with asciminib in the ASCEMBL clinical trial was thrombocytopenia, leading to discontinuation in 3.2% of patients. Overall, 5.8% of patients discontinued asciminib in the ASCEMBL trial for a side effect; this compares with 21.1% in the bosutinib arm; a currently approved 3rd line therapy. Arteriothrombotic events (ATEs) occurred in 3.2% of patients receiving asciminib and 1.3% of patients receiving bosutinib. While not significant, it will be important to continue to monitor for and report ATEs in patients on asciminib as for other TKIs.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Asciminib is also FDA approved in this setting.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are safety and demonstration of efficacy by assessment of BCR-ABL by RT-qPCR for BCR-ABL. These were both measured in the ASCEMBL clinical trial (Cortes et al, Blood 2021; Aug18:blood2020009984).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA 451?	TA-451 is for ponatinib. Since this was published in 2017, there has been a further update of the Phase 2 PACE clinical trial. The reference is Cortes et al, Blood 2018;132:393-404.
21. How do data on real-world experience compare with the trial data?	Our experts believe that for TKIs they are broadly similar, although the real-world data tends to have an older patient population, and proportions of patients achieving molecular endpoints such as major molecular remission (MMR) tend to be slightly lower in real-world data as compared to clinical trials. The data is also confounded as trials of new TKIs tend to be run at large academic centres, whereas in the real world both academic centres and district general hospitals manage patients on TKIs, bringing in another level of bias.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. As mentioned earlier, the approval of this technology would allow more tolerable and effective treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an

	alternative TKI that would not manifest itself on asciminib would benefit considerably with regards to future morbidity and medical intervention.
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Asciminib has demonstrated superiority in a phase 3 clinical trial versus bosutinib in the third line setting for treatment of chronic phase CML
- Asciminib has a favourable safety profile compared with other available second and third generation TKIs
- The management and molecular monitoring of patients on asciminib is the same as for existing, approved TKIs
- Asciminib would offer a new and well-tolerated treatment approach for many patients failing existing TKIs or who were unsuitable for existing TKIs due to co-morbidities
- Asciminib works against Abl kinase domain mutations, including T315I, and will have a spectrum of efficacy over other TKIs.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-RCP-RCR-ACP**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-RCP-RCR-ACP**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aims of treatment of CML are to stop progression to a more aggressive acute phase of leukaemia and to control chronic myeloid leukaemia, such that patients have normal life expectancy with very low or absent levels of disease detectable. After initially preventing progression, therapy should allow for maintenance of quality of life (QoL). Subsequently deep molecular responses can be gained to ensure no loss of response, and finally allow for a more tolerable potential for treatment free remission (TFR), but this option is only available for intolerant (and not resistant) patients.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Our experts would consider a clinically significant treatment response (at a minimum) to be achievement of complete cytogenetic response (CCyR) by one year on therapy. This means that on bone marrow cytogenetics 0/20 cells assessed carry the Philadelphia chromosome. Achievement of CCyR in CML has been associated with better survival outcomes. Achievement of a major molecular response (MMR) is termed an optimal response, as per the recommendations and definition of several guidelines (British Society of Haematology [BSH] 2020; European LeukaemiaNet [ELN] 2020. MMR is a standardised low number of BCR-ABL transcripts defined

x cm, or a reduction in disease activity by a certain amount.)	as < 0.1% on the International Scale (IS). This is thought to be a 'safe haven' where the chance of progression and loss of response is extremely low. The next goal is to also induce deep molecular response (DMR) defined as <0.01% , which if sustained would allow patients to stop therapy. This would not be appropriate in any patient with resistance, but in patients who are intolerant to therapy, who are finally treated with a tolerable TKI, this is a definite possibility.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, we have five tyrosine kinase inhibitors (TKIs) currently available to treat chronic myeloid leukaemia. They are all inhibitors of the ATP binding site of BCR-ABL, and hence patients on these drugs are at risk of resistance from the same mutations or compound mutations. Asciminib is allosteric inhibitor of BCR-ABL, termed a STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor so binds to a different part of the BCR-ABL molecule. Therefore, the resistance profile is different. In addition, the toxicity profile for asciminib is different to other BCR-ABL TKIs and may be favourable in terms of cardiovascular toxicity (compared to nilotinib and ponatinib) or pleural effusion (compared to dasatinib). Many patients have already cycled through the five approved TKIs, but have failed treated, either through resistance or intolerance. Therefore, there is a need for an alternative, well tolerated therapy. In further detail: **resistance to previous treatment**- patients can be resistant with or without a BCR-ABL kinase domain mutation (KDM). Asciminib bypasses KDM including the T315I mutation to which only ponatinib is effective. Ponatinib, a third-generation agent is significantly associated with arterial occlusive events (AOE), mainly heart attack, stroke, and peripheral arterial disease, which can occur up to 30% of patients. Asciminib does not have this specific side-effect of cardio-vascular (CV) adverse events (AE), so it will be of tremendous benefit to patients. It will also by-pass all other KDM to which the other second-generation (2G)TKI may or may not be sensitive to (nilotinib, dasatinib and bosutinib) . The CML specialist opinion is that 2G-TKI all have equivalent efficacy, although no head- to -head trials between the 2G-TKIs have been undertaken. Asciminib has shown greater potency and tolerability in a clinical trial against bosutinib (ASCEMBL trial) in the > second line treatment setting. This offers a fantastic opportunity for patients who are resistant to 2 previous TKIs. Next: **tolerability;** patients QoL on asciminib has been remarkably improved. Patients have managed to come off supportive care treatments required for other 2G-TKIs such as Erythropoietin and G-SCF support (given sub-cutaneously) for anaemia and neutropenia. In particular, overwhelming fatigue on other TKIs does not seem to be present, with negligible cardio-pulmonary toxicity on asciminib. The unmet need continues to be a tolerable potent agent against CML, and asciminib appears to fulfil these requirements.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	It is expected that asciminib would be used in third on later lines of therapy for CML patients with resistance or intolerance to existing TKIs. Currently, in the third line setting patients would receive one of the existing approved TKIs (imatinib, nilotinib, dasatinib, bosutinib, ponatinib). The choice dependent on prior toxicities, known BCR-ABL kinase domain mutations, and previous sequence of TKIs. Chronic myeloid leukaemia is currently treated with tyrosine kinase inhibitors (TKIs) in the NHS. Until April 2012 Imatinib was the only 1st line NICE approved drug available, but Nilotinib, a 2G-TKI, was also approved by NICE for 1st line use in April 2012. Since then, first line dasatinib, a 2G-TKI with an alternative side-effect profile has also been approved. The 2G-TKIs are more effective in inducing more rapid and deep responses, but also are less well tolerated. Approximately 75- 80% of patients respond satisfactorily to Imatinib /Nilotinib/Dasatinib 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 10 years of first line imatinib therapy, only around 50% of patients remain on imatinib for the reasons mentioned. Side effects on dasatinib include irreversible Pulmonary arterial hypertension, and pleural effusions, for which the biggest risk is age > 60 years. Side-effects on nilotinib include diabetes and AOE as mentioned before. Patients who are refractory or intolerant of their 1st line treatment (imatinib, nilotinib or dasatinib) are eligible to receive bosutinib (for imatinib failure, if nilotinib or dasatinib are not indicated), and alternative 2G-TKI, where the other TKIs are not indicated. Side-effects on bosutinib include an increase in liver function tests, and diarrhoea. Following failure of imatinib for resistance, the chance of any 2G-TKI inducing a complete cytogenetic response (CCyR) is 50%. After failure of a second line 2G-TKI in this setting for resistance, the chance of

	any alternative 2G-TKI inducing a CCyR is 10-30%. The chance of ponatinib working in this setting third line is more than 50%. The choice of TKI >second line for resistance is guided by a KDM, patients' base-line co-morbidities and the side-effect profile of the individual TKI. Ponatinib is the only TKI available for the t315I KDM, but the occurrence of this mutation is very low (5%). The majority of resistant patients do not have a KDM and resistance mechanisms are bcr-abl independent. In more detail, other TKIs have a spectrum of mutations that they cover – imatinib and nilotinib usually share activity, dasatinib is resistant to F317L for e.g. and bosutinib to V299L for e.g. Only ponatinib covers the T315I mutation thus farm the other TKIs are resistant to the T315I mutation. The choice of next TKI for resistance depends on the sensitivity of the KD mutation – asciminib covers all KD mutations, including T315I due to its mode of action. Finally, TFR is the next goal of chronic myeloid leukaemia therapy and is tyrosine kinase inhibitor (TKI) independent; patient suffer from withdrawal syndrome in 30% of cases, and it is very unlikely that this will occur on asciminib, due to asciminib's mode of action, with no common off - target activity.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, within the UK, we follow the European LeukemiaNet and British Society for Haematology Guidelines. Most Health Boards have developed their own clinical management guideline based on these national and international guidelines. ELN Guideline: Hochhaus et al, Leukemia 2020;34:966-84. BSH Guideline: Smith et al, British Journal of Haematology 2020;191:171-93.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined, but once patients reach the third line setting for TKI, there may be differences in opinion between clinicians as to which is the most appropriate TKI for an individual patient. For some patients, allogeneic stem cell transplantation may also be considered an appropriate treatment, especially if patients have already demonstrated resistance to 2 or more second generation TKIs.

• What impact would the technology have on the current pathway of care?	A recent clinical trial ASCEMBL (Cortes et al, Blood 2021; Aug18:blood2020009984), has recently demonstrated the superiority of asciminib to bosutinib in the third line setting. Therefore, if approved, it is likely that asciminib would be used quite extensively in the third line setting for treatment of CML. It is also likely to be used in later lines of therapy. Asciminib wouldn't change the care pathway but would be available as an alternative in the third-line setting.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, asciminib would be integrated into the existing care pathway for CML. It has already been used in a few patients, either as part of the ASCEMBL clinical trial, or in the Novartis asciminib compassionate use programme, where patients with chronic phase CML could access asciminib if they had failed all available, approved TKIs. Asciminib would be used in the exact same way as any other TKI. It is predicted that patients will require a) less input from primary care to manage CV risk factors b) have less concomitant medication to manage CV risk (aspirin, statins, anti-hypertensives) c) have further investigations such Doppler US scan, echocardiography d) attend haematology out-patients far less often as they will not require as much intervention for management of other TKI toxicity, as asciminib is very well tolerated.
• How does healthcare resource use differ between the technology and current care?	The only difference will be the cost of asciminib as compared to existing, approved TKIs. The costs of monitoring and staff resources will be the same.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Asciminib should be used in secondary care – haematology clinics, and specialist myeloid clinics. It is not appropriate for use in primary care.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant investment. Space in pharmacy to store drug. Training of pharmacy staff in dispensing, and training of clinicians in prescribing, side effects, etc. The technology will be straightforward to use once it becomes available since it is a simple tablet medication, taken as an out-patient. There are no required concomitant medications or other clinical requirements. Any side-effects of therapy are similar to any other available TKI, however, it is likely that the AE profile is less, making it an easier treatment to use. Monitoring of treatment response is the same as for the other well established tyrosine kinase inhibitors.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Asciminib has shown superiority to bosutinib in the third line setting (Cortes et al, Blood 2021; Aug18:blood2020009984). Our experts would therefore anticipate these benefits seen in the ASCEMBL clinical trial would translate into improved responses and better quality of life in the real world.
• Do you expect the technology to increase length of life more than current care?	Yes, although this question can only be answered with increased follow- up of patients. As stated before , patients survival is more affected than co-morbidities and in parallel toxicity of existing TKI therapy. As asciminib does not seem to aggravate co-morbidities, and appears well tolerated in patents with CV and renal disease, it will allow for less treatment interruption leading to increased remission, and less adverse event which would invariably affect the length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. The side effect profile of asciminib is better than some of the existing TKIs. It does not seem to have the risk of arterial thrombotic events associated with ponatinib and nilotinib, the side effect of diarrhoea seen with most patients starting bosutinib, or the risk of developing a pleural effusion seen with patients on dasatinib (Smith et al, British Journal of Haematology 2020;191:171-93). Overall, it has a favourable safety profile, which may improve HR-QoL for patients experiencing toxicities as compared to existing approved TKIs.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is limited data for the use of asciminib in patients with advanced phase CML (AP and BP). The drug may be less effective in these patients. A higher dose of asciminib may be required for patients with a T315I BCR-ABL kinase domain mutation. This needs to be assessed in ongoing clinical trials. In the main, once patients fail 2 or more TKIs, they are destined to stay on long-term TKI therapy. With age, co-morbidities increase, so asciminib will benefit the future of younger CML patients. Separately, 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 a potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an alternative TKI that would not manifest itself on asciminib would benefit considerably with regards to future morbidity and medical intervention. Other TKIs have a spectrum of mutations that they cover – imatinib and nilotinib usually share activity, dasatinib is resistant to F317L for e.g. and bosutinib to V299L for e.g. Only ponatinib covers the T315I mutation thus far- the other TKIs are resistant to the T315I mutation. The choice of next TKI for resistance depends on the sensitivity of the KD mutation – asciminib covers all KD mutations, including T315I due to its mode of action, and tolerability. Our experts believe that no data exists for the use of asciminib in children.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Asciminib will be the same to use as existing approved TKIs in current care. There are no practical implications for use. It has a twice daily dosing strategy comparable to the approved TKI nilotinib. Monitoring would be the same as for existing approved TKIs.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The decision to start or stop therapy will be based on BCR-ABL RT-qPCR results. A patient considered to have TKI treatment failure according to ELN criteria would be considered for treatment with asciminib in the third or later line setting. The patient would be expected to achieve milestone improvements in BCR-ABL levels as dictated by the ELN 2020 guideline in order to continue on asciminib. In the ELN treatment guideline (Hochhaus et al, Leukemia 2020;34:966-84), in the third line setting, failure to achieve/maintain a BCR-ABL level of <1% would be considered treatment failure. Patients developing side effects which are considered intolerable would also stop treatment with asciminib and an alternative would be sought from existing TKIs, not previously used in the patient. There would be no additional testing for asciminib as compared to existing TKIs.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are	No

unlikely to be included in the quality-adjusted life year (QALY) calculation?	As previously mentioned however, the QoL of life in CML patients is likely to improve on asciminib, and due to tolerability a greater response is likely to be achieved, and allogeneic transplantation avoided.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Our experts believe that this is an important drug, which has demonstrated superiority in a randomised phase 3 clinical trial against an existing accepted third line therapy. The drug works in a slightly different way and appears to have a favourable safety profile compared to existing second and third generation TKIs currently used in this setting. As asciminib works in a different way to other TKIs, it is innovative – asciminib can overcome kinase domain mutations (KDM), and has less organ toxicity, which has been also detailed in response et the other questions this far. It is likely that there will be less surgical, neurological and cardiological intervention in comparison to ponatinib, the third generation TKI.
• Is the technology a 'step-change' in the management of the condition?	Potentially yes, as it is a 'first in class' drug.

• Does the use of the technology address any particular unmet need of the patient population?	Yes, it provides a new therapy for those patients that have failed all existing TKIs, either through resistance or intolerance. Thus, has the potential to improve survival and quality of life in these patients with poor prognosis CML. As mentioned earlier, the approval of this technology would allow more tolerable and effective treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an alternative TKI that would not manifest itself on asciminib would benefit considerably with regards to future morbidity and medical intervention.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Asciminib has a side effect profile like other TKIs. Most side effects are grade 1 and grade 2, manageable with dose reductions or interruptions to improve side effects and quality of life. The commonest grade 3/4 adverse event with asciminib in the ASCEMBL clinical trial was thrombocytopenia, leading to discontinuation in 3.2% of patients. Overall, 5.8% of patients discontinued asciminib in the ASCEMBL trial for a side effect; this compares with 21.1% in the bosutinib arm; a currently approved 3rd line therapy. Arteriothrombotic events (ATEs) occurred in 3.2% of patients receiving asciminib and 1.3% of patients receiving bosutinib. While not significant, it will be important to continue to monitor for and report ATEs in patients on asciminib as for other TKIs.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Asciminib is also FDA approved in this setting.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are safety and demonstration of efficacy by assessment of BCR-ABL by RT-qPCR for BCR-ABL. These were both measured in the ASCEMBL clinical trial (Cortes et al, Blood 2021; Aug18:blood2020009984).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA 451?	TA-451 is for ponatinib. Since this was published in 2017, there has been a further update of the Phase 2 PACE clinical trial. The reference is Cortes et al, Blood 2018;132:393-404.
21. How do data on real-world experience compare with the trial data?	Our experts believe that for TKIs they are broadly similar, although the real-world data tends to have an older patient population, and proportions of patients achieving molecular endpoints such as major molecular remission (MMR) tend to be slightly lower in real-world data as compared to clinical trials. The data is also confounded as trials of new TKIs tend to be run at large academic centres, whereas in the real world both academic centres and district general hospitals manage patients on TKIs, bringing in another level of bias.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. As mentioned earlier, the approval of this technology would allow more tolerable and effective treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation. Furthermore, patients at risk of/experiencing a significant side-effect on an

	alternative TKI that would not manifest itself on asciminib would benefit considerably with regards to future morbidity and medical intervention.
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Asciminib has demonstrated superiority in a phase 3 clinical trial versus bosutinib in the third line setting for treatment of chronic phase CML
- Asciminib has a favourable safety profile compared with other available second and third generation TKIs
- The management and molecular monitoring of patients on asciminib is the same as for existing, approved TKIs
- Asciminib would offer a new and well-tolerated treatment approach for many patients failing existing TKIs or who were unsuitable for existing TKIs due to co-morbidities
- Asciminib works against Abl kinase domain mutations, including T315I, and will have a spectrum of efficacy over other TKIs.

Thank you for your time.

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Evidence Review Group's Report

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

FINAL REPORT

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None

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Dr Fiona Dignan, Consultant Haematologist, Manchester University NHS Foundation Trust acted as clinical advisor for this STA, providing clinical support and commentary. Martin Njoroge assisted with the cost-effectiveness sections of the report.

Rider on responsibility for report

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

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Contributions of authors

Peter Murphy performed the cost-effectiveness analyses and wrote report sections related to it.

Alexis Llewellyn wrote background and decision problem sections of the report and contributed generally to clinical sections of the report.

Nick Meader wrote report sections relating to the ASCEMBL trial and contributed to clinical sections of the report.

Robert Hodgson led the economic analysis and wrote cost-effectiveness sections of the report.

Mark Simmonds led the review of clinical effectiveness, oversaw the report as a whole, and wrote sections on the report relating to synthesis and indirect comparisons.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

Acronym	Definition
ABL1	Abelson
AE	Adverse event
AIC	Akaike's information criterion
Allo-SCT	Allogeneic stem cell transplant
AP	Accelerated phase
ATP	Adenosine triphosphate
BCR	Breakpoint cluster region
BD	Twice-daily
BIC	Bayesian information criterion
BMA	Bone marrow aspirate
BP	Blast phase
CCyR	Complete cytogenetic response
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CP	Chronic phase
CRUK	Cancer Research UK
CSR	Clinical study report
CyR	Cytogenetic response
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
ELN	European LeukemiaNet
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FISH	Fluorescence in situ hybridisation
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRT	Interactive response technology
ITC	Indirect treatment comparison
KM	Kaplan-Meier
LYG	Life-year gained
MAIC	Matched-adjusted indirect comparison
MCyR	Major cytogenetic response

Acronym	Definition
MDASI	M.D. Anderson Symptom Inventory
MMR	Major molecular response
MR	Molecular response
NE	Not estimable
NHB	Net-health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OD	Once-daily
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PD	Progressed disease
PFS	Progression-free survival
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome positive
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RFS	Relapse free survival
SAE	Serious adverse event
SCT	Stem-cell transplant
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36-Item
SLR	Systematic literature review
SmPC	Summary of product characteristics
STAMP	Specifically targeting the ABL myristoyl pocket
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

1 EXECUTIVE SUMMARY

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Key Issues ID3813	**Summary of issue**	**Report sections**
1	Absence of evidence on patients with the T315I mutation The company did not provide evidence for the effectiveness, safety and cost-effectiveness of asciminib in patients with the T315I mutation. Ponatinib is currently the only NICE recommended TKI for patients with a T315I mutation, and the relative effectiveness of ponatinib and asciminib in these patients is uncertain. The company has now confirmed that reimbursement is not sought for patients with the T315I mutation. This issue is retained for reference only.	2.3, 3.2, 3.4
2	Bias and quality concerns with the ASCEMBL trial The ERG identified design limitations in the ASCEMBL trial, including: possible baseline imbalances, lack of blinding, and potential for biased decision making for TTD. These all impact the reliability of the results of the trial	3.2
3	Lack of evidence on survival outcomes Survival outcome data (OS, PFS) were very immature in the ASCEMBL trial, and results were not compared to comparator interventions. While the ERG acknowledges that long survival times in CML limit the value of survival outcomes in this assessment, the lack of data reduces the possibility of robust comparisons between asciminib and comparator interventions.	3.2, 3.4
4	Use of time to discontinuation (TTD) to inform the economic analysis The company's indirect comparisons with other TKIs and the company's economic model rely heavily on time to	2.3, 3.2, 3.4

	treatment discontinuation (TTD). TTD was not an outcome specified in the scope. No evidence was provided to support the validity of TTD as a marker of long-term survival. The ERG is concerned that TTD may not be a robust measure of efficacy.	
5	Severe limitations of the matched adjusted indirect comparison (MAIC) analyses The results of MAIC analyses are highly uncertain. The ERG concludes that they may not be valid and are of insufficient quality to draw reliable conclusions. Problems include: Incomplete set of comparator studies No comparison with HMRN data Limited set of variables adjusted for Limited or incomplete reporting of outcomes (only MMR, CCyR and TTD) Limited reporting of relative estimates of effectiveness.	3.4
6	Model structure The company's preferred model structure is based on TTD followed by assumptions of post-discontinuation survival (referred to as the 'cumulative survival model'). This approach is subject to considerable uncertainty because of the paucity of evidence linking TTD to survival. It also has practical limitations and imposes structural restrictions on the model. The alternative model presented by the company, which is based on response to treatment (referred to as the 'surrogate survival model'), has some evidence linking response outcomes to survival but relies on external data. All results generated by both models are subject to considerable uncertainty.	4.2.2
7	Removal of retreatment The company's approach to modelling subsequent treatments uses the same basket of treatments regardless of the primary treatment received. This implicitly allows retreatment with the primary treatment. This is inconsistent with clinical practice.	4.2.4
8	Use of log-logistic to model TTD The lognormal model was selected by the company to model observed TTD from the ASCEMBL trial. Model selection was based on model fit and clinical plausibility. The ERG, however, considers the log-logistic model a better selection as it has a better statistical fit and results in similar survival predictions to the lognormal model.	4.2.6.2
9	Assumed duration of post-discontinuation survival	4.2.6.3

	The cumulative survival model makes assumptions regarding post-discontinuation survival. In the company base case, this is assumed to be 7 years to align with a previous appraisal. The ERG, however, considers this subject to uncertainty in light of evidence from the PACE trial and HRMN which suggests survival may be longer than the company's assumption.	
10	Use of Niederwieser 2021 for SCT survival The company based SCT survival on Jabbour 2011 data to align with a previous appraisals in CML. The ERG is concerned that this is a relatively old study which reports on relatively few patients. The ERG considers Niederwieser 2021 to be a better source of evidence as it is a more recent study and reports outcomes for a greater number of patients.	4.2.8.2
12	Comparator dosing It is assumed in the company's model that the relative dose intensities of ponatinib, nilotinib and dasatinib are 100%. This does not align with the dose intensity observed in the relevant pivotal trial (PACE) and does not reflect the assumptions made in the appraisal of ponatinib. Regarding nilotinib and dasatinib, it is unclear if the assumption of 100% is appropriate.	4.2.8.1

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The ERG considers there to be considerable uncertainty when modelling cost effectiveness but prefers to use the surrogate survival model. The company's preferred approach is to use the cumulative survival model.
- The ERG prefers to model subsequent treatment by removing the option of retreatment with the primary treatment. The company's preferred approach is to use the same basket of treatments regardless of primary treatment.
- The ERG extrapolates observed TTD using a log-logistic model fitted to the KM data from ASCEMBL, whereas the company prefer using a log normal model.
- The ERG prefers to us the Niederwieser et al. to inform the outcomes of patients who receive SCT, the company model uses Jabbour 2011 et al.to inform these outcomes.
- The ERG agreed with the company that it is appropriate to implement age-related utility decrements. The ERG, however, considers the most appropriate way to do this is to apply the decrements as a multiplier, rather than additive as in the company base case.

- The ERG prefers to model a reduced relative dose intensity of ponatinib, rather than assuming 100% as in the company base-case. In the cumulative survival model, the ERG assumes the dose reduces to 33% after 1 year. In the surrogate survival model, the ERG assumes the dose is 33% for those with a response (CCyR, PCyR and CHR) and 67% for those without a response (NR) after 1 year.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life using the quality-adjusted life year (QALY) with the established standard of care. An ICER is the additional cost associated with a new treatment for every additional QALY gained.

Overall, the technology is modelled to affect QALYs depending on the model approach adopted. In the cumulative survival model, this is achieved through:

- Increasing overall survival by increasing TTD (bosutinib, dasatinib and nilotinib comparisons only);
- Having a more favourable long-term safety profile compared to some of the other treatments.

In the surrogate survival model, impact on QALYs depends on:

- CCyR response rates which impact to increase PFS and OS;
- Having a more favourable long-term safety profile compared to some of the other treatments.

Overall, the technology is modelled to affect costs due to:

- Drug acquisition costs;
- Use of SCT which is reduced in more effective treatments (asciminib and ponatinib)
- Greater disease management costs accrued due to longer survival (bosutinib, dasatinib and nilotinib comparisons only).

The modelling assumptions that have the greatest effect on the ICER are:

- The use of the surrogate survival model;
- The removal of retreatment from the pool of subsequent treatments;
- The use of the Niederwieser 2021 data to model SCT survival;
- Reducing the relative dose intensity of ponatinib.

1.3 The decision problem: summary of the ERG's key issues

Issue 1: Absence of evidence on patients with the T315I mutation

Report section	2.3, 3.2, 3.4
Description of issue and why the ERG has identified it as important	The company did not provide evidence for the effectiveness, safety and cost-effectiveness of in patients with the T315I mutation. This subgroup of patients are likely to be important when making clinical decisions. Ponatinib is currently the only NICE recommended TKI for patients with a T315I mutation, and the relative effectiveness of ponatinib and asciminib in these patients is uncertain. The ERG expects that evidence on the effectiveness of asciminib within this subgroup may be required. The company has now confirmed that reimbursement is not sought for patients with the T315I mutation. This issue is retained for reference only.
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	Not applicable

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2: Bias and quality concerns with the ASCEMBL trial

Report section	3.2
Description of issue and why the ERG has identified it as important	The ERG identified design limitations in the ASCEMBL trial, including: possible baseline imbalances, lack of blinding, and potential for biased decision making for TTD. These all impact the reliability of the results of the trial
What alternative approach has the ERG suggested?	The ERG acknowledges that blinding was not feasible in ASCEMBL, but notes that this means that analysis should be focused on outcomes less likely to be influenced by knowledge of treatment. In particular, TTD might potentially be influenced by knowledge of which treatment was received, which could have led to biased results (see Issue 4). The ERG requested that suitable regression models be used to investigate whether prognostic factors where ASCEMBL was imbalanced at baseline (e.g. time since diagnosis, number of pervious TKIs) might have influenced the results. The company did not provide these analyses.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests that the ASCEMBL trial data be re-analysed to account for all known imbalances in key prognostic factors between groups. This would ensure that the most appropriate and robust estimates of difference between asciminib and bosutinib are made available. The necessary data for these analyses should already be available.

Issue 3: Lack of evidence on survival outcomes

Report section	3.2, 3.4
Description of issue and why the ERG has identified it as important	Survival outcome data (OS, PFS) were very immature in the ASCEMBL trial, and results were not compared to comparator interventions. The ERG acknowledges that long survival times in this clinical area limit the value of survival outcomes in this assessment. However, the lack of data reduces the possibility of robust comparison of asciminib with comparator interventions.
What alternative approach has the ERG suggested?	As survival data from ASCEMBL matures (e.g. at 1 and 2 year follow-up) this data should be analysed, and compared to other interventions using MAIC analysis (see Issue 5).
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that no analyses are possible at present, but updated survival data should be analysed and reported as soon as is feasible (at 1 and 2-year's follow-up of the ASCEMBL trial).

Issue 4: Focus on time to discontinuation (TTD) as a measure of effectiveness

Report section	2.3, 3.2, 3.4
Description of issue and why the ERG has identified it as important	The company's indirect comparisons with other TKIs and the company's economic model rely heavily on time to treatment discontinuation (TTD). TTD was not specified in the scope. No evidence was provided to support the validity of TTD as a marker of long-term survival. The ERG is concerned that TTD may not be a robust measure of effectiveness.
What alternative approach has the ERG suggested?	The ERG considers that outcomes that are more robust and relevant to patients should be of primary interest in this assessment. This includes response outcomes (MMR, CCyR) and survival outcomes (OS, PFS). This includes choice of outcomes for the cost-effectiveness analysis (see Issue 6)
What is the expected effect on the cost-effectiveness estimates?	See issue 6.
What additional evidence or analyses might help to resolve this key issue?	Analyses should be presented that focus on robust measures of response, particularly for MAIC analyses (See Issue 5)

Issue 5: Severe limitations of the matched adjusted indirect comparison (MAIC) analyses

Report section	3.4
Description of issue and why the ERG has identified it as important	The results of MAIC analyses are highly uncertain. The ERG concludes that they may not be valid and are of insufficient quality to draw reliable conclusions. Problems include: Incomplete set of comparator studies; No comparison with HMRN data; Limited set of variables adjusted for; Limited or incomplete reporting of outcomes (only MMR, CCyR and TTD); Limited reporting of relative estimates of effectiveness.
What alternative approach has the ERG suggested?	The ERG considers that a complete MAIC needs to be performed, as the analyses provided by the company are insufficient to draw reliable conclusions.
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The ERG thinks that a more comprehensive MAIC approach is required. This should include: Using more studies for comparison (and more than one per comparator); A MAIC compared to the HMRN data Performed for all outcomes (TTD, MMR, CCyR and OS and PFS when data become available);

	Sensitivity analyses should be performed to investigate the impact of changing the number and choice of adjustment factors in the MAICs. In all cases a clear presentation of data for comparators is required (such as a formal data extraction form), as is a clear description of the chosen MAIC model for each analysis, and a clear presentation of all results, including presenting both unadjusted and adjusted results.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 6: Model structure

Report section	4.2.2
Description of issue and why the ERG has identified it as important	The model structure presented by the company (referred to as the cumulative survival model) is subject to considerable uncertainty as it derives comparative effectiveness from TTD. The paucity of evidence regarding the reliability of TTD as a clinical endpoint means there is considerable scope for comparative estimates of TTD to be biased. In addition, the comparative evidence supporting these comparisons is limited and potential subject to bias. Lack of time-to-event data for TTD for all comparators also means extrapolation of evidence is limited to an exponential model.
What alternative approach has the ERG suggested?	The ERG considered there to be an alternative approach to modelling cost-effectiveness, which relies on response to treatment rather than TTD (referred to as the surrogate survival model). Modelling cost-effectiveness on response aligns with the most recent appraisal of a TKI in this population, which was the third-generation TKI, ponatinib. Not only is there recent precedent for using a surrogate survival model, evidence shows an association between CCyR and MMR and long-term OS. At the request of the ERG, the company presented a surrogate survival model. It is important to note that this approach is also subject to uncertainty as the model relies on external evidence generated in a 2nd line population.
What is the expected effect on the cost-effectiveness estimates?	This acts to reduce the ICERs in comparisons with b and ponatinib. The ICER for comparisons with nilotinib remains approximately the same and the ICER for Dasatinib is increased.
What additional evidence or analyses might help to resolve this key issue?	Evidence supporting the surrogate value of TTD would help support the company's approach. More reliable comparative evidence on TTD for relevant comparators would also be informative.

Issue 7: Retreatment with primary therapy

Report section	4.2.4.2
Description of issue and why the ERG has identified it as important	In modelling the subsequent treatment patients receive, the company have assumed that the basket of subsequent treatments available is the same regardless of the primary treatment received. The implication of this is that patients can be retreated with their primary treatment. Clinical advice to the ERG considers this assumption unrealistic. The ERG is also conscious that the current approach may artificially amplify the impact of any cost differences between comparators treatments, distorting the results of the economic analysis.
What alternative approach has the ERG suggested?	The ERG considers it more appropriate to revise the basket of subsequent treatments modelled to remove the possibility of retreatment.
What is the expected effect on the cost-effectiveness estimates?	The result of the ERG's preferred approach is that it increases the ICER for the comparison with bosutinib and reduces the ICER for comparisons with Dasatinib and nilotinib. The ICER can also be seen to reduce the ICER for comparisons with ponatinib, however as this is in the southwest quadrant of the cost-effectiveness plane (i.e. less costly and less effective) a reduction in the ICER means ponatinib becomes, relatively speaking, more cost-effective.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input regarding the appropriateness of retreatment with the primary treatment would be informative.

Issue 8: Extrapolation of TTD

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	In order to extrapolate observed TTD data from the ASCEMBL trial, the company fitted a log-normal model to the available KM data. The log-normal model was selected according to the company based on model fit criteria (AIC and BIC) and because it aligned with clinical opinion on expected survival estimates.
What alternative approach has the ERG suggested?	The ERG notes the log-logistic model results in similar survival expectation to the log-normal model (and in fact slightly closer to the company's clinical expert survival estimates) and has a better fit according to AIC and BIC statistics.
What is the expected effect on the cost-effectiveness estimates?	The ERG considers it more appropriate to use the log-logistic model to extrapolate TTD.
What additional evidence or analyses might help to resolve this key issue?	Using the log-logistic model has a minimal impact on the ICER in the company's base case.

Issue 9: Assumed duration of post-discontinuation survival

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	The cumulative survival model includes the assumption of a fixed post-discontinuation survival period of 7 years. This assumption is based on ERG estimates of mean OS from TA401 and was accepted by committee. The ERG, however, has concerns that this estimate is overly pessimistic given the substantive changes to the pathway and improvements in care. This position is supported by evidence from both the HMRN and the PACE trial.
What alternative approach has the ERG suggested?	To illustrate the impact of increasing post-discontinuation survival, the ERG implemented several of alternative scenarios which maintain the company's assumed time in PPS (i.e. 16 months) but increase total post discontinuation survival. These were informed by evidence on OS from the PACE trial. These scenarios vary post-discontinuation survival from 7 years to i) 10.1 years, and ii) 14.6 years.
What is the expected effect on the cost-effectiveness estimates?	This scenario acts to reduce the ICERs for comparison with bosutinib and dasatinib and results in a moderate increase in the ICER for comparisons with nilotinib. This scenario also increases the ICER for comparisons with ponatinib but as this falls in the south-west quadrant of the cost-effectiveness plane this results in asciminib appearing more cost-effective compared to ponatinib.
What additional evidence or analyses might help to resolve this key issue?	There remains uncertainty regarding the most appropriate survival assumptions in this population given current treatment pathways. Further, clinical insight into expected survival in this population is likely to eb useful. Further, long-term data on OS in patients in the population would also be informative.

Issue 10: Use of Niederwieser 2021 for SCT survival

Report section	4.2.6.4
Description of issue and why the ERG has identified it as important	Under both the cumulative survival and surrogate survival modelling approaches it is assumed a proportion of patients go on to receive SCT. Survival for those receiving SCT is based on data provided in Jabbour *et al*. While Jabbour et al. has been used in previous TA, the ERG is concerned that this is a relatively old study which reports on relatively few patients (n = 47). As a result, the ERG considered there to be uncertainty in the survival estimates of those with SCT based on this data.
What alternative approach has the ERG suggested?	The ERG therefore looked for any alternative sources of evidence. The Niederwieser *et al.* identified by the ERG, is a significantly more recent study and reports outcomes for greater number of patients (n = 147). Therefore, the ERG considers Niederwieser et *al.* a superior source of evidence. The Niederwieser study, reports no difference in SCT outcomes for patients receiving SCT in the CP and AP, but inferior outcomes for patients receiving SCT in the BP. This inconsistent with the company's model. The ERG prefers to align with Niederwieser et *al* given the absence of alternative evidence.
What is the expected effect on the cost-effectiveness estimates?	The results show a modest decrease in the ICERs
What additional evidence or analyses might help to resolve this key issue?	Further, evidence on survival outcomes of CML patients receiving SCT would be informative. The ERG is, however, unaware of any such evidence.

Issue 11: Age-adjusted utilities

Report section	4.2.7
Description of issue and why the ERG has identified it as important	To account for the impact of ageing on HRQol, the model applies age adjustments to all utility values. The company's approach was to apply these using an additive approach in which a utility decrement is estimated relative to the utility of a 51-year-old (staring age) in the general population. This decrement is then subtracted from each health state utility value to generate an age-specific value. The ERG considers the application of age-related utility decrements to be appropriate given the long-time horizon considered in the economic analysis. However, the approach adopted to achieve this is not considered appropriate. The company's additive approach assumes that the impact of age is constant across all health states. Age-related utility decrements are typically applied as a multiplier rather in an additive way. with the precedent set for this approach reported in a large number of previous technology appraisals.
What alternative approach has the ERG suggested?	The ERG revised the implementation of the age-related decrements so that they are applied as a multiplier.
What is the expected effect on the cost-effectiveness estimates?	The results show a modest decrease in the ICERs.
What additional evidence or analyses might help to resolve this key issue?	Not applicable.

Issue 12 Comparator dosing

Report section	4.2.8
Description of issue and why the ERG has identified it as important	The modelling of the costs of comparators requires the specification of the relative dose intensity. In the company base case a relative dose intensity of 100% is assumed for ponatinib, nilotinib and dasatinib. The ERG has reasons to consider this assumption subject to uncertainty. a) Dose of ponatinib The assumption of 100% dose intensity of ponatinib does not align with the dose intensity observed in the relevant pivotal trial (PACE) or TA451. Clinical advice suggests that many patients receiving ponatinib will receive a lower dose, receiving either a 30 or 15-mg dose (significantly lower than the (full) 45mg dose outlined in the SmPC). Further, while specific details of dosing in the PACE trial are not reported in detail, it is clear that dose reductions were applied to the vast majority of patients. All patients who had achieved a cytogenetic response or better were lowered to a 15 mg maintenance dose from October 2013 onwards. A dose intensity of 100% is therefore likely to overestimate the acquisition costs associated with ponatinib.

	b) Dose of nilotinib and dasatinib It is unclear if the assumption of 100% dose intensity for nilotinib and dasatinib is appropriate. Clinical advice to the ERG suggesting that dose modifications and reductions would occur in at least a proportion of patients. Appropriate evidence to inform alternative assumptions is, however, limited.
What alternative approach has the ERG suggested?	The ERG considered a number of alternative scenarios to address the dosing issues. a) Dose of ponatinib In the cumulative survival model, the ERG implemented a simple scenario in which the dose intensity is reduced for all receiving treatment from 45mg (100%) to 15mg (33%) at i) 1 year, ii) 2 years and iii) 3 years. This has the impact of bringing the modelled acquisition cost of ponatinib down. Although it is a simplistic scenario, it illustrates the impact of dose reductions on the ICER. In the surrogate survival mode, the ERG assumes those with a response (CCyR, PCyR, CHR) receive a 15mg dose of ponatinib and those with no response receive 30mg. This aligns with the dosing reductions in the PACE trial. b) Dose of nilotinib and Dasatinib The ERG considers a scenario in which the dose of nilotinib and dasatinib are assumed to be equivalent to the observed dose of bosutinib in ASCEMBL. The dose of bosutinib was selected as it is a 2nd generation TKI, like dasatinib and nilotinib. This scenario is used to illustrate the impact of the company's assumption of 100% dose intensity on the ICER.
What is the expected effect on the cost-effectiveness estimates?	For scenario a) a ponatinib dose reduction reduces the ICER considerably in both the cumulative survival model and the surrogate survival model. As this is the south-west quadrant of the cost-effectiveness plane, this scenario results in ponatinib being more cost-effective compared to asciminib. In scenario b) the ICER increased considerably for comparisons with dasatinib but had a minimal impact on the ICER for comparisons with nilotinib.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on the dosing of ponatinib, nilotinib and dasatinib in clinical practice would be help refine the ERG's scenarios. Further

1.6 Summary of ERG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the ERG are described in Section 5.3. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2. The results of the ERG's exploratory analyses including the ERG's preferred base case are presented below.

ERG Scenarios

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Change from company base case
Company base case						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	2,654	n/a
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	582	n/a
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	49,445	n/a
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	271,410*	n/a
Error correction						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-2,753
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	88	-494
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	48,961	-484
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	271,026*	-384
Scenario 1: Surrogate survival model						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-14162
Asciminib vs dasatinib						

Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	37,740	+37,158
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	49,261	-184
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	748,333*	+476,923
Scenario 2: Equivalence in effectiveness						
Asciminib vs bosutinib						
Bosutinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	11,052	+10,470
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	38,926	-10,519
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-2,494,048
Scenario 3: Removing retreatment from subsequent treatment						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	10,810	8155
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-15,179
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	20,919	-28,526
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	205,233*	-66,177
Scenario 4: Log-logistic model for TTD						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	1,224	-1,431
Asciminib vs dasatinib						
Dasatinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a

Asciminib vs Nilotinib						
Nilotinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib						
Ponatinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Scenario 5: Use of Niederwieser 2021 for SCT survival						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	2,485	-169
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	189	-392
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	45,884	-3,561
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	252,355*	-19,055
Scenario 6a: 14.6 years post discontinuation survival						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-19186
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-17174
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	50,828	1382
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	369,627*	98216
Scenario 6b: 10.1 years post discontinuation survival						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-7287
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-6477
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-

Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	50,015	570
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	308,180*	36770
Scenario 7: Age adjustment						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	2,605	-50
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	569	-12
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	48,484	-962
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	265,551*	-5859
Scenario 8a: Ponatinib dose reduced to 15mg after 1 year						
Asciminib vs bosutinib						
Bosutinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib						
Nilotinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	74,952*	-196,458
Scenario 8b: Ponatinib dose reduced to 15mg after 2 years						
Asciminib vs bosutinib						
Bosutinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib						
Nilotinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib						

Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	122,390*	-149,020
Scenario 8c: Ponatinib dose reduced to 15mg after 3 years						
Asciminib vs bosutinib						
Bosutinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib						
Nilotinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	160,296*	-111,114
Scenario 9: Nilotinib and Dasatinib equivalent to Bosutinib dose						
Asciminib vs bosutinib						
Bosutinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	13,212	+12,631
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	49,749	+304
Asciminib vs ponatinib						
Ponatinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

*ICER falls in the south-west quadrant of the cost-effectiveness plane

ERG base case and exploratory analysis on the base case

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Change from company base case
ERG preferred base case: Error correction, Scenario 1, 3, 4, 5, 7, 8						
Asciminib vs bosutinib						
Bosutinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-6,227

Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	30,538	29956
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	35,035	-14410
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-351,500
Exploratory analysis: ERG preferred base case + Scenario 2						
Asciminib vs bosutinib						
Bosutinib	n/a	n/a	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	40,296	39715
Asciminib vs Nilotinib						
Nilotinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	39,784	-9661
Asciminib vs ponatinib						
Ponatinib	[redacted]	[redacted]	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	315,255	+586,665

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

*ICER falls in the south-west quadrant of the cost-effectiveness plane

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

2.1.1 Critique of description of underlying health problem

The company submission (CS, Document B, pp.15-20), provides a generally clear and appropriate description of the underlying health problem, which is briefly summarised in this section.

Chronic myeloid leukaemia (CML) is a rare cancer of the blood characterised by the uncontrolled proliferation of myeloid cells in the bone marrow and subsequent release into peripheral blood. [1-3] CML is defined by the presence of the Philadelphia chromosome (Ph), an acquired abnormality in haematopoietic stem cells,[4] which results from a translocation involving the ABL1 (Abelson) protooncogene on chromosome 9, and the breakpoint cluster region (BCR) gene on chromosome 22.[5] This translocation leads to the formation of the fusion protein BCR-ABL, an active cytoplasmic tyrosine kinase, leading to the growth and differentiation of haematopoietic cells.[4, 6, 7]

CML has three phases, which depend on the number of immature blasts in the bone marrow or peripheral blood; chronic phase (CP), accelerated phase (AP), or blast phase (BP).[8] Approximately 90% of CML patients are diagnosed while in CP; 9% are diagnosed in the AP and 1% in the BP. The CP phase is characterised by an overproduction of myeloid cells in the peripheral blood, whilst mature granulocytes are still produced.[9, 10] Failure to treat CP successfully can to progression to AP and may be followed by BP, where differentiation of myeloid and/or lymphoid cells stops, and immature leukaemic blasts accumulate in the bone marrow and subsequently spread to tissues and organs.[9] Left untreated,, the disease course from the CP to more advanced stages (AP and BP) without treatment is 3.5–5 years.[5, 11]

There are approximately 709 new cases of CML each year in England, with an annual incidence rate of 1.3 per 100,000. In the UK, the median age at diagnosis is 59.1 years; males tend to be more affected (55% of cases).[12] In the UK, CML accounts for approximately 226 deaths per year.[12] CML in the CP is relatively slow-evolving, with an OS rate of 89% at 8 years.[13]However, for patients whose disease progresses to AP or BP, median survival is significantly reduced.[14]

2.1.2 Critique of current service provision

The CS (Document B, pp.20-24) provides a generally appropriate overview of current service provision for people with CML, which is briefly summarised in this section.

Allogeneic stem cell transplant (allo-SCT) is the only therapy with curative potential for CML. However, it is associated with a substantial risk of morbidity and mortality and is therefore limited by patient suitability and choice as well as the availability of suitable donors.[15] Oral tyrosine kinase inhibitors (TKIs) have become the mainstay for the treatment of CML. Currently, five TKIs (imatinib, dasatinib, nilotinib, bosutinib and ponatinib) are recommended by NICE for the treatment of CML.[16-19]

The choice of first-line TKI therapy for CP patients is primarily guided by pre-existing medical conditions. Imatinib is recommended for the majority TKI-treatment naïve patients.[20] Comparative evidence for the relative efficacy of third and later line TKIs is limited, therefore, no treatment guidelines provide well-defined treatment recommendations regarding the TKI of choice at these stages of the treatment pathway.[20-23] Clinical advice to the ERG indicated that choice of second- and subsequent lines of TKI in patients resistant to/intolerant to previous treatment depend primarily on comorbidities and the adverse event profile of TKI therapies. For instance, the ERG clinical adviser noted that dasatinib may not be used in people with respiratory comorbidities, and that ponatinib may be considered further along the pathway due to its worse safety profile, notably in individuals with cardiac comorbidities. Other deciding factors may include tolerability to prior treatments, as well as physician and patient preferences.[23]

2.1.2.1 NICE guidance

NICE guidelines for the treatment of CML in adult patients are presented in CS (Document B, pp.22-23), and summarised in Table 1 below.

TKIs are recommended at all lines of therapy; imatinib, dasatinib, or nilotinib are recommended at first-line; and dasatinib, nilotinib, bosutinib, or ponatinib are recommended in second- or later line therapy.[22] Ponatinib is currently the only recommended treatment for individuals with a T315I mutation.[18]

Haematological Malignancy Research Network (HMRN) audit data from September 2004 to August 2019 shows that most patients (89.6%) with CML-CP in England receive first-line treatment with imatinib, followed by second-line treatment with nilotinib (58.2%) or dasatinib (29.3%) [24]; in some cases, individuals may be retreated with a previous TKI.

Although not recommended by NICE, allo-SCT will be considered for a subset of patients following failure to prior TKI therapy. Clinical advice to the ERG noted that, due to its high mortality and morbidity rates, this option would be more likely to be considered as a treatment of last resort.

Table 1 NICE treatment guidelines for CML in adults

Guideline (Year)	Treatment	Recommendations
Untreated (first-line)		
TA426 (2016) and TA70 (2003)	Imatinib (1GTKI)	Recommended for: • Untreated (first-line) Ph+ CML-CP • Ph+ CML-CP adults who initially present in the AP or BP • Adults who present in the CP and then progress to the AP or BP
TA426 (2016)	Dasatinib (2GTKI)	Recommended for untreated (first-line) Ph+ CML-CP
	Nilotinib (2GTKI)	
Previously treated (second- or later line)		
TA425 (2016)	Dasatinib (2GTKI)	Recommended for adults with CP or AP Ph+ CML who: • Cannot have imatinib or • are imatinib-resistant
	Nilotinib (2GTKI)	
TA401 (2016)	Bosutinib (2GTKI)	Recommended for adults with CP, AP, and BP Ph+ CML when: • They have previously received ≥1 TKI, and • imatinib, nilotinib, and dasatinib are not clinically appropriate
TA451 (2017)	Ponatinib (3GTKI)	Recommended for adults with CP, AP, and BP CML when: • Resistant to dasatinib or nilotinib • Dasatinib or nilotinib are not tolerated, and subsequent treatment with imatinib is not clinically appropriate • Positive for the T315I gene mutation

Source: NICE treatment pathway for CML.[22]; adapted from CS document B, Table 4. Abbreviations: 1/2/3GTKI, first/second/third generation tyrosine kinase inhibitor; AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; NICE, National Institute for Health and Care Excellence; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.

2.2 Background

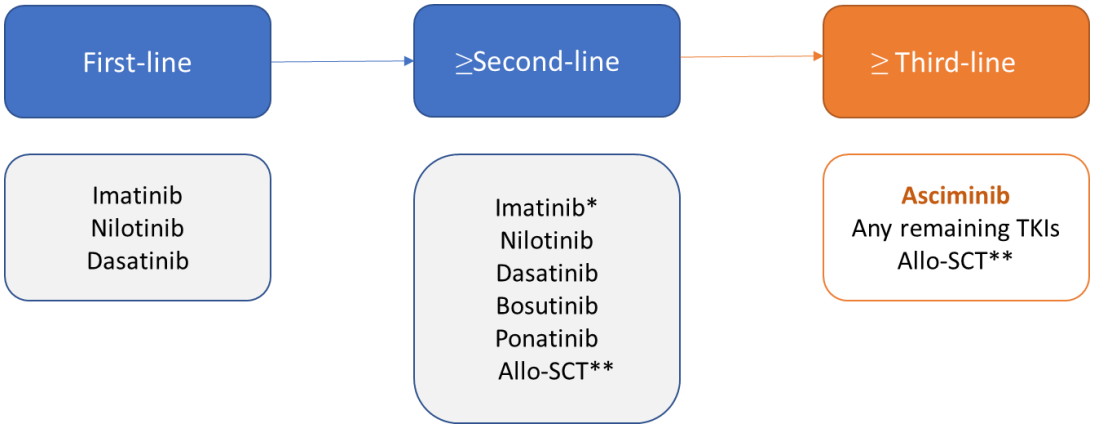
2.2.1 Asciminib

Asciminib is an oral TKI and BCR-ABL1 inhibitor that specifically targets the myristoyl pocket of BCR-ABL1 (STAMP). Asciminib targets both native and mutated BCR-ABL1, including the T315I mutant.[25] The recommended dose for patients with Ph+ CML-CP previously treated with ≥2 TKIs is 80 mg, available as a 2 x 40 mg dose regimen 12 hours apart or as an 80 mg once daily dose regimen.

2.2.2 Critique of the company's positioning of asciminib in the treatment pathway

The anticipated indication for this submission is [redacted] [redacted][26] Therefore, the company placed asciminib as an option in third and subsequent lines in the treatment of adults with adults with Ph+ CML-CP. Clinical advice to the ERG found the company's positioning was likely to be appropriate, with most patients receiving asciminib as either third- or fourth-line treatment. The company's positioning of asciminib is presented in Figure 1 below:

Figure 1 Clinical pathway of care for managing Ph+ CML-CP (including the proposed positioning of asciminib)



Source: modified from CS Document B, Figure 4 *The ERG clinical adviser noted that imatinib may be used in a small subset of 2nd line patients; the company stated that in clinical practice, imatinib is used for the treatment of second-line patients who are intolerant to a prior TKI therapy, but not in the case of prior TKI resistance. ** Allo-SCT is used in clinical practice but is not part of the NICE clinical pathway of care. Abbreviations: Allo-SCT, allogeneic stem cell transplantation; Ph+ CML-CP, Philadelphia chromosome positive chronic myeloid leukaemia-chronic phase.

2.2.3 Unmet need

The company's description of unmet need (Document B, pp.24-26) in CML individuals with two or more prior lines of TKI is broadly appropriate.

Among CML patients receiving first-line imatinib therapy in England, approximately 40% experienced loss of response within the first-year of treatment.[24] Broadly 30%–50% patients discontinue imatinib within 5 years, with 5–7% due to TKI intolerance and 15–20% due to TKI resistance.[27] Each subsequent TKI therapy line can lead to increased resistance, lower rates of treatment response, and decreased survival. Resistance rates are higher during second-line treatment, with 60–70% of individuals failing to achieve a major molecular response (MMR) with 2 years of follow-up.[28-31] Higher rates of progression and death are observed in patients with third line TKI therapy failure.[32-34]

Due to their lack of specificity, current TKIs have off-target activities leading to long-term complications and intolerance.[27, 32, 33, 35, 36] For patients with resistance or intolerance to second line therapy, there are few remaining options with favourable risk-benefit profile. Because of this, patients may need to continue their 2L or 3L therapy despite experiencing AEs, frequently at reduced and less effective doses.[37] Sequential TKI treatment is often associated with the emergence of new mutations. The BCR-ABL1 T315I mutation, associated with a worse prognosis and is of particular concern. T315I is present in approximately 20% of mutations, and its prevalence is higher in more heavily pre-treated patients.[24, 38-40] T315I confers resistance to all TKIs currently approved by NICE except ponatinib.[40] Due to the increased risk of arterial occlusion associated with ponatinib (and other approved TKIs), patients with cardiovascular risk factors have even fewer treatment options.[23]

2.2.4 Regulatory submissions

In October 2021, the Food and Drug Administration granted accelerated approval to asciminib for individuals with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs), and for adult patients with Ph+ CML in CP with the T315I mutation. A regulatory application for the anticipated UK licence indication was submitted to the MHRA in July 2021.

The company has subsequently informed the ERG about the MHRA early access to medicines scheme (EAMS) scientific opinion published on 24 January 2024, which excludes individuals with the T315I mutation: “asciminib is indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) without T315I mutation previously treated with two or more tyrosine kinase inhibitors.”

2.3 Critique of company’s definition of decision problem

Table 2 presents a summary of the decision problem, and a commentary on the extent to which the company submission matches the final scope issued by NICE.

Overall, the ERG found that the evidence submitted broadly reflects the decision problem, although the ERG has a number of concerns, particularly the use of TTD as a surrogate marker of survival.

2.3.1 Population

Clinical advice to the ERG confirmed that the clinical evidence presented in the CS broadly reflects the population described in final scope, although compared with the HMRN audit of third-line TKI patients,[24] the ASCEMBL trial population was younger (by a median of 4.2 years) and fitter (ECOG 0-1: 99.1% in ASCEMBL vs. 87.1% in HMRN audit) on average.

The main asciminib trial (ASCEMBL),[41] which informed the company's economic model, excluded individuals with T315i mutation. This is a clinically important population, with higher resistance to TKIs and worse prognosis.[38-40] Among NICE approved TKIs, only ponatinib is recommended for the T315I mutation. Although an earlier phase 1 trial of asciminib presented response data for a subset of 28 CML individuals with a T315I mutation (trial X2101)[25], this limits the applicability of the trial evidence to the final scope population.

The ERG notes that the company have now clarified that reimbursement is not sought for patients with T315I mutation.

2.3.2 Intervention

The intervention characteristics presented in the submission reflect the decision problem. The recommended dose for asciminib in patients with Ph+ CML-CP previously treated with ≥2 TKIs is 80 mg, available as a 2 x 40 mg dose regimen 12h apart or as an 80 mg once daily dose regimen.[26] The focus of the CS was on the dose regimen of 2x40 mg 12h apart.

2.3.3 Comparators

The comparators described in the company's submission match the final scope. However, the ERG is concerned that the company submission may not reflect all relevant published evidence. This is further discussed in Section 3.3.

2.3.4 Outcomes and validity of surrogate endpoints

Due to the relatively slow disease course of CML-CP, the OS and PFS trial evidence is very immature and insufficient to inform long-term disease progression and survival outcomes. To address this limitation, the company added the following surrogate outcomes to the decision problem: major molecular response (MMR), cytogenetic response (CyR), complete cytogenetic response (CCyR) and time to treatment discontinuation (TTD). MMR and CyR are commonly used surrogate endpoints in clinical practice and trials of CML, and CyR has been used in some prior TAs (TA241 and TA251) and HTAs of TKIs.[42-44]

In response to request for clarification from the ERG, the company provided evidence to support the association between response endpoints and longer-term survival outcomes, mainly based on one systematic review that aimed to validate CCyR and MRR as surrogate markers of OS in patients with CML-CP receiving first-line TKIs.[45] The systematic review by Oriana et al.(2013) included three cohort studies and two RCTs of TKIs, with a median follow-up ranging from 28 to 110 months. Based on observational analyses comparing responders with non-responders, the review found a consistent association between CCyR and MMR and long-term (1–7 years) overall survival, and a stronger association with OS for CCyR compared with MMR overall. Based on pooled associations between CCyR and MMR and overall survival, long-term extrapolations showed comparable predicted mean duration of survival (21–23 years) following first-line treatment with imatinib, dasatinib, or nilotinib at 57 years of age.

Although the systematic review by Oriana et al. provides some evidence to validate the use of cytogenetic and molecular response as surrogate markers of long-term survival, it has a number of limitations in the context of this appraisal. Survival outcomes were not stratified by depth of response, and the follow-up of the observational evidence was still limited to capture long-term survival in most CML-CP individuals. The review may be out of date (searches were conducted up to May 2012), only included first-line TKI patients, rather than the population of CML-CP patients with ≥2 TKI, and only included three TKIs (imatinib, dasatinib, or nilotinib).

No evidence was provided for the validity of TTD as a marker of long-term survival. The ERG is concerned that TTD may not be a robust measure of efficacy, as it may be confounded by multiple variables including treatment tolerance, safety, patient characteristics, availability of and suitability for subsequent treatments, and clinician and patient preferences. The company's comparisons with other TKIs listed in the scope and the company's economic model rely heavily on TTD.

Table 2 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with Ph+ CML-CP previously treated with two or more TKIs	As per NICE final scope	N/A	Clinical advice to the ERG confirmed that the clinical evidence presented in the CS broadly reflects the population described in final scope, although compared with the HMRN audit of third-line TKI patients,[24] the ASCEMBL trial population was younger (by a median of 4.2 years) and fitter (ECOG 0-1: 99.1% in ASCEMBL vs. [redacted] in HMRN audit) on average. Individuals who would be eligible to asciminib would likely receive it as 3rd or 4th line TKI therapy, although the respective distribution of populations likely to receive asciminib as 3rd versus 4th line and beyond is uncertain. The main Asciminib trial (ASCEMBL) excluded individuals with T315I mutation. The company justified this decision due to existing evidence of lack of efficacy in the comparator treatment (bosutinib). Individuals with a T315I mutation are a clinically important population, with higher resistance to TKIs and worse prognosis. This limits the applicability of the trial evidence to the final scope population. In their factual accuracy check (FAC) response, the company have clarified that they are not seeking reimbursement for this group.
Intervention	Asciminib	As per NICE final scope	N/A	The intervention described in the company's submission matches the intervention described in the final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Comparator(s)	• Bosutinib • Dasatinib • Nilotinib • Ponatinib	As per NICE final scope	N/A	The comparators described in the company's submission match the final scope. The ASCEMBL trial was a head-to-head comparison between asciminib and bosutinib. Evidence for dasatinib, nilotinib and ponatinib was included in a matched-indirect treatment comparison (MAIC). However, the comparator evidence has important limitations, and the ERG has concerns that the studies included in the company's MAIC may not reflect all relevant published evidence (see ERG report Sections 3.2-3.4). ERG clinical advice suggests that allo-SCT is likely to be considered as treatment of last resort for a subset of fitter and younger patients, therefore the exclusion of allo-SCT is likely to be appropriate.
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates • Time to response • Adverse effects of treatment • Health-related quality of life	As per NICE final scope, with two additional outcome measures (MMR and TTD)	MMR: Since the introduction of imatinib, nearly all imatinib-treated patients achieve normalised blood counts and most achieve a complete cytogenetic response. There is evidence that achieving a MMR predicts superior long-term clinical outcomes. TTD: OS and PFS trial data from ASCEMBL are immature; TTD is an important clinical outcome and is used within the	PFS and OS data from the trial evidence is very immature and insufficient to inform long-term survival outcomes. The MAIC and economic model rely heavily on TTD data. TTD is not a robust measure of efficacy. TTD is not commonly used in clinical practice, and may be confounded by multiple variables including treatment tolerance, safety, and clinician and patient preferences. The company did not show evidence supporting the association between TTD and longer-term PFS and OS in CML.

			economic model to capture that overall survival is the sum of time on treatment and survival post-discontinuation of third-line treatment.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year, and that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per NICE final scope	N/A	In line with NICE scope.
Special considerations including issues related to equity or equality				N/A

Abbreviations: CML, chronic myeloid leukaemia; CP, chronic phase; CS, company submission; MMR, major molecular response; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation.

3 CLINICAL EFFECTIVENESS

After receiving the company submission (CS), the ERG submitted several points for clarification (PFC) to the company. Any additional or corrected data provided by the company have been incorporated into the analyses and discussion of this ERG report where appropriate.

3.1 Critique of the methods of review(s)

The company conducted a systematic review to identify the available clinical evidence for the safety and effectiveness of current treatment options for patients with chronic myeloid leukaemia in the chronic phase (CML-CP). The systematic review methods are summarised in CS section B.2.1 and B.2.2. Further detail is available in Appendix D. This section provides a brief summary and critique of the systematic review methods.

The ERG considered review methodology used to be broadly appropriate. However, there were variations in judgments on quality assessments between the company and ERG for some outcomes.

3.1.1 Searches

The search strategies to identify studies of asciminib and comparators for the treatment of CML-CP were included in Appendix D of the CS.

Several limitations were identified by the ERG which may have affected the ability of the searches to comprehensively retrieve all relevant studies, particularly non-English language papers and any non-RCT/observational studies. It is therefore possible that some relevant studies were not identified. Further details can be found in Table 3 below.

Table 3 ERG appraisal of evidence identification

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	PARTLY	- The segment of MEDLINE that was searched was not reported, so unclear if all parts of MEDLINE were searched (e.g. In Process, Epub Ahead of Print, non-indexed records).
Were appropriate sources searched?	PARTLY	- Sources of previous Health Technology Assessments were not searched e.g.: International HTA (INAHTA) database, HTA Database, websites of HTA agencies. - ClinicalTrials.com was not searched. - Limited searching for previous systematic reviews. Epistimonikos, Database of Abstracts of Reviews of Effects (DARE) and the Cochrane Database of Systematic Reviews (CDSR) were not searched. As the searches of MEDLINE and Embase were restricted to RCTs and non-RCT/observational studies, they may have missed relevant systematic reviews.

Was the timespan of the searches appropriate?	YES	Databases were searched from inception to 9th November 2020 and then updated to cover the period to 13th May 2021.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	- Chronic Myeloid Leukaemia (P) AND (asciminib (I) OR relevant comparators (C)) AND (RCTs OR non-randomised/observational studies (S)) - Seven extra comparators were included in the search strategies which were not in the NICE scope. It was unclear why they were included in the search strategies. - The comprehensiveness of the search could have been improved by removing the limit to RCTs and non-RCTs/ observational studies to allow retrieval of all study designs. Ineligible study designs could then have been more reliably identified and excluded at the screening stage.
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	PARTLY	- A limit to English language publications was applied to the searches. This matched the inclusion criteria, however would have caused any relevant studies published in other languages to be missed. - For the update search, retrieval was limited to studies published from the year 2020 onwards. However, this would have missed any studies studies published prior to 2020, that were not on the databases at the time of the original search.
Were any search filters used validated and referenced?	UNCLEAR	- It appears that the RCT and non-RCT/observational filters used in the MEDLINE and Embase search strategies were informed by several different filters which were then adapted. Therefore, it is likely the adapted filters were not validated. However, the terms used in the RCT filters appear to be comprehensive. - Previous research has shown that non-RCT/observational study design search filters are not sensitive enough for use in systematic reviews.[46]

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Study selection

The selection criteria were appropriate and mainly reflected the NICE scope. Study design criteria were also broad including RCTs, single-arm and Phase I trials, and observational studies.

The company RCT (ASCEMBL) was the only trial included in the systematic review that compared active interventions head-to-head. An additional 13 single-arm clinical trials and 23 observational studies were also included in the systematic review. Data from the Haematological Malignancy Research Network cohort (two UK Cancer Networks in the Yorkshire and Humber region) were also discussed in the CS, although not formally included in the systematic review.

3.1.2 Quality assessment

The ERG identified limitations with the quality assessment.

The company used two tools for assessing the quality of the studies included in their systematic review: the Cochrane risk of bias tool for RCTs,[47] and the Newcastle-Ottawa scale[48] for non-randomised studies. The ERG notes that the Cochrane risk of bias version used and the Newcastle-Ottawa tools are somewhat out-of-date, and have been superseded by more up-to-date quality assessment tools.[49, 50] The Newcastle-Ottawa assessment scored each study from 1 (poor) to 8 (good quality). The approach of scoring studies may be misleading; for instance, a study with a single significant design flaw may be less reliable than studies with several small limitations, yet have a higher overall quality score.

3.1.3 Evidence synthesis

Given the lack of head-to-head evidence for all comparators specified in the NICE scope except for bosutinib, evidence synthesis focused on a series of matching-adjusted indirect treatment comparisons (MAICs) that compared the effectiveness of asciminib with ponatinib, nilotinib, and dasatinib. These were based on four studies: ASCEMBL (see CS), PACE[51], Giles 2010[52], and Rossi 2013[53], with a further study by Ibrahim et al. (2010)[54] at the request of the ERG. The ERG summary and critique of these evidence syntheses are provided in section 3.3 and 3.4 below.

Responding to an ERG point for clarification, the company also provided summaries of other included studies in Table 1 of the response to points of clarification (PFC) document. The company also provided further information on a study of the asciminib compassionate use programme[55-57]in response to question A10 of the PFC document. The company clarified that they did not consider this study to be applicable to the UK population. The company pointed out that the patient population were older, it was conducted in Spain, and 90% of patients received ≥ 3 prior TKIs. Although the ERG agrees these factors (with the exception of region) may have impacted on generalisability to the UK population, given the limited data available in this area it should have informed the CS.

In addition, the company did not present data from their Phase I study (X2101) as it was the first trial in human participants. However, pooled safety data from this Phase I study and ASCEMBL are presented in Appendix N of the CS.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Data reported in the CS focused on an RCT (ASCEMBL) conducted by the company (see section 3.2.1.

3.2.1 ASCEMBL

3.2.1.1 Design

The design of the ASCEMBL trial is presented in the CS, Document B, pp. 35 to 43. The ASCEMBL trial is an open-label, international, phase III randomised trial comparing the efficacy and safety of asciminib 40 mg BD vs bosutinib 500 mg once-daily (OD). The trial included 233 individuals with Ph+ CML-CP previously treated with two or more TKIs.

The ASCEMBL trial used an open label design, neither patients nor study personnel were blinded to treatment allocation. The company argued it was not possible to blind participants to their intervention status. Bosutinib requires to be taken with food while asciminib requires to be taken fasted (see CS section B.2.13).

Patients randomised to the bosutinib treatment arm that met treatment failure criteria (according to 2013 ELN recommendations)[15] had the option to switch to asciminib where clinically appropriate.

Randomisation was stratified according to major cytogenetic response (MCyR) at baseline (defined as 0 to 35% Ph+ metaphases). The company provided further information on the randomisation procedure after an ERG clarification question. In summary, after an investigator had confirmed that participants met the eligibility criteria, patients were assigned a randomisation number using an Interactive Response Technology (IRT) provider linked to a treatment arm and medication number. The randomisation number was not communicated to the caller (see clarification response for further details).

The ASCEMBL trial is ongoing (96-week analysis planned in second quarter of 2022). The CS presents data from the 24-week primary endpoint, patient related outcomes, pharmacokinetics, and resource utilisation (25th May 2020 data cut-off). Other efficacy and safety outcomes were at 48 weeks (6th January 2021 data cut-off).

The ERG's main concern regarding the design of the ASCEMBL trial was the potential impact of an open-label design on TTD outcomes.

In response to request for clarification, the company stated that randomisation and objective efficacy endpoints mitigate any risks associated with the lack of blinding. The ERG agrees that objective outcomes (such as CCyR or MMR) are unlikely to be significantly impacted by a lack of blinding.

3.2.1.2 Study quality and risk of bias

The CS judged there was an unclear risk of performance bias for all outcomes. However, the ERG had some concerns regarding performance bias for the time to treatment discontinuation (TTD) outcome. The risk that decisions to discontinue treatment may, in some cases, have been influenced by patients' and study personnel's knowledge of treatment assignment cannot be excluded. The open-label trial design may have led to an underestimate of TTD in patients who received bosutinib.

An additional quality assessment issue was that company clarifications on methods of allocation concealment in the ASCEMBL trial raised further ambiguities. In response to PFC question A7, the company stated: "methods were not used to conceal allocation to asciminib or bosutinib treatment arms". This would lead the ERG to rate the trial at high risk of selection bias due to lack of allocation concealment. However, by contrast, the company's description of the randomisation process stated that patients were randomised by a centralised system after being classified as meeting inclusion criteria for the trial. These methods would lead the ERG to rate the trial at low risk of selection bias, as randomisation was appropriate. On balance, the ERG concluded that the risk of section bias is low.

Contrary to the company, the ERG has some concerns regarding a number of imbalances at baseline between the asciminib and bosutinib arms, which may have introduced bias. These are discussed in section 3.2.1.3.

3.2.1.3 Population and generalisability to the NHS

Eligibility criteria for inclusion to the ASCEMBL trial are provided in Table 4 (for further details see CS Table 8).

Table 4 Key Eligibility criteria in ASCEMBL

Inclusion criteria	Exclusion criteria
• Adults with CML-CP, who had received prior treatment with ≥2 ATP binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib), and were treatment failure or intolerant to the most recent TKI • ECOG PS of ≤2 • Evidence of typical BCR-ABL1 transcript (e14a2 and/or e13a2)	• Known presence of the T315I or V299L mutation at any time prior to study entry • Known second CP of CML after previous progression to AP/BP • Previous treatment with a haematopoietic SCT or patient planning to undergo allo-SCT • Presence of cardiac or cardiac repolarisation abnormality

Abbreviations: CML-CP: chronic myeloid leukaemia, chronic phase; ATP: adenosine triphosphate; TKI: tyrosine kinase inhibitor; ECOG PS: Eastern cooperative oncology group performance status; BCR: breakpoint cluster region; ABL1: Abelson; AP: accelerated phase

The ERG's clinical advisor agreed that the eligibility criteria were reasonable. However, although she agreed that there was justification for excluding patients with cardiac abnormalities, the clinical advisor considered this a sizeable proportion of the CML population in clinical practice. So, it is unclear whether data from ASCEMBL generalize to this important patient subgroup.

Similarly, the company excluded patients with the T315I mutation because bosutinib is known to be less effective in this patient group. This is an acceptable justification. However, there are no RCT data on the effectiveness of asciminib in this patient group, so it is unclear if data from the ASCEMBL trial generalizes to this subgroup. The company have subsequently clarified that reimbursement is not sought for patients with the T315I mutation.

Demographic and clinical characteristics of the patients included in ASCEMBL are summarised in Table 5. There are a number of imbalances in key characteristics (including sex, time since initial diagnosis and number of prior TKIs, and proportion of patients without a CCyR at baseline) that may favour asciminib. Although there was no evidence that these imbalances were statistically significant, the ERG has some concerns that they may have cumulatively biased response rate estimates in favour of asciminib.

Table 5 Key baseline characteristics of patients included in ASCEMBL trial (FAS)

Variable	Asciminib (N=157)	Bosutinib (N=76)	P-value
Mean age in years (SD)	[redacted]	[redacted]	[redacted]
Females (%)	[redacted]	[redacted]	[redacted]
Race n (%):			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	
Black or African American	[redacted]	[redacted]	
American Indian/Alaska Native	[redacted]	[redacted]	
Other/Unknown	[redacted]	[redacted]	
Ethnicity:			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	

Not reported/unknown	[redacted]	[redacted]	
ECOG performance status, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	
2	[redacted]	[redacted]	
Time since initial diagnosis, mean years (SD)	[redacted]	[redacted]	[redacted]
Number of lines of prior TKI therapy, n (%)			
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	
4	[redacted]	[redacted]	
≥5	[redacted]	[redacted]	
MCyR, n(%)			
Yes	44 (28.0)	21 (27.6)	[redacted]
No	78 (49.7)	46 (60.5)	
Missing[†]	35 (22.3)	9 (11.8)	
Number not in CCyR, n(%)	[redacted]	[redacted]	[redacted]

Abbreviations: FAS: full analysis set; SD: standard deviation; ECOG: Eastern cooperative oncology group; TKI: Tyrosine kinase inhibitor; MCyR: Major cytogenetic response; CCyR: Complete cytogenetic response

More females were assigned to asciminib (52.2%) compared with bosutinib (40.85%). Subgroup analyses found that at 24 weeks, difference in MMR rate [redacted] asciminib in females (RD [redacted]) but not males ([redacted]). Although these estimates lack precision and are based on a subgroup analysis, this raises some concerns that this imbalance may have favoured asciminib.

The proportion of patients who were not in CCyR (defined as 0% Ph+ metaphases) at baseline was lower in the asciminib arm (65.6%) compared with bosutinib (81.6%). The company did not report whether this difference was statistically significant. Analyses of CCyR at follow-up only included patients without CCyR at baseline, which mitigates the risk of bias due to CCyR imbalances at baseline for this outcome, although the company did not report whether the characteristics of the asciminib and bosutinib participants included in the analyses of CCyR were balanced at baseline. The ERG has some concerns that other analyses, notably MMR or TTD, which included all randomised patients, may have been biased by differences in baseline CCyR rates, although multivariate analyses

that adjusted for MCyR at baseline as well as other key variables (including sex and number of prior TKIs) showed no significant impact on MMR.

The ERG's clinical advisor also considered treatment history to be an important predictor. Asciminib patients had a shorter (6.2 years) mean time to diagnosis and a higher proportion receiving a maximum of two prior TKIs (52.2%) compared with bosutinib patients (mean time to diagnosis=7.0 years; maximum of two prior TKIs=39.5%). These baseline differences theoretically favour asciminib. Time to diagnosis was not explored as a potential prognostic factor in subgroup or regression analyses. Subgroup analyses did not find large differences in MMR rate between patients receiving two prior or three prior TKIs.

There was a potential imbalance in proportion of Hispanic or Latino patients (asciminib: 9.6% vs bosutinib: 22.4%) that was borderline statistically significant (p=0.05). However, given the number of statistical tests for baseline comparisons, the ERG recognises that some differences would be statistically significant by chance (i.e. 1 in 20). Ethnicity was not included as a subgroup analysis therefore it is unclear whether outcome data differed between these subgroups.

3.2.2 ASCEMBL Clinical effectiveness results

This section provides a summary and critique of the clinical effectiveness results of ASCEMBL, presented in the CS, Document B, pp.56-72. Table 6 presents a summary of the ASCEMBL key efficacy results at 24, 48- and 60-weeks follow-up.

Table 6 Summary of efficacy: 24, 48 and 60 weeks (ASCEMBL, FAS unless stated)

Outcomes	Asciminib (n=157)	Bosutinib (n=76)	Difference (95% CI)
MMR, n (%)	24 weeks: 43 (27.39) 48 weeks: [redacted] 60 weeks: [redacted]	24 weeks: 11 (14.47) 48 weeks: [redacted] 60 weeks: [redacted]	24 weeks: RD=12.85 (2.40 to 23.29) 48 weeks: RD=[redacted] 60 weeks: RD= [redacted]
MR, n (%)	24 weeks: 14 (8.9) 48 weeks: [redacted] 60 weeks: [redacted]	24 weeks: 1 (1.3) 48 weeks: [redacted] 60 weeks: [redacted]	- - -
CCyr, n(%) **CCyR analysis set[#]: asciminib=103 Bosutinib=62**	24 weeks: 42 (40.78) 48 weeks: [redacted] 60 weeks: not reported	24 weeks: 15 (24.19) 48 weeks: [redacted] 60 weeks: not reported	24 weeks: RD 17.30 (3.62 to 30.99) 48 weeks: RD [redacted] 60 weeks: not reported

TTD, % event free (95% CI)	1 year: [redacted]	1 year: [redacted]	1 year: HR=[redacted]
PFS, % (95% CI)	[redacted]	[redacted]	-
OS, % (95% CI)	[redacted]	[redacted]	-
MDASI-CML, mean change from baseline (95% CI)	-0.65 (-1.01 to -0.29)	-0.16 (-0.67 to 0.36)	-
EQ-5D-5L, mean (SD)	24 weeks: [redacted] 48 weeks: [redacted]	24 weeks[redacted] 48 weeks: [redacted]	-

Abbreviations: FAS: full analysis set; MMR; major molecular response, MR: molecular response; CCyR: complete cytogenetic response, TTD: time to treatment discontinuation, PFS=progression-free survival, OS: overall survival, MDASI-CML: MD Anderson Symptom Inventory-Chronic Myeloid Leukaemia, RD: risk difference, HR: hazard ratio; CI=confidence interval. #CCyR analysis set: subset of FAS, patients who were not in CCyR at baseline

MMR rate

This section provides a summary and critique of the clinical effectiveness results of ASCEMBL, presented in the CS, Document B, pp.56-72. Table 6 presents a summary of the ASCEMBL key efficacy results at 24, 48- and 60-weeks follow-up.

Table 6 shows that asciminib was associated with a higher MMR rate (24 weeks: RD=[redacted]; 48 weeks: [redacted]compared to bosutinib. However, the actual difference between groups was uncertain, 95% CIs were also compatible with negligible differences between groups.

CCyR rate

CCyR rate was higher in the asciminib (40.78%) than bosutinib group (24.19%) by 24 weeks in the subset of patients with no CCyR at baseline (CCyR analysis set). However, the between group difference declined by 48 weeks (asciminib: [redacted] vs bosutinib: [redacted]). Although the asciminib group still had a higher CCyR rate, the extent to which response rates differed in comparison with bosutinib was uncertain as the 95% CI was very wide (RD [redacted]).

Time to Discontinuation

Bosutinib patients ([redacted]) were less likely to remain event free compared with asciminib patients ([redacted]) at one year ([redacted]). For further details, see CS Figure 7 and Table 28.

As discussed above, (section 3.2.1.1), the ERG is concerned that TTD may have been biased due to the lack of blinding of participants and study personnel.

Progression Free Survival (PFS) and Overall Survival (OS)

The maturity of the data meant little could be concluded on PFS and OS. At 48 weeks, [redacted] in the asciminib arm and [redacted] in the bosutinib arm met criteria for PFS. There were more deaths in the asciminib arm ([redacted]) compared with bosutinib ([redacted]), but trial data are insufficiently mature to reliably identify differences between groups. Fatal adverse events are further discussed in Section 3.2.3.

Quality of life

There were no clear differences between groups on quality of life measures. According to the MDASI manual,[58] differences were not statistically significant ([redacted]; estimated by ERG) and unlikely to be clinically important. The MDASI manual suggests minimal clinically important differences (MCID) of SMD=0.5 or MDs ranging from 0.98 to 1.21 which are far higher than values observed in ASCEMBL. However, the ERG were unable to identify MCIDs specifically for the CML patient population. Between-group differences in EQ-5D-5L were also [redacted].

3.2.3 X2101 effectiveness results

As identified in sections 2.3.1 and 3.2.1.3, ASCEMBL excluded patients with the T315I mutation. Hence there are uncertainties on the effectiveness of asciminib in this population. However, the company have also conducted an earlier Phase I trial (X2101) that included this patient subgroup.[25]

The ERG notes that the company are not seeking reimbursement for patients with the T315I mutation. This section is therefore intended for reference only.

The company did not discuss the results from this trial in the CS, because it was the first human dose escalation study of asciminib. The ERG acknowledges the limitations of the study. However, since this is the only data available on the effectiveness of asciminib in T315I patients, results are summarised in Table 7.

Table 7 Discontinuation, MMR and CCyR data for asciminib according to T315I mutation and previous TKI status in CP-CML individuals

Outcome	Patients without T315I mutation	Patients with T315I mutation

	Total N=113	≤2 previous TKIs, N=32	>2 previous TKIs, N=81	Total N=28	≤2 previous TKIs, N=12	>2 previous TKIs, N=16
Patient remained in study, n (%)	88 (78)	-	-	19 (68)	-	-
MMR rate: By 6 months, n/ total n, (%)	37/99 (37)	13/25 (52)	24/74 (32)	5/20 (25)	4/10 (40)	1/10 (10)
By 12 months, n/ total n, (%)	44/91 (48)	15/25 (60)	29/66 (44)	5/18 (28)	4/9 (44)	1/9 (11)
CCyR rate: n/ total n, (%)	77/110 (70)	-	-	11/25 (44)	-	-

Source: Hughes et al. (2019)[25]. Abbreviations: MMR: major molecular response; CCyR: complete cytogenetic response; TKI: tyrosine kinase inhibitor

Twenty-eight CML-CP patients with the T315I mutation were included in the trial, 12 patients had received ≤ 2 previous TKIs and 16 patients >2 TKIs. Fewer patients with T315I mutation remained in the study (68% vs 78% for those without that mutation), but discontinuation was not reported by previous TKI status. MMR rate was also lower in patients with T315I mutation compared with those without (by 6 months: 25% vs 37%, by 12 months: 28% vs 48%) and even lower in patients with the T315I mutation who have received >2 prior TKIs (by 6 months: 10% vs 32%, by 12 months: 11% vs 44%). Similar patterns were found for CCyR rate (patients with T315I= 44% vs patients without T315I=70%).

However, the small number of patients with T315I mutation, and subgroup data not reported in a manner consistent to ASCEMBL (i.e. ≥ 2 prior TKIs) makes any conclusions drawn from the data very uncertain.

3.2.4 Adverse effects

Table 8 summarises data on adverse effects from ASCEMBL, X2101, and a pooled analysis of these studies. The proportions are similar across these two studies and the pooled analysis. Therefore, the text below will focus on data from ASCEMBL.

Asciminib patients were [redacted] to experience at least one event (Grade ≥ 3=[redacted]) compared with bosutinib patients (Grade ≥ 3=[redacted]), and also less likely to have at least one serious adverse event (asciminib: Grade ≥ 3=[redacted] bosutinib (Grade ≥ 3=[redacted]). Patients receiving asciminib were also less likely to discontinue due to an adverse event ([redacted]) than those receiving bosutinib ([redacted]).

Four patients receiving asciminib died compared to one death in bosutinib patients. The greater number of deaths in the asciminib group is cause for concern given the short follow up duration and prognosis in this population. Two deaths in asciminib patients were due to underlying disease in patients who had discontinued treatment, the other two deaths occurred during treatment (arterial embolism, ischemic stroke). The death in the bosutinib patient occurred during treatment (septic shock).

The ERG's clinical advisor highlighted several specific adverse effects that were of importance. Thrombocytopenia was almost [redacted] more [redacted] in asciminib (Grade ≥ 3=[redacted]) than in bosutinib patients (Grade ≥ 3=[redacted]). Hypertension was a little [redacted] in asciminib (Grade ≥ 3= [redacted]) compared with bosutinib (Grade ≥ 3= [redacted]). Hepatotoxicity was less common in asciminib patients (Grade ≥ 3= [redacted]) compared with those receiving bosutinib (Grade ≥ 3 = [redacted]).

Rates of pancreatic toxicity (asciminib: Grade ≥ 3= [redacted], bosutinib: Grade ≥ 3= [redacted]) and ischemic heart and CNS conditions were similar in both groups (asciminib: Grade ≥ 3= [redacted], bosutinib: Grade ≥ 3= [redacted]).

Table 8 Summary of adverse events in ASCEMBL, Study X2101, and pooled data

Adverse effect	ASCEMBL				Study X2101		Safety Pool			
	Asciminib 40mg BD (n=[redacted])		Bosutinib 500mg OD (n=[redacted])		Asciminib 80mg OD (n=[redacted])		Asciminib 40mg BD (n=[redacted])		Asciminib all patients (n=[redacted])	
	All grades, n (%)	Grade ≥ 3, n (%)	All grades, n (%)	Grade ≥ 3, n (%)	All grades, n (%)	Grade ≥ 3, n (%)	All grades, n (%)	Grade ≥ 3, n (%)	All grades, n (%)	Grade ≥ 3, n (%)
Number of patients with at least one event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least one serious event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common events Thrombocytopenia Neutropenia Headache Fatigue Hypertension Arthralgia Diarrhoea Nausea Nasopharyngitis Anaemia Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events of special interest Myelosuppression GI toxicity Hypersensitivity Haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Hepatoxicity Pancreatic toxicity Oedema and fluid retention Ischemic heart and CNS conditions Cardiac failure (clinical events)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]		[redacted]		-	-	-	-	-	-
BD=twice a day, OD=once a day, n=sample size, GI= gastrointestinal, CNS=central nervous system										

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Studies used for indirect comparison were chosen from those identified from the overall systematic review. The ERG is satisfied that the systematic review process to identify these trials was reasonably conducted (See Section 3.1).

The company assessed the quality of the studies using a version of the Newcastle-Ottawa scale, [48] as (apart from ASCEMBL) most were non-randomised, single-arm studies. The assessment scored each study from 1 (poor) to 8 (good quality). Only 3 studies scored 6 or more. Although quality scores may not be reliable and should be interpreted with caution, the ERG considers that this highlights the general limitations of single-arm cohort studies, and general poor reporting of these studies.

This means that all indirect comparisons were based on single-arm studies, so comparison methodology was limited to MAIC analysis, and meta-analyses and network meta-analyses could not be performed.

The systematic review identified 35 papers covering 23 studies. However, only 4 studies (ASCEMBL, PACE,[51] Giles et al. (2010)[52], and Rossi et al. (2013)[53] were used for the MAIC in the CS, with a further study by Ibrahim et al. (2010)[54] used in MAICs performed at the request of the ERG.

A summary of the studies included in the initial MAIC is reported in the CS, Appendix D, pp.39-41. All comparator studies included in the indirect treatment comparison were uncontrolled, non-randomised studies; two were phase II, single-arm trials, [51, 52] and two were prospective observational studies.[53, 54] All studies included individuals who were resistant or intolerant to two or more TKIs, and all except one only included individuals in the CP.[53] T315I mutations were eligible in all except one comparator study.[54] Median follow-up ranged from 12 to 56.8 months.

The ERG requested clarification on why most studies included in the SR were excluded from the MAICs. Key reasons for exclusion were:

1. All bosutinib trials were excluded as direct evidence on bosutinib is available in ASCEMBL. The ERG disagrees with this exclusion. We note that if a full network meta-analysis had been feasible trials of bosutinib providing indirect evidence would have been included. Therefore, a MAIC of bosutinib studies could provide useful supporting evidence, even if it would be less reliable than the direct comparison within ASCEMBL.
2. Four studies were excluded because "<80% of patients matched the target population and did not report baseline characteristics for the target population". While this may be reasonable, the ERG notes that adjustments could have been made using the overall baseline characteristics, unless there were clear reasons to consider them unrepresentative.
3. Seven studies were excluded for being too small (<20 persons), not reporting baseline data, or being Phase I trials. These were all reasonable grounds for exclusion.
4. Three studies did not report TTD. However, these did report other outcomes, and could have been used in MAIC analyses. One (Ibrahim 2010) was used in the revised MAIC analyses.

The ERG notes that it disagrees with some of these grounds for exclusion, and considers that more identified studies could reasonably have been used for MAIC analysis. MAICs could have used more than one trial per comparator intervention, which would have aided comparison and clarified whether adjustments made were robust.

The ERG also notes that the HMRN data discussed in the CS were not used for any indirect comparisons with ASCEMBL.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The ERG notes that the company in the CS reported performing a matched adjusted indirect comparison (MAIC) analysis to compare asciminib to other interventions. This was achieved by adjusting the results from the ASCEMBL trial and comparing these to suitable single-arm studies of other interventions.

The ERG had several concerns with how the MAIC analyses were performed and reported, as follows:

The MAIC analyses was performed only for time to discontinuation of treatment, as that was the primary outcome used for economic modelling. However, time to discontinuation was not an outcome specified in the NICE scope, and no evidence has been provided to demonstrate its correlation with survival outcomes (such as overall survival), nor that it is a clinically or patient-relevant outcome in

its own right. The ERG therefore requested that the company provide indirect comparison analyses (MAIC and unadjusted) for asciminib for all key outcomes: specifically, MMR, overall and progression-free survival.

The MAIC reported in the CS was limited in the number of sources compared to the ASCEMBL trial; with only one study compared to ASCEMBL for each comparator intervention. The CS also did not compare asciminib to the results from the HMRN database. The ERG therefore considered the company's indirect comparison analysis to be incomplete. The ERG requested summary outcome data for all identified studies, so naïve unadjusted comparisons between interventions could be performed.

While the CS described the MAIC process it did not report the full MAIC results. The CS reported adjusted time to discontinuation curves for asciminib in the ACSEMBL trial, but only limited data for comparator interventions, nor any estimates of relative effectiveness. The ERG was therefore unable to fully compare interventions using data in the CS, and requested that the company provide complete results for the MAIC analyses, including readjusted and unadjusted results from ASCEMBL and results from comparator studies. Th ERG notes that some of the limitations in reporting were due to limited outcome reporting in the included comparator trials.

Given these concerns, the ERG's assessment of the indirect comparison evidence is based on material supplied by the company after requests for clarification, rather than the CS. The company provided the following data:

1. Summary results (MMR, CCyR, OS, PFS) for all studies identified in the systematic review
2. Naive unadjusted comparison of asciminib with comparators for selected studies (MMR, TTD)
3. MAIC of asciminib with comparators for selected studies (MMR, CCyR, TTD)

The following sections critique these data.

3.4.1 Naïve unadjusted indirect comparison of all identified studies

Figure 2 summarises all the outcome data reported by the company for all 36 studies (including ASCEMBL) identified by the company systematic review (See Section 3.1). For each available outcome (MMR, CCyR, OS and PFS) it plots the percentage of patients with that outcome at the follow-up time (in months). The colours indicate the different interventions. Circles are the ASCEMBL data; triangles are studies used in the company MAIC; squares are all other studies.

Table 9 shows the results of linear regressions of outcome against intervention and time. It shows the mean effect of asciminib and the comparison of other interventions to asciminib (except for OS, where comparisons are with bosutinib). Regressions were weighted by sample size. Negative

differences indicate that asciminib is superior to the comparator; positive numbers that asciminib is inferior.

Figure 2 Summary of all outcome data from the studies identified in the systematic review

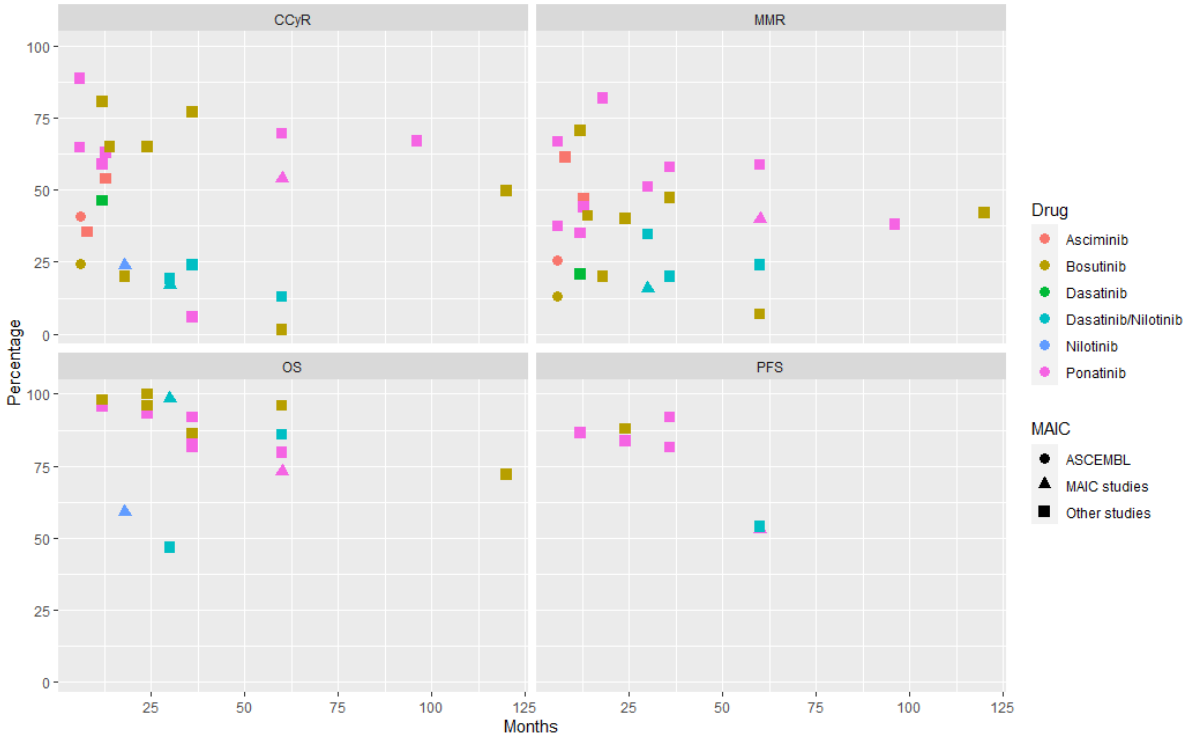


Table 9 Linear regression analysis of indirect comparisons from SR data

Outcome	Comparison	Mean effect (italics) / Mean difference (bold) (%)	SE (p-value)
MMR after 1 year	Asciminib	*45.8*	10.6 (0.0004)
	Bosutinib vs Asciminib	**-2.22**	12.83 (0.86)
	Dasatinib/Nilotinib vs Asciminib	**-26.03**	20.48 (0.22)
	Ponatinib vs Asciminib	**7.28**	13.55 (0.60)
CCyR after 1 year	Asciminib	*51.5*	3.89 (0.001)
	Bosutinib vs Asciminib	**7.98**	16.02 (0.62)
	Dasatinib/Nilotinib vs Asciminib	**-17.93**	22.3 (0.43)
	Ponatinib vs Asciminib	**10.50**	17.97 (0.57)
OS after 5 years	Bosutinib	*87.0*	2.9 (<0.001)
	Dasatinib/Nilotinib vs Bosutinib	**9.50**	16.51 (0.58)
	Ponatinib vs Bosutinib	**-12.39**	4.76 (0.024)

Abbreviations: SR: Systematic review; SE: standard error; MMR: major molecular response; CCyR: complete cytogenetic response; OS: overall survival

It should be remembered when considering Figure 2 and Table 9 that these are naïve unadjusted comparisons of studies with potentially very different participants and characteristics. This makes interpretation of these results uncertain. However, the ERG notes several key points:

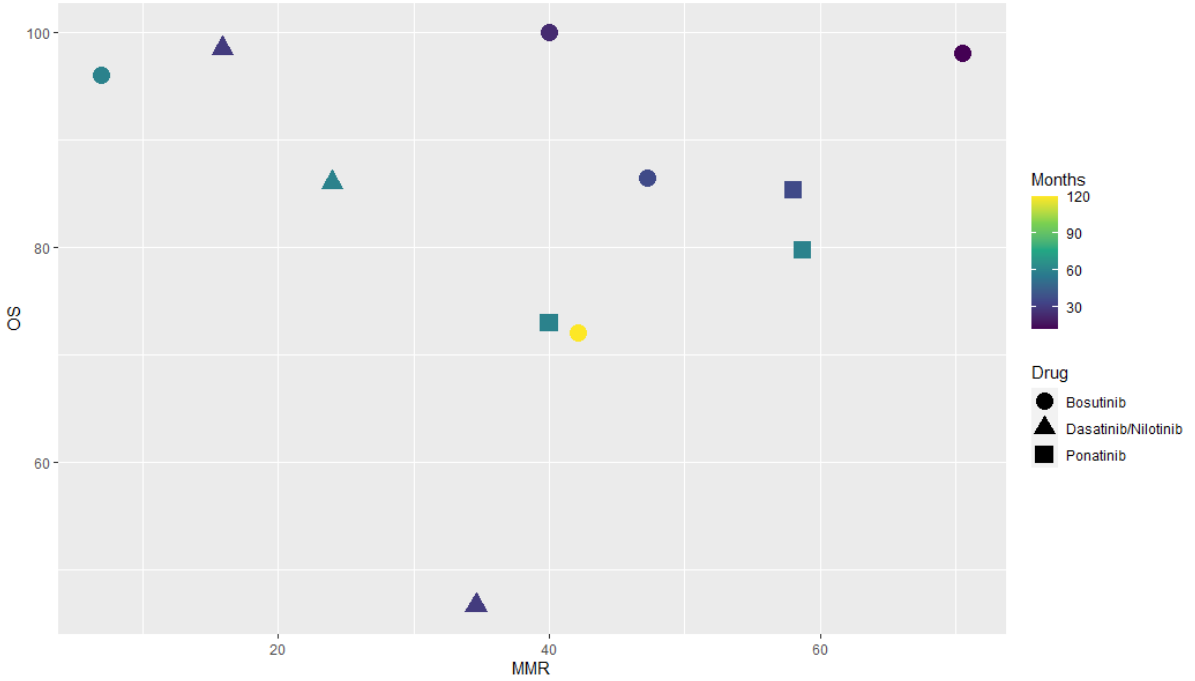
There is evidence of substantial variation both between and within interventions for all outcomes, suggesting that their effectiveness may be highly uncertain, and perhaps strongly dependent on patient characteristics.

The results for ASCEMBL, for both MMR and CCyR are notably poorer, in both arms, than for other studies. For example, [redacted] of patients on bosutinib achieved MMR in ASCEMBL, compared to over 40% in most other studies. This may be due to the short follow-up time, or to patient characteristics.

The regression analyses suggest that asciminib is broadly similar to bosutinib for MMR and CCyR response; may be superior to dasatinib and nilotinib; and may be inferior to ponatinib. However, the substantial variation across studies meant that none of the comparisons were statistically significant. For overall survival ponatinib was inferior to bosutinib, despite being superior to it for MMR. This may be because the interventions are used at different line of therapy, or patients have more advanced disease in trials of ponatinib, but highlights the difficulty of using MMR as a surrogate for later survival.

Figure 3 shows the association between MMR and OS, for studies that reported both outcomes. There is no correlation between the two outcomes. This assessment is limited because it used data aggregated at study level, rather than patient-level data, but further raises concerns about using MMR as a surrogate for later survival.

Figure 3 MMR vs OS in studies in the systematic review



3.4.2 Naïve unadjusted indirect comparisons provided by the manufacturer

The ERG notes that naïve unadjusted comparisons between studies and interventions may give misleading results where studies vary in key prognostic factors, such as line of therapy or disease severity. However, given the ERG's concerns with parts of the MAIC process (see Sections 3.3 and 3.4), we requested that the company provide full unadjusted results for all studies included in the MAIC, to permit comparison. Some of the data supplied by the company in response to this request were incorrect. As this was subsequently clarified by the company at time of factual accuracy checking, those errors have been corrected here.

As discussed in Section 3.3, the company used only four studies (one per comparator) in the MAIC analysis. The data from those studies, and ASCEMBL, are presented in Table 10. Some data were not supplied by the company, but could be extracted from publications, or the CS. These are shown in red. The ERG notes that it cannot confirm the quoted MMR of 19% in the PACE trial, as this does not appear to have been directly reported. The ERG notes that the overall MMR in PACE was 40%, with a median time to MMR of 5.5 months, and 34% had MMR after 1 year.

The ERG notes the substantial limitations in this data; for example, Giles 2010 did not report MMR as an outcome. Because the company chose to focus on TTD as the outcome of interest for the MAIC it is largely impossible for the ERG to properly assess how results in ASCEMBL compare to other interventions for the outcomes specified in the scope, particularly survival outcomes and MMR.

Table 10 Naive unadjusted comparison supplied by the company

		ASCEMBL	PACE (Ponatinib)	Giles 2010 (Nilotinib)	Rossi 2013 (Dasatinib)
OS	1-year survival, % (95% CI)		Around 80	At least 59	At least 98.5
	5-year survival, % (95% CI)		Around 73		
PFS	1-year survival, % (95% CI)	NA	80	NA	NA
	5-year survival, % (95% CI)	NA	53 (45, 60)	NA	NA
MMR	MMR (6 months), % (95% CI)	27.4	19 (15, 26)	NA	15.9
TTD	Median (months) (95% CI)	Not reached	32.1 (0.1, 73.0)	11 (<1.0, 29.2)	14

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival; MMR: major molecular response; TTD: time-to-treatment discontinuation

3.4.2.1 Adverse events

The company also provided a comparison of adverse events in the clarification document (see clarifications question A15, Table 20). As this table was extensive it is only partly reproduced here in Table 11, for more common or serious adverse events, limited to adverse events occurring in more than 5% of patients, and SAEs occurring in more than one patient. The Giles and Rossi papers had limited data on adverse events, so ASCEMBL is compared only to PACE here.

Overall, asciminib appears to have a better adverse event profile than ponatinib, across almost all adverse event types. However, as this is an indirect comparison, the possibility that patients in PACE were more susceptible to adverse events due to their underlying characteristics cannot be ruled out.

Table 11 Naïve comparison of adverse events in ASCEMBL and PACE

Type of AE	Number (%) of events	
	ASCEMBL (asciminib)	PACE (ponatinib)
Nonhematologic AEs any grade, n (%)		
Abdominal pain	9 (5.8)	125 (46)
Rash	12 (7.7)	127 (47)
Constipation	NA	112 (41)
Headache	29 (18.6)	116 (43)
Dry skin	7 (4.5)	114 (42)
Fatigue	21 (13.5)	81 (30)
Hypertension	19 (12.2)	99 (37)
Pyrexia	6 (3.8)	70 (26)
Arthralgia	19 (12.2)	90 (33)
Nausea	18 (11.5)	79 (29)
Diarrhoea	18 (11.5)	54 (20)
Increased lipase	8 (5.1)	73 (27)
Vomiting	11 (7.1)	50 (19)
Myalgia	8 (5.1)	65 (24)

Pain in extremity	13 (8.3)	65 (24)
Pruritus	8 (5.1)	NA
Asthenia	9 (5.8)	NA
Peripheral oedema	9 (5.8)	NA
Nonhematologic AEs grade 3/4, n (%)		
Abdominal pain	0	28 (10)
Hypertension	9 (5.8)	37 (14)
Increased lipase	6 (3.8)	34 (13)
Vomiting	2 (1.3)	4 (1)
Hematologic TEAEs, any grade, n (%)		
Thrombocytopenia	36 (23.1)	123 (46)
Neutropenia	30 (19.2)	53 (20)
Anaemia	15 (9.6)	53 (20)
Hematologic TEAEs, grade 3/4, n (%)		
Thrombocytopenia	28 (17.9)	95 (35)
Neutropenia	24 (15.4)	45 (17)
Anaemia	2 (1.3)	28 (10)
SAEs, %		
Pancreatitis	NA	7
Atrial fibrillation	0	6
Pneumonia	1 (0.6)	6
Angina pectoris	NA	5
Pyrexia	2 (1.3)	NA
Urinary tract infection	2 (1.3)	NA

AE: adverse event; TEAE: treatment-emergent adverse event; SAE: serious adverse event

3.4.3 Naïve unadjusted indirect comparison with HMRN data

The ERG requested that the company provide a naive unadjusted indirect comparison of ASCEMBL with the HRMN data described in the CS. This was because the ERG considers the HMRN data to be likely to be the best evidence on the effectiveness of comparator interventions in the UK. Table 12 summarises the data provided. The company also provided survival outcome data from HMRN, but this could not be compared to ASCEMBL due to its short follow-up time, so survival outcomes are not presented here.

Table 12 Naïve unadjusted comparison with HMRN data

TKI	**Third-line**			**Fourth-line**	
	MMR (6 months) % (CI)	**MMR (12 months), % (CI)**	**TTD Median months (CI)**	**MMR (6 months) %**	**TTD Median months (CI)**
Asciminib (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval: TKI: tyrosine kinase inhibitor; MMR: major molecular response; TTD: time-to-treatment discontinuation

At third line asciminib appears inferior to bosutinib, dasatinib and nilotinib for MMR , although confidence intervals are wide, so this inferiority is not conclusive. At fourth line, asciminib remains inferior to dasatinib and nilotinib for MMR, but asciminib appears superior to bosutinib . No confidence intervals were supplied for fourth-line data, so the uncertainty cannot be assessed.

Both MMR and TTD were poor for ponatinib in the HMRN data, but there were only nine patients who received ponatinib.

Interpretation of these results is complicated by the fact that results for asciminib are not distinguished for line of therapy, so exact results for asciminib could be different. If asciminib resembles other treatments, results in third line could be better than estimated, but poorer in fourth line. The generally small sample sizes in the HMRN data set also mean that it is difficult to draw any firm conclusions on how asciminib compares to other interventions.

3.4.4 Matched adjusted indirect comparisons (MAIC): general critique

In the original company submission, the company performed a MAIC analysis comparing asciminib to comparator interventions for time to discontinuation. The ERG had several concerns with the MAIC as presented. This section details those concerns.

3.4.4.1 Use of TTD as an outcome

The MAIC presented by the company reported only TTD as an outcome. The ERG notes that this was not an outcome in the original scope, nor was its choice justified by the company. It appears to have been used solely because the submitted economic model was based on TTD. No evidence has been provided to demonstrate that TTD is a reasonable surrogate outcome, for survival, or any other outcome in the scope. Other concerns with using TTD as an outcome have been discussed earlier (see Section 3.2.1.2).

The ERG therefore thinks the value of TTD as a clinical outcome is questionable, and requested that MAIC analyses also be performed for outcome specified in the scope or reported in ASCEMBL, specifically MMR, OS and PFS. The company supplied a MAIC for MMR and also for CCyR, but not for survival outcomes, due to the immaturity of survival data in ASCEMBL.

3.4.4.2 Selection of trials used in the MAIC

The systematic review identified 35 papers covering 23 studies. However, only 4 studies (ASCEMBL, PACE,[51] Giles et al. (2010)[52], and Rossi et al. (2013)[53] were used for the MAIC in the CS, with a further study by Ibrahim et al. (2010)[54] used in MAICs performed at the request of the ERG. See Section 3.3 for a discussion of the grounds for exclusion given by the company.

The company did not produce a MAIC to compare asciminib in ASCEMBL to the HMRN data. The company also declined to perform such a MAIC when the ERG requested it. This was mainly on the grounds that the company considered that data from clinical studies is likely to be more relevant or reliable than that from a registry. The ERG questions this claim, and does not consider it to be strong grounds not to attempt a MAIC analysis, particularly as the sample sizes in HMRN are similar to those in the selected studies (except for ponatinib).

Overall, therefore, the ERG has some concerns that the MAIC analyses were unnecessarily limited, and more studies could have been included.

3.4.4.3 Critique of the MAIC methodology

Overall, the MAIC analyses appear to have been conducted correctly. The initial selection of prognostic factors intended for use in the adjustment appeared reasonable, with no obvious factors missing that might influence the results.

The ERG notes that there were several prognostic factors where ASCEMBL differed substantially from other studies, particularly: having more patients with 3 or more previous TKIs, fewer with imatinib resistance/intolerance, fewer patients with gene mutations, more patients with EGOC 0 status, and a younger age profile. Differences are summarised in Table 13 (taken from CS Appendix I)

Table 13 - Comparison of baseline characteristics in MAIC trials

Characteristics	Asciminib				Ponatinib	Omacetaxine	Nilotinib	Dasatinib
Trial/Study								
Patients								
Prior TKI = 2								
Prior TKI >=2								
TKI resistant to Nilo/Dasa								
TKI intolerant only (Nilo/Dasa)								
Imatinib resistant								
Imatinib intolerant								

Dasatinib resistant	[redacted]						[redacted]	
Dasatinib intolerant	[redacted]						[redacted]	
Nilotinib resistant	[redacted]							[redacted]
Nilotinib intolerant	[redacted]							[redacted]
MCyR @ baseline	[redacted]						[redacted]	
PCyR @ baseline		[redacted]	[redacted]	[redacted]	[redacted]			
No mutation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of mutation = 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
ECOG = 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Median Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: company submission, Appendix I

Following a request for clarification from the ERG, the company presented a formal assessment of the overlap between the populations of the comparator trials included in the MAIC against ASCEMBL, including the distribution of key covariates and standardised mean differences before after matching (Clarification response, pp. 42-44). The company's assessment of overlap shows that the effective sample size (ESS) for ASCEMBL after weighting was significantly reduced in all comparisons (ESS=48 to 74 where reported, out of a total of 157 participants in ASCEMBL). This indicates that the population overlap in the MAIC was limited, and that adjusted effect estimates after weighting may not be robust.

When attempting to perform the MAIC analyses the company found models adjusting for all factors did not converge, and models with fewer factors had to be considered. The company chose to favour models with maximal effective sample size (ESS); that is, models which retain the maximum equivalent numbers of patients in ASCEMBL after adjusting. While such an approach is reasonable in order to retain maximum robustness, it meant that several key factors could not be adjusted for. In particular, none of the MAICs adjusted for age, ECOG status or gene mutations. The ERG considers that these are likely to be important prognostic factors, and there is evidence (Table 13) that they differed between trials. This could therefore have led to substantial bias in the MAIC analyses.

The ERG notes that methodological detail was only provided for the MAICs of TTD. No details on the models used for the subsequent MAICs of MMR or CCyR has been provided.

Overall, the ERG considers that there are substantial problems with the conduct of the MAIC analysis performed by the company. They are sufficient to raise major concerns as to the validity and robustness of the analyses, and therefore the ERG considers that they are unlikely to be reliable for determining the true effectiveness of asciminib.

3.4.5 Matched adjusted indirect comparisons (MAIC): results

The company provided a MAIC for TTD in the original submission, a MAIC for MMR on request from the ERG, and a MAIC for CCyR to support the revised economic model. The company declined to perform MAICs for survival outcomes due to the immaturity of the data in the ASCEMBL trial.

Table 14 presents the ERG's estimates of the MAIC results for TTD. For asciminib, data is extracted from Kaplan-Meir curves in the CS. The ERG notes that some data provided by the company were incorrect. Where this has been clarified, the data here have also been corrected.

Table 14 Summary of TTD MAIC results

Comparator	Intervention (Trial)	Median TTD (months)
	Asciminib (Unadjusted)	[redacted]
Ponatinib	(PACE)	32.1
	Asciminib (adjusted)	[redacted]
Dasatinib	(Rossi)	14
	Asciminib (adjusted)	[redacted]
Nilotinib	(Giles)	11
	Asciminib (adjusted)	[redacted]

The results suggests that patients may stay on ponatinib for longer than asciminib. Median TTD was [redacted] when ASCEMBL data were adjusted for comparison with dasatinib and nilotinib. This would suggest asciminib has longer TTD than either dasatinib or nilotinib, but no confidence intervals were available, so this is uncertain. The ERG also notes that TTD was substantially longer in the HMRN data for both dasatinib (1.7 years) and nilotinib (3 years).

Table 15 summarises the MAICs performed for MMR and CCyR. The ERG cannot confirm the figure of 18.7% MMR for ponatinib given in the CS, but the PACE trials states that 40% of patients achieved MMR, with a median time to MMR of 5.5 months. The ERG notes that these results were supplied without confidence intervals. Few details were provided about the methods used for these MAIC analyses.

Table 15 Summary of MAIC results for MMR and CCyR

	Asciminib vs Bosutinib (unadjusted from ASCEMBL)		Asciminib vs Ponatinib (PACE)		Asciminib vs Dasatinib/Nilotinib (Ibrahim)	
	Asciminib	Bosutinib	Asciminib	Ponatinib	Asciminib	Dasatinib/Nilotinib
MMR	[redacted]	14.5%	[redacted]	18.7%	[redacted]	20.8%
CCyR	[redacted]	33.87%	[redacted]	43.26%	[redacted]	30.9%

The adjusted results for CCyR for dasatinib/nilotinib [redacted], particular when considering that other MAICs produced [redacted] in effect estimates. As no information on the conduct of this MAIC was provided, the ERG cannot check the validity of this result. Using the unadjusted results suggests that there is a possibility that asciminib gives better MMR and CCyR rates than dasatinib/nilotinib, but, without confidence intervals, this is uncertain. The data on ponatinib are too uncertain to draw any firm conclusions.

3.5 Additional work on clinical effectiveness undertaken by the ERG

As the ERG did not have access to the ASCEMBL data we were unable to perform any further statistical analyses, or to check the MAIC analyses.

Additional work was limited to performing naïve indirect comparisons. See Section 3.4.1 for details of these analyses.

3.6 Conclusions of the clinical effectiveness section

3.6.1 Decision problem

The company placed asciminib as an option in third and subsequent lines in the treatment of adults with adults with Ph+ CML-CP. ERG found the company's positioning was likely to be appropriate, with most patients receiving asciminib as either third- or fourth-line treatment. The likely distribution of patients who would receive asciminib as third versus fourth-line and beyond is uncertain.

Overall, the ERG found that the evidence submitted broadly reflects the decision problem. However, the company's comparisons with other TKIs listed in the scope and the company's economic model rely heavily on TTD, which was not a specified outcome in the final scope. No evidence was provided for the validity of TTD as a marker of long-term survival. The ERG believes that TTD may not be a

robust measure of treatment efficacy, and that CCyR and MMR may be more appropriate alternative intermediate endpoints.

The clinical evidence presented in the CS broadly reflects the population described in final scope. The asciminib trial evidence included patients who may be fitter, younger and with fewer comorbidities than the population who would be eligible for asciminib in practice.

3.6.2 ASCEMBL trial

The ASCEMBL trial excluded patients with cardiac comorbidities and patients with the T315I mutation. These exclusions are justified in aiming to ensure comparability between treatments.

The ERG has concerns about a number of potential imbalances in baseline characteristics, that, cumulatively, may have favoured participants who received asciminib. The trial used an open-label design. This may have biased TTD estimates.

Very few patients in the trial had progressed disease or had died. There was therefore insufficient data to conclude on whether there were differences between asciminib and bosutinib on PFS and OS. The ASCEMBL trial suggested that asciminib was more clinically effective than bosutinib for most outcomes (e.g. MMR, CCyR, TTD). However, the magnitude and clinical significance of between group differences were very uncertain due to wide 95% CIs and potential risk of bias for some outcomes.

Asciminib patients were less likely to experience adverse events, serious adverse events, and less likely to discontinue due to adverse events. However, Grade ≥ 3 thrombocytopenia was almost three times as common in asciminib compared with bosutinib. The ERG's clinical advisor considered this an important adverse effect.

Overall, the ACEMBL trial suggested some superiority of asciminib over bosutinib in terms of TTD, clinical response (MMR and CCyR) and reduced adverse events. However, the ERG has concerns about potential bias in the trial, particularly for TTD, and so concludes that asciminib should not be assumed to be definitively superior to bosutinib.

3.6.3 Indirect comparisons

Naïve unadjusted comparisons between ASCEMBL and other studies of asciminib with trials of other TKIs identified by systematic review demonstrated considerable variation in response (MMR, CCyR) and survival outcomes (OS, PFS) both between and within TKIs. This variation means that a robust indirect comparison of asciminib with other TKIs is difficult, even if matched adjusted analyses can be performed.

The naïve comparison suggested that asciminib may be similar in response (MMR and CCyR) to bosutinib, superior to dasatinib and nilotinib, and possibly inferior to ponatinib. However, no difference was statistically significant, and this comparison makes no adjustment for differences in patient characteristics across trials. Comparing adverse events for asciminib and ponatinib suggested that asciminib may have a better adverse event profile. A comparison of survival outcomes was not possible, due to the immaturity of the ASCEMBL data.

The MAIC analyses reported in the CS were limited to adjustments of TTD. The ERG notes that TTD was not an outcome defined in the original scope, and it appears to have been included mainly because it was the outcome used to structure the economic model. Differences in TTD between TKIs could be confounded by a number of factors, including availability of other subsequent treatments. As discussed above, TTD may not be a suitable surrogate for response or survival outcomes. The ERG considers it to be an inappropriate choice of outcome for indirect comparison.

The ERG had numerous concerns with the conduct of the MAIC analyses. Only four trials were used, one per comparator TKI, and it is unclear whether these are representative of the other TKIs, or how results might vary had other trials been used. In particular, no MAIC was performed to compare ASCEMBL to the HMRN data. The trials used also varied between outcomes, with different trials used for TTD analysis than for MMR/CCyR analysis, creating inconsistencies in results and interpretation. Overlap between ASCEMBL and trial included in the MAIC was limited. There were problems with convergence in MAIC models, and the factors adjusted for varied between analysis and may not be sufficient to properly adjust for differences between studies.

Given these concerns with the reporting and conduct of the MAIC analyses, and the limitations of naïve indirect comparison, the ERG considers that there is currently no robust evidence to reliably assess the clinical differences between asciminib and other interventions.

4 COST EFFECTIVENESS

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

The company performed systematic literature reviews (SLR) to identify relevant economic evaluations of treatments for CML. The details of the methods and results of the SLRs are reported in the CS, Appendix G and summarised below.

4.1.1 Searches

The CS included the searches to identify economic evaluations of tyrosine kinase inhibitors (TKIs) for CML in Appendix G.

The searches may have missed potentially relevant studies due to the way that study design search filters were adapted and incorporated into the strategies for MEDLINE and Embase. Validated search filters that have been designed and tested for use in sensitive search strategies are available and would have been a more reliable method of limiting to economic evaluations, particularly for identifying those published since the NHS Economic Evaluations Database closed in 2015.

The ERG appraisal of the searches can be found in Table 16 below.

Table 16 ERG appraisal of evidence identification

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	Yes	Errors were corrected and missing information was provided in the response to the PFCs.
Were appropriate sources searched?	Partly	- No search of the International HTA (INAHTA) database, however several websites of international HTA agencies were searched to identify previous HTAs. - The reference lists of included studies were not checked to identify further relevant economic evaluations.
Was the timespan of the searches appropriate?	Unclear	The searches covered the period from 2010 to May 2021. No justification for limiting from 2010 was reported in Appendix G.
Were appropriate parts of the PICOS included in the search strategies?	Yes	CML (**P**opulation) AND economic evaluations (**S**tudy design).
Were appropriate search terms used?	Yes	
Were any search restrictions applied appropriate?	Not applicable	

Were any search filters used validated and referenced?	Unclear	Several search filters were referenced in the response to the PFCs, therefore it was unclear whether the final filters used in the search strategies were validated. The combining and adapting of several search filters is not considered an optimal method of searching comprehensively for economic evaluations.

4.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria applied are summarised in the CS, Appendix G, Table 3 and follow the usual PICOS framework. In brief, the review included published economic analyses of selected treatments for CML. Treatments considered included: asciminib, nilotinib, imatinib, dasatinib, bosutinib, ponatinib, Interferon (broad-spectrum), Allo-SCT, omacetaxine, and best supportive care (including hydroxycarbamide). The review did not focus specifically on any line of treatment and therefore considered a broader population than the NICE scope.

A date limit of 2010 was applied, and the review considered only abstracts presented in English. The selection of studies was undertaken in two stages, with two reviewers independently assessing abstracts and titles for inclusion followed by full-text assessment by two reviews independently. Any differences in reviewer decisions were reconciled by a third review at both stages of the selection process.

The ERG considers that the inclusion/exclusion criteria are appropriate and relevant to the decision problem.

4.1.3 Studies included and excluded in the cost-effectiveness review

A total of 45 economic evaluations were identified in the review. This included 29 unique studies and 16 Health Technology assessments. The most relevant economic analyses identified were several previous NICE, including bosutinib (TA401)[16] and ponatinib (TA451)[18]. The CS identify these two TAs to be of particular significance as they exemplify the two distinct approaches that have been adopted to model CML. Central to these different approaches is how they extrapolate short-term trial data given the relatively long-life expectancy associated with CML.

The first approach is the cumulative survival approach. This approach was used for decision making in TA401[16] and was also one of the model structures considered in TA426[17]. The cumulative survival approach assumes that life expectancy post discontinuation of treatment is independent of the initial treatment received. Under this approach, the effectiveness of each treatment is captured by time-to-treatment discontinuation (TTD), with total survival time estimated as the sum of a treatment specific TTD and a fixed (treatment independent) survival period.

The second approach is the surrogate modelling approach which uses a response-based model. Under this approach, response to treatment is used to predict progression-free survival (PFS), assuming a common (treatment independent) surrogate relationship between each specific response category and progression-free survival. Under this approach, treatment specific PFS is determined according to the proportion of patients achieving each level of response and is the sum of the PFS curves associated with each level of response. This approach was used for decision-making in TA 451 and was considered in both TA 401[16] and TA 426. [17]

Each of these approaches makes specific assumptions and, as such, has different strengths and weaknesses. These are discussed in detail in Section 4.2.2, where the validity of the company's modelling approach is assessed.

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

4.2.1 NICE reference case checklist

Table 17 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 17 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits to treated individuals were considered.
Perspective on costs	NHS and PSS	NHS and PSS costs have been considered.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	A cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model uses a 50-year time horizon. Less than 2.4% of patients are expected to survive beyond this period.
Synthesis of evidence on health effects	Based on a systematic review	The company initiated a systematic review to identify relevant sources of comparator data.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Values used for CP health states were based on EQ-5D-5L data collected in the ASCEMBL trial. These values were cross-walked to EQ-5D-3L values using the van Hout et al. [59]mapping function. Values for AP and BP health states were obtained from Szabo 2010 [60] which used a Time Trade-Off approach to elicit utility values.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Values for CP health states were derived from EQ-5D data directly obtained from patients in the ASCEMBL trial [41]. Values

		for AP and BP health states were elicited directly from members of the public.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	CS appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	CS appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs were based on UK sources including the BNF and NHS reference costs. Resource use rates were adapted from data utilised in TA451 (ponatinib).
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits have been discounted at 3.5% per annum. Scenario analysis was performed applying an annual discount rate of 0% and 5%.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company presented a model for the original submission based on an approach the company have identified as the "*cumulative survival approach*". This model is considered to be the company's preferred method of modelling the cost-effectiveness of asciminib. Following the response to clarification questions and at the request of the ERG, the company also presented a second model, referred to as the "*surrogate survival approach*". Both of these models are described below and a critique of the approaches and uncertainties are presented.

Cumulative survival approach

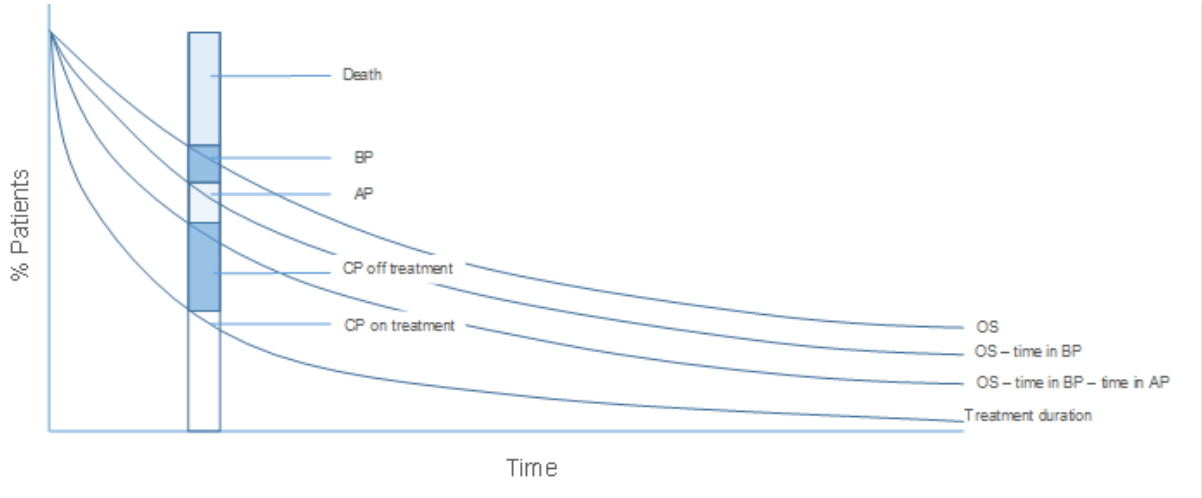
The company developed a de novo cost-effectiveness model in Microsoft Excel to simulate the long-term outcomes of CML-CP patients previously treated with two or more TKIs. The model structure is based on a set of partitioned survival models (PSM).

The first PSM, models patients who do not undergo an allo-SCT for the duration of the model time horizon. In this PSM, patient outcomes are modelled through several mutually exclusive health states: chronic phase (CP), accelerated phase (AP), blast phase (BP) and death. Within the CP, patients can be classed as on-treatment or off-treatment, the latter for those who have discontinued their primary treatment but remain in the CP.

The proportion of patients in each health state is determined directly from the survival curves. The proportion in the CP is based on time to discontinuation (TTD) curves, which are informed by a combination of parametric models fitted to observed treatment discontinuation data from ASCEMBL

and median TTD reported in the literature (see Section 4.2.6 for further details). Following discontinuation, the model assumes death occurs 7 years on average post-discontinuation. This is independent of the treatment received and is the central assumption of the cumulative survival approach; OS is therefore the cumulation of TTD and the fixed 7-year post-progression survival period. Within the 7-year post-discontinuation survival period, it is assumed 10 months is spent in the AP and 6 months are spent in the BP. Figure 4 illustrates the PSM structure. This illustrates that it is only TTD (CP on treatment) as illustrated in Figure 4, which varies by treatment; all other stages (e.g. CP off treatment, AP and BP) remain constant irrespective of treatment selected.

Figure 4 Illustration of partitioned survival model structure (Figure 17 from the CS, pg. 120)



Abbreviations: AP, advanced phase; BP, blast phase; CP, chronic phase; OS, overall survival.

The second set of PSM models is used to reflect the outcomes of patients undergoing allo-SCT. This can occur at either the point of discontinuation of primary treatment or at the point of progression to AP or BP. In the allo-SCT PSMs, patient outcomes are modelled through three distinct health states: relapse-free, relapsed disease and death. Like the first PSM, the proportion of patients in each health state in the second PSM is determined directly from the survival curves, which are based on survival outcomes reported in the literature. There are two distinct versions of the allo-SCT PSM to account for the phase in which allo-SCT is received. The first reflects the outcomes of patients who receive allo-SCT during the CP phase and the second those who receive allo-SCT in either the AP or BP. Details of the survival outcomes informing the allo-SCT PSM can be found in Section 4.2.6.

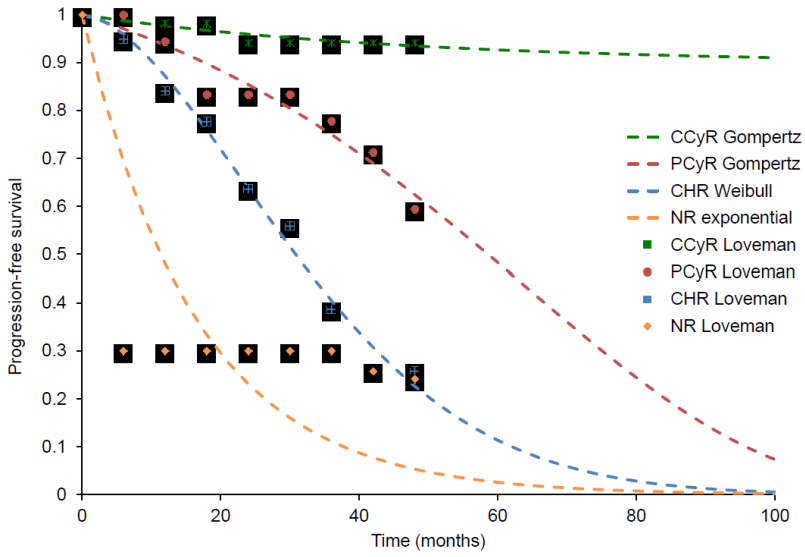
Surrogate survival approach

In response to clarification questions at the request of the ERG, the company presented an alternative economic analysis that uses an alternative model structure. This second model uses a surrogate survival model, which is based broadly on the model used in TA451 (ponatinib).[18] The model has some similarities with the cumulative survival approach, in that there are two PSMs: one for patients who have not undergone an allo-SCT; one for those undergoing allo-SCT. The surrogate survival approach, however, makes different assumptions about how the period prior to progressive disease (AP and BP) is determined.

In patients who do not undergo allo-SCT the duration of PFS is modelled as a function of cytogenetic and haematological response. The model used four response categories i) complete cytogenic response (CCyR), ii) partial cytogenetic response (PCyR), iii) complete haematological response (CHR), and iv) no response (NR). The patients classified into each of the four response categories are assumed to follow distinct PFS curves (Figure 2) based on the parametric extrapolation of pseudo-patient-level data digitised from TA451.[18] Progression-free survival for the whole cohort was therefore based on the distribution of patients achieving each level of response and represents a weighted average of the survival outcomes associated with each response category.

Figure 5 - PFS as a function of response to treatment as reported in TA451 (ponatinib) (Figure 1, PFC response, pg. 60)

Figure 5-7. Comparison of the BMS-034 study data and the fitted parametric functions



CCyR, complete cytogenetic response; CHR, complete haematologic response; NR, non-response; PCyR, partial cytogenetic response.

Separate curves for progression to BP and OS for the four response categories were generated from each of the modelled PFS curves. Curves for progression to BP and OS were assumed to follow an exponential distribution with rates chosen to ensure that the respective curves generated a mean time

to event which was 10 months and 6 months after the respective mean progression to AP. A curve for progression to AP, a curve for progression to BP and a curve for OS were therefore constructed from the respective four curves for patients according to the proportions in each response category. The second PSM, to represent patients undergoing allo-SCT is implemented in a similar way to the cumulative survival approach.

4.2.2.1 Points for critique

The ERG has several concerns regarding both model structures presented by the company. The critique will be structured as follows. First, a critique of the cumulative survival approach will be presented followed by a critique of the surrogate survival approach. Following the discussion of these two approaches, additional points for critique are raised which are present in both models.

Cumulative survival approach

The cumulative survival approach adopted by the company relies on several strong assumptions. A detailed exposition of these assumptions and the ERG's concerns regarding their plausibility is presented below.

Appropriateness of TTD as a surrogate outcome

As described above, the cumulative survival approach captures the relative clinical effectiveness of each treatment through TTD and that following discontinuation, survival is not influenced by the treatment received. Under the cumulative survival approach, TTD is therefore the fundamental driver of cost-effectiveness, determining the vast majority of incremental QALY benefits and costs associated with each treatment. The logic underpinning this approach assumes that progression to the accelerated phase of the CML is delayed in patients achieving a response to treatment, and that duration of that response may be proxied by the duration of treatment. The ERG acknowledges the plausibility of this relationship and the precedent set out in previous technology appraisals (TA401, TA426). The ERG is, however, concerned by the lack of direct evidence supporting these associations and in particular the lack of any direct evidence linking TTD with PFS and OS (see Section 2.3). This lack of evidence substantively undermines the validity of this approach and means that the justification for this approach relies upon its previous use in TA401 [16], TA426 [17] and the basic clinical logic as described above.

The ERG is further concerned about the reliability of TTD as a clinical endpoint and considers that there is considerable scope for comparative estimates of TTD to be biased. These concerns stem from the fact TTD is not a marker of disease activity or patient status and is inherently a subjective endpoint that is heavily dependent on several circumstances. Importantly, while the ERG accepts that TTD is likely to be indicative of treatment failure and loss of response, other factors such as tolerability, the incidence of comorbidities and availability of alternative treatments may also impact

TTD. Consequently, TTD is likely confounded as a measure of clinical benefit. Moreover, these confounding factors are likely inherent to the population being considered and the time and place they were treated, including the availability of subsequent treatments. This significantly limits the reliability of using TTD as a clinical endpoint and the reliability of cross-study comparisons as has been done in the base-case analysis.

In addition to the above, the ERG also considers that the cumulative survival approach has important practical limitations as the approach relies on the availability of evidence of TTD for the treatment and comparators. In the comparison between asciminib and bosutinib, this evidence was drawn from Kaplan-Meier data on TTD available from the ASCEMBL trial [41]. This data was then extrapolated by fitting standard parametric survival models, with the log-normal function adopted in the base-case analysis based on visual and statistical fit, as well as clinical opinion. Kaplan-Meier data for other comparators was, however, not available for the other comparators (ponatinib, nilotinib, and dasatinib). Modelled TTD in these comparisons was therefore based on assuming TTD followed an exponential function estimated using reported median TTD in the respective trials;[32, 52, 53] a full discussion of the selected models is presented in Section 4.2.6.

This inconsistency in model selection for TTD is of considerable concern for the ERG, particularly given the impact of this assumption on total QALYs and costs accrued. Importantly, the use of alternative parametric functions for each comparison is one of several factors that prevent a fully incremental comparison from being presented, see Section 5.1 for further discussion. In response to clarification, the company asserted that exponential models do not generate implausible extrapolations, but they did indicate that they may be conservative in failing to capture the long treatment durations in patients who respond particularly well to third-line therapy. A scenario conducted by the company implemented exponential survival models for TTD in the place of lognormal models for asciminib and bosutinib had minimal impact on the ICER at the list price or PAS price. The ERG acknowledges the limited impact on the ICER in this specific comparison but highlights that the inability of the model to consider other comparisons means this is still a source of uncertainty that cannot be explored. Further, this scenario does not address the issues that this approach prevents a fully incremental analysis from being considered.

Post-discontinuation survival

An important assumption of the cumulative survival approach is that post-discontinuation survival is not influenced by previous treatment. That is, life expectancy following discontinuation of asciminib is equal to life expectancy following discontinuation of any of the comparator treatments. As has been acknowledged in previous technology appraisals (TA401)[16] the validity of this assumption is largely unknown; it is plausible that post-progression survival may be longer or shorter following discontinuation of asciminib compared with relevant comparator treatments. In response to

clarification questions, the company stated there is no direct evidence indicating whether post-discontinuation survival is likely to be constant across different treatments, irrespective of TTD. The company, however, considered the basic premise of the model as is reasonable and consistent with clinical practice and evidence from earlier lines of treatment. The company did acknowledge the possibility that increasing time on third-line treatment may reduce the time from initiation of fourth-line therapy to progression of the disease and death but considered there was little direct data to verify or refute this assumption. This assumption remains an area of uncertainty and may impact the ICER although the direction and magnitude of the bias are unknown.

Surrogate survival approach

The surrogate survival approach is consistent with the most recent appraisal of a TKI in this population, which was the third-generation TKI, ponatinib (TA451)[18]. This approach relies on the strength of the relationship between response status and PFS. There are two things to consider in this approach: whether response can be considered a reasonable surrogate for PFS; and whether the data used to inform the surrogate relationship extracted from TA451[18] are appropriate. The latter is discussed briefly below and in more detail in Section 4.2.6.

Appropriateness of response as a surrogate outcome

As discussed in Section 2.3, several previous studies have provided evidence of a relationship between cytogenetic and molecular response and survival outcomes. In particular, the systematic review published in 2013 by Oriana *et al.*[45] shows strong evidence of an association between CCyR long-term OS. Evidence from the HMRN[24] also appears to support this association with patients achieving an MMR demonstrating improved PFS and OS. This contrasts with TTD, where there is a paucity of evidence linking it to improved survival outcomes. Further, the clinical utility of response as an indicator of effectiveness is widely acknowledged. This is indicated by the widespread use of response as a primary and/or secondary outcome in the relevant CML trials literature. This includes the ASCEMBL trial [41, 61] where the proportion of patients achieving MMR at 24 weeks is the primary outcome. More fundamentally, response is a more objective measure of clinical benefit, which is less likely to vary over time and across settings. This makes comparison's across studies more plausible and reduces the potential for confounding.

In the context of the economic analysis, there are, however, limitations associated with the use of a response-based model. Specifically, limitations in the evidence available to support this model structure. As highlighted in the company submission, the only adequate evidence available to support a response-based assessment is from a second-line population which may represent an optimistic estimate of progression in a third-line. Further, this data is relatively immature resulting in few events for patients that achieve a full cytogenic response. Extrapolation of this data is therefore subject to

considerable additional uncertainty. These issues motivate the company's decision to favour a cumulative survival approach.

Post progression survival

Like the cumulative survival approach, the surrogate survival approach makes assumptions about survival in the post-progression period. Specifically, and similar to the cumulative survival approach it is assumed that patients' survival is on average 16 months irrespective of the time spent in pre-progression health states. As in the cumulative survival approach, this assumption of a fixed post survival period is uncertain and there is the potential for the post-progression survival to vary depending upon the duration of the pre-progression period. This assumption is, however, less strong than one made in the cumulative survival approach which covers the entire period post discontinuation of primary (third line) treatment.

Conclusions

The company consider the cumulative survival approach to be a conservative and simplistic approach to modelling. This is evidenced through the sole difference in effectiveness being TTD and post-discontinuation survival including the time spent in the various phases of CML is constant across asciminib and comparators. The ERG disagrees that this approach is necessarily conservative but acknowledges the relative simplicity of this approach model. The cumulative survival approach is, however, subject to several important limitations that significantly increase the uncertainty associated with this approach. Foremost amongst these are uncertainties regarding the surrogate value of TTD as a predictor of PFS and OS, as well as concerns about the validity of comparing TTD across studies. In contrast, the response-based approach has substantively more grounding in the literature and has much clearer value as a clinical outcome. As a result, the ERG favours the surrogate modelling approach over the cumulative survival approach. This is, however, a finely balanced decision, that requires a significant element of judgement. In Section 6.2 the ERG, therefore, explores scenarios using both the cumulative and surrogate and modelling approach.

4.2.3 Population

The modelled population included patients with [redacted]This population aligns with the market authorisation for asciminib and the population outlined in the NICE scope.

The primary source of clinical data used to populate the model was the ASCEMBL trial, from which the estimates of the effectiveness of asciminib and bosutinib were derived. Additionally, the model drew on evidence from Giles *et al.*,[52] Rossi *et al.*[53] and Cortes *et al.*[28, 32]. These studies respectively informed estimated TTD for nilotinib, dasatinib and ponatinib. The modelled population drew age and

gender characteristics from the ASCEMBL trial (mean age 51, proportion female 52%). These parameters informed the mortality cap imposed and applied age-related quality of life adjustments.

Reflecting the population in ASCEMBL, the modelled population comprises a heterogeneous group of patients at different points in the treatment pathway. This includes patients treated in a third-line setting, as well as patients treated in subsequent lines. This approach acknowledges the heterogenous treatment pathway and that asciminib may be used at several different points in the pathway. This approach, however, does not permit comparison of asciminib at each alternative position in the treatment pathway, e.g. asciminib as 3rd vs 4th line treatment option. The CS comments that this is consistent with previous TAs conducted in CML.

4.2.3.1 Points for critique

Relevance of comparators to the whole population

NICE recommendations for bosutinib and ponatinib do not permit use in all third-line patients. Specifically, NICE recommendations for bosutinib and ponatinib require that dasatinib and nilotinib are not appropriate. This has important implications for the population eligible for asciminib and implies that there are two subpopulations reflecting the clinical relevance of dasatinib and nilotinib. Currently, the economic analysis does not reflect this distinction and importantly does not explicitly account for the fact these patient groups may have distinct clinical characteristics. For example, patients ineligible for dasatinib and nilotinib are likely to have received fewer previous treatments and to have a lower burden of comorbidities. Further, in terms of the decision problem, it suggests that a fully incremental analysis, including all four comparators, is not appropriate because patients cannot be eligible for all four comparators simultaneously. At the clarification stage, the ERG requested that the company comment on the relevance of a fully incremental analysis given the NICE guidance associated with bosutinib and ponatinib. The company response noted that the current pairwise comparisons (see Section 5) are consistent with the NICE scope and allow asciminib to be compared with all relevant comparators. The company however acknowledge that for individual patients the choice of TKI is likely to be restricted to therapies clinically indicated and those not previously tried.

T315I mutation

The ASCEMBL trial explicitly excludes patients with the T315I and therefore does not provide evidence of effectiveness in this population. Because the modelled population is based on ASCEMBL, this implies that the economic analysis does not provide evidence of cost-effectiveness in the T315I subgroup. This is consistent with the anticipated marketing authorisation and the NICE scope. Given the noted differences in disease pathology and differences in efficacy observed in this patient group, the ERG does not consider it appropriate to assume that the cost-effectiveness results for the main population are transferable to the T315I subgroup. The ERG also notes that the decision problem for this population is likely to differ from that of the main population. Specifically, the

comparators associated with this population are likely are to differ from that of the main population and to be restricted to ponatinib as well as best supportive care.

Blended population

The company's economic model does not consider the potential for asciminib to be used at different stages of the treatment pathway. Typically, an economic analysis will consider each alternative position in the pathway separately. This approach allows differences in the patient population, comparators, and ultimately cost-effectiveness to be fully reflected in each analysis.

The formal application of this approach may, however, not be appropriate in the present circumstances. The limitations of both ASCEMBL means there is limited evidence for each specific line of therapy, which increases the uncertainty associated with modelling a specific line of therapy. The limited availability of data from the comparator studies also imposes significant restrictions, limiting the feasibility of evaluating each subgroup of patients. Such an approach may also not be appropriate given the complexity of the CML pathway, which together with the strict eligibility criteria associated with both bosutinib and ponatinib, implies that eligibility for treatment with asciminib is likely to occur at different points in the treatment pathway. Evaluation of asciminib at a specific line of therapy is therefore unlikely to fully reflect the decision problem faced by the NHS.

For these reasons, it is the ERG's opinion that the use of a blended population (where asciminib is considered at multiple alternative positions simultaneously) is appropriate, if not ideal. The ERG, however, highlights that the use of a blended population implies that the analysis cannot reflect heterogeneity in the cost-effectiveness of asciminib across subgroups of patients. Further, this approach limits the ability to evaluate the impact of any uncertainty in the composition of the modelled population, e.g. the proportion of 3rd vs 4th line patients. This latter point may be of particular relevance given that line of therapy may determine which comparator treatments are relevant. See Section 2.2 and 2.3 for further discussion on the positioning of asciminib.

4.2.4 Interventions and comparators

There have been several previous technology appraisals in CML, with specific guidance covering all four comparators. Dasatinib and nilotinib were both appraised in TA425 [19], where they were principally considered in a second-line setting. Recommendations for dasatinib and nilotinib permit use in imatinib-resistant or intolerant chronic myeloid leukaemia. As retreatment is rare in CML, treatment with dasatinib and nilotinib in a third-line setting is only relevant when they have not been used in a first or second-line setting.

Bosubtinb was considered in NICE TA401[16] and is recommended as a treatment option for CML when: i) patients have received>1 TKI, and (ii) when imatinib, dasatinib and nilotinib are not clinically indicated.

Ponatinib was considered in TA451[18] and is recommended in line with marketing authorisation. This permits use following either failure (resistance or intolerance) of dasatinib or nilotinib, or in any patient where the T315I gene mutation is present. The use of ponatinib is, however, typically reserved for patients who have exhausted alternatives. This is reflected in TA451, where the comparators presented to the committee included bosutinib, best supportive care (BSC) and allo-SCT. This lack of overlap in the recommendations for the considered comparators has consequences for the modelled population.

The dosing of each therapy is summarised in Table 18. All treatments were modelled as a flat dose with costs adjustment to account for relative dose intensity. See Section 4.2.8 for further details.

Table 18 Summary of modelled interventions and comparators

Treatment	Dose
Asciminib	40mg dose administered orally twice a day (80 mg per day)
Bosutinib	500 mg orally once a day
Ponatinib	45 mg orally once a day
Nilotinib	400 mg orally twice a day (800 mg per day)
Dasatinib	100 mg orally once a day.

4.2.4.1 Points for critique

The ERG considers the interventions and comparators included in the economic model to be broadly appropriate and consistent with the decision problem. As noted above, BSC and allo-SCT were considered in TA451[18]. The committee, however, concluded that both alternatives were not relevant to the decision problem. Clinical advice received by the ERG confirmed that these alternatives are of limited relevance to the modelled population. BSC is typically reserved for patients where all treatment options have been exhausted. This is inconsistent with the expected position of asciminib as a 3rd/4th line treatment, where TKI agents are typically available. BSC may, however, be relevant to the T315I mutation subpopulation where treatment options are more limited. This population is, however, not currently modelled by the company as it is not expected to be included in the marketing authorisation, see Section 4.2.3. Allo–SCT may also be used in a 3rd/4th line setting as indicated by the HMRN dataset [24]. The population eligible to receive allo-SCT is, however, likely to represent a distinct population. This reflects the inherent risks associated with SCT and the limited availability of the treatment due to the need for a matched donor.

4.2.4.2 Subsequent lines of therapy

Patients within the economic model are assumed to receive secondary therapy after discontinuation of primary treatment. Patients are also assumed to receive additional therapy upon transition to the AP and BP health states, or upon relapse, following allo-SCT. Modelled subsequent treatments included a range of pharmacological treatments, as well as allo-SCT. The proportion of patients receiving pharmacological treatment vs allo-SCT was assumed to be constant and was, therefore, independent of primary treatment received. See Section 4.2.6.4 for rates applied.

Patients moving to pharmacological therapy were assumed to receive a basket of treatments reflecting the sequential use of alternative TKIs. This basket of subsequent treatments modelled reflected the distribution used in clinical practice. The basket included imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. The relative proportion of patients on each TKI was informed by data from HMRN [24], with adjustments made to account for the recent availability of ponatinib. The proportion receiving each treatment was varied for each specific health state but importantly did not vary according to the primary treatment received. Following the transition to AP and BP, patients were eligible to receive further treatment with TKIs but could also receive FLAG-Ida (fludarabine, cytarabine, filgrastim and idarubicin). The proportion of patients receiving each therapy is summarised in Table 19.

Patients receiving TKI in the off-treatment CP, AP, BP or relapsed Allo-SCT health state were assumed to receive treatment for the entire period they reside in that specific health state. As an exception to this rule, patients receiving FLAG-Ida are assumed to receive two cycles of treatment only.

Table 19: Subsequent treatment assumptions across health states (adapted from Table 85 pg. 167 of the CS)

Health state	Proportion					
	Nilotinib	Dasatinib	Ponatinib	Imatinib	Bosutinib	FLAG-Ida
Chronic phase off-treatment	21%	18%	25%	5%	30%	0%
AP	10%	30%	30%	0%	20%	10%
BP	0%	20%	80%	0%	0%	50%
Allo-SCT post relapse	25%	25%	25%	0%	25%	0%

Abbreviations: CP, chronic phase, PD, progressed disease; SCT, stem cell transplant.

Points for critique

As noted above, the company simplistically assumes that all patients will receive the same basket of subsequent treatments regardless of the primary treatment received. While this assumption is consistent with the cumulative survival approach it also implies that a proportion of patients will be retreated with their primary treatment in subsequent lines. Clinical advice received by the ERG,

however, suggests that this assumption is unrealistic and that retreatment is rare in clinical practice. This is evidenced by data from the HRMN dataset[24] where only 10% of 3rd line patients (excludes patients receiving 3rd line imatinib) are retreated with a previously failed TKI. Further, while the ERG is cognisant of the assumptions of the cumulative survival approach, it prefers an approach that matches the clinical pathway. This is because the current approach does not reflect the fact that the availability of asciminib alters the treatment pathway. Specifically, patients who receive asciminib as a third-line option will have a wider range of treatment options than patients who receive one of the comparators. The ERG is also conscious that the current approach may artificially amplify the impact of any cost differences between comparators treatments distorting the results of the economic analysis. In section 6 the ERG presents an alternative scenario in which patients cannot be retreated with their primary therapy.

4.2.5 Perspective, time horizon and discounting

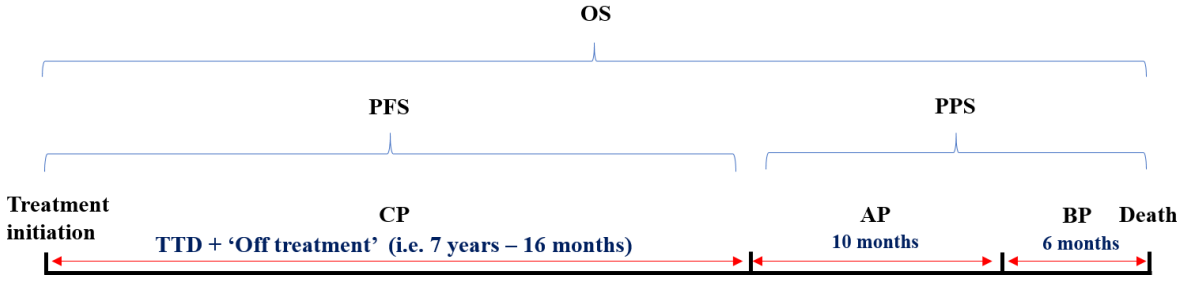
Consistent with the NICE methods guide[62], the company's analysis adopted an NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%. The impact of alternative discount rates (0% and 5%) was assessed in scenario analysis.

A lifetime horizon of 50 years was chosen to capture all relevant differences in costs and benefits between comparators. The use of a lifetime horizon is considered appropriate by the ERG and necessary to account for the chronic nature of CML and the potential for patients to achieve long-lasting remission of symptoms.

4.2.6 Treatment effectiveness and extrapolation

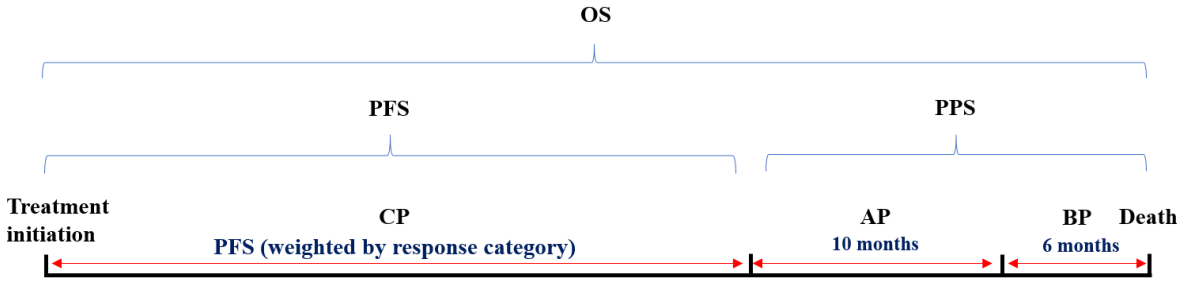
As has been detailed in Section 4.2.2, the company presented two versions of the economic model: the cumulative survival approach and the surrogate survival approach. Each model relies on different clinical effectiveness data and assumptions regarding time spent in PFS. The individual structures of the models have been discussed elsewhere (Section 4.2.2) but a summary of the underlying time spent in each phase of the respective models can be seen in Figure 6 and Figure 7.

Figure 6 Modelled time spent in each phase of CML in the cumulative survival model



AP, accelerated phase; BP, blast phase; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TTD, time-to-discontinuation.

Figure 7 Modelled time spent in each phase of CML in the surrogate survival model



AP, accelerated phase; BP, blast phase; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TTD, time-to-discontinuation.

4.2.6.1 Progression-free survival

In the absence of directly observed PFS data from the ASCEMBL trial[41], the cumulative survival approach and the surrogate survival approach rely on individual data to act as a proxy for directly observed results. Both of the approaches and the effectiveness data used to model asciminib and comparators are discussed.

Cumulative survival

Progression-free survival in the cumulative survival approach is based on TTD plus time spent in the CP 'off treatment'.

i) Time to discontinuation

Data on TTD were available from ASCEMBL for up to 37 months and 34 months, for asciminib and bosutinib, respectively[61]. Figure 8 shows the TTD Kaplan-Meier data from ASCEMBL. The company jointly fitted seven parametric survival models (exponential, Weibull, Gompertz, lognormal, log-logistic, gamma, and generalised gamma) to the TTD data for asciminib and bosutinib. Note, joint models were fitted including a covariate representing asciminib vs bosutinib as tests indicated proportional hazards could not be rejected.

Figure 8 ASCEMBL TTD KM data (Figure 19, pg. 126, CS)

[redacted]

The resulting extrapolated data based on the seven parametric models fitted to asciminib and bosutinib can be seen in Figure 9 and Figure 10, respectively.

Figure 9 Extrapolated TDD for asciminib from ASCEMBL (Figure 21, pg. 128, CS)

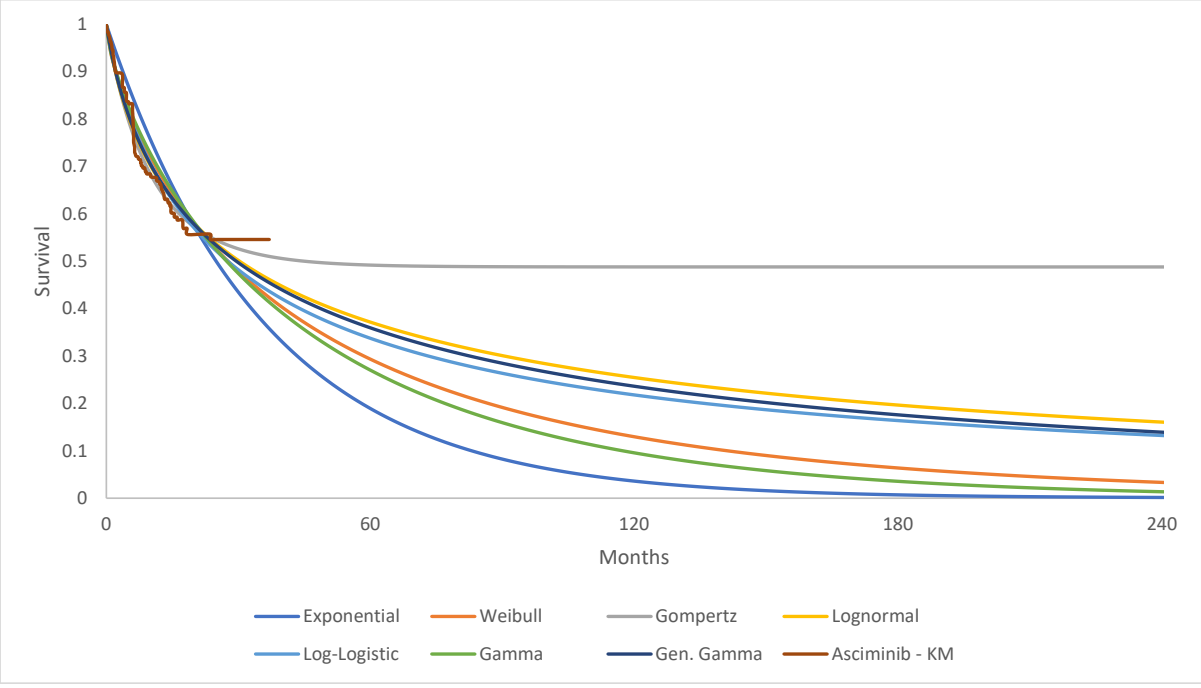
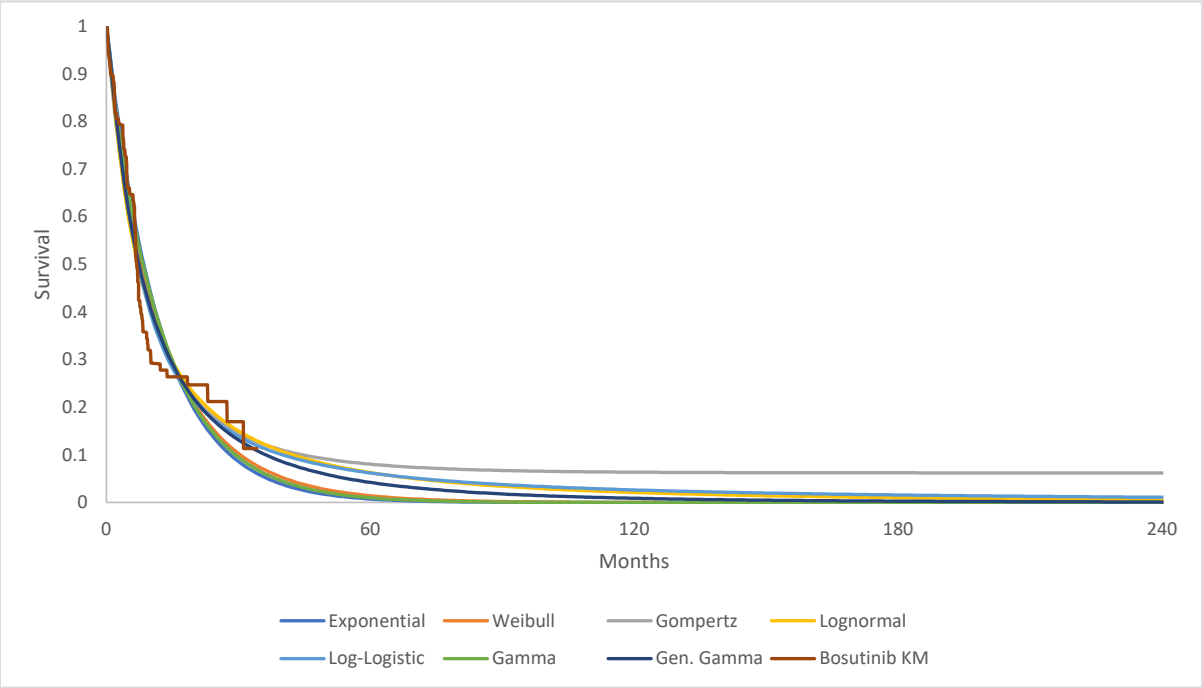


Figure 10 Extrapolated TDD for bosutinib from ASCEMBL (Figure 22, pg. 128, CS)



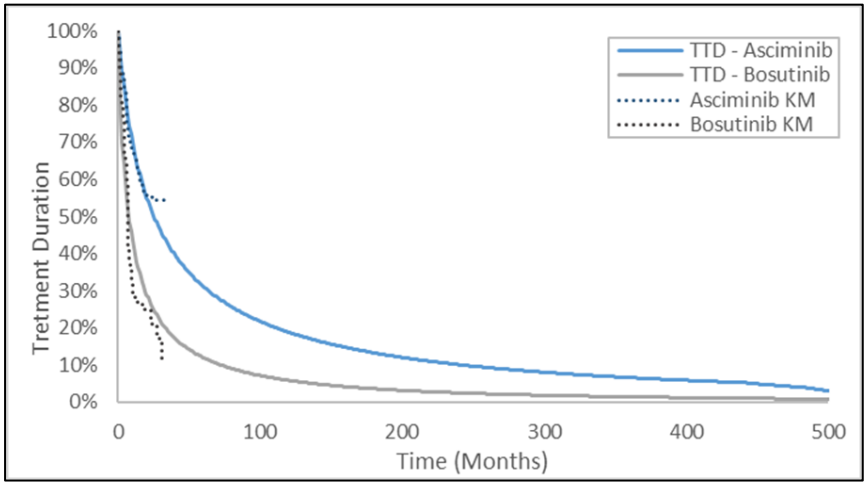
The company selected log-normal distributions for both asciminib and bosutinib. This was despite Gompertz providing the best model fit based on AIC, BIC and visual inspection. The log-normal (ranked 4th based on fit criteria) was considered the most plausible based on clinical opinion. This advised that around a quarter of patients would be expected to gain long term control of their disease on asciminib, and around 1 in 20 patients would gain long term control of their disease on bosutinib at 5 years. Based on the log-normal model, two, five and 10-year survival were estimated to be 54%, 37% and 25%, respectively for asciminib. For bosutinib, corresponding survival was estimated to be 19%, 6% and 2%.

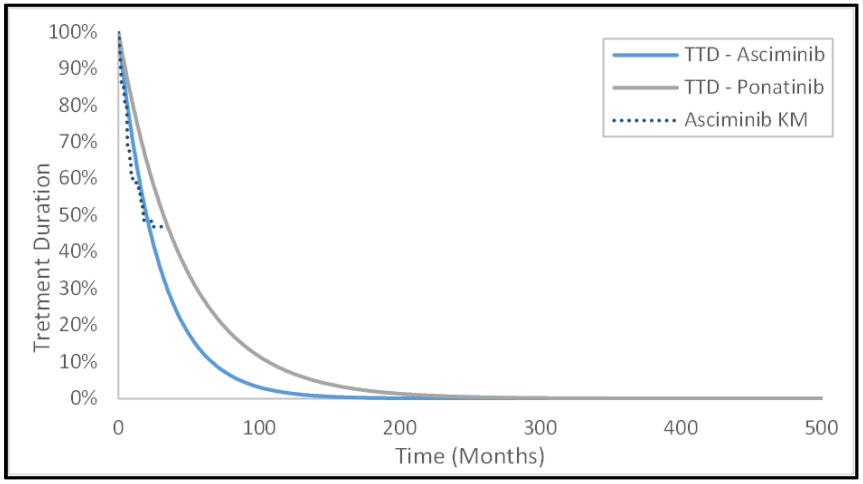
For dasatinib, nilotinib, and ponatinib, Kaplan-Meier data on TTD were unavailable in the literature; therefore, the following median TTD values were obtained from the literature:

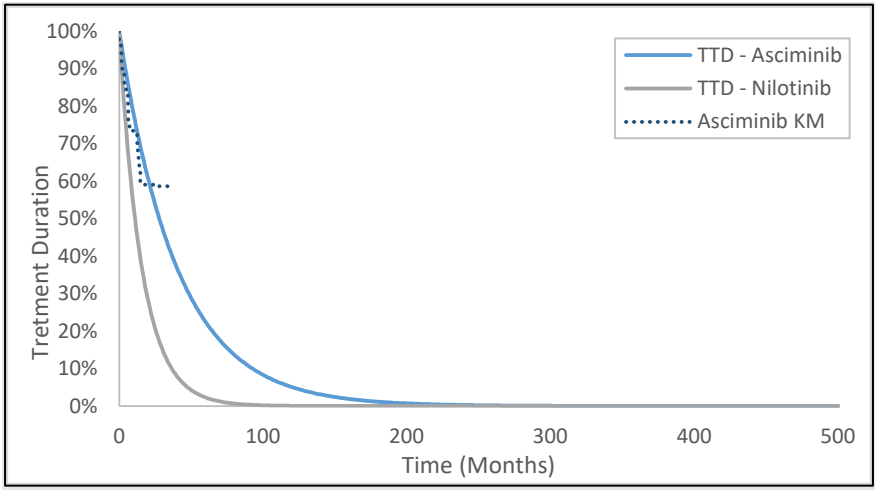
- Dasatinib: 14 months (Rossi *et al.*)[53]
- Nilotinib: 11 months (Giles *et al.*)[52]
- Ponatinib: 32.1 months (Cortes *et al.*)[32]

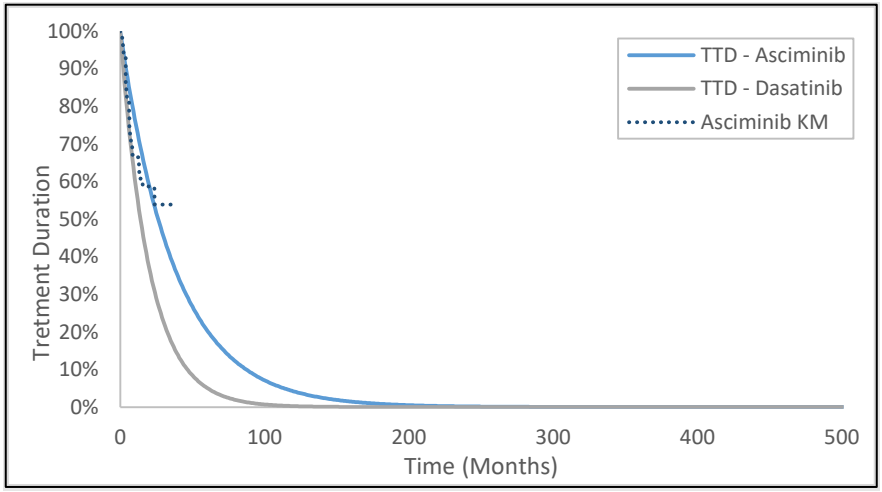
Exponential distributions were then calculated based on these median values. For comparisons with each of the three comparators listed above, the company re-weighted the asciminib TTD data using a MAIC (see Section 4.2.6.4 and Section 3.4 for further details). Parametric models were then fitted to the re-weighted asciminib data, and model fit was assessed. In the base case analysis, the company selected an exponential distribution to match the distribution used for the comparators. Figure 11 presents the resulting base case TTD extrapolations used in the economic model.

Figure 11 Base case TTD extrapolations for asciminib vs bosutinib, ponatinib, nilotinib and dasatinib (Figures 23, 26, 29 & 32, pg. 130–137, CS)









Points for critique

Appropriateness of the modelled TTD

As has been described, the ERG is concerned about the reliability of TTD as a measure of clinical effectiveness and the appropriateness of the selected studies used to inform estimates of TTD.

Estimated TTD for bosutinib as derived from the randomised ACEMBL trial is notionally the most reliable comparison with asciminib. The median TTD of bosutinib in the ASCEMBL trial was [redacted] this matches broadly with evidence considered in TA401[16] and TA451[18] where a median time treatment of 8.3 months was considered. Data from other studies, however, may suggest that this is underestimated. For example, Hochhaus *et al.*[63], which recruited a similar population, reports a median TTD of 24 months at the third line and 12.3 months at the fourth line. Evidence from the HMRN[24] would also suggest that observed TTD is shorter than observed in practice, see Table 5.

More broadly, evidence from the HRMN[24] does not align with TTD reported in the literature identified by the company. This is illustrated in Table 20, which shows that the company's preferred median TTD for dasatinib, nilotinib and bosutinib are all lower in the literature than in the HMRN data. The ERG does not necessarily consider the HMRN data to be a superior data source as there may be concerns regarding the external validity of the data (some participants were enrolled from as early as 2004), but it does illustrate the scope for considerable differences in TTD and the difficulties of making comparisons across studies.

Table 20 Modelled and HMRN TTD

Intervention	Model TTD (median)	HMRN Median (years)
Asciminib	25 months (2.1 years)	n/a
Dasatinib	14 months (1.2 years)	1.4 years (0.4 - 4.2)
Nilotinib	11 months (0.9 years)	2.7 years (1.1 - 4.9)
Bosutinib	8.5 months (0.7 months)	3.1 years (0.2 - n/a)
Ponatinib	32.1 months (2.7 years)	0.6 years (0.0 - 1.3)

Abbreviations: HMRN, Haematological Malignancy Research Network; TTD, time to discontinuation

Further, as detailed in Section 3.4.4. the ERG has several substantive concerns with the MAIC used to adjust the ASCEMBL population. Specifically, the ERG highlights problems with convergence in MAIC models, and substantive concerns regarding the factors adjusted for, which may not be sufficient to properly adjust for differences between studies. Further, there appears to be inconsistency in the magnitude of the adjustments when compared to other MAICs. For example, the CCyR adjustments for dasatinib and nilotinib are much more extreme than changes in MMR or across CCyR and MMR in the ponatinib adjustment. These issues are sufficient to raise major concerns as to the

validity and robustness of these analyses, and therefore the ERG considers that the MAICs are unlikely to be reliable for determining the true effectiveness of asciminib.

The issues are also further compounded by the use of a single datum to determine TTD in the comparisons with dasatinib, nilotinib and ponatinib. This reliance on a single datum of median TTD imposes the use of the exponential model for these comparators which is inconsistent with the company's preferred assumptions in the comparison with bosutinib where the log-normal function is used. To mitigate the impact of this issue the company also switches the extrapolation of the asciminib trial data to an exponential function for these comparisons, to align with NICE TSD14. This approach is, however, somewhat unsatisfactory and has a sizeable impact on the total QALYs gained and the costs associated with asciminib. Further, when confidential PAS schemes are implemented in the model it also has a moderate impact on the ICER. These differences in the ICER further exemplify the problems associated with generating suitable comparisons using TTD given the uncertainties in the available data.

In summary, the use of TTD is associated with significant challenges and uncertainties that serve to undermine the reliability of the cost-effectiveness analysis. Given these sizable uncertainties, the ERG considers that consideration should be given to the response-based approach outlined in Section 4.2.2. Moreover, given the issues with the MAICs, and the absence of alternative evidence the ERG is of the view that consideration should be given to both naïve comparisons as well as comparisons where equivalence is assumed across interventions. The ERG explores several additional scenarios in Section 6 considering these uncertainties in the effectiveness estimates.

Model selection

The parametric models selected in the company's base case for asciminib vs bosutinib were based on fit criteria and clinical plausibility. However, the ERG notes the log-normal model used in the base case is the 5th and 4th best-fitting model according to AIC and BIC, respectively. The log-normal model was selected as a result of the company's expectation that approximately '*a quarter of patients would gain long term control of their disease on asciminib, and on bosutinib around 1 in 20 patients would gain long term control of their disease at 5 years.*' It is the ERG's view that the log-logistic would have been a preferable model choice given the stated criteria as it produces a 5-years proportion remaining on asciminib closer to 25% and a comparable proportion on bosutinib at 5 years compared to the log-normal model, see Table 21. The log-logistic model is also the 2nd best fitting model according to AIC and BIC. The selection of the log-logistic model has a moderate impact on the company's base case ICER. The impact of this model selection on the company's and ERG's ICERs can be seen in Section 6.2.

Table 21 Proportion on treatment according to parametric model selection (Table 57, CS, pg. 129)

	Survival						
	Asciminib						
	Exponential	**Weibull**	**Gompertz**	**Lognormal**	**Log-Logistic**	**Gamma**	**Gen. Gamma**
2 years	51%	54%	55%	54%	53%	54%	54%
5 years	19%	29%	49%	37%	34%	27%	36%
10 years	4%	13%	49%	25%	22%	10%	24%
	Bosutinib						
2 years	14%	16%	18%	19%	18%	15%	18%
5 years	1%	1%	8%	6%	6%	1%	4%
10 years	0%	0%	6%	2%	3%	0%	1%

Surrogate survival

i) Response

Progression-free survival in the surrogate survival approach is based on modelled PFS by response category (see Section 4.2.2 for further discussion of the structure). The company extracted data from TA451 [18], which considered 12-month PFS data by response category (CCyR, PCyR, CHR and NR). The data were obtained from CA180034 study,[64] a randomised open-label phase 3 study of dasatinib in patients with imatinib-resistant or -intolerant CP-CML (see Section 3.2 for further discussion). The company digitised the Kaplan-Meier data and fitted the same parametric models to the data as those selected in TA451[18]. That is, gompertz for CCyR; gompertz for PCyR; Weibull for CHR; and exponential for NR. These models and the Kaplan-Meier data can be seen in Figure 5.

Response data, in the form of CCyR and PCyR for asciminib and bosutinib, were obtained from ASCEMBL. MAICs were undertaken to derive CCyR and PCyR for asciminib vs each comparator (ponatinib, nilotinib, and dasatinib; see Section 3.4 and Section 4.2.6.4). Data on ponatinib for the MAIC was taken from the PACE study [65]. Data for nilotinib and dasatinib for the MAIC were taken from Ibrahim 2010[54].

The proportion of patients achieving CCyR, PCyR, CHR, and NR was obtained from TA451[18] for ponatinib and bosutinib. The relative proportion that achieved PCyR, CHR, and no response (NR) for patients not achieving a CCyR were calculated for ponatinib and bosutinib, and also an average of the two arms was taken for each value. The resulting response rates used in the model can be seen in Table 22.

Table 22 Response rates (adapted from Table 25, PFC response, pg. 62)

	CCyR	PCyR	CHR	NR
Asciminib versus bosutinib				
Asciminib	45.63%	9.71%	26.05%	18.61%
Bosutinib	33.87%	8.06%	32.58%	25.48%
Asciminib versus ponatinib				
Asciminib	41.86%	9.87%	28.15%	20.12%
Ponatinib	43.26%	10.01%	28.37%	18.36%
Asciminib versus nilotinib				
Asciminib	62.63%	3.05%	20.02%	14.30%
Nilotinib	30.90%	9.89%	34.53%	24.67%
Asciminib versus dasatinib				
Asciminib	62.63%	3.05%	20.02%	14.30%
Dasatinib	30.90%	9.89%	34.53%	24.67%

Abbreviations: CCyR, complete cytogenetic response, CHR, complete haematological response; PCyR, partial cytogenetic response; NR, no response.

The data on the proportions of patients achieving CCyR, PCyr, CHR, and NR was used to weight the curves modelled for each response group. Note each response curve has its own curve generated for progression to AP and BP and these are weighted according to the proportions of responders in each category (see Section 4.2.6.2).

Points for critique

Surrogate relationship between response and survival

The fundamental uncertainty in the evidence presented in the company's surrogate survival model is the reliance on the data from TA451[18]. As previously discussed in Section 2.3 and Section 4.2.2, there is some limited evidence to support a surrogate relationship between response status and relevant survival outcome (PFS and OS). Specifically, a systematic review [45], has suggested there is evidence of a strong association between CCyR and OS. While it is important to acknowledge that the model relies on the association between CCyR and PFS (not OS) the ERG considers this evidence supportive of this relationship and also notes other data including that from both the CA180034 study[64] and HRMN[24] appear to support this relationship.

Despite the evidence outlined above, it is important to acknowledge that the CA180034 [64] evidence used to inform the model are external data rather than direct evidence of asciminib in a relevant population. This inevitably increases the uncertainty associated with this approach. Further, it is also important to acknowledge that the population recruited to the CA180034 [64]trial was not a third line population but instead included patients who had received dasatinib following one prior targeted

therapy, imatinib. While a substantive number of patients had also received other non-target therapies including interferon (53%) and chemotherapy (23%) this population is less heavily pre-treated than the one population considered in the decision problem. The resulting PFS may therefore be somewhat overly optimistic. Further, the follow up in the CA180034 [64] trial is limited and in the context of full cytogenetic response there are a few events increasing uncertainty associated with the extrapolation of this evidence, see below for further discussion.

Model fit

The parametric survival models fitted to the PFS data were the company-preferred models used in TA451.[18] In TA451,[18] the ERG in that appraisal deemed the selected models to be inappropriate and criticised the company for model selection on AIC and BIC only and not taking clinical expert advice on the plausibility of the survival curves into account. Several alternative models were deemed plausible by the ERG in TA451[18] (see Table 23). The committee concluded that the company had neither properly explored the effect of alternative parametric distributions nor justified its chosen distribution. The ERG is therefore concerned about the company's selected parametric functions. It is, however, unclear which models were accepted by the committee in TA451.[18]

Table 23 Parametric models used in the company base case, alternative models presented by the company and the models deemed plausible in TA451

Response category	Company-preferred model inTA451[18] and the model used in surrogate survival model for asciminib	Alterative model(s) presented in surrogate survival model for asciminib	Models deemed plausible by ERG in TA451[18]
CCyR	Gompertz	Exponential	Gompertz, log-normal, log-logistic, Weibull
PCyR	Gompertz	Log logistic, exponential	Gompertz, log-normal, log-logistic, Weibull
CHR	Weibull	Log logistic, exponential	Gompertz, log-normal, log-logistic, Weibull
NR	Exponential	Weibull, Gompertz	Exponential, log-normal

Abbreviations: CCyR, complete cytogenetic response, CHR, complete haematological response; PCyR, partial cytogenetic response; NR, no response.

To assess the clinical plausibility of the parametric models presented in the company's surrogate survival model, the landmark survival for each model by response category is presented in Table 24. It is worth noting that it is unclear to the ERG why the company selected the exponential, Weibull, Gompertz and log-logistic models for inclusion in the company executable model and why the company did not consider all the models deemed plausible by the committee in TA451[18] (Table 23). Owing to time constraints in the appraisal process, the ERG was unable to have clinical expert opinion comment on the most plausible PFS estimates for each response category. Despite this, it is clear to see a number of the survival estimates lack face validity, these include the Gompertz and

Weibull for NR. As a result, this remains an area of uncertainty, though ERG notes the impact of using alternative parametric models has limited impact on the ICER.

Table 24 Landmark survival by response status

	Exponential	Weibull	Gompertz	Log-Logistic
CCyR				
2 years	96%	n/a	**96%**	n/a
5 years	91%	n/a	**93%**	n/a
10 years	83%	n/a	**91%**	n/a
PCyR				
2 years	82%	n/a	**85%**	84%
5 years	61%	n/a	**49%**	56%
10 years	38%	n/a	**1%**	30%
CHR				
2 years	58%	**64%**	n/a	63%
5 years	25%	**11%**	n/a	17%
10 years	6%	**0%**	n/a	4%
NR				
2 years	**23%**	29%	29%	n/a
5 years	**3%**	27%	29%	n/a
10 years	**0%**	25%	29%	n/a

The numbers outlined in the highlighted boxes are those selected in the company base case Abbreviations: CCyR, complete cytogenetic response, CHR, complete haematological response; PCyR, partial cytogenetic response; NR, no response.

Comparison of cumulative survival data to surrogate survival data

The ERG considers there to be a high degree of uncertainty regarding the use of both TTD and response evidence to inform the economic results. As detailed extensively in Section 3, TTD is subject to considerable bias as a comparative marker of effectiveness. It is the ERG's opinion that although there is logic behind the use of TTD, it does not offer a robust and objective outcome with which to model comparative effectiveness. Yet, despite the clear benefits of using response to treatment as an objective outcome measure for the use of comparative analysis, the ERG does agree with the company in that there is also considerable uncertainty in basing decisions on external evidence of dasatinib which was generated in a second-line population.

There is also the concern that when the interventions are ranked based on their TTD or CCyR, there does not appear to be consistency in the rankings. Table 25 shows the observed TTD or CCyR rates for each comparator, naive unadjusted rates are used to simplify this comparison. This demonstrates that the ranking of the alternatives is dependent upon the measure of clinical effectiveness used. The

ranking of the three 2nd generation TKI's (bosutinib, nilotinib and dasatinib), is particularly impacted by the choice of outcome, with bosutinib moving from the least effective to 3rd most effective depending upon whether CCyR response rates are considered. These inconsistencies in the clinical evidence exemplifies the uncertainty being presented by the company and the difficulties of making inferences about relative effectiveness. Given these substantive uncertainties, the ERG considers there to be value in a scenario where equivalence is assumed in the effectiveness of asciminib and comparators. Specifically, the ERG considers that it may be appropriate to assume that asciminib and ponatinib are broadly equivalent and that bosutinib, nilotinib and dasatinib are broadly equivalent. Relative effectiveness between the two groups can then be drawn from the ASCEMBL trial [41]. This scenario accepts that is a lack of robust evidence to support differences in effectiveness and also helps navigate the restrictions imposed by the current evidence regarding parametric model selection (i.e. exponential models for comparisons with dasatinib, nilotinib and ponatinib; see Section 4.2.6.1 for details).

Table 25 Ranked TTD and CCyR

Intervention	TTD (median)	Rank	CCyR	Rank
Asciminib	[redacted]	2	[redacted]	1
Bosutinib	[redacted]	5	[redacted]	3
Ponatinib	32.1 months	1	43.26%	2
Nilotinib	11 months	4	30.90%	4
Dasatinib	14 months	3	30.90%	4

4.2.6.2 Post-progression survival

In both modelling approaches, the company assume a fixed duration of time spent in the AP and BP. Mean time in the AP and BP states was assumed to be 10 months and 6 months, respectively. The company based this assumption on the appraisal of bosutinib (TA401).[16] This assumption is present in both the cumulative survival and surrogate survival models.

Points for critique

The assumed average life expectancy of those in post-progression survival, i.e. 16 months for those in the AP with 6 months of that spent in the BP, has been accepted by the committee in the appraisal of bosutinib for 3rd line CML. Further, clinical advice indicated that this was a reasonable estimate for patients not undergoing SCT. At the clarification stage, the noted that evidence from the PACE trial[65] may help inform estimates of post-progression survival and requested that the company conduct appropriate analysis to explore the potential of this data. The analysis conducted by the company at the clarification stage using data from the PACE trial[65] suggests post-progression survival may be significantly longer with estimates generated between 46 and 84 months. This is significantly longer than the 16 months used in the company base case. The company, however, noted that progression

was broadly defined in the PACE trial to include "*Progression from CP was defined as death, development of AP or BP, loss of complete hematologic response (in absence of cytogenetic response), loss of MCyR, or increasing white blood cell count without complete hematologic response".* The company considered that the estimates generated are likely to be inflated because of this broad definition of progression. The ERG agrees with the company on this issue and does not consider the PACE trial estimates to be reflective of survival in the AP and BP. In the absence of alternative evidence, the ERG, therefore, accepts the assumptions of the base-case analysis.

4.2.6.3 Overall survival

The OS in the cumulative survival model is based on TTD plus an additional 7 years (Figure 6). The assumption of 7 years survival post-discontinuation is based on ERG estimates of mean OS from TA401.[16] This was informed by Kantarjian *et al.*[66] which reported OS in 67 patients discontinuing imatinib in the CP. Importantly, reported OS was for patients who received neither SCT nor TKI treatment following imatinib discontinuation. In the TA401 appraisal, the duration of post-progression survival was subject to significant scrutiny reflecting the uncertainties in both the extrapolation of the reported evidence and inconsistencies in the population. Specifically, the company in that appraisal argued that these estimates were overly optimistic. Clinical expert opinion, however, suggested the assumption of 7 years post-discontinuation survival was reasonable and it was accepted by the committee.

Points for critique

While the ERG acknowledges the precedent for the use of 7 years and the committee's previous conclusions in TA401,[16] the ERG has substantive concerns regarding the Kantarjian *et al* data.[66] As noted above the population focuses on a group of patients who do receive subsequent TKI's, with subsequent treatments including tipifarnib; hydroxyurea; lonafarnib; decitabine; cytarabine; homoharringtonine and interferon-α. These technologies no longer represent practice in the UK and are not included in the current NICE treatment pathway. Moreover, the age of Kantarjian *et al.,*[66] which recruited patients from as early as 1999, generally raises concerns about the validity of using Kantarjian *et al*.[66] to estimate post-progression survival and is concerned that these estimates are overly pessimistic given the substantive changes to the pathway and improvements in care. This position is supported by evidence from both the HMRN[24] and the PACE trial[65] both of which indicate that survival is substantively longer as predicted by the economics analysis. The HMRN data reports that [redacted] of fourth-line patients are alive at 5 years. Median survival in this population is therefore still yet to be reached at 60 months and even assuming 50% median survival of 5 years implies that mean OS is very likely to be greater than seven years. Evidence from the PACE is similarly optimistic. The PACE trial[65] reported a 5-year OS of 73% suggesting median OS is significantly over 5 years. Further, following a request from the ERG, the company fitted parametric models to the OS

data from the PACE trial. This extrapolated evidence produced estimates of mean OS that ranged from 14 to 19 years from the commencement of third-line therapy. These estimates are inconsistent with the company economic analysis which suggests total LYG in on ponatinib of [redacted] years. Given these estimates, the ERG considers it very likely that the post-progression survival is greater than 7 years, and explores several alternative scenarios in Section 6 to address this uncertainty.

4.2.6.4 Allogeneic stem cell transplant

Within the company's original model, it is assumed a proportion of patients go on to receive an SCT. Patients are eligible to receive SCT upon entering each of the following health states: CP off treatment, AP and BP. The proportion of patients undergoing SCT in each health state was informed by evidence from the HMRN dataset. In the company's original base case the proportion of patients In the CP off treatment health state [redacted] were assumed to undergo SCT, with a [redacted] assumed to ago SCT upon entering both the AP and BP health states. These probabilities were, however, modified following clarification in response to queries raised by the ERG. The ERG questioned the assumption of using a constant probability of receiving SCT throughout the entire time horizon of the model as this implied that patients could continue to receive SCT well into old age which is clinically implausible. For example, in the original model, [redacted] received SCT over the age of 65 and [redacted] over the age of 75. Clinical advice to the ERG indicated that while fitness, not age is the primary eligibility criteria for SCT these proportions are significantly higher than what would be expected in practice. In response to these concerns, the company revised their base case to account for the declining probability of receiving SCT with increased age. This is done by applying a linear tapering of the probability of undergoing SCT. This taper reduces the probability of receiving SCT by 7.5% per year starting from age 50.

As described in Section 4.2.2, patients receiving SCT are assumed to transition to a sub-model that determines outcomes for patients receiving SCT. The model uses two separate sub-models to account for outcomes in patients receiving SCT. The first applies to patients receiving SCT in the CP, while the second is used to determine outcomes in the AP and BP. Both of these sub-models use the same structure and are based on three-state PSM consisting of the following health states: relapse-free, relapsed disease, and death. State occupancy is determined by relapse-free survival (RFS) and OS curves which for both sub-models was based on separate data from Jabbour *et al.*[67] The data from Jabbour *et al.*[67] was extrapolated using standard parametric curves which were fitted to the available KM data Model selection was based on AIC, BIC and clinical plausibility, see Tables 65 of the CS for relevant fit statistics. The company selected the generalised gamma distribution for the RFS and OS curves in the CP sub-model, and the lognormal distribution for the RFS and OS curves in the progressed disease model.

Points for critique

While the Jabbour *et al.*[67] study has been used in previous TA, the ERG is concerned that this is a relatively old study that reports on relatively few patients (n = 47). The ERG, therefore, looked for alternative sources of data to inform these assumptions and identified Niederwieser *et al.*[68] as a possible alternative. Niederwieser *et al.*[68] is a significantly more recent study and reports outcomes for a greater number of patients (n = 147). At the clarification stage, the ERG, therefore, requested that the company implement scenarios in which the Niederwieser *et al.*[68] study is used in place of Jabbour *et al* [67]. In their response the company presented two approaches to including i) non-blast crisis survival is used for CP and blasts crisis survival is used for AP and BP; ii) non-blast crisis survival is used for CP and AP and blast crisis survival is used for BP. The former is aligned to the approach adopted by the company in their base case, while the second is informed by the findings of the Niederwieser *et al.*[68] study which does not find any difference in the outcomes of patients receiving SCT in the CP and AP. The impact of this scenario on the ICER can be seen in Section 6.2. The results of these scenarios are presented in Section 5 and show a modest decrease in the ICER using the Niederwieser data. Given the advantage of the Niederwieser study, the ERG considers this the most appropriate source of evidence to inform post SCT survival outcomes.

Regarding whether SCT either AP and BP or CP and AP outcomes should be equivalent, the ERG notes that the Niederwieser study not does provide conclusive evidence to support either scenario and only suggests that there is an absence of evidence to suggest CP and AP outcomes are different. Both sets of assumptions therefore would represent reasonable interpretations of the available evidence. In terms of the ICER, the ERG notes that these alternative scenarios only have a modest impact, and therefore the ERG accepts the company's base-case assumptions for simplicity and does not explore this issue further in additional scenario analysis.

4.2.6.5 Adverse events

The adverse event frequencies for asciminib and bosutinib were obtained from the ASCEMBL trial. Those for ponatinib were obtained from the PACE study. For nilotinib and dasatinib, adverse events were obtained from Giles *et al.*[52] and Tan *et al.*,[69] respectively. The latter was not taken from Rossi 2013 [53] as they were not reported in this study. Rates applied in the model are reported in Table 67 of the CS. These rates were used to inform utility decrements and costs associated with AE's. The ERG is satisfied with sources used to inform AE rates and notes that these have a nominal impact on the resulting estimates of cost-effectiveness.

4.2.7 Health related quality of life

4.2.7.1 Health-related quality of life associated with health states

The company used data from the ASCEMBL trial to populate the utility values applied in the pre-progression health states. In line with the model structure outlined in Section 4.2.2, the HRQoLs values applied in the pre-progression states were stratified into two groups: those '*on treatment*' and those '*off treatment*'. *On treatment* is used to represent those in receipt of their allocated primary treatment and is based on baseline values observed in ASCEMBL. *Off treatment,* utilities are applied on discontinuation of primary treatment until progression of disease and were based on observed values from ASCEMBL. For the utilities collected in ASCEMBL, EQ-5D-5L data were, mapped to EQ-5D-3L values using the van Hout *et al*. algorithm,[70] and analysed using a mixed-effects model.

For utility values applied in the AP and BP health states the company drew on values reported in Szabo *et al.*[60] This study was identified in the company review of HRQoL evidence, which searched for utility values in a general CML population including patients in receipt of 1st, 2nd and 3rd line therapy (see CS Appendix H). The Szabo *et al.*[60] study recruited from the general population and implemented a TTO analysis for several health states. Specifically, the company selected values for patients unresponsive to treatment in the AP and BP.

For patients receiving SCT, the company drew on values reported in T451 which used published values from the literature. Separate values were applied for patients who were relapse-free and those that had relapsed. The model, however, did not account for when SCT was received (pre-progression vs post-progression).

Table 26 summarises the health-related quality of life (HRQoL) data associated with health states in the company's model.

Table 26 Health-related quality of life associated with health states (adapted from Table 78, pg. 162 of the CS)

Health State	Utility value:	Source/Assumption
CML-CP (on treatment)	0.838	ASCEMBL
CML-CP (off treatment)	0.809	
CML-AP	0.66	Szabo et al.[60]
CML-BP	0.43	
SCT relapse free	0.71	Derived from TA451[18]
SCT relapsed	0.59	

Points for critique

The ERG considers that the applied utility values are broadly reasonable. The ERG, however, does not consider that there is sufficient evidence to apply different utility values in the on and off-

treatment health states. As stated in the CS, the data to support this difference is limited, with only 14 patients contributing to the off-treatment health state. As a result of this small sample size, the difference in utility values is not statistically significant. The ERG is also not clear on the clinical rationale for this distinction. The off-treatment health statement only implies a patient has discontinued their primary treatment. It does not imply that patients are off treatment completely. The impact of this assumption is, however, small. The ERG, therefore, does consider this issue further.

Age-adjustment

The model applies age adjustments to all utility values used in the model. These account for the impact of ageing on HRQol. These are applied using an additive approach in which a utility decrement is estimated relative to the utility of a 51-year-old (staring age) in the general population using data from Ara and Brazier.[71] This decrement is then subtracted from each health state utility value to generate an age-specific value.

Points for critique

The ERG considers the application of age-related decrement appropriate, given the long-time horizon considered in the economic analysis. The ERG, however, does not consider the company's implementation of the age-related decrements to be appropriate. The company's additive approach assumes that the impact of age is constant across all health states. Age-related utility decrements are typically applied as a multiplier rather in an additive way, with the precedent set for this approach reported in a large number of previous technology appraisals. This approach assumes that the impact of age on HRQoL is not constant across all health states and instead is proportional to the health state utility. This is done on the assumption that the marginal impact of ageing on HRQoL is lower in individuals who have diminished HRQoL. In Section 6.2, the ERG revises the implementation of the age-related decrements so that they are applied as a multiplier.

4.2.7.2 Health-related quality of life associated with adverse events

Table 74 of the CS summarises the impact of adverse events on health outcomes in the model. The company assumed the effect of severe AEs (Grade 3 or 4) on HRQoL was not captured by the EQ-5D data collected in ASCEMBL and included it separately in the model. All disutilities associated with AEs are applied as utility decrements in the first cycle of the model. The total decrement applied was estimated by multiplying an AE specific utility decrement by the frequency of that event. See Section 4.2.6.5 for details of rates used. Utility decrements applied were sourced from previous TAs and published literature. Where utility decrements were not available, a utility decrement of 0.05 was applied. This is consistent with the assumptions made in TA426 [17]. The total QALY decrement due to adverse events is reported in Table 27. In all cases, the total disutility applied is small and less than 0.1 of a QALY.

Table 27: Total AE related disutilities (Reproduction of Table 75 of the CS)

Treatment	QALY loss
Asciminib	–0.0345
Bosutinib	–0.0453
Ponatinib	–0.0722
Nilotinib	–0.0807
Dasatinib	–0.0292

Abbreviations: QALY, quality-adjusted life year.

Points for critique

The ERG is unclear on the rationale for including separate utility decrements for adverse events, given that the health state utility values are based on HRQoL data collected in ASCEMBL. The use of this data should capture any differences in HRQoL resulting from AE's and shows no significant differences between asciminib and bosutinib. The ERG recognises that the ASCEMBL trial data cannot account for the AE profile associated with dasatinib, nilotinib, and ponatinib. However, the small differences in the decrements applied to each treatment suggest that these AE profiles are not sufficiently different to impact decision making. Further, the lack of data available to inform the applied decrements undermines the validity of the company approach as the impact of AE's is more a function of their frequency rather than severity. Given these issues, the ERG would have favoured a simplified approach in which all AE related utility decrements are removed. This issue is not explored further due to the small impact on the ICER.

4.2.8 Resources and costs

The company's model included drug acquisition and administration costs, allo-SCT costs, health state costs (which account for the management and monitoring of patients with CML), and adverse event costs.

4.2.8.1 Drug acquisition and administration costs

Asciminib acquisition costs were sourced from Novartis and estimated based on a dose of 40 mg twice daily. Asciminib acquisition costs presented were inclusive of a confidential PAS discount. This lowered the per pack price from [redacted] to [redacted] This is equivalent to a [redacted] discount off the list price.

Acquisition costs for other pharmacological treatments, including all four comparator treatments, were sourced from either eMIT or the BNF. Aligning with dosing recommendations, the modelled dose of dasatinib and imatinib was dependent upon the disease phase (chronic or progressed). The costs per cycle for each drug and by disease phase are presented in Table 28. Confidential PAS discounts are available for all of the relevant comparators. All analyses presented by the company are

exclusive of this discount. Results inclusive of this discount are included in a confidential appendix to this report.

Consistent with previous TAs and reflecting that all treatments are taken orally, no acquisition costs were included for any pharmacological treatment. Drug costs were applied per monthly cycle and accounted for reductions in dose intensity. Drug costs applied did not account for wastage.

Table 28: Daily cost of drugs Adapted from Table 80 pg. 163 of the CS)

Drug	Daily dose (Mg/MU) - CP	Daily dose (Mg/MU) - Progressed Disease	Daily cost – CP	Daily cost – AP and BP
Asciminib	80.00		[redacted]	
Bosutinib	500.00		£122.74	
Ponatinib	45.00		£168.33	
Dasatinib	100.00	–	£83.50	–
Dasatinib	–	140.00	–	£83.50
Nilotinib	400.00		£43.44	
Imatinib	400.00	–	£3.76	–
Imatinib	–	600.00	–	£5.60

Abbreviations: CP, chronic phase; AP, accelerated phase; BP, blast phase.

To account for dose reductions and treatment breaks, relative dose intensity (RDI) was used to adjust acquisition costs. RDI for asciminib and bosutinib was based on data from ASCEMBL (See Table 81 of the CS for rates applied). Relative dose intensity for other comparators was assumed to be 100%.

Points for critique

Dose intensity: ponatinib

The modelled dose intensity of ponatinib is assumed to be 100%. This does not align with the dose intensity observed in the relevant pivotal trial (PACE) [65] and does not reflect the assumptions made in TA451 [18]. As discussed in Section 2.2.3, ponatinib is associated with several serious AE's. Reflecting these concerns about AEs, SmPC guidance for ponatinib recommends that dose modifications or interruption be considered for the management of haematological and non-haematological toxicities. Clinical advice suggests that many patients receiving ponatinib will receive a lower dose, receiving either a 30 or 15-mg dose (significantly lower than the (full) 45mg dose outlined in the SmPC). Further, while specific details of dosing in the PACE trial are not reported in detail, it is clear that dose reductions were applied to the vast majority of patients. All patients who had achieved a cytogenetic response or better were lowered to a 15 mg maintenance dose from October 2013 onwards. A dose intensity of 100% is therefore likely to overestimate the acquisition costs associated with ponatinib. To account for this, the ERG implements scenario analyses in section 6, exploring alternative ways of modelling expected reductions in the maintenance dose of ponatinib.

Dose intensity: nilotinib and dasatinib

The dose intensity for both nilotinib and dasatinib was assumed to be 100%. It is, however, unclear if this is appropriate, with clinical advice suggesting that dose modifications and reductions would occur in at least a proportion of patients. Appropriate evidence to inform alternative assumptions is limited. The Giles *et al.*[52] and Rossi *et al.*[53] studies used to inform the TTD parameters did not report any meaningful data on dose intensity. In TA 251,[72] dose intensities of 99% and 92% were modelled for nilotinib and dasatinib. These values, however, reflect a first-line population, and it is unclear how relevant they are to a third-line plus population. A reasonable alternative to the company's base-case assumptions may be to use reported dose intensity for bosutinib. This assumes that the tolerability of nilotinib and dasatinib is comparable to that of bosutinib. Scenario analyses exploring these alternative assumptions are reported in Section 6.

Drug wastage

The company's model assumes that missed doses will result in fewer packs of asciminib and bosutinib being used. This is equivalent to assuming no drug wastage. Clinical advice to the ERG indicated that the stock-piling of pills could be possible but expected that some drug wastage would be associated with dose interruptions. At the clarification stage, the company provide a scenario analysis to explore this issue. The company scenario analysis adopted a simplified approach in which no savings accrued from missed doses. This assumes that all treatments had a dose intensity of 100%. The results of this scenario are presented in Section 5 and indicate that drug wastage is likely to increase the ICER associated with asciminib.

4.2.8.2 Allo-SCT costs

The costs of allo-SCT are assumed to be a one-off cost of £109,279 and are based upon values reported in a 2014 NHS blood and transplant report (inflated to current prices). The applied costs align with those used in TA451.[18]

Based on clinical advice, the model assumes that the patients receiving allo-SCT in either the AP or BP require additional care. In the AP, it is assumed patients require a month of myeloablative therapy to stabilise their condition. In the BP, this is increased to two months. Each month of myeloablative therapy was costed as a 30-day inpatient stay at a total cost of £17,279.30 per month.

Points for critique

The ERG is satisfied with the costs applied for allo-SCT. Clinical advice given to the ERG confirmed the additional costs associated with delivering SCT in patients with progressive disease and considered the sources used reasonable.

4.2.8.3 Health state costs: disease management costs

Disease management and monitoring costs identified by the company as supportive of the condition were: outpatient visits nurse-led, outpatient visits haematologist led, hospital and hospice stay, emergency department visits, full blood counts, blood transfusions, bone marrow aspiration, PCR and FISH testing, cytochemistry analysis, blood film examinations, blood chemistry, kinase domain mutation analysis and platelet transfusions. The resource rates applied were principally sourced from TA451 and updated to reflect current clinical practice. In line with TA451, resource use varied per treatment status (on vs off) and the presence of progressive disease. Unit costs applied were obtained from the most recent NHS reference cost schedule [73] and the Personal Social Services Research Unit (PSSRU) handbook.[74]

Resource use rates applied in the model are described in Table 86 of the CS, with unit costs reported in Table 87. A summary of the health state costs applied is presented in Table 29 below.

Table 29: Total health state costs per cycle (reproduction of Table 88 CS, pg. 171)

	Health state	Unit cost per month (£)
CML-CP	On 3L treatment	277.75
	Off 3L treatment	637.60
	Post allo-SCT - Relapse-free	42.80
	Post allo-SCT – Relapsed	2,916.72
Progressed disease	AP	2,916.72
	BP	17,049.44
	Post allo-SCT - Relapse-free	42.80
	Post allo-SCT – Relapsed	2,916.72

Abbreviations: 3L, third-line; AP, advanced phase; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase, PD, progressed disease; SCT, stem cell transplant

Points for critique

Alignment with TA451

The ERG is satisfied that the values from TA451[18] are likely to represent the most relevant data to populate these inputs, as the resource review identified no alternatives. The ERG, however, highlights that the differences in model structure mean the values are applied to a different set of health states. This is of specific relevance to the off-treatment health state, which corresponds to non-response in the TA451[18] model. One implication of this is that costs applied in the off-treatment health state are substantially higher than for the on-treatment health state. The ERG considers this inconsistent with the treatment pathway as it fails to acknowledge the sequential use of treatments. The off-treatment health state does not imply that a patient is off all treatments. It only means that they have discontinued primary treatment. The ERG, however, further notes the general insensitivity of the model to these inputs and therefore does not explore this issue further.

4.2.8.4 Adverse events

Adverse events modelled included all grade 3 and 4 AE's. The rates of AEs were drawn from the pivotal trials – see Section 4.2.8.4 for details. The costs associated with AEs were drawn from NHS reference costs [73] and PSSRU and are reported in Tables 89 and 90 of the CS.

Points for critique

The ERG is satisfied with the unit costs applied with respect to AE. For a critique of AE, rates applied see Section 4.2.8.4.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company updated base case as presented in the clarification response. The updated base case includes several changes to the base case presented in the CS. These are as follows:

i) A correction to minor calculation error identified by the company;
ii) The implementation of half cycle correction;
iii) Alternation of the assumptions relating to allo-SCT so that the likelihood of receiving SCT decreases as patients age.

The presented results are inclusive of the PAS for asciminib but do not include PAS discounts for comparator treatments (bosutinib, dasatinib, nilotinib, ponatinib) or CMU discounts associated with imatinib which is included as a subsequent treatment. Results with the PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix separate from this report.

5.1.1 Deterministic results

The company does not present a fully incremental analysis including all relevant comparators. Instead, the company presents a series of pairwise ICERs for asciminib versus each of the comparators: bosutinib, dasatinib, nilotinib, ponatinib. The use of pair-wise comparison implies that the company views these comparisons as representing separable decision problems (patients eligible for one of the comparators are not eligible for any of the others), requiring separate decisions concerning the use of asciminib in these distinct populations. The ERG does not consider the characterisation of the decision problem appropriate. As discussed in Section 4.2.3, the ERG considers that there are two relevant populations: i) those in which dasatinib, nilotinib is clinically indicated and ii) patients where dasatinib and nilotinib are not clinical indicated. The ERG understands the complexities of developing fully incremental comparisons given the limitations of the data but considers this to be a major weakness of the presented analysis increasing the uncertainty associated with the cost-effectiveness of asciminib. This issue is exemplified when comparing total QALY and costs estimates for asciminib across each comparison which vary considerably. This principally reflects different assumptions made regarding TTD.

The results of the company base case cost-effectiveness analysis are summarised in Table 30. Compared with bosutinib, dasatinib and nilotinib the results suggest asciminib is associated with increased costs (cost difference of [redacted] respectively) but also greater benefits

(QALY difference of [redacted] respectively). The company's base case ICER comparing asciminib with bosutinib, dasatinib and nilotinib are respectively [redacted], [redacted], and [redacted] per QALY. In all three comparisons, the higher costs are primarily a result of the higher acquisition costs associated with asciminib, while the greater benefits are primarily a result of extending TTD and overall survival. In the comparison with ponatinib, the results of the company base case suggest that asciminib is associated with reduced costs (cost difference of -£138, 189) but also reduced benefits (QALY difference of [redacted]). The resulting ICER is therefore in the southwest quadrant where a higher ICER is indicative of asciminib being increasingly cost-effective. The company's base case ICER comparing asciminib with ponatinib is £271,410 per QALY gained.

Table 30 Company base-case results: deterministic pairwise analysis (Asciminib PAS only)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs Nilotinib							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

* Southwest quadrant

5.1.2 Probabilistic results

The company performed a probabilistic sensitivity analysis (PSA), running 1,000 iterations for each pairwise comparison. The results of the mean probabilistic ICER for asciminib compared to each of the comparators are presented in Table 31. In the comparison with bosutinib, asciminib had a [redacted] probability of being cost-effective at a threshold of £20,000 per QALY and [redacted] probability at a willingness-to-pay threshold of £30,000 per QALY (Figure 12). In the comparison with dasatinib, asciminib had a [redacted] probability of being cost-effective at a £20,000 per QALY threshold and a [redacted] probability at £30,000 per QALY willingness-to-pay threshold (Figure 13). In the comparison with nilotinib, asciminib had a [redacted] probability of being cost-effective at a £20,000 per QALY threshold and a [redacted] probability at £30,000 per QALY willingness-to-pay threshold (Figure 14). In the

comparison with ponatinib, asciminib had a [redacted] probability of being cost-effective at both a £20,000 and £30,000 per QALY threshold (Figure 15).

Table 31 Company base-case result: probabilistic

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib					
Bosutinib	[redacted]	[redacted]			
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib					
Dasatinib	[redacted]	[redacted]			
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib					
Nilotinib	[redacted]	[redacted]			
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib					
Ponatinib	[redacted]	[redacted]			
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Southwest quadrant.

Figure 12. Cost-effectiveness acceptability curve for asciminib vs. bosutinib

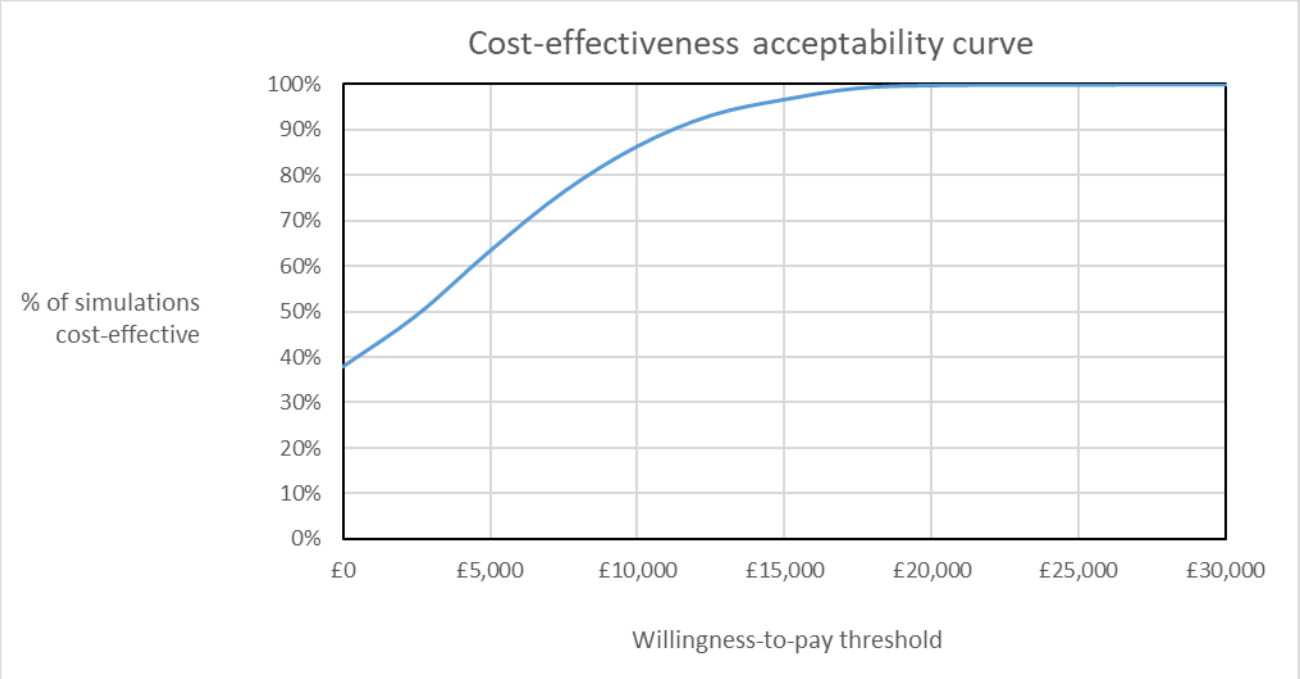


Figure 13. Cost-effectiveness acceptability curve for asciminib vs. dasatinib

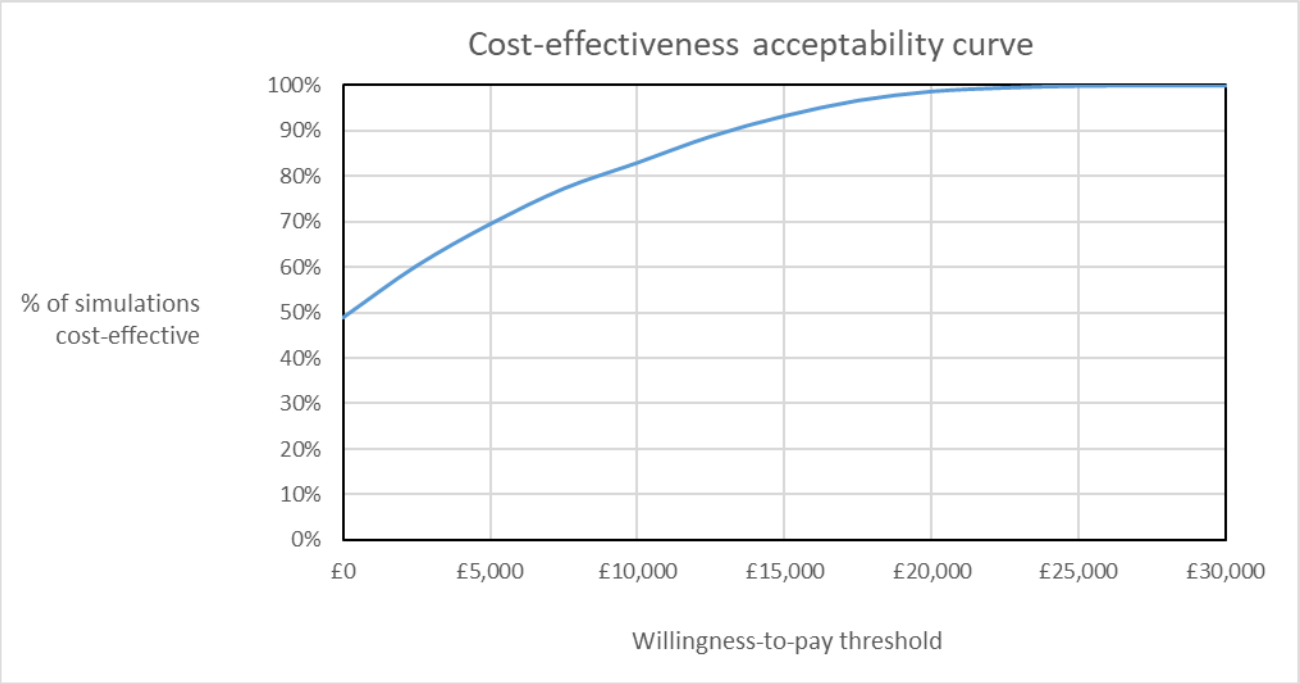


Figure 14. Cost-effectiveness acceptability curve for asciminib vs. nilotinib

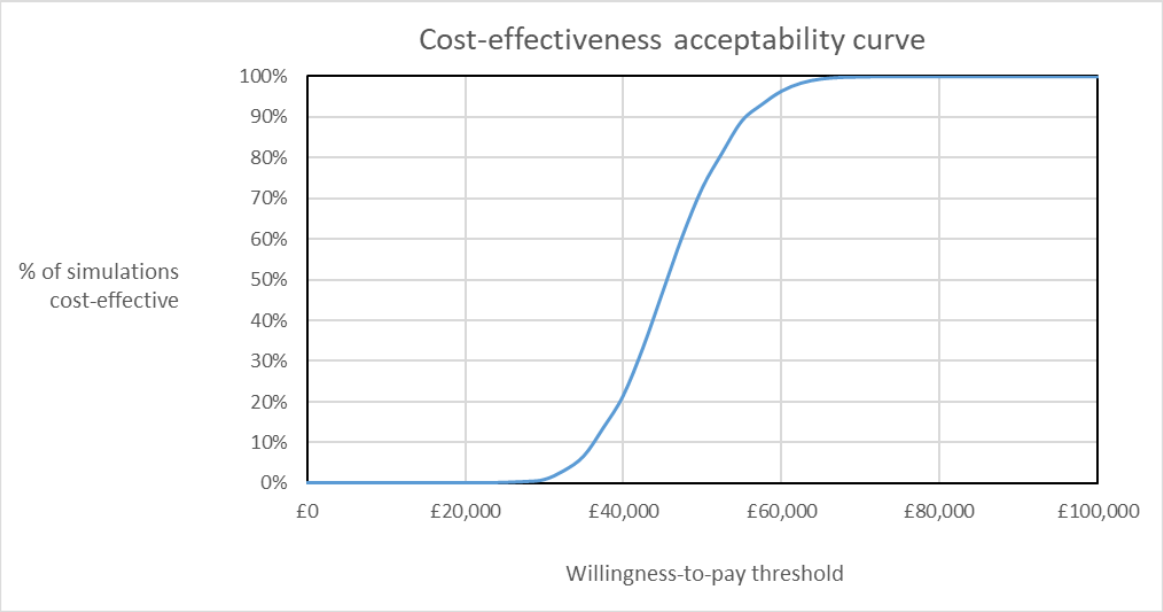


Figure 15. Cost-effectiveness acceptability curve for asciminib vs. ponatinib

5.1.3 Subgroup analyses

The company did not present any subgroup analyses.

5.2 Company's additional analyses

5.2.1 Response based analysis

At the clarification stage, the ERG requested that the company present several scenarios considering alternative assumptions and parameter inputs. The first of these considered the use of a response-based model, the details of which are outlined in Section 4.2.2. The results of this analysis are presented in Table 32.

Table 32 Company's scenario analysis response-based model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib							

Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

5.2.2 Alternative post-progression survival assumptions

The company base-case model assumes that post-progression survival is, on average, 16 months (10 months in the AP phase and 6 months in the BP). These assumptions were informed by previous NICE TA's in CML. At the clarification stage, the ERG noted that the PACE trial may provide alternative and more up-to-date estimates of average life expectancy and requested the company to incorporate these estimates into the economic analysis. The company's response noted that progression was defined broadly in the PACE study and that this may inflate estimates of post-progression survival but implemented these analyses in line with the base-case model structure. The results of this analysis generated substantial higher estimates of PFS and OS than predicted by either the cumulative survival or response-based model with estimates of post-progression survival ranging from 46 to 86 months. The company considered this upper estimate to be clinically implausible and therefore presented two scenarios assuming either a 46 month or 74 month post-progression survival period. Results of this analysis are presented in Table 33.

Table 33 Company's scenario analysis using PACE to model progressive disease

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib assuming a total of 46 months with progressed disease							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs bosutinib assuming a total of 74 months with progressed disease							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib assuming a total of 46 months with progressed disease							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib assuming a total of 74 months with progressed disease							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib assuming a total of 46 months with progressed disease							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib assuming a total of 74 months with progressed disease							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Asciminib vs ponatinib assuming a total of 46 months with progressed disease							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib assuming a total of 74 months with progressed disease							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

5.2.3 Alternative SCT assumptions

The Niederwieser *et al.*[68] study provides an alternative source of data on CML patients who receive allo- SCT. One observation of the Niederwieser *et al*.[68] study is that outcomes for patients who receive SCT in the CP are not statistically different from patients in the AP phase. Niederwieser *et al.,*[68] however, does observe a difference in outcomes for patients receiving SCT in the BP. These results stand in contrast to assumptions made in the model where SCT outcomes are assumed to differ according to whether patients are in the pre-progressed health states (CP off treatment) or have progressive disease (AP and BP). At the clarification stage, the ERG requested the company implement a scenario in which the outcomes of patients in the CP and AP are the same, with different outcomes assumed for the BP. The results of this analysis are reported in Table 34.

Table 34 Company's scenario analysis rerouting patients to SCT_CP submodel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

Extending the scenario described above, the ERG further requested that the company replace the Jabbour *et al.*[75] data with data from Niederwieser *et al.*[68] In response, the company provide two scenarios utilising the data from Niederwieser *et al.* Scenario 1 implements the Niederwieser *et al.*[68] survival data while also retaining the company base-case assumption that SCT survival outcomes differ according to whether patients are pre-progressed (CP off-treatment) or progressed (AP and BP). Scenario 2 implements the Niederwieser *et al.*[68] survival data but instead assumes that survival outcomes following Allo-SCT are the same in the CP and AP. Results of this analysis are reported in Table 35.

Table 35 Company's scenario analysis Niederwieser 2021 for SCT outcomes

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib Scenario 1							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs bosutinib Scenario 2							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib scenario 1							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib scenario 2							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib scenario 1							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib scenario 2							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib scenario 1							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib scenario 2							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

5.2.4 Drug wastage

At the clarification stage, the ERG raised concerns regarding the savings associated with reduced dose intensity and requested the company present an appropriate scenario analysis to assess the impact of these assumptions. In response, the company provided a scenario analysis where it is assumed that relative dose intensity is 100% for all comparators. The results of this analysis are presented in Table 36.

Table 36 Company's scenario analysis RDI of 100% for all treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib							
Bosutinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs dasatinib							
Dasatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs nilotinib							
Nilotinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib vs ponatinib							
Ponatinib	[redacted]	[redacted]	[redacted]				
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

5.3 Model validation and face validity check

5.3.1 Validation undertaken by the company

The CS stated that the outcomes of the model were clinically validated to ensure the face validity of predictions. This was undertaken by comparing OS data from the model with published data and real-world data from HMRN, long term trial data from comparator trials, and was further supported by expert clinical opinion.

5.3.2 Internal validation undertaken by the ERG

As part of the ERG assessment of the economic analysis, the ERG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. Several minor model errors were identified as part of the ERG's validation checks. These related to the transition probabilities applied in several health states, which failed to account for general population mortality. This meant that

patients resided in some health states too long/ This specifically impacted survival functions with either declining or constant hazards were selected to inform the probability of remaining in a health state. The impact of this issue was relatively minor in the context of the cumulative survival model but had a larger effect when using the response-based approach. All identified errors were corrected by the ERG, and a revised model was supplied to the company for verification. Revised results correcting for these errors are reported in Section 6.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section 4.2. The elements where the ERG felt that there was an alternative approach that was more appropriate or where the ERG considered it an important area of uncertainty but it is unclear which approach is most appropriate are explored below.

Descriptions of the exploratory analyses are described in Section 6.1 and the impact of these analyses on the company's base case are presented in Section 6.2 along with the ERG's preferred base case. Note, a number of scenarios were implemented by the company in response to PFCs. These scenarios are included in the following section to illustrate the impact on the company and ERG base case and to allow the combination of such scenarios with the ERG's exploratory scenarios.

The ERG has provided the results as an ICER and as net health benefit (NHB). This is because a major problem associated with mean cost-effectiveness ratios is that the incremental cost-effectiveness ratios cannot be constructed from difference between the mean cost-effectiveness ratios in each pairwise arm of the model (Asciminib compared to either Bosutinib or Dasatinib or Nilotinib or Ponatinib). The NHB statistic offers a solution to this problem. The net health benefit statistic is calculated as:

$$NHB: \Delta E - \frac{\Delta C}{\lambda} > 0$$

Where ΔE is the change in health effects; ΔC is the change in costs; and λ is the cost-effectiveness threshold. The difference in average net health benefit in experimental treatment (Asciminib) and the average net health benefit of the standard care treatment (e.g. Bosutinib) will give the overall incremental net health benefit [1]. The net health benefit is also easier to interpret, as higher values are always better.

6.1 Exploratory and sensitivity analyses undertaken by the ERG

As an initial step, the ERG implemented corrections to the model calculations. The nature of these errors are described in Section 5.3.2. The ERG then conducted the following exploratory analyses.

1. Surrogate survival model

In response to the ERG's concerns regarding the cumulative survival model, the company presented a surrogate survival model based on response outcomes, to match the model used in the most recent appraisal of a TKI in 3rd or later line CML, ponatinib (TA451). A detailed description of the model

structure can be found in Section 4.2.2 and the evidenced used to populate the model in Section 4.2.6.1.

2. Equivalence in effectiveness

As described in Section 4.2.6.1, the ERG has substantive concerns regarding the validity of the of the non-randomised comparisons used to inform the model and does not consider that the MAIC undertaken are sufficiently robust to eliminate the risk of confounding bias. To explore this uncertainty the ERG presents a set of illustrative scenarios in which equivalence in TTD is assumed between asciminib and ponatinib; and equivalence is assumed between bosutinib, nilotinib and dasatinib. This scenario uses data from ASCEMBL to model TTD, with data for asciminib used to populate values for both asciminib and ponatinib while TTD for bosutinib is used to model outcomes bosutinib, nilotinib and dasatinib. This scenario not only has the benefit of navigating the considerable risk of bias in TTD, which includes the issues regarding the MAIC, but also circumvents the imposed modelling restrictions that currently only permits ponatinib, nilotinib and bosutinib to have an exponential model for TTD.

3. Removing retreatment from subsequent treatment

As described in Section 4.2.4, the company assumes that all patients will receive the same basket of subsequent treatments regardless of the primary treatment received. The ERG implements a scenario in which the primary treatment is removed from the distribution of subsequent treatments. The remaining subsequent treatments are then reweighted to ensure the cumulative total sums to 100%.

4. Log-logistic model for TTD

In Section 4.2.6.1, the ERG describes the inconsistency between the company's justification for selecting their preferred parametric model and the model selected for TTD. The company claimed selection was based on plausibility and fit and selected the log normal model. However, the log-logistic resulted in survival predictions that were closer to survival expectations and had a better fit according to AIC and BIC. Therefore, the ERG prefers the use of the log-logistic model for TTD for both asciminib and bosutinib. This scenario is only applicable to the comparison of asciminib with bosutinib.

5. Use of Niederwieser 2021 for SCT survival

Section 4.2.6.5 described the recent addition to the literature of the Niederwieser 2021 evidence which the ER considers to be more suitable than the Jabbour 2011 evidence given it is more up-to-date and consists of larger patient numbers. The scenario was implemented by the company in response to the ERG's clarification questions.

6. Post-discontinuation survival

The assumption of 7 years post-discontinuation survival was based on reported survival in the Kantarjian *et al.* study.[66] The ERG is concerned about the relevance of the Kantarjian *et al.*[66] given the age of that study and the significant changes to practice. Further, more recent evidence from the PACE trial[32] suggests that OS survival may be substantially longer than the predicted by the company model suggesting that an average of 7 years post-discontinuation survival maybe overly conservative. To explore this uncertainty, the ERG implements scenarios in which the 7-year post-discontinuation is extended. The ERG conducts two scenarios based on survival predictions generated by extrapolating evidence from the PACE trial[32] (see PFCs, pg. 83). Two scenarios are conducted to reflect the uncertainty in the extrapolation of the PACE trial data. Scenario 6 (a) assumes a total average OS of 221 months, Scenario 6 (b) assumes a total OS of 167 months. Average post-discontinuation was calculated based on reported TTD on treatment in the PACE trial[32] (32.1 months) assuming that TTD followed an exponential distribution. The median TTD reported in PACE was converted to mean TTD (46.3 months) and was subtracted from the 221 months and 167 months. Estimated post-progression survival was therefore 174.7 months (14.6 years) in scenario 6a and 120.7 months (10.1 years) in scenario 6(b).

7. Age-adjustment

In Section 4.2.7, the ERG outlined the company's additive approach to implementing age-related utility decrements. The ERG considers it more appropriate to apply the age-related utility decrements as a multiplier, to align with the precedent set in a large number of previous appraisals. The approach assumes the impact of age on HRQoL is proportional to the health state utility rather than constant across health states.

8. Dose intensity of ponatinib

In Section 4.2.8.1.1, the ERG detailed issues with the company assumption that dose intensity of ponatinib is maintained at 100% (45mg). This assumption does not align with the PACE trial. Within the trial, participants started with a dose of 45mg, then reduced to 15 mg for those with a response to ponatinib, 30mg for those without a response. Changes in the dose schedule were imposed to reduce risks of adverse events. Clinical advice to the ERG aligns with the assumption of 15mg being a more appropriate dose.

As the exact dosing schedule in PACE is unknown, the ERG implements a number of scenarios in which it is assumed patients are treated with 100% dose intensity (45mg) for a time period, followed by a reduction to 33% (15mg) after that. The ERG implements scenarios in which the reductions occur at a) 1 year, b) 2 years and c) 3 years. Note, this approach is implemented in the cumulative

survival model. In the surrogate survival model, it is assumed all individuals with a CCyR, PCyR and CHR receive 15mg, those without a response receive 30mg. The dose reductions will occur at 1 year as this aligns with the time period over which response status can be ascertained. Note these scenarios do not reduce the dose of ponatinib when it is used as a subsequent treatment.

9. Dose intensity of nilotinib and Dasatinib

As described in Section 4.2.8.1.2, it is unclear if the company's assumption of 100% dose intensity of nilotinib and Dasatinib is appropriate. The ERG therefore explores a scenario in which the relative dose intensity of nilotinib and dasatinib matches that reported for bosutinib in the ASCEMBL trial.

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

The results of the scenario analyses are presented in Table 37 for asciminib compared to bosutinib, ponatinib, nilotinib and dasatinib. These results exclude the confidential PAS discounts for bosutinib, ponatinib, nilotinib and Dasatinib. The ERG understands the confidential PAS for nilotinib could be included as the manufacturer of asciminib is also the manufacturer of nilotinib. However, for consistency the results presented below include the asciminib PAS only. Results including all discounts are presented in a confidential appendix. All results are presented deterministically.

Table 37 ERG exploratory scenarios

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Change from company base case	NHB with k = £20,000/QALY (QALYs)	Change in NHB from company base case	NHB with k = £30,000/QALY (QALYs)	Change in NHB from company base case
Company base case										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	2,654	n/a	1.29	n/a	1.36	n/a
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	582	n/a	0.55	n/a	0.56	n/a
Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	49,445	n/a	-1.25	n/a	-0.55	n/a
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	271,410*	n/a	6.40	n/a	4.10	n/a
Error correction										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-2,753	1.40	+0.11	1.40	+0.04
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	88	-494	0.57	+0.01	0.57	+0.01

Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	48,961	-484	-1.23	+0.02	-0.54	+0.01
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	271,026*	-384	6.39	-0.01	4.09	-0.01
Scenario 1: Surrogate survival model										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-14162	1.81	0.51	1.59	0.23
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	37,740	+37,158	-2.17	-2.72	-0.63	-1.19
Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	49,261	-184	-3.71	-2.46	-1.63	-1.08
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	748,333*	+476,923	5.91	-0.49	3.89	-0.21
Scenario 2: Equivalence in effectiveness										
Asciminib vs bosutinib										
Bosutinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	11,052	+10,470	0.38	-0.18	0.53	-0.03
Asciminib vs Nilotinib										

Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	38,926	-10,519	-0.92	+0.33	-0.29	+0.26
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-2,494,048	4.22	-2.18	2.83	-1.27
Scenario 3: Removing retreatment from subsequent treatment										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	10,810	8155	0.69	-0.61	0.95	-0.41
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-15,179	0.99	+0.43	0.85	+0.29
Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	20,919	-28,526	-0.04	+1.21	0.26	+0.81
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	205,233*	-66,177	4.72	-1.68	2.97	-1.12
Scenario 4: Log-logistic model for TTD										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	1,224	-1,431	1.27	-0.03	1.29	-0.07
Asciminib vs dasatinib										
Dasatinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib										

Nilotinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib										
Ponatinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
<u>Scenario 5: Use of Niederwieser 2021 for SCT survival</u>										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	2,485	-169	1.36	+0.07	1.43	+0.07
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	189	-392	0.61	+0.05	0.61	+0.05
Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	45,884	-3,561	-1.17	+0.07	-0.48	+0.07
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	252,355*	-19,055	6.35	-0.05	4.05	-0.04
<u>Scenario 6a: 14.6 years post discontinuation survival</u>										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-19186	1.90	0.61	1.62	0.26
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-17174	0.75	0.20	0.64	0.08
Asciminib vs Nilotinib										

Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	50,828	1382	-0.97	0.28	-0.44	0.11
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	369,627*	98216	6.20	-0.20	4.02	-0.08
Scenario 6b: 10.1 years post discontinuation survival										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-7287	1.58	+0.29	1.48	+0.12
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-6477	0.64	0.09	0.59	0.04
Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	50,015	570	-1.12	0.13	-0.50	0.05
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	308,180*	36770	6.31	-0.09	4.06	-0.04
Scenario 7: Age adjustment										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	2,605	-50	1.32	0.03	1.39	0.03
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	569	-12	0.57	0.01	0.57	0.01
Asciminib vs Nilotinib										

Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	48,484	-962	-1.23	0.02	-0.53	0.02
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	265,551*	-5859	6.39	-0.01	4.09	-0.01
Scenario 8a: Ponatinib dose reduced to 15mg after 1 year										
Asciminib vs bosutinib										
Bosutinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib										
Dasatinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib										
Nilotinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	74,952*	-196,458	1.40	-5.00	0.76	-3.33
Scenario 8b: Ponatinib dose reduced to 15mg after 2 years										
Asciminib vs bosutinib										
Bosutinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib										
Dasatinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib										

Nilotinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	122,390*	-149,020	2.61	-3.79	1.57	-2.53
Scenario 8c: Ponatinib dose reduced to 15mg after 3 years										
Asciminib vs bosutinib										
Bosutinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib										
Dasatinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs Nilotinib										
Nilotinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	160,296*	-111,114	3.57	-2.83	2.21	-1.89
Scenario 9: Nilotinib and Dasatinib equivalent to Bosutinib dose										
Asciminib vs bosutinib										
Bosutinib	n/a	n/a	-	-	-	-				
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a				
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	13,212	+12,631	0.19	-0.36	0.32	-0.24

Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	49,749	+304	-1.26	-0.01	-0.56	-0.01
Asciminib vs ponatinib										
Ponatinib	n/a	n/a	-	-	-	-				
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NHB, net health benefit; QALYs, quality-adjusted life-years.

*ICER falls in the south-west quadrant of the cost-effectiveness plane

The ERG base case results are presented in Table 38. These results exclude the confidential PAS discounts for bosutinib, nilotinib, dasatinib and ponatinib.

In addition to the ERG base case, the ERG presents the results of the illustrative scenario of assuming equivalence in effectiveness (i.e. Scenario 2). Note, its implementation on the ERG base case means the model is assuming equivalence in CCyR, PCyR, CHR and NR. That is, equivalence between ponatinib and asciminib, and separately equivalence between nilotinib, dasatinib and bosutinib, to allow the use of the ASCEMBL data. The ERG considers that this scenario has less merit in the surrogate survival model than the cumulative survival model given the strengths of response as an objective measure of effectiveness (compared to TTD) but the results nevertheless have benefits in that they do not rely on the results of the MAIC.

Table 38 ERG base case and exploratory scenario on the base case

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Change from company base case	NHB with k = £20,000/QALY (QALYs)	Change in NHB from company base case	NHB with k = £30,000/QALY (QALYs)	Change in NHB from company base case
ERG preferred base case: Error correction, Scenario 1, 3, 4, 5, 7, 8										
Asciminib vs bosutinib										
Bosutinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-6,227	1.27	-0.03	1.20	-0.16
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	30,538	29956	-1.15	-1.70	-0.04	-0.60
Asciminib vs Nilotinib										
Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	35,035	-14410	-1.72	-0.47	-0.38	0.17
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-351,500	-0.91	-7.31	-0.67	-4.77
Exploratory analysis: ERG preferred base case + Scenario 2										
Asciminib vs bosutinib										
Bosutinib	n/a	n/a	-	-	-	-	-	-	-	-
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib										
Dasatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	40,296	39715	-3.35	-3.91	-1.13	-1.69
Asciminib vs Nilotinib										

Nilotinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	39,784	-9661	-3.34	-2.09	-1.10	-0.55
Asciminib vs ponatinib										
Ponatinib	[redacted]	[redacted]	-	-	-	-	-	-	-	-
Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	315,255	+586,665	-0.56	-6.96	-0.36	-4.46

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NHB, net health benefit; QALYs, quality-adjusted life-years.

*ICER falls in the south-west quadrant of the cost-effectiveness plane

6.3 Conclusions of the cost effectiveness section

The company submitted a de novo partitioned survival cost-effectiveness model. The ERG deems that the submitted evidence broadly reflects the decision problem defined in the final scope and meets the requirements of the NICE reference case. The ERG's review of the CS identified several key uncertainties, which the ERG has sought to address in the revised base case and scenario analyses.

One key area of uncertainty is the modelling approach adopted. The company's base-case analysis approach is based on the cumulative survival approach. This approach relies heavily on TTD being predictive of relevant survival outcomes (PFS and OS). The company was, however, unable to provide any direct evidence to support the predictive value of TTD. Further, the ERG is also concerned that TTD is not a marker of disease activity or patient status and is inherently a subjective endpoint that is heavily dependent on several circumstances. Consequently, TTD is likely to be confounded as a measure of clinical benefit. This undermines the reliability of using TTD as a clinical endpoint and increases the difficulty of generating unbiased comparisons across studies.

Reflecting on these concerns, the ERG proposed using an alternative approach in which cytogenetic response is used to predict PFS. This surrogate modelling approach has been adopted in the most recent NICE TA for CML (TA 451).[18] This response-based approach has several advantages over the cumulative survival approach. The clinical utility of cytogenic response as an indicator of effectiveness is widely recognised and is a more objective measure of effectiveness. This reduces the potential for confounding when making non-randomised comparisons, which is necessary for several comparators. Importantly the surrogate value of response is supported in the published literature, with several previous studies demonstrating a relationship between response and relevant survival outcomes. The ERG, therefore, favours the surrogate (response-based) approach over the cumulative survival approach.

A further important assumption of the cumulative survival approach is the duration of post-progression following discontinuation of primary treatment. In the company analysis, this period is assumed to be seven years. This assumption is informed by data from Kantarjian *et al.*,[66] which had been used in previous appraisals to support similar assumptions. The ERG is concerned about the relevance of the Kantarjian *et al.*[66] study to current practice. Improvements in care and increased availability of TKI's is likely to mean that estimates of survival based on Kantarjian *et al.*[66] may be overly conservative. Evidence from both the HMRN[24] and the PACE trial[32] and HMRN network appear to affirm these concerns, suggesting patients live for substantially longer than predicted by the economic model. The ERG, therefore, explores a range of scenarios that seek to utilise the data from the PACE trial to inform assumptions about the duration of post-progression survival.

A further important area of uncertainty relates to the dose intensity of comparator treatments ponatinib, nilotinib and dasatinib. As discussed in Sections 3.4.2.1 and 4.2.8.1, ponatinib is associated with several serious AEs. Reflecting these concerns about AEs, SmPC guidance for ponatinib recommends that dose modifications or interruption be considered. Further, clinical advice suggests that lower doses of ponatinib are regularly used in practice. Evidence from the PACE trial[32] indicates that dose reductions were imposed on nearly all patients reflecting concerns raised by the FDA. Evidence to support alternative assumptions regarding the dosing of ponatinib is, however, limited as the dose reductions applied in the PACE[32] is not reported in detail. The ERG, therefore, considers a range of scenarios exploring alternative ways of modelling expected reductions in the maintenance dose of ponatinib. The lack of data to inform these assumptions means that substantive uncertainty remains regarding the appropriate dosing of ponatinib. Further, clinical input in evaluating the most appropriate dose would help reduce this uncertainty.

Similarly, assumptions around the dosing dasatinib and nilotinib are also subject to uncertainty. The company's model assumes a relative dose intensity of 100% for the treatments implying no dose reductions or interruptions. This position is inconsistent with clinical advice received by the ERG. This suggests that a proportion of patients receiving dasatinib and nilotinib will require dose modifications. Appropriate evidence to inform alternative assumptions is limited. The ERG, therefore, implemented an exploratory analysis using dose intensity reported for bosutinib as a proxy. These scenarios assume that the tolerability of nilotinib and dasatinib is comparable to that of bosutinib. This may be reasonable given that all three agents are second-generation TKI's with similar modes of action.

A final uncertainty explored relates to the basket of treatments patients receive following discontinuation of primary treatment. The company model assumes a common basket of subsequent treatments is used based on data adapted from the HMRN.[24] While this approach is consistent with the cumulative survival approach, these assumptions are inconsistent with clinical practice where retreatment with previously used therapies is rare. The ERG, therefore, prefers to revise the distribution of subsequent treatments to remove the possibility of retreatment.

Other areas of uncertainty and limitations, which have a smaller impact on the results, are the choice of extrapolation for TTD; the methods used to adjust for age-related reductions in quality of life; and, the data used to inform outcomes following SCT. These issues were explored in scenario analysis presented by either the company or the ERG and were all demonstrated to have a modest impact on the cost-effectiveness of asciminib See Table 37 and Table 38.

Despite the ERG's attempt to address the key uncertainties, limitations in the evidence base meant that some uncertainties could not be fully explored. Several of the cost-effectiveness estimates are

based on an uncontrolled naïve comparison. While the ASCEMBL trial provides relatively robust estimates of TTD for asciminib and bosutinib, comparisons with other comparators are generated via indirect comparisons using single-arm data. To account for the differences in participant characteristics across studies, the company attempts to adjust the available data for asciminib through a series of MAICs. These MAICs, however, adjust for relatively few covariates. These comparisons are therefore not sufficiently robust to minimise the impact of confounding. The ERG is also concerned about the lack of overlap between the ASCEMBL trial and the single-arm studies used in the comparisons. For example, the PACE trial[32] used in the ponatinib comparison includes a substantial number of T315I. These patients were, however, explicitly excluded from the ASCEMBL trial and therefore not represented in the population. For these reasons, the ERG considers these non-comparisons inherently unreliable and very likely to be subject to considerable confounding bias of unknown direction and magnitude. Further, because of the limitations of the adjusted analysis, the ERG considers that consideration should be given to scenarios where equivalence is assumed between all 2nd generation TKI's. Similarly, the ERG considers that it may also be appropriate to consider scenarios in which ponatinib is assumed equivalent to asciminib.

A further area of uncertainty that could not be explored by the ERG relates to the model population and its generalisability to practice. Specifically, the ERG notes NICE recommendations for bosutinib and ponatinib do not permit use in all third-line patients, restricting use to patients where dasatinib and nilotinib are not appropriate. Note, ponatinib is also recommended in patients with the T315I mutation. This implies that there are two subpopulations eligible for asciminib reflecting the clinical relevance of dasatinib and nilotinib. These subpopulations are not explicitly reflected in the economic model and may differ in important characteristics.

The impact of these uncertainties is considered in a series of exploratory analyses. The results of these illustrated that several of the ERG's alternative assumptions impacted significantly on the results of the economic analysis. Specifically, assumptions made regarding the model structure (cumulative survival vs. surrogate survival), the basket of subsequent treatments modelled, and the dosing of ponatinib have a very substantive impact on the estimated ICER. Taking the ERG base-case, which uses a response-based approach, the pairwise comparison with bosutinib leads to asciminib dominating bosutinib producing greater health benefits at lower cost. Pairwise comparisons with dasatinib and nilotinib result in ICERs of £30,558 and £35,035 per QALY respectively. In the pairwise comparison with ponatinib, asciminib is estimated to be less effective and more expensive than ponatinib implying that asciminib is dominated by ponatinib. These results are exclusive of PAS discount for comparators and subsequent treatments. See confidential appendix for results of all presented analyses including all available PAS discounts.

7 END OF LIFE

The ERG considers that asciminib does not meet end-of-life criteria. Median life expectancy for people with CML treated with TKIs appears to be considerably longer than 5 years. The survival data on asciminib from the ASCEMBL trial are currently too limited and immature to determine whether asciminib will extend life, when compared to other TKIs.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 3 February 2022** using the below 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 committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Absence of evidence on patients with the T315I mutation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ERG state: *"The company did not provide evidence for the effectiveness, safety and cost-effectiveness of in patients with the T315I mutation. This subgroup of patients are likely to be important when making clinical decisions. Ponatinib is currently the only NICE recommended TKI for patients with a T315I mutation, and the relative effectiveness of ponatinib and asciminib in these patients is uncertain. The ERG expects that evidence on the effectiveness of asciminib within this subgroup may be required."* Location: Section 1.1 (Page 11), Section 1.3 (Page 15), Section 2.3.1 (Pages 36 and 38)	We propose that this be removed as an issue as this is not a subgroup in which reimbursement is being sought for asciminib.	The license of asciminib is not expected to include this subgroup. The population are therefore out of scope for this appraisal. The pivotal clinical trial (ASCEMBL) also excluded patients with the T315I mutation.	At the time of writing, the anticipated indication for asciminib was [redacted] and did not mention any restrictions by mutation status. We thank the company for highlighting the recent MHRA early access to medicines scheme (EAMS) scientific opinion published on 24 January 2024, which states that asciminib is *indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) without T315I mutation previously treated with two or more tyrosine kinase inhibitors.* As this is a scientific opinion rather than a licensed indication, we have decided to leave discussion of individuals with a T315I mutation in the report, for completeness, and to

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			allow the committee to consider this subgroup, if it wishes. We have clarified in Sections 1.1, 1,3, 2.3.1, 3.2.1.3, 3.2.3 and Table 2 that the company are not seeking reimbursement for this group.
The ERG state: "*Asciminib targets both native and mutated BCR-ABL1, including the T315I mutant."* Location: Section 2.2.1 (Page 34)	We suggest removing the second part of the sentence, as the T315I mutation group is not a relevant subgroup for this submission.	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	Not a factual accuracy: and see response above
The ERG state: "*In October 2021, the Food and Drug Administration granted accelerated approval to asciminib for individuals with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs), and for adult patients with Ph+ CML in CP with the T315I mutation. A regulatory application for the anticipated UK licence indication was submitted to the MHRA in July 2021."* Location: Section 2.2.4 (Page 35)	We propose more detail should be added to this paragraph based on the recent early access to medicines scheme (EAMS) approved indication.	The MHRA EAMS has approved asciminib for a more specific indication: *"treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) without T315I mutation previously treated with two or more tyrosine kinase inhibitors"*. The EAMS number is: 00101/006 and was granted on the 19th of January 2022.	We have added a note to Section 2.2.4 referring to the recent HMRA EMA scientific opinion.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ERG state: "*Overall, the ERG found that the evidence submitted broadly reflects the decision problem, although the ERG has a number of concerns, notably regarding the exclusion of individuals with the T315i mutation from the ASCEMBL trial and the use of TTD as a surrogate marker of survival."* Location: Section 2.3 (Page 35)	We propose that the part of the sentence referring to the mutation group be removed, as this is not a subgroup of interest and therefore it is not considered an issue that the population is not generalisable to that group. Proposed wording: *Overall, the ERG found that the evidence submitted broadly reflects the decision problem, although the ERG has a number of concerns, notably ~~regarding the exclusion of individuals with the T315i mutation from the ASCEMBL trial and~~ the use of TTD as a surrogate marker of survival.*	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	We have removed the reference to T315I in Section 2.3: See also response above
The ERG state: "*Similarly, the company excluded patients with the T315I mutation because bosutinib is known to be less effective in this patient group. This is an acceptable justification. However, there are no RCT data on the effectiveness of asciminib in this patient group, so it is unclear if data from the ASCEMBL trial generalizes to this subgroup."* Location: Section 3.2.1.3 (Page 47)	We propose the last sentence be replaced by "*However, there are no RCT data on the effectiveness of asciminib in this patient group, so it is unclear if data from the ASCEMBL trial are generalisable to this subgroup."* With: *This was also a patient group excluded from ASCEMBL, and the licensed indication is not expected to include this subgroup, and therefore the data from ASCEMBL are not expected to be generalisable to this subgroup.*	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	See response above

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
X2101 effectiveness results. Location: Section 3.2.2 (Page 51)	The ERG discusses the results of study X2101, a Phase I trial (X2101) that included the T315I patient subgroup. We propose this section be removed, as this is not a subgroup expected to be part of the licensed indication and therefore not relevant to the analysis.	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	See response above
The ERG state: *"The clinical evidence presented in the CS broadly reflects the population described in final scope, although the ASCEMBEL trial excluded patients with a T315I mutation, a population with higher unmet need. The asciminib trial evidence also included patients who may be fitter, younger and with fewer comorbidities than the population who would be eligible for asciminib in practice."* Location: Section 3.6.1 (Page 68)	We propose that the first sentence be amended, as the T315I mutation group is not a subgroup of interest to the analysis, and therefore it's exclusion from the trial should not be considered a limitation of the trial. Proposed wording: "*The clinical evidence presented in the CS broadly reflects the population described in the final scope, ~~although the ASCEMBEL trial excluded patients with a T315I mutation, a population with higher unmet need~~. The asciminib trial evidence also included patients who may be fitter, younger and with fewer comorbidities than the population who would be eligible for asciminib in practice."*	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	We have removed the reference to T315I in Section 3.6.1: See response above
The ERG state: *"The ASCEMBL trial excluded patients with cardiac comorbidities and patients with the T315I mutation. Although these exclusions are justified in aiming to ensure comparability between treatments*	We propose that the second sentence be amended, as the data from ASCEMBL are not expected to be generalisable to this subgroup. Proposed wording: *The ASCEMBL trial excluded patients with cardiac comorbidities and patients with the T315I*	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	We have removed the reference to T315I in Section 3.6.2: See response above

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
it is unclear whether the ASCEMBL data generalise to this important subgroup." Location: Section 3.6.2 (Page 68)	*mutation. ~~Although T~~These exclusions are justified in aiming to ensure comparability between treatments ~~it is unclear whether the ASCEMBL data generalise to this important subgroup~~, as this is not a subgroup included as part of this analysis.*		
The ERG state: *"Because the modelled population is based on ASCEMBL, this implies that the economic analysis does not provide evidence of cost-effectiveness in the T315I subgroup. This is inconsistent with the anticipated marketing authorisation and the NICE scope."* Location: Section 4.2.3.1 (Page 81)	The scope does not explicitly include the T315I mutation subgroup, and the anticipated marketing authorisation makes no reference to the T315I mutation subgroup. We ask that the ERG remove the entire sub-section on the T315I mutation or adds clarification that the T315I subgroup is not part of the expected license for asciminib.	The scope does not explicitly include the T315I mutation subgroup. During the scope consultation, Novartis commented that there were no subgroups of interest. The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	We have removed reference to the T315I mutation subgroup being included in the marketing authorisation in Section 4.2.3.1.
The ERG state: *"As discussed in Section 4.2.3, the ERG considers that there are three relevant populations: i) those in which dasatinib, nilotinib is clinically indicated, ii) patients where dasatinib and nilotinib are not clinical indicated, iii) patients with the T315I mutation."* Location: Section 5.1.1 (Page 107)	Population 3 is not relevant, as this is not a subgroup that is expected to be part of the licensed indication, and should be removed from this list. As for populations 1 and 2, we would like to emphasise that comparisons are presented with all comparators mentioned in the scope.	The T315I mutation group is not a relevant subgroup for this submission, as described in row 1 of this table.	We have removed reference to the T315I mutation subgroup in Section 5.1.1.
The ERG state: *"Further, the modelled population excludes*	The T315I mutation group is not a subgroup of interest to the analysis.	The T315I mutation group is not a relevant subgroup for this	We have removed reference to the T315I mutation subgroup being a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients with the T315I mutation. The T315I is clinically significant because it is associated with resistance to currently available TKIs except for ponatinib and therefore its omission is important. Further, because of the noted differences in disease pathology, and differences in efficacy observed in this patient group, the ERG does not consider it appropriate to assume that the cost-effectiveness results for the main population are transferable to the T315I subgroup." Location: Section 6.3 (Page 134)	Therefore the lack of generalisability to this subgroup should not be considered an issue. We propose this paragraph be removed.	submission, as described in row 1 of this table.	relevant subgroup for this decision in Section 6.3.

Issue 2 Bias and quality concerns with the ASCEMBL trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ERG state: *"The ERG acknowledges that blinding was not feasible in ASCEMBL, but notes that this means that analysis should be focused on outcomes less likely to be influenced by knowledge of treatment. In particular, TTD might potentially be influenced by knowledge of which treatment was received, which could have led to biased results (see Issue 4)."* Location: Section 1.4 (Page 16)	The statement: *"In particular, TTD might potentially be influenced by knowledge of which treatment was received, which could have led to biased results (see Issue 4)"* is factually inaccurate. This statement should be removed as an issue.	Please see row 3 of issue 2 in this document. Only patients who fulfilled the objective lack of efficacy criteria, i.e. lab based BCR-ABL1 level milestones per ELN were allowed to switch to bosutinib.	Not a factual inaccuracy. This comment does not relate to treatment switching, but only to the fact that a decision to discontinue treatment can be subjective.
The ERG state: "*The CS judged there was an unclear risk of performance bias for all outcomes. However, the ERG had some concerns regarding performance bias for the time to treatment discontinuation (TTD) outcome. The risk that decisions to discontinue treatment may, in some cases, have been influenced by patients' and study personnel's knowledge of treatment assignment cannot be excluded. The open-label trial design may have led to an underestimate of TTD in patients who received bosutinib.*	The following statements are factually inaccurate: "*One of the treatment failure criteria was discontinuation for any reason."* *"…and subjective non-response (discontinuation for any reason) criteria"* We propose the removal of the whole statement: *"Patients in the bosutinib arm who met treatment failure criteria had the option to switch to asciminib. One of the treatment failure criteria was discontinuation for any reason. Given patients knowledge of their treatment status, the ERG's clinical advisor agreed it was possible some patients assigned to bosutinib may have chosen to discontinue in*	Only patients who fulfilled the objective lack of efficacy criteria, i.e. lab based BCR-ABL1 level milestones per ELN were allowed to switch to bosutinib. The criteria of discontinuation for any reason stated here is related to the definition of treatment failure as associated with the full analysis set (FAS) and not with eligibility criteria to be offered switch to asciminib. Section 7.1.2.2 of the Protocol Version 3 provides the detailed conditions to be fulfilled for switch of treatment (1). Patients discontinuing for any other reason than lack of efficacy were not allowed to switch	Not a factual inaccuracy. The ERG notes that the criteria for treatment failure listed in section B.2.4.1.4 of the CS and section 9.7.6 of the CSR includes discontinuation for any reason. We also note that we state in Section 3.2.1.2 that: *"ASCEMBL did not allow bosutinib arm participants to switch to asciminib unless*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Patients in the bosutinib arm who met treatment failure criteria had the option to switch to asciminib. One of the treatment failure criteria was discontinuation for any reason. Given patients knowledge of their treatment status, the ERG's clinical advisor agreed it was possible some patients assigned to bosutinib may have chosen to discontinue in order to receive asciminib, a new treatment. Therefore, there is a risk that the rate of discontinuation may have been inflated and TTD underestimated in the bosutinib arm. ASCEMBL did not allow bosutinib arm participants to switch to asciminib unless they met criteria for treatment failure which included objective non-response (e.g. BCR-ABL 1 ratio >10% IS and/or 65% Ph+ metaphases at 6 months) and subjective non-response (discontinuation for any reason) criteria. This might have reduced some of the risk that lack of blinding could have affected decisions to switch to asciminib." Location: Section 3.2.1.2 (Page 46)	*order to receive asciminib, a new treatment. Therefore, there is a risk that the rate of discontinuation may have been inflated and TTD underestimated in the bosutinib arm. ASCEMBL did not allow bosutinib arm participants to switch to asciminib unless they met criteria for treatment failure which included objective non-response (e.g. BCR-ABL 1 ratio >10% IS and/or 65% Ph+ metaphases at 6 months) and subjective non-response (discontinuation for any reason) criteria. This might have reduced some of the risk that lack of blinding could have affected decisions to switch to asciminib."*	to bosutinib. Patients must have met ≥1 of the following criteria. Failure is defined as follows: • Three months after the initiation of therapy or thereafter: No CHR or >95% Ph+ metaphases. • Six months after the initiation of therapy or thereafter: BCR-ABL1 ratio >10% IS and/or >65% Ph+ metaphases. • Twelve months after initiation of therapy or thereafter: BCR-ABL1 ratio >10% IS and/or >35% Ph+ metaphases. • At any time after the initiation of therapy, loss of CHR, CCyR or PCyR. • At any time after the initiation of therapy, detection of new BCR-ABL1 mutations which potentially cause resistance to study treatment (asciminib or bosutinib). • At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests. • At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+.	*they met criteria for treatment failure which included objective non-response"* However, we consider that the paragraph indicated by the company may be causing confusion, and we have decided to remove it. We do not appear to have received Protocol version 3 therefore we cannot comment on its contents.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		There is no subjective non-response associated with patients in the bosutinib arm that defines treatment failure allowing for the option to switch.	
The ERG state: *"An additional quality assessment issue was that company clarifications on methods of allocation concealment in the ASCEMBL trial raised further ambiguities. In response to PFC question A7, the company stated: "methods were not used to conceal allocation to asciminib or bosutinib treatment arms". This would lead the ERG to rate the trial at high risk of selection bias. However, the company's description of the randomisation process stated that patients were randomised by a centralised system after being classified as meeting inclusion criteria for the trial. These methods would lead the ERG to rate the trial at low risk of selection bias. Despite inconsistent descriptions of allocation concealment methods, the ERG concluded that methods for concealing allocation are likely to be appropriate."* Location: Section 3.2.1.2 (Page	We believe that this paragraph is confusing the allocation method to treatment, with the blinding of treatment. These are not the same issues. Proposed wording: ~~*Despite inconsistent descriptions of allocation concealment methods,*~~ *the ERG concluded that methods for concealing allocation are likely to be appropriate."*	A lack of blinding does not create a selection bias, providing allocation mechanisms were robust, which they were. Therefore we disagree that there is '*inconsistent descriptions of allocation concealment'* as there are two different issues being discussed of blinding to the treatments, and how allocation to the treatments was undertaken.	We do not think that the text in the ERG report implies that a lack of blinding creates selection bias. However, we have edited section 3.2.1.2 to clarify the distinction between allocation concealment and randomisation methods.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
46)			

Issue 3 Focus on time to discontinuation (TTD) as a measure of effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The company's indirect comparisons with *other TKIs and the company's economic model rely heavily on time to treatment discontinuation (TTD). TTD was not specified in the scope. No evidence was provided to support the validity of TTD as a marker of long-term survival. The ERG is concerned that TTD may not be a robust measure of effectiveness."* Location: Section 1.4 (Page 17)	Regarding the point that TTD was not an outcome specified in the scope, we would like to point out that as part of the scope consultation Novartis had suggested the addition of TTD as an outcome (the consultation is available on the NICE website). However this was not added into the scope by NICE, as it was stated that *"The list of outcomes are examples and not intended to be an exhaustive list."* We propose references to TTD not being in the scope should be removed.	As the list of outcomes in the scope are not an exhaustive list, then other outcomes can also be relevant.	Not a factual inaccuracy. We think that it is important to highlight that the key outcome reported by the company was not a key outcome identified by NICE.

Issue 4 Severe limitations of the matched adjusted indirect comparison (MAIC) analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ERG state: "*The CS only reported the adjusted time to discontinuation curves for asciminib in the ACSEMBL trial, and not the equivalent data for comparator interventions, nor any*	Proposed wording: *"The CS only reported the adjusted time to discontinuation curves for asciminib in the ACSEMBL trial, and not the equivalent data for comparator interventions, nor any estimates of relative effectiveness, as*	Reporting of the equivalent data for the comparators was not possible as median TTD was all that was available for the	We have edited Section 3.4 and 3.4.5 to address this error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
estimates of relative effectiveness" Location: Section 3.4 (Page 56) *"Despite the ERG requesting the data, the MAIC for TTD was incomplete, as it reported the adjusted data for ASCEMBL, but not TTD data from the comparator trials"* Location: Section 3.4.5 (Page 66)	*this was not possible due to lack of data reporting in the comparator trials."* We propose the latter paragraph mentioned be removed.	comparators. This should be reflected in the text.	
Median TTD is quoted as *16.6 months* for asciminib from ASCEMBL (unadjusted) Location: Section 3.4.2 (Table 10), Section 3.4.3 (Table 12), Section 3.4.5 (Table 14)	Asciminib median TTD had not been reached at the last data cut available from ASCEMBL, therefore there is no median TTD to be reported.	In the clarification questions, unadjusted data for median TTD with asciminib from ASCEMBL was 16.6 months. This has been carried forward into data within the ERG report in Tables 12 and 14. We would like to point out that this value is incorrect. Asciminib median TTD had not been reached at the last data cut available from ASCEMBL (48-weeks data cut), therefore there is no median TTD to be reported, and this value was incorrect and should be removed from the tables.	Table 20 of the company points for clarification document (6/12/21) gives the median TTD in ASCEMBL as 16.6 months. The ERG naturally assumed that table was correct. We have edited Tables 10, 12 and 14 to reflect this error. We clarify at Sections 3.4.2 and 3.4.5 that incorrect data were supplied. Some text (Section 3.4.3) has been edited to remove discussion of TTD which is no longer relevant.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			We note that lack of clarity and accuracy in data provision further undermines the validity of MAIC analyses
The ERG state: *"The results suggests that patients may stay on ponatinib for longer than asciminib. Median TTD was not reached when ASCEMBL data were adjusted for comparison with dasatinib and nilotinib. This would suggest asciminib has slightly longer TTD than either dasatinib or nilotinib, but no confidence intervals were available, so this is uncertain."* Location: Section 3.4.5 (Page 67)	Proposed wording: "*The results suggests that patients may stay on ponatinib for longer than asciminib. Median TTD was not reached when ASCEMBL data were adjusted for comparison with dasatinib and nilotinib. This would suggest asciminib has ~~slightly~~* ***substantially*** *longer TTD than either dasatinib or nilotinib, but no confidence intervals were available, so this is uncertain."*	Follow-up was 35 months in ASCEMBL and median TTD for asciminib was not reached before or after adjustment. This suggests substantially longer TTD than dasatinib or nilotinib at 11 and 14 months, respectively.	The "slightly" has been deleted. We disagree that "substantially" is reasonable, given high uncertainty in median TTD, and lack of confidence intervals.
The ERG compare TTD for asciminib derived from the ASCEMBL trial with TTD data from HMRN. The comparison is made without reference to the bosutinib arm in ASCEMBL which would anchor a MAIC. This is a naïve comparison, which is understandable. However, the company believes the comparison would be strengthened if an anchored comparison was undertaken relative to the	Replacement of the first paragraph on Page 63 with the following: *"Data from HMRN indicate superior TTD for bosutinib in comparison with dasatinib, nilotinib and ponatinib at third and fourth line.* • *The ASCEMBL trial demonstrated a significant improvement in TTD for asciminib compared to bosutinib.* • *A naïve comparison would therefore indicate improved TTD for asciminib*	A comparison of outcomes across very different types of studies is strengthened by consideration of relative effectiveness using a common treatment or anchor. Consequently, the Company would argue that consideration of relative effectiveness compared to bosutinib provides a better comparison of asciminib with nilotinib, dasatinib, and ponatinib. The Company accepts that this is a naïve comparison. However, an	Not a factual inaccuracy. While we appreciate the company's point regarding anchored vs unanchored comparisons, a key purpose of our approach is to highlight the substantial differences in outcomes between HMRN data and trial data.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
common bosutinib arm in both data sources. Location: Section 3.4.3 (Page 63)	*compared to nilotinib, dasatinib and ponatinib.* • *Data on MMR in HMRN suggest bosutinib is inferior to dasatinib and nilotinib.* • *Data in ASCEMBL demonstrated superiority of asciminib over bosutinib for MMR.* • *Overall, a naïve comparison with HMRN would suggest asciminib provides improved TTD over nilotinib, dasatinib and ponatinib.* • *The effectiveness of asciminib compared to nilotinib, dasatinib and ponatinib with regard to MMR is less clear."*	anchored comparison would indicate superiority of asciminib over nilotinib, dasatinib, and ponatinib. This is a very different inference to the unanchored comparison and has greater validity.	

Issue 5 Retreatment with primary therapy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ERG has amended the analysis to ensure that no patients receive treatment with the TKI they received at third line of therapy. The company considers this unrealistic and that an assumption that the distribution of subsequent treatments are independent of third-line treatment is closer to reality.	The Company requests reconsideration of the company base case in which the distribution of TKIs assumed for treatment following discontinuation of third-line therapy is independent of the third-line therapy received.	The Company understands that patients failing to achieve a response to multiple lines of TKI therapy are increasingly likely to receive the same TKI as that received at an earlier stage in their therapy as therapeutic options narrow. This is evidenced in the data cited in the ERG report which show that at third-line, 10% of patients are treated with a TKI they have received previously. Logically, this proportion must rise as patients progressively exhaust TKI treatment options. For some patients, the pool of alternative TKIs may also be narrowed due to contraindications for particular therapies. For these reasons, the Company suggests that the proportion of patients retreated at fourth-line or subsequently with the therapy received at third-line is likely to be higher than zero and likely to exceed 10%. On this basis, the Company believes that the assumptions underpinning the original CS are closer to reality than an assumption of 0% retreatment with the TKI used at third-line.	Not a factual inaccuracy. Clinical advice received by the ERG suggests that retreatment with the primary treatment is unrealistic and that retreatment is rare in clinical practice

Issue 6 Comparator dosing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The ERG has implemented a very simple adjustment to account for the potential for reduction in RDI for patients on ponatinib. This significantly overestimates the savings accruing from a reduction in RDI.	Implementation of a reduction in RDI for ponatinib by dividing by 1.54 instead of by 3. Application to both the cumulative survival approach and to the surrogate survival approach. The current implementation of the ERG's approach is to divide RDI for ponatinib by 3 if dose intensity is assumed to fall at two or three years. If it falls at one year a calculation is made in which RDI is divided by 3/2 for patients with no response to treatment and by 3 for the remaining patients. The Company proposes applying a denominator of 1.54 following the reduction in dose intensity regardless of whether this is modelled to occur after 1, 2 or 3 years.	Ponatinib is available in three doses of 45 mg, 30 mg, and 15 mg. From the BNF, the price for the 30 tablets at both the 45 mg and 30 mg dose is the same, £5,050. The price of 30 tables at the 15 mg dose is £2,525 (half the price of the 45 mg dose). MHRA guidance, as reported in the BNF, suggests reducing the initial 45 mg dose in patients achieving a major cytogenetic response. It is unlikely that all patients reducing their dose will move to 15 mg rather than 30 mg, and for the latter patients, the cost is unchanged. It is plausible to assume that most patients achieving a MCyR will reduce their dose (although possibly not all to 15 mg). It is unlikely that most patients failing to achieve a MCyR will reduce their dose to 15 mg. Therefore, the Company proposes the following amendment to scenario 8 as implemented by the ERG: • Patients achieving a MCyR are assumed to move to 15 mg doses and the cost is halved. Patients not achieving a MCyR are assumed to remain on 30 mg or 45 mg doses and their costs are	Not a factual inaccuracy. The ERG, however, acknowledges the uncertainty in the dosing of ponatinib and is open to considering alternative scenarios. The ERG encourages the company to implement their preferred scenario at the technical engagement stage.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		unchanged. The proportion of patients achieving a MCyR in the PACE trial at 4 years was 70% in patients with 2 prior TKIs (lower in patients with more than two prior TKIs) (2). • Therefore, the Company proposes that the denominator be changed from 3 to 1.54 (calculated as the inverse of the sum of one half multiplied by 70% plus 30% [1/(0.5*0.7)+(1*0.3)]) to implement a reduction in costs to half of the original costs for the proportion of patients achieving a MCyR.	
The ERG state: *"In the surrogate survival mode, the ERG assumes those with a response (CCyR, PCyR, CHR) receive a 15mg dose of ponatinib and those with no response receive 30mg. This aligns with the dosing reductions in the PACE trial."* Location: Section 1.5 (Page 24)	PACE trial data on dosing are misinterpreted. The Company requests consideration of a change to the implementation of the dose reduction for ponatinib in scenario 8 and asserts that the current assumptions do not align with the PACE trial as the report suggests.	The PACE trial investigators implemented dose reductions where possible in October 2013. Patients achieving a MCyR were changed to a 15 mg dose and patients not achieving a MCyR were changed to a 30 mg dose. The four-year results show the proportion of patients in the CML-CP group at third-line achieving a MCyR was 70% (and lower for patients at fourth-line and later) (2). The Company believes that patients failing to achieve even a PCyR are equivalent to those failing to meet MCyR and they would have been	Not a factual inaccuracy. As above, the ERG encourages the company to explore alternative scenarios at the technical engagement stage.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		moved to the 30 mg dose rather than the 15 mg dose (3).	

Issue 7 Parameterisation of response based model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The description of the implementation of the surrogate survival approach is not quite correct. The ERG states: *"The proportion of patients achieving CCyR, PCyR, CHR, and NR was obtained from TA45118 for ponatinib and bosutinib. For asciminib, dasatinib and nilotinib, the proportion of patients not achieving CCyR was distributed across the categories of PCyR, CHR and NR according to the relative proportions obtained from TA451."* Location: Section 4.2.6.1 (Page 92)	Proposed wording: *"The proportions of patients achieving CCyR, PCyR, CHR, and NR were obtained from TA451 for ponatinib and bosutinib. The relative proportion that achieved PCyR, CHR, and no response (NR) for patients not achieving a CCyR were calculated for ponatinib and bosutinib, and also an average of the two arms was taken for each value. ~~For asciminib, dasatinib and nilotinib, the proportion of patients not achieving CCyR was distributed across the categories of PCyR, CHR and NR according to the relative proportions obtained from TA451."~~* In the asciminib arm of every comparison, the observed proportion of those not achieving CCyR or PCyR with asciminib was distributed between CHR and NR according to the average relative proportions of the ponatinib and bosutinib arms observed in TA451 (4). When compared with bosutinib, the observed proportion of those not achieving CCyR with bosutinib was distributed between PCyR, CHR, and NR according to the relative proportions of the bosutinib arm observed in TA451 (4). When compared with ponatinib, the observed proportion of those not achieving CCyR on ponatinib was distributed between PCyR, CHR, and NR according to the relative	Description of methods is misleading.	We have amended the text as outlined by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	proportions of the ponatinib arm observed in TA451 (4). When compared with dasatinib or nilotinib, the observed proportion of those not achieving CCyR for either dasatinib or nilotinib was distributed between PCyR, CHR, and NR according to the relative average proportions of the ponatinib and bosutinib arms observed in TA451 (4).		

Issue 8 Errors in Company submitted documents

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect data in submitted clarification questions document. Location: A15 (Table 20)	Asciminib median TTD had not been reached at the last data cut available from ASCEMBL, therefore there is no median TTD to be reported.	In the clarification questions, comparisons of unadjusted data had reported asciminib median TTD from ASCEMBL of 16.6 months. This has been carried forward into data within the ERG report in Tables 12 and 14. We would like to point out that this value is incorrect. Asciminib median TTD had not been reached at the last data cut available from ASCEMBL, therefore there is no median TTD to be reported, and this value was incorrect. We apologise for this error.	We have amended the text as outlined by the company. (Table 12 and Table 14).
Daily cost of asciminib. Location: ERG report (Section 4.2.6.1 [Table 28]; NICE submission: Section B3.5.1 [Table 80]	The value should be amended to £135.01	The value of £121.67 was incorrectly reported in the CS. The correct cost, used in the economic analysis, is £135.01 per day. We apologise for this error.	We have amended the text as outlined by the company. (Table 28)
Incorrect median TTD value for asciminib in the MAIC versus ponatinib. NICE submission: • "*Median TTD for asciminib was not reached in the ASCEMBL trial. Post-MAIC with ponatinib, median TTD for asciminib was 18.3 months compared…"* Location: Executive summary	Median TTD for asciminib was 17.6 months when compared to ponatinib in the MAIC, not 18.3 months. The incorrect value appears twice in the company submission. The correct value is that which appears on page 93.	Median TTD for asciminib was 17.6 months when compared to ponatinib in the MAIC, not 18.3 months. We apologise for this error.	No amendment necessary.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
(Page 9) • "*Median TTD for asciminib was not reached in the ASCEMBL trial. Post-MAIC with ponatinib, median TTD for asciminib was 18.3 months…'* Location: Section B2 (Page 28)			

Issue 9 Incorrect data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"MMR rate (24 weeks: RD=12.24, 95% CI 2.19 to 22.30; 48 weeks: [redacted])" Location: Section 3.2.2 (Page 50)	MMR rate (24 weeks: RD=12.85, 95% CI 2.40 to 23.29; 48 weeks: [redacted])	Data are incorrect	Thank you for highlighting these issues. Corrected
Neutropenia value is incorrect: "*27 (14.4)"* Location: Section 3.2.4 (Table 8)	Should be corrected to: **34 (17.2)**	Data are incorrect	Corrected to: 34 (18.2).
Arthralgia value is incorrect: "*42 (22.5)"* Location: Section 3.2.4 (Table 8)	Should be corrected to: **29 (15.5)**	Data are incorrect	Corrected
Deaths with bosutinib: *"0"* Location: Section 3.2.4 (Table 8)	Should be corrected to: **1**	Data are incorrect	Corrected
TTD value is incorrect: "*1"* Location: Section 3.4.2 (Table 10)	Should be corrected to: **14**	Data are incorrect	Corrected
Asciminib vs ponatinib 74 months; second ponatinib incorrectly labelled (should be asciminib). • Total costs: "[redacted]" • QALYS: "[redacted]" Location: Section 5.2.2 (Table 33)	As per table 47 in the Company's clarification response, this value should be: [redacted] [redacted]	Data are incorrect	Corrected (Table 33)
The Company cannot replicate nilotinib scenarios ***Asciminib vs nilotinib scenario 1*** Nilotinib [redacted] Asciminib [redacted] **Asciminib vs nilotinib scenario 2** Nilotinib [redacted] Asciminib [redacted]	Values derived from model when replicate these scenarios are: **Asciminib vs nilotinib scenario 1** Nilotinib [redacted] Asciminib [redacted] **Asciminib vs nilotinib scenario 2**	We were not able to replicate the results.	Thank you for highlighting the error in the transcription of the results. These have now been changed to reflect the corrected results as

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Location: Section 5.2.3 (Table 35)	Nilotinib [redacted] Asciminib [redacted]		generated by the model. (Table 35)

Issue 10 Textual/typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"*This acts to reduce the ICERs in comparisons with nilotinib and ponatinib. The ICER for comparisons with nilotinib remains approximately the same and the ICER for Dasatinib is increased."* Location: Section 1.5 (Page 19)	This acts to reduce the ICERs in comparisons with **bosutinib** and ponatinib.	Nilotinib is mentioned twice in the paragraph. The ICER versus bosutinib reduces and the ICER versus nilotinib stays similar.	Thank you for highlighting these errors. Amended.
The Company is unsure whether the second column of the table aligns with the first column headings Location: Section 1.5 (Page 20)	The text in column two of the second row ('*What alternative approach has the ERG suggested?*') beginning '*The ERG is also conscious…*', should be in the row above. Same for the subsequent rows in that table (i.e. the text in each row looks like it belongs in the row above).	The text in row two onwards should all be in the previous row to its current location.	The text in row two onwards has been moved to the row above. The following has been added to the table in the final row: '*Further clinical input regarding the appropriateness of retreatment with the primary treatment would be informative*.'
"These scenarios post-discontinuation survival from 7 years to i) 11.2 years, and ii) 15.7 years." Location: Section 1.5 (Page 21)	These scenarios **vary** post-discontinuation survival from 7 years to i) **10.1** years, and ii) **14.6** years.	Word missing. The values mentioned do not match the values actually tested and reported later on in the report.	Amended.
ASCEMBL misspelt Location: multiple occasions	All instances of ACSCEMBL, ASCEMBEL and ASCEBML should be corrected to **ASCEMBL**	Should be amended for consistency.	Amended.
Row heading incorrectly labelled: "*Number of prior TKIs, n (%)"* Location: Section 3.2.1 (Page 48)	Number of **lines of** prior TKI therapy, n (%)	Data presented for both asciminib and bosutinib refer to number of lines of prior TKI therapy, not number of prior TKIs.	Amended.
Asciminib misspelt Location: multiple occasions	**Asciminib**	Misspelt word.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect date of reference: "*(Ibrahim 2019)"* Location: Section 3.3 (Page 55)	(Ibrahim **2010**)	Should be amended for accuracy.	Amended
Incorrect wording: "…*surrogate relationship between each specific response category and overall survival."* Location: Section 4.1.3 (Page 73)	Surrogate relationship between each specific response category and **progression-free** survival.	This statement refers to PFS, not OS.	Amended
Cytogenetic misspelt. Location: Section 4.2.2 (Page 79)	**Cytogenetic**	Misspelt word.	Amended
Bosutinib misspelt Location: multiple occasions	**Bosutinib**	Misspelt word.	Amended
Missing word: "T*he ERG notes that the Niederwieser study does provide conclusive evidence…"* Location: Section 4.2.6.4 (Page 99)	The ERG notes that the Niederwieser study does **not** provide conclusive evidence	"Not" is missing, and the statement is incorrect without it.	Amended
Missing word: "…s*tudies used to inform the TTD parameters did report any meaningful data…"* Location: Section 4.2.8 (Page 104)	Studies used to inform the TTD parameters did **not** report any meaningful data…	"Not" is missing, and the statement is incorrect without it.	Amended
Myeloablative misspelt Location: Section 4.2.8.2 (Page 104)	**Myeloablative**	Misspelt word.	Amended
Missing word: "*The implementation of half correction…"* Location: Section 5.1 (Page 107)	The implementation of half **cycle** correction;	Cycle is missing, and the statement is incorrect without it.	Amended
Incorrect cross-reference: "*The nature of these errors are described in Section 0."* Location: Section 6.1 (Page 117)	Please amend Section 0 to the correct cross-reference.	Incorrect cross-section	Amended

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incomplete cross-referencing: "*As discussed in Sections x and Y, ponatinib…"* Location: Section 6.3 (Page 133)	Please amend Sections X and Y to the correct cross-references.	No cross references provided.	Amended

References

1. Novartis. Data on file. Asciminib/ABL001 Oncology Clinical Trial Protocol CABL001A2301. 2018.
2. Hochhaus A, Cortes J, Kim D, Pinilla-Ibarz J, le Coutre P, Paquette R, et al. Efficacy and safety of ponatinib in CP-CML patients by number of prior tyrosine kinase inhibitors: 4-year follow-up of the phase 2 PACE trial. Blood. 2015;126(23):4025.
3. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre PD, Paquette R, Chuah C, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018;132(4):393-404.
4. National Institute for Health and Care Excellence. TA451 Ponatinib committee papers. Available at: https://www.nice.org.uk/guidance/ta451/documents/committee-papers (last accessed 24th Nov 2021).

Technical engagement response form

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm on 14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 2: Concerns with the ASCEMBL trial	**Yes**	The ASCEMBL trial used a robust randomisation procedure, and the resulting patient baseline characteristics were not significantly different across trial arms. As part of the clinical study record (CSR), the company submitted logistic regression analysis of major molecular response (MMR) adjusting only for the stratification factor (major cytogenic response [MCyR] at baseline), and further analysis in which the following additional covariates were adjusted for: • sex, • number of prior tyrosine kinase inhibitors (TKIs), • and reason for discontinuation of last TKI. Previous analysis submitted as part of the CSR demonstrated an odds ratio (OR) for MMR with asciminib of [redacted] (95% confidence interval (CI): [redacted] after stratification on MCyR at baseline, and an OR of [redacted] (95% CI: [redacted] after further adjustment for sex, number of prior TKIs, and reason for discontinuation of prior TKI. The ERG acknowledged that multivariate analysis presented in the CSR led to no meaningful change in the OR of MMR with asciminib. However, the ERG raised concerns regarding baseline imbalances and highlighted the importance of time since first diagnosis. Novartis has undertaken further multivariate analysis of the ASCEMBL data, using logistic regression, where time since first diagnosis was added as a covariate in

Key issue	Does this response contain new evidence, data or analyses?	Response
		addition to the previous analysis presented in the CSR, and hence addresses the primary concern of the ERG regarding baseline imbalances. The treatment effect remained statistically significant (OR=[redacted] 95% CI: [redacted]) when time since first diagnosis at baseline was included in the analysis. Detailed results are provided in Table 1. The analysis confirms the expected relationship between MMR and both MCyR at baseline and number of prior TKIs. Baseline MCyR is associated with a significantly higher chance of MMR at 6 months. A trend to a lower chance of MMR for patients at fourth-line is supported by a significant reduction for patients at fifth-line. Patients discontinuing their previous TKI for reasons of resistance and are less likely to achieve MMR than those discontinuing due to intolerance. The results suggest a trend towards increased chance of MMR associated with longer time since diagnosis. The additional analysis supports the original finding that treatment with asciminib is associated with a significant improvement in MMR at 6 months. The treatment effect remains significant after controlling for key baseline characteristics.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>Table 1: Odds ratio of MMR rate at 24 weeks adjusted for the stratification factor (MCyR at randomisation) and other important variables, including time since first diagnosis at baseline (Full analysis set)
<table>
<tr><th>Variable</th><th>Odds ratio</th><th>95% CI</th></tr>
<tr><td>Treatment with asciminib</td><td></td><td></td></tr>
<tr><td>Strata (MCyR at baseline)</td><td></td><td></td></tr>
<tr><td>Sex (female)</td><td></td><td></td></tr>
<tr><td>Line of therapy (fourth)†</td><td></td><td></td></tr>
<tr><td>Line of therapy (fifth)†</td><td></td><td></td></tr>
<tr><td>Reason for discontinuation of previous TKI (intolerance)</td><td></td><td></td></tr>
<tr><td>Time since first diagnosis at baseline (each year increase)</td><td></td><td></td></tr>
</table>
†The reference case for the analysis is treatment at third-line.
Abbreviations: CI, confidence interval; MCyR, major cytogenic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

Novartis would like to reiterate that the ASCEMBL trial is the first head-to-head trial in this area, and that evidence for other TKIs has been obtained from single-arm trials. As such, and taking into account the results of the reanalysis requested, Novartis believes that the data from the ASCEMBL trial and the conclusions drawn from it are robust.</td></tr>
<tr><td>Key issue 3: Lack of evidence on survival outcomes</td><td>No</td><td>The available data from the ASCEMBL trial for both overall survival (OS) and progression-free survival (PFS) were extremely immature in the 48-week data cut:
• OS was and in the asciminib and bosutinib arms, respectively</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		• PFS was [redacted] % and [redacted] % in the asciminib and bosutinib arms, respectively. The immaturity of the data is expected given the good prognosis for patients with CML. As acknowledged by the ERG, no new evidence can be provided at this stage. Previous submissions for patients in CML-chronic phase (CP) have encountered this issue and have used a surrogate outcome to estimate OS.
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	**No**	The ERG states that *'outcomes that are more robust and relevant to patients should be of primary interest in this assessment. These include response outcomes (MMR, CCyR) and survival outcomes (OS, PFS).'* Although TTD was not an outcome considered in the scope, the company considers it to be an important clinical outcome in the treatment of CML. TTD has been shown to be important to patients, and is a marker for survival. Analysis supporting the use of TTD as a proxy measure of OS has been published in non small cell lung cancer and in renal cell carcinoma (1-3). There is also ample evidence that successful treatment with TKIs can slow the progress of CML and significantly increase OS (4-6). Patients report a return to normal social and work routines once a stable treatment regime is established, with periods of uncertainty associated with the risk of developing resistance and having to stop treatment (4-6). Hence the company considers TTD to be an important patient outcome, and the link to OS to be consistent with clinical understanding of disease progression and the impact of TKI treatment. Additional data from the matched adjusted indirect comparison (MAIC) on key outcomes of response were provided to the ERG following clarification questions. Further evidence comparing TTD for asciminib with nilotinib and dasatinib in the form of a MAIC using data from HMRN is provided in Appendix E and Key issue 5

Key issue	Does this response contain new evidence, data or analyses?	Response
		part 2. There is precedence for the use of TTD in cost-effectiveness analysis in CML. As previously noted, the generally slow progression of CML in the CP necessitates the use of a proxy outcome to estimate OS. Previous submissions have used one of two approaches: • A cumulative survival approach based TTD • A surrogate survival approach based on response to treatment. The most recent previous submission in CML, TA451 (ponatinib) (7), used a surrogate survival approach. The next most recent submission in CML, TA401 (bosutinib) (8), applied the cumulative survival approach in the manufacturer's resubmission, following guidance from the ERG. Both approaches inevitably introduce structural uncertainty. The company submission used the cumulative survival approach. Strengths of this approach include: • The approach is simple and transparent, and has been supported by a United Kingdom (UK) clinician (9). • The duration of survival, post discontinuation of the index treatment, can be adjusted to reflect current clinical expectations of post-discontinuation survival. The approach is also subject to limitations, notably the subjectivity of TTD as a measure of response compared with other measures, such as MMR. In response to concerns regarding the cumulative survival approach, the company has submitted a model using the surrogate survival approach. The model mirrors the approach applied in the manufacturer's submission for ponatinib (TA451) (7). In

Key issue	Does this response contain new evidence, data or analyses?	Response
		particular, the company scenario analysis uses the same categories of response to treatment and the same data as TA451 to model the relationship between response and OS. Results from the surrogate survival model are broadly consistent with those from the cumulative survival model with regard to the key comparator, bosutinib: the company preferred base case ICER using the asciminib PAS price vs bosutinib is £5,659, and when considering the response based model asciminib is dominant. Bosutinib is considered the key comparator to asciminib, as nilotinib and dasatinib are typically used at prior lines, and ponatinib is generally the TKI of last resort due to its side effect profile. In addition, bosutinib is the only comparator based on a head-to-head comparison from the ASCEMBL trial.
Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	**Yes**	The ERG raised a number of issues with the MAIC undertaken. These included: 1. Incomplete set of comparator studies 2. No comparison with Haematological Malignancy Research Network (HMRN) data 3. Limited set of variables adjusted for 4. Limited or incomplete reporting of outcomes (only MMR, complete cytogenic response [CCyR], and TTD) 5. Limited reporting of relative estimates of effectiveness. Each of these issues will be addressed in turn. **1. The ERG disagreed with some of the grounds for exclusion of studies from the systematic review of the indirect comparison** The ERG questioned the exclusion of studies reporting outcomes for bosutinib. The identified studies that included bosutinib were all single arm studies; none would have supported an anchored comparison between asciminib and another

Key issue	Does this response contain new evidence, data or analyses?	Response
		TKI. The bosutinib studies were excluded on the grounds that direct evidence was available from ASCEMBL, the only randomised trial available including a head-to-head comparison with the most relevant alternative TKI, bosutinib. Comparison with previous clinical studies of bosutinib would have required an unanchored MAIC. Guidance from NICE in TSD18 (10) highlights the risk of bias in unanchored comparisons, hence the company avoided unanchored comparisons where this was feasible (vs bosutinib). The ERG also queried the reasons for excluding studies reporting outcomes for other TKIs. The company excluded studies based on small size, inappropriate comparator, inappropriate population, or lack of baseline data on the relevant patient subgroup. The company would like to provide further explanation and clarity on the justification for exclusion of each study: • Garg et al 2009 (11) presented data for 48 patients of whom 34 received dasatinib in third line and 14 received nilotinib in third line. Only 25 of the 48 patients were in the CP, and 3 had the T315I mutation. Outcome data were reported for patients in CP; however, it was unclear if this group included the patients with the T315I mutation, and baseline characteristics were not reported for the subgroup of patients in CP. The company excluded this study on the grounds of study size, potential presence of patients with T315I mutation, and the lack of subgroup-specific baseline data. • Lee et al 2014 (12) described outcomes for patients undergoing allo-SCT, and only 50 of the 97 patients had received prior TKIs. The company excluded this study on the basis that allo-SCT was not considered a third-line comparator to asciminib. • The CML-202 study (13) reported results for omacetaxine, a non-relevant intervention. The study was excluded on this basis.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• Ribeiro et al 2015 (14) reported outcomes for 25 patients of which 18 were in CP. Response and baseline data were not separately reported for the patients in CP, and hence the study was excluded. Three studies did not report TTD but did report other relevant outcomes. Of these studies, Ibrahim 2010 (15) was selected to inform response-based outcomes with nilotinib and dasatinib in a MAIC with asciminib (15). That analysis then informed the scenario analysis using the surrogate survival model. The remaining two studies were subject to significant limitations: • The PEARL study (16) reported outcomes for 48 patients in CP treated with ponatinib. The population included only 5 patients treated with 2 prior TKIs, and 29 patients treated with 3 prior TKIs. The company chose to exclude this study on the grounds of the low number of patients at third-line, and the availability of a large study of ponatinib in a predominantly third-line CML population (PACE). • Tan 2019 (17) reported response data for 24 patients receiving dasatinib in third-line. However, data at 3, 6 and 12 months were only reported for selected patient subgroups; data reported for all third-line patients appears to be cumulative response over varying patient follow-up. The reported data were considered insufficient to support comparison with outcomes at 6 months for ASCEMBL, and hence the study was excluded. In summary, whilst the company acknowledges that some studies have been excluded, this was for robust reasons. **2. A comparison with HMRN has been undertaken using an anchored MAIC** The availability of data on bosutinib in HMRN allowed an anchored MAIC to be performed between asciminib and other TKIs in HMRN. Anchoring allows

Key issue	Does this response contain new evidence, data or analyses?	Response
		adjustment for unobserved patient characteristics that may differ across comparators (10). The findings of the anchored MAIC comparing asciminib (ASCEMBL trial arm) with dasatinib or nilotinib data (HMRN dataset) for TTD, and MMR by 6 months (Appendix E), were supportive of the findings of the primary unanchored MAIC for these comparators, using the clinical trial comparator data identified in the SLR. For TTD, asciminib offered [redacted] compared with dasatinib and nilotinib in the majority of unadjusted and adjusted comparisons. Unadjusted results for MMR by 6 months were favourable for asciminib in comparison with dasatinib and nilotinib. However, adjusted results were [redacted], reflecting the modest sample size in HMRN and the reduction in effective sample size (ESS) in ASCEMBL after matching. The comparison with HMRN is subject to several limitations, including non-randomisation of the patients in the study, but the results provide further evidence of the effectiveness of asciminib, alongside the primary analysis comparing outcomes with data available from the clinical literature. **3. Limited set of variables adjusted for** The ERG raised concerns that not all prognostic factors had been adjusted for. Unfortunately, it was not possible to adjust for all the variables identified by clinicians as potentially prognostic because weights could not be estimated to match baseline characteristics with the comparator trial for all the variables, or the resulting ESS was considered too small. Variables were ranked according to importance by a clinician, and variable selection was prioritised to include the most influential variables.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>

4. Limited or incomplete reporting of outcomes (only MMR, CCyR, and TTD)

The ERG suggested that analyses be performed for all outcomes (TTD, MMR, CCyR and OS and PFS when data become available). As alluded to in the response to key issue 3, data on OS and PFS were extremely immature for ASCEMBL in the 48-week data cut. The data were considered insufficient to support comparison with data on comparators from published studies, and hence no comparisons of OS and PFS were undertaken.

5. Limited reporting of relative estimates of effectiveness.

Data on TTD in the clinical studies selected for nilotinib, dasatinib, and ponatinib were limited to median values. [redacted], and after weighting to match patient values in the clinical studies for nilotinib and dasatinib. Consequently, reporting of the results of the MAIC was limited to Kaplan-Meier (KM) curves for TTD before and after weighting. The available summary data on median TTD are reported in Table 2. Table 3 provides the proportion of asciminib-treated patients who discontinued at the time of the median TTD for the relevant comparator before and after weighting in each of the MAICs.

Table 2: Comparator median TTD and adjusted and unadjusted median TTD of asciminib

Comparator	Median TTD (months)	Asciminib unadjusted median TTD (months)	Asciminib adjusted median TTD (months)
Ponatinib	32.1	[redacted]	[redacted]
Nilotinib	11		[redacted]
Dasatinib	14		[redacted]

Abbreviations: TTD, time to discontinuation.

</td></tr>
</table>

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>Table 3: Comparator median TTD and % on treatment from adjusted and unadjusted asciminib curves at comparator median
<table>
<tr><th>Comparator</th><th>Month median TTD is reached for comparator</th><th>% on treatment from unadjusted asciminib curve</th><th>% on treatment from adjusted asciminib curve per MAIC</th></tr>
<tr><td>Ponatinib</td><td>32.1</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Nilotinib</td><td>11</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Dasatinib</td><td>14</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
†The unadjusted ASCEMBL KM used for the ponatinib MAIC is based on a sub-population from ASCEMBL.
Abbreviations: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; TTD, time to discontinuation.</td></tr>
<tr><td>Key issue 6: The model structure is subject to considerable uncertainty</td><td>No</td><td>The immaturity of the OS and PFS data in the ASCEMBL trial necessitates the use of a proxy outcome to extrapolate survival. The cumulative survival approach, in which TTD is used to extrapolate OS, has some advantages, as outlined in response to key issue 4. Analysis supporting the use of TTD as a proxy measure of OS has been published in non-small cell lung cancer and in renal cell carcinoma (1-3). As noted for key issue 4, the development of resistance or intolerance to treatment and the resulting risk of disease progression is a concern for patients (3). The cumulative survival approach was favoured by the ERG in the appraisal of bosutinib and formed the basis of the economic analysis which supported the approval of bosutinib. The company accepts that the use of proxy measure to estimate OS introduces uncertainty. The company had undertaken an additional scenario analysis which uses response data to estimate OS, rather than TTD. The scenario analysis helps to address the issue of structural uncertainty and supports the conclusion that asciminib is a cost-effective alternative to treatment with bosutinib.</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		There is ample evidence that successful treatment with TKIs can slow the progress of CML and significantly increase OS (4-6). Patients report a return to normal social and work routines once a stable treatment regime is established, with periods of uncertainty associated with the risk of developing resistance and having to stop treatment (4-6). Hence the company considers TTD to be an important patient outcome and the link to OS to be consistent with clinical understanding of disease progression and the impact of TKI treatment.
Key issue 7: Removal of retreatment	**No**	The ERG considered it unrealistic that patients can subsequently be retreated with the TKI used at third-line. The company notes that a patient organisation response to the initial ERG report indicates that patients are retreated with the same TKI, *'Some patients have even had to go back onto previous TKIs they were intolerant to as the side-effects were comparatively better than other TKIs…'* The company also notes that data in HMRN cited in the ERG report confirm rechallenge with a previously used TKI at subsequent lines. Subsequent treatment in the model represents TKIs used at fourth-line and later. The company accepts that the choice of third-line TKI will influence subsequent treatment. The number of patients using a TKI at fourth-line or later is likely to be lower if that TKI has been used at third-line. However, it is unlikely to be zero. The company regards the company's own assumption and the assumption of the ERG as simplifications representing upper and lower bounds on the true number of patients subsequently treated with a TKI used at third-line. The true number of patients rechallenged at subsequent treatment with the third-line TKI will fall somewhere between the company's estimate and zero. However, the company has used the ERG assumption within the updated base case.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	**No**	The company's preferred model for extrapolation of TTD was selected on the basis of clinical opinion, which reflected the proportion that would gain long-term control of their disease. The ERG argued that the log-logistic distribution resulted in time to treatment discontinuation estimates that were closer to clinical opinion, and had a better fit according to AIC and BIC. As the ERG state, using the log-logistic model has a minimal impact on the ICER in the company's base case. However, the company agrees that an argument can be made to select the log-logistic model on the basis of model fit criteria as well as providing similar extrapolated values over time, and hence the joint log-logistic distribution is used in the updated base case.
Key issue 9: Duration of post-discontinuation survival	**Yes**	The company's estimate of post-discontinuation survival was based primarily on clinical opinion. The company accepts that there is uncertainty around this value. Data on OS following commencement of fourth-line therapy is available for 48 patients in HMRN. The data extend to 8 years follow-up, and a KM curve is available. The company has digitised the KM curve and generated pseudo patient data for OS. Five survival models were fitted to the data (the generalised gamma model failed to converge). The results of the survival analysis are presented in Appendix D. Survival models were used in conjunction with population lifetable data to simulate survival of a cohort commencing treatment at fourth line. Mean survival varied from [redacted] years with an exponential survival function, to [redacted] years with a lognormal survival function, and [redacted] years with a Gompertz survival function. The exponential model exhibited the best fit to the data according to AIC, with the lognormal model second best. The company considers these estimates to be overly optimistic, as they are considerably higher than those provided by clinical opinion. Consequently, the

Key issue	Does this response contain new evidence, data or analyses?	Response
		company considers the clinician's estimate of 7 years to be the best available estimate of post-discontinuation survival (9).
Key issue 10: Use of Niederwieser 2021 for stem-cell transplant survival	**No**	The company accepts the selection of Niederwieser 2021 (18) as a superior source of data to estimate outcomes of SCT.
Key issue 11: Age-adjusted utilities	**No**	The company acknowledges that different approaches can be used when adjusting HRQoL over time. The company's model uses an additive approach, while the ERG preferred a multiplicative approach. The company recognises that both approaches are appropriate, but note that a multiplicative approach is recommended in the updated NICE method guide, and therefore the company accepts the use of a multiplicative adjustment model in place of an additive model for age adjustment of health state utility values.
Key issue 12: Comparator dosing	**Yes**	As outlined within the fact-checking stage, the ERG has implemented a very simple adjustment to account for the potential reduction in relative dose intensity (RDI) for patients on ponatinib. The ERG's approach was to divide RDI for ponatinib by 3 for patients moving to the 15 mg dose and by 3/2 for patients moving to the 30 mg dose. This approach does not reflect the relative cost of the different doses of ponatinib. During the Technical Engagement call, the ERG acknowledged the uncertainty in the dosing of ponatinib and invited the company to present a preferred scenario. This is presented below. • Ponatinib is available at three doses of 45 mg, 30 mg, and 15 mg. From the British National Formulary (BNF), the price for 30 tablets at both the 45 mg

Key issue	Does this response contain new evidence, data or analyses?	Response
		and 30 mg dose is the same, £5,050. The price of 30 tablets at the 15 mg dose is £2,525 (half the price of the 45 mg dose). • Current Medicines and Healthcare products Regulatory Agency (MHRA) guidance recommends a dose reduction to 15 mg in patients in the CP achieving a major cytogenic response (MCyR). • Data to inform the effectiveness of ponatinib was from PACE (19). The PACE trial started in 2010 with patients receiving a starting dose of 45 mg. Dose reductions were implemented in October 2013 in response to evidence of adverse events (AEs) linked to ponatinib. The dose reduction is described in 5-year results report. The methods section reports, "*Unless benefit-risk analysis justified treatment with a higher dose, the following dose reductions were recommended: 15 mg once daily for CP-CML patients **with** MCyR, and 30 mg once daily for CP-CML patients **without** MCyR, accelerated phase (AP)-CML patients, and blast phase (BP)-CML patients*." • The company considers the MHRA guidance to be in alignment with the dose reduction implemented in PACE. Dose reductions with a material impact on cost are assumed to occur only in patients in CP achieving a MCyR. Assumptions applied to cumulative survival model and surrogate survival scenario analysis • MCyR is deemed to be equivalent to at least partial cytogenic response (PCyR), and hence patients achieving at least a PCyR (i.e. those achieving PCyR or CCyR) have a MCyR. MCyR in the literature has also included CCyR and PCyR (20). • Patients achieving a MCyR are assumed to move to 15 mg doses and the cost is halved. Patients in CP not achieving a MCyR, and all patients in the accelerated and blast phase were assumed to either remain on the 45 mg

Key issue	Does this response contain new evidence, data or analyses?	Response
		dose, or move to the 30 mg dose. There is no impact on costs of a dose reduction from 45 mg to 30 mg. • The CEM estimates the proportion of patients achieving a CCyR and a PCyR at 12 months to allow extrapolation of OS in the scenario analysis using the surrogate survival method. These proportions were summed to estimate the proportion of patients achieving MCyR at 12 months with ponatinib ([redacted]). Scenarios were considered in which: • No dose reduction was assumed • Dose reduction assumed 1 year after initiation of ponatinib • Dose reduction assumed 2 years after initiation of ponatinib • Dose reduction assumed 3 years after initiation of ponatinib. Analysis was undertaken at both list price and patient access scheme (PAS) price for asciminib. Scenarios were run using: A. The cumulative survival model with the ERG error correction B. The surrogate survival model (scenario 1 from the ERG report) C. And with the ERG's preferred scenarios (1, 4, 5, and 7 applied). The latter analysis applies: • The ERG error correction. • The ERG's assumption of zero retreatment with the TKI used at third line, • The data from Niederwieser (2021) (18) for parameterising the stem cell transplant (SCT) sub models (note that in conjunction with the Niederwieser data, patients undergoing allogenic (allo) SCT at transition to the accelerated phase were assumed to have the same outcomes (OS

Key issue	Does this response contain new evidence, data or analyses?	Response
		and relapse free survival) as patients undergoing allo-SCT at discontinuation of third line therapy). • The multiplicative adjustment to utility for aging. A summary of the scenarios presented are in Table 4.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Table 4: Summary of ponatinib dosing scenarios
<table>
<tr><th rowspan="2">Ponatinib dose scenarios</th><th colspan="3">ERG scenarios</th></tr>
<tr><th colspan="2">Company submitted base case (including ERG error correction)</th><th>ERG preferred base case</th></tr>
<tr><th></th><th>Cumulative survival model (A)</th><th>Surrogate survival model (B)</th><th>Surrogate survival model (C)</th></tr>
<tr><td>No dose reduction</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td></tr>
<tr><td>Dose reductions at 1 year</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td></tr>
<tr><td>Dose reductions at 2 years</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td></tr>
<tr><td>Dose reductions at 3 years</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td><td>• At asciminib PAS
• At asciminib list price</td></tr>
</table>
Abbreviations: EAG, External Review Group; ERG, Evince Review Group; PAS, Patient access Scheme.

Results are provided in Appendix A.

In the majority of scenarios considered for dose reductions, ponatinib is more expensive than asciminib. All ICERs where ponatinib is more expensive are in the southwest quadrant, with ICERs exceeding [redacted]. There is only one scenario where asciminib is [redacted] per QALY, in which the ERG-preferred scenarios are applied; the list price of asciminib is applied; and the dose reduction with ponatinib is assumed to occur after 1 year. In all scenarios in which
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		the PAS discount was applied to asciminib, asciminib was considered cost-effective.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1:	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2:	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Click or tap here to enter text.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

<table>
<tr><th>Key issue(s) in the ERG report that the change relates to</th><th>Company's base case before technical engagement</th><th>Change(s) made in response to technical engagement</th><th>Impact on the company's base-case incremental cost-effectiveness ratio (ICER)</th></tr>
<tr><td>NA</td><td>Incremental cost vs nilotinib (asciminib at list price):
[redacted]
Incremental cost vs nilotinib (asciminib at PAS price):
[redacted]</td><td>An error was identified in the model, whereby the cost of nilotinib was not being applied correctly. This has been corrected.

Full results of applying this correction to the scenarios run by the ERG are reported in Appendix B.</td><td>
<table>
<tr><th>Original base-case ICER</th><th>New ICER</th><th>Change</th></tr>
<tr><td colspan="3">Results vs nilotinib</td></tr>
<tr><td colspan="3">Asciminib at list price</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>–18.1%</td></tr>
<tr><td colspan="3">Asciminib at PAS price</td></tr>
<tr><td>£49,445</td><td>£27,798</td><td>–43.8%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td>NA</td>
<td></td>
<td>Error correction by the ERG has been included in an updated base case.</td>
<td rowspan="3">Impact of section: Summary of changes to the company’s cost-effectiveness estimate.

Table 5: Results vs TKIs

<table>
<tr><th>Original base-case ICER</th><th>New ICER</th><th>Change</th></tr>
<tr><td colspan="3">Results vs bosutinib</td></tr>
<tr><td colspan="3">Asciminib at list price</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>8.0%</td></tr>
<tr><td colspan="3">Asciminib at PAS price</td></tr>
<tr><td>£2,654</td><td>£5,659</td><td>113.2%</td></tr>
<tr><td colspan="3">Results vs ponatinib</td></tr>
<tr><td colspan="3">Asciminib at list price</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>–83.0%</td></tr>
<tr><td colspan="3">Asciminib at PAS price</td></tr>
<tr><td>£271,410</td><td>£111,470</td><td>–58.9%</td></tr>
<tr><td colspan="3">Results vs nilotinib</td></tr>
<tr><td colspan="3">Asciminib at list price</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>–48.0%</td></tr>
<tr><td colspan="3">Asciminib at PAS price</td></tr>
<tr><td>£49,445</td><td>Dominant</td><td>–</td></tr>
<tr><td colspan="3">Results vs dasatinib</td></tr>
<tr><td colspan="3">Asciminib at list price</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>–24.2%</td></tr>
<tr><td colspan="3">Asciminib at PAS price</td></tr>
<tr><td>£582</td><td>Dominant</td><td>–</td></tr>
</table>
</td>
</tr>
<tr>
<td>Key issue 7: Removal of retreatment</td>
<td>The company base case included retreatment at fourth-line or later with a third-line treatment.</td>
<td>Clinical advice, HMRN data, and patient organisation responses to the ERG draft report, have shown that people are retreated with the same drug again in later lines.
However, the company accepts the ERG’s view that TKI selection at third line is likely to reduce selection at a later stage. Consequently, the company has included the ERG’s view as part of an updated base case.</td>
</tr>
<tr>
<td>Key issue 8: Use of log-logistic to extrapolate time to treatment</td>
<td>The log-normal distribution was used in the company base case for the comparison with bosutinib.</td>
<td>The company accepts that an argument can be made to select the log-logistic model on the basis of model fit criteria, and has included the ERG’s view as part of an updated base case.</td>
</tr>
</table>

Key issue 10: Use of Niederwieser 2021 for stem-cell transplant survival	The company base case used Jabbour et al as the source for outcomes of stem cell transplant (21).	The company accepts the selection of Niederwieser 2021 (18) as a superior source of data to estimate outcomes of stem cell transplant, as part of an updated base case. The company notes that Niederwieser differentiates outcome data for allo-SCT according to whether or not patients had reached the blast phase. Hence the company includes, as part of an updated base case, the rerouting of patients undergoing allo-SCT at progression to the accelerated phase. These patients join patients undergoing allo-SCT in CP rather than those undergoing allo-SCT in the blast phase.	
Key issue 11: Age-adjusted utilities	The company base case included an additive model for age adjustment of health state utility values.	The company accepts the use of a multiplicative adjustment model in place of an additive model for age adjustment of health state utility values, as part of an updated base case.	

Key issue 12: Comparator dosing	The company base case assumed that there was no dose reduction on ponatinib.	An updated base case includes assumptions around ponatinib dose reduction as based on MHRA guidance that the dose is reduced to 15 mg for patients achieving MCyR. Dose reduction is assumed to be 1 year after initiating ponatinib.	
Company's base case following technical engagement (or revised base case)	Incremental QALYs: • Asciminib vs bosutinib: 1.33 • Asciminib vs ponatinib: –0.55 • Asciminib vs nilotinib: 0.91 • Asciminib vs dasatinib: 0.61	Incremental costs: **Asciminib at list price:** • Vs bosutinib: [redacted] • Vs ponatinib: [redacted] • Vs nilotinib: [redacted] • Vs dasatinib: [redacted] **Asciminib at PAS price:** • Vs bosutinib: £7,549 • Vs ponatinib: –£61,154 • Vs nilotinib: –£2,803 • Vs dasatinib: –£9,970	Please provide company revised base-case ICER See full results in Appendix C. **Asciminib at list price:** • Vs bosutinib: [redacted] • Vs ponatinib: [redacted] • Vs nilotinib: [redacted] • Vs dasatinib: [redacted] **Asciminib at PAS price:** • Vs bosutinib: £5,659 • Vs ponatinib: £111,470 • Vs nilotinib: Dominant • Vs dasatinib: Dominant

Sensitivity analyses around revised base case

Please see Appendix C.

Appendix A: Ponatinib dosing scenarios

1. Cumulative survival model results (no ERG preferred assumption except error correction)

Table 6: Scenario analysis with dose reduction for ponatinib using cumulative survival model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	Asciminib list price					Asciminib PAS price				
Submitted base case: cumulative survival approach (no dose reduction										
Ponatinib	[redacted]	6.75	–	–	–	[redacted]	6.75	–	–	–
Asciminib	[redacted]	6.24	[redacted]	–0.51	[redacted]	[redacted]	6.24	–£137,967	–0.51	£271,026
Reduction of ponatinib dose occurring 1 year after initiating treatment										
Ponatinib	[redacted]	6.75	–	–	–	[redacted]	6.75	–	–	–
Asciminib	[redacted]	6.24	[redacted]	–0.51	[redacted]	[redacted]	6.24	–£96,301	–0.51	£189,176
Reduction of ponatinib dose occurring 2 years after initiating treatment										
Ponatinib	[redacted]	6.75	–	–	–	[redacted]	6.75	–	–	–
Asciminib	[redacted]	6.24	[redacted]	–0.51	[redacted]	[redacted]	6.24	–£106,899	–0.51	£209,996
Reduction of ponatinib dose occurring 3 years after initiating treatment										
Ponatinib	[redacted]	6.75	–	–	–	[redacted]	6.75	–	–	–
Asciminib	[redacted]	6.24	[redacted]	–0.51	[redacted]	[redacted]	6.24	–£114,802	–0.51	£225,520

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years.

2. Surrogate survival model results (no ERG preferred assumption except error correction)

Table 7: Scenario analysis with dose reduction for ponatinib using surrogate survival model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	Asciminib list price					Asciminib PAS price				
Surrogate survival scenario with no dose reduction										
Ponatinib	[redacted]	6.96	_	–	–	[redacted]	6.96	–	–	–
Asciminib	[redacted]	6.82	[redacted]	–0.14	[redacted]	[redacted]	6.82	–£120,085	–0.14	£848,775
Reduction of ponatinib dose occurring 1 year after initiating treatment										
Ponatinib	[redacted]	6.96	–	–	–	[redacted]	6.96	–	–	–
Asciminib	[redacted]	6.82	[redacted]	–0.14	[redacted]	[redacted]	6.82	–£78,419	–0.14	£554,274
Reduction of ponatinib dose occurring 2 years after initiating treatment										
Ponatinib	[redacted]	6.96	–	–	–	[redacted]	6.96	–	–	–
Asciminib	[redacted]	6.82	[redacted]	–0.14	[redacted]	[redacted]	6.82	–£89,017	–0.14	£629,185
Reduction of ponatinib dose occurring 3 years after initiating treatment										
Ponatinib	[redacted]	6.96	–	–	–	[redacted]	6.96	–	–	–
Asciminib	[redacted]	6.82	[redacted]	–0.14	[redacted]	[redacted]	6.82	–£96,920	–0.14	£685,042

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

3. ERG preferred assumptions results

Table 8: Scenario analysis with dose reduction for ponatinib using error correction, ERG scenarios 1, 4, 5 and 7, and assuming equivalent outcomes for patients undergoing allo-SCT in CP and AP

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	List price					PAS price				
Surrogate survival scenario with no dose reduction										
Ponatinib	[redacted]	7.05				[redacted]	7.05			
Asciminib	[redacted]	6.87	[redacted]	–0.18	[redacted]	[redacted]	6.87	–£85,356	–0.18	£470,019
Reduction of ponatinib dose occurring 1 year after initiating treatment										
Ponatinib	[redacted]	7.05				[redacted]	7.05			
Asciminib	[redacted]	6.87	[redacted]	–0.18	[redacted]	[redacted]	6.87	–£43,689	–0.18	£240,580
Reduction of ponatinib dose occurring 2 years after initiating treatment										
Ponatinib	[redacted]	7.05				[redacted]	7.05			
Asciminib	[redacted]	6.87	[redacted]	–0.18	[redacted]	[redacted]	6.87	–£54,288	–0.18	£298,942
Reduction of ponatinib dose occurring 3 years after initiating treatment										
Ponatinib	[redacted]	7.05				[redacted]	7.05			
Asciminib	[redacted]	6.87	[redacted]	–0.18	[redacted]	[redacted]	6.87	–£62,191	–0.18	£342,458

Abbreviations: allo-SCT, allogenic stem cell transplant; AP, accelerated phase; CP, chronic phase; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Appendix B: Nilotinib cost correction scenarios

Following submission of the original evidence, an error was identified in the economic model whereby the cost of nilotinib was calculated incorrectly. This error persisted in the ERG adaptation of the model. Consequently, the company has rerun each of the scenarios examined by the ERG in their technical report for the comparison with nilotinib. Scenarios 4 and 8 were not rerun as these scenarios do not include a comparison with nilotinib.
Note that all numbered scenarios include the error correction from the ERG.

Table 9: Base case and additional scenarios for comparison with nilotinib after amendment of nilotinib costs

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	Asciminib list price					Asciminib PAS price				
Company base case										
Nilotinib	[redacted]	5.76	–	–	–	[redacted]	5.76	–	–	–
Asciminib	[redacted]	6.61	[redacted]	0.85	[redacted]	[redacted]	6.61	£23,582	0.85	£27,798
Error correction (amendment of capping of OS at population values for life expectancy)										
Nilotinib	[redacted]	5.75	–	–	–	[redacted]	5.75	–	–	–
Asciminib	[redacted]	6.60	[redacted]	0.85	[redacted]	[redacted]	6.60	£23,185	0.85	£27,320
Scenario 1: Surrogate survival model										
Nilotinib	[redacted]	5.98	–	–	–	[redacted]	5.98	–	–	–
Asciminib	[redacted]	8.16	[redacted]	2.18	[redacted]	[redacted]	8.16	£88,425	2.18	£40,485
Scenario 2: Equivalence in effectiveness										
Nilotinib	[redacted]	5.63	–	–	–	[redacted]	5.63	–	–	–
Asciminib	[redacted]	6.60	[redacted]	0.98	[redacted]	[redacted]	6.60	£23,175	0.98	£23,753
Scenario 4: Removing retreatment from subsequent treatment										
Nilotinib	[redacted]	5.75	–	–	–	[redacted]	5.75	–	–	–
Asciminib	[redacted]	6.60	[redacted]	0.85	[redacted]	[redacted]	6.60	–£1,016	0.85	Dominant
Scenario 5: Use of Niederwieser 2021 for SCT survival (outcomes of allo-SCT from AP assumed same as those from BP as in ERG report)										
Nilotinib	[redacted]	5.46	–	–	–	[redacted]	5.46	–	–	–
Asciminib	[redacted]	6.37	[redacted]	0.91	[redacted]	[redacted]	6.37	£23,134	0.91	£25,496
Scenario 6a: 14.6 years post discontinuation survival										
Nilotinib	[redacted]	7.97	–	–	–	[redacted]	7.97	–	–	–
Asciminib	[redacted]	8.60	[redacted]	0.63	[redacted]	[redacted]	8.60	£13,376	0.63	£21,194

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	Asciminib list price					Asciminib PAS price				
Scenario 6b: 10.1 years post discontinuation survival										
Nilotinib	[redacted]	6.78	–	–	–	[redacted]	6.78	–	–	–
Asciminib	[redacted]	7.53	[redacted]	0.75	[redacted]	[redacted]	7.53	£18,771	0.75	£25,075
Scenario 7: Age adjustment										
Nilotinib	[redacted]	5.93	–	–	–	[redacted]	5.93	–	–	–
Asciminib	[redacted]	6.80	[redacted]	0.87	[redacted]	[redacted]	6.80	£23,185	0.87	£26,789
Scenario 9: nilotinib and dasatinib equivalent to bosutinib dose										
Nilotinib	[redacted]	5.75	–	–	–	[redacted]	5.75	–	–	–
Asciminib	[redacted]	6.60	[redacted]	0.85	[redacted]	[redacted]	6.60	£26,161	0.85	£30,827
ERG preferred base case: Error correction, Scenario 1, 3, 4, 5, 7, 8										
Nilotinib	[redacted]	5.85	–	–	–	[redacted]	5.85	–	–	–
Asciminib	[redacted]	8.14	[redacted]	2.29	[redacted]	[redacted]	8.14	£61,873	2.29	£27,017
Exploratory analysis: ERG preferred base case + Scenario 2										
Nilotinib	[redacted]	5.82	–	–	–	[redacted]	5.82	–	–	–
Asciminib	[redacted]	8.14	[redacted]	2.32	[redacted]	[redacted]	8.14	£55,235	2.32	£23,816

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Appendix C: Base case results

Table 10: Base case results from company preferred base case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	List price					PAS price				
Asciminib vs bosutinib										
Bosutinib	[redacted]	6.26	–	–	–	[redacted]	6.26	–	–	–
Asciminib	[redacted]	7.59	[redacted]	1.33	[redacted]	[redacted]	7.59	£7,549	1.33	£5,659
Asciminib vs ponatinib										
Ponatinib	[redacted]	6.83	–	–	–	[redacted]	6.83	–	–	–
Asciminib	[redacted]	6.28	[redacted]	–0.55	[redacted]	[redacted]	6.28	–£61,154	–0.55	£111,470
Asciminib vs nilotinib										
Nilotinib	[redacted]	5.76	–	–	–	[redacted]	5.76	–	–	–
Asciminib	[redacted]	6.67	[redacted]	0.91	[redacted]	[redacted]	6.67	–£2,803	0.91	Dominant
Asciminib vs dasatinib										
Dasatinib	[redacted]	5.98	–	–	–	[redacted]	5.98	–	–	–
Asciminib	[redacted]	6.59	[redacted]	0.61	[redacted]	[redacted]	6.59	–£9,970	0.61	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Sensitivity analysis

Probabilistic sensitivity analysis

Table 11: Probabilistic base case results from company preferred base case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	List price					PAS price				
Asciminib vs bosutinib										
Bosutinib	[redacted]	6.27	–	–	–	[redacted]	6.27	–	–	–
Asciminib	[redacted]	7.60	[redacted]	1.33	[redacted]	[redacted]	7.59	£7,549	1.33	£5,659
Asciminib vs ponatinib										
Ponatinib	[redacted]	6.83	–	–	–	[redacted]	6.82	–	–	–
Asciminib	[redacted]	6.29	[redacted]	-0.54	[redacted]	[redacted]	6.28	–£62,616	-0.54	£116,748
Asciminib vs nilotinib										
Nilotinib	[redacted]	5.76	–	–	–	[redacted]	5.77	–	–	–
Asciminib	[redacted]	6.69	[redacted]	0.93	[redacted]	[redacted]	6.70	–£2,803	0.91	Dominant
Asciminib vs dasatinib										
Dasatinib	[redacted]	5.98	–	–	–	[redacted]	5.98	–	–	–
Asciminib	[redacted]	6.60	[redacted]	0.63	[redacted]	[redacted]	6.61	–£9,678	0.63	Dominant

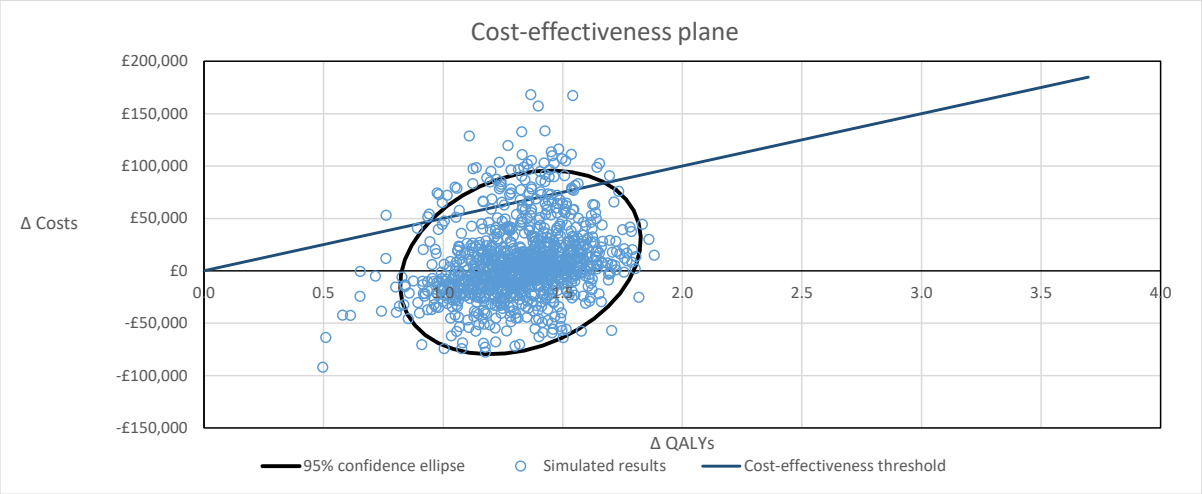
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Asciminib vs bosutinib

Figure 1: Cost-effectiveness plane – asciminib (list price) vs bosutinib

Abbreviations: QALYs, quality-adjusted life years.

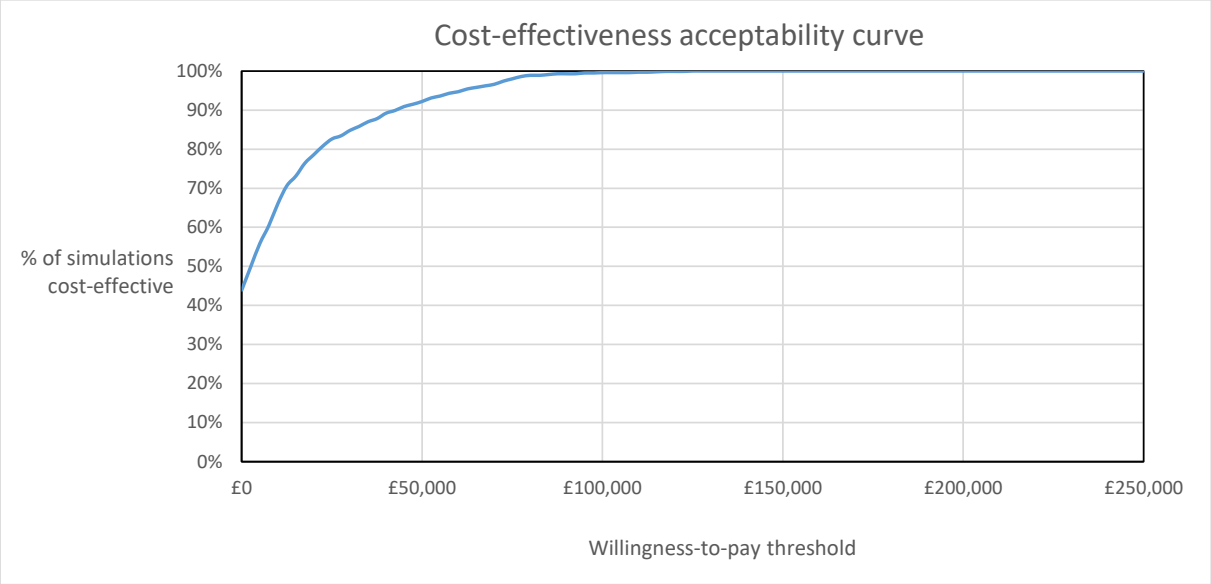
Figure 2: Cost-effectiveness plane – asciminib (PAS price) vs bosutinib



Abbreviations: PAS, Patient Access Scheme; QALYs, quality-adjusted life years.

Figure 3: Cost-effectiveness acceptability curve – asciminib (list price) vs bosutinib

Figure 4: Cost-effectiveness acceptability curve – asciminib (PAS price) vs bosutinib



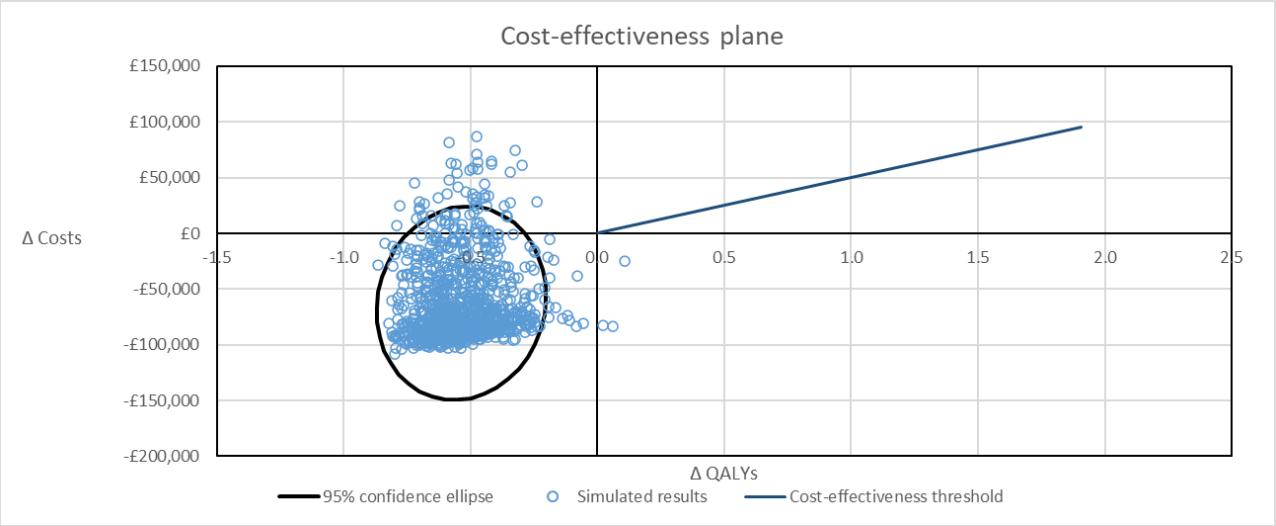
Abbreviations: PAS, Patient Access Scheme.

Asciminib vs ponatinib

Figure 5: Cost-effectiveness plane – asciminib (list price) vs ponatinib

Abbreviations: QALYs, quality-adjusted life years.

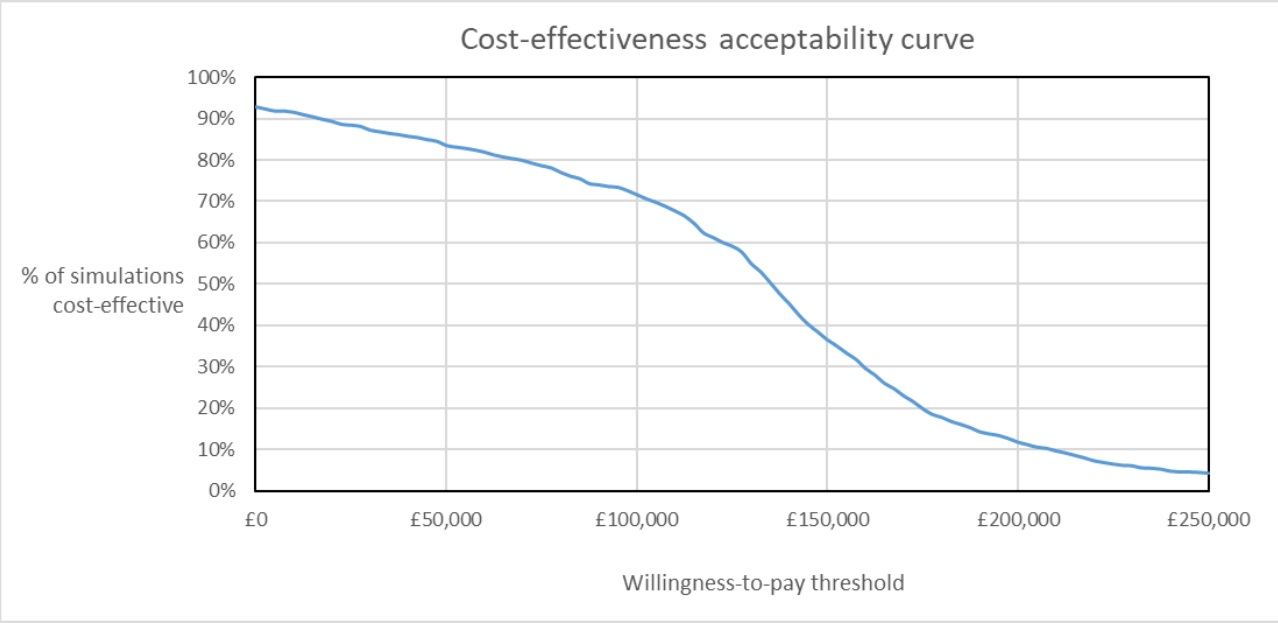
Figure 6: Cost-effectiveness plane – asciminib (PAS price) vs ponatinib



Abbreviations: PAS, Patient Access Scheme; QALYs, quality-adjusted life years.

Figure 7: Cost-effectiveness acceptability curve – asciminib (list price) vs ponatinib

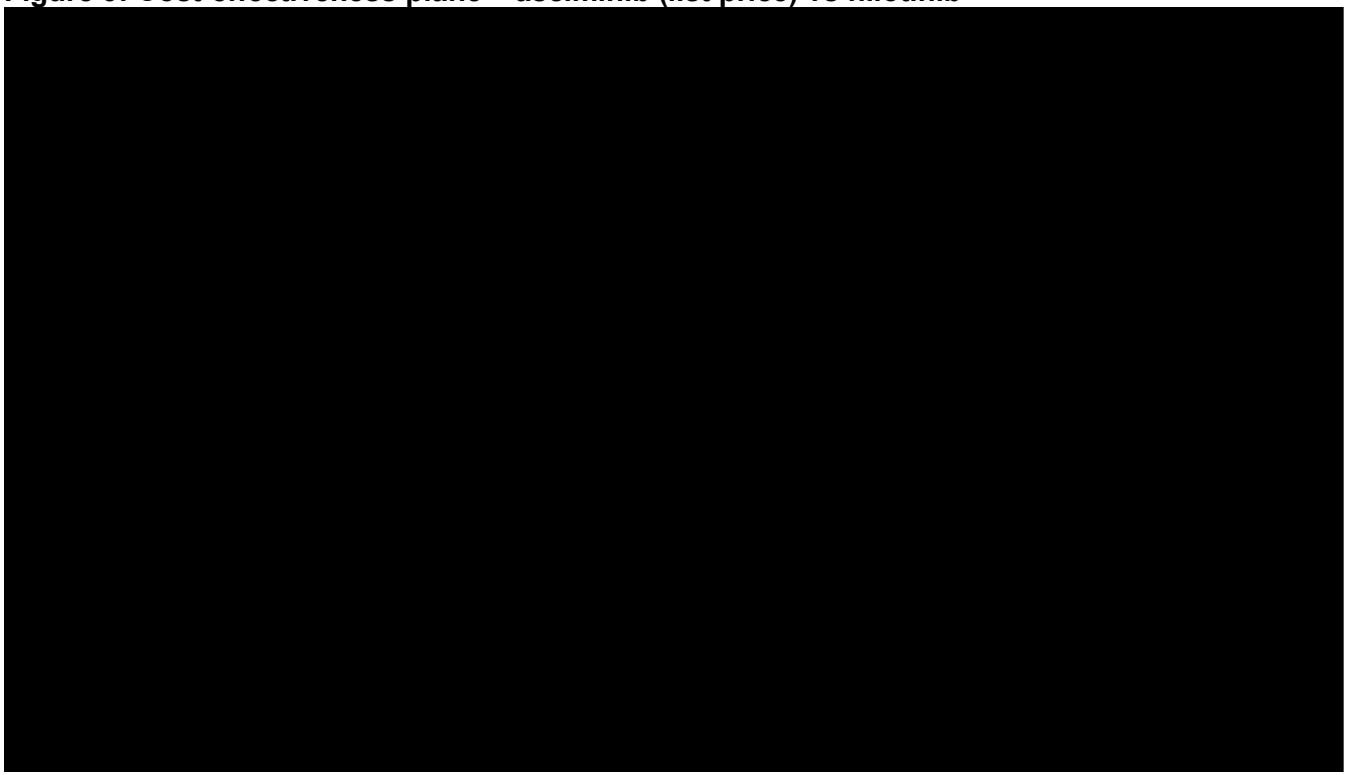
Figure 8: Cost-effectiveness acceptability curve – asciminib (PAS price) vs ponatinib



Abbreviations: PAS, Patient Access Scheme.

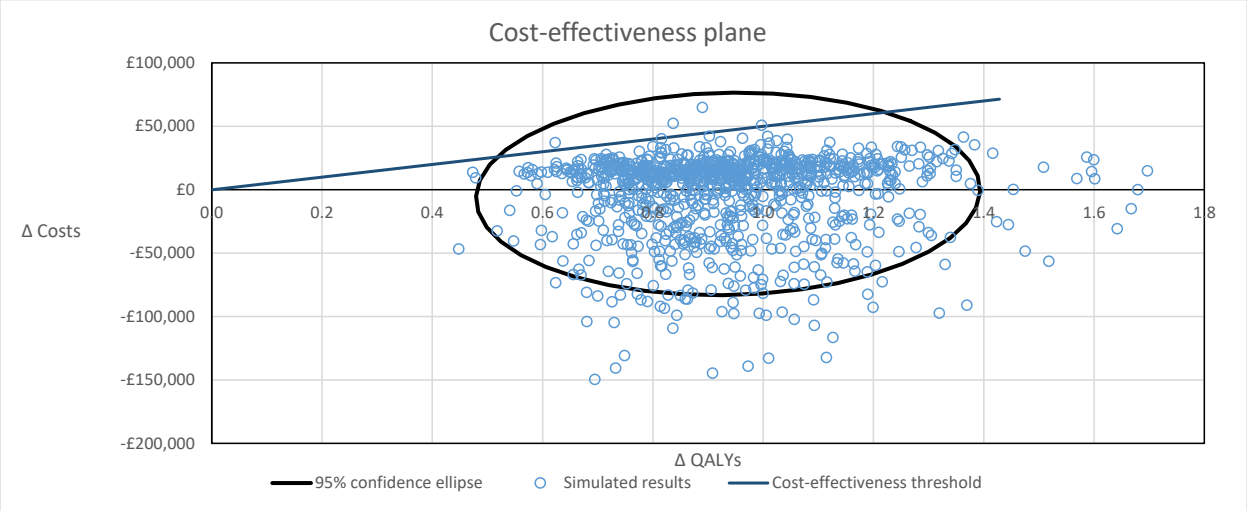
Asciminib vs nilotinib

Figure 9: Cost-effectiveness plane – asciminib (list price) vs nilotinib



Abbreviations: QALYs, quality-adjusted life years.

Figure 10: Cost-effectiveness plane – asciminib (PAS price) vs nilotinib



Abbreviations: PAS, Patient Access Scheme; QALYs, quality-adjusted life years.

Figure 11: Cost-effectiveness acceptability curve – asciminib (list price) vs nilotinib

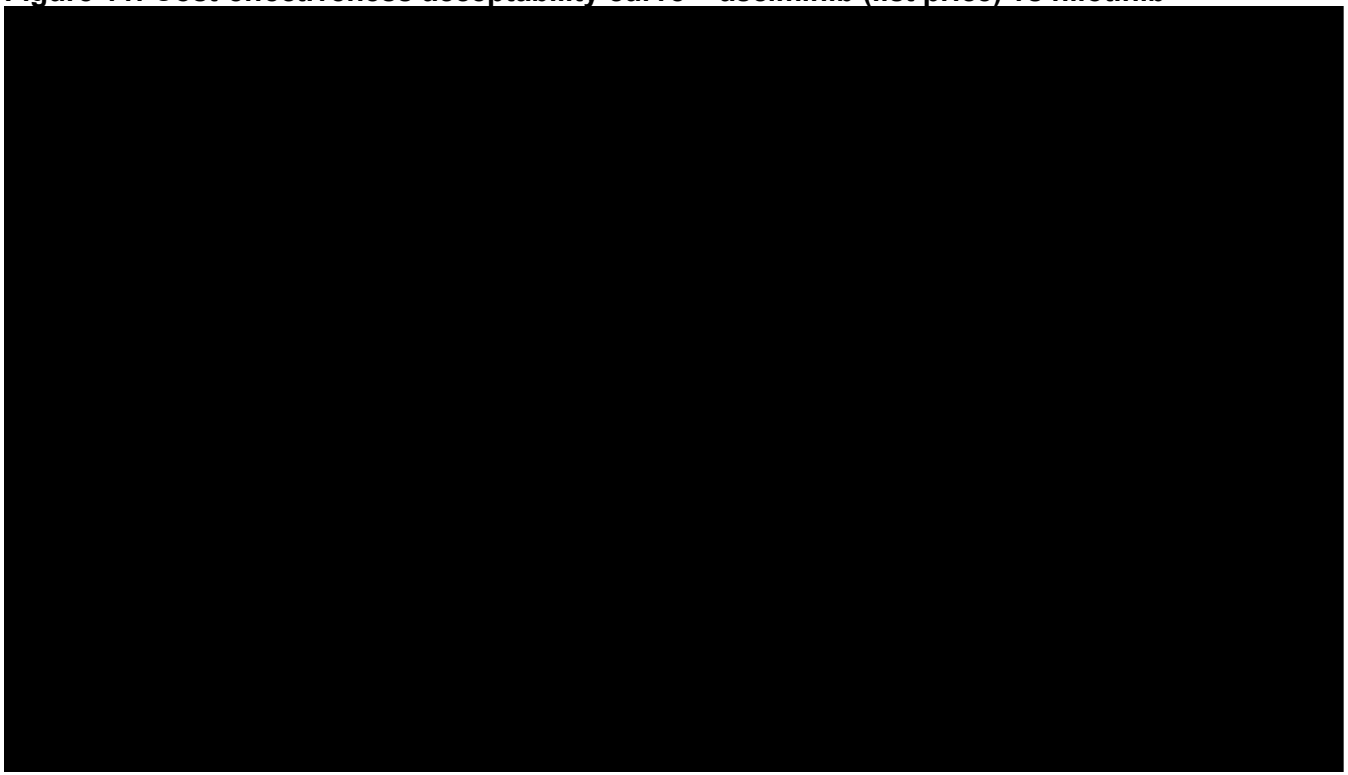
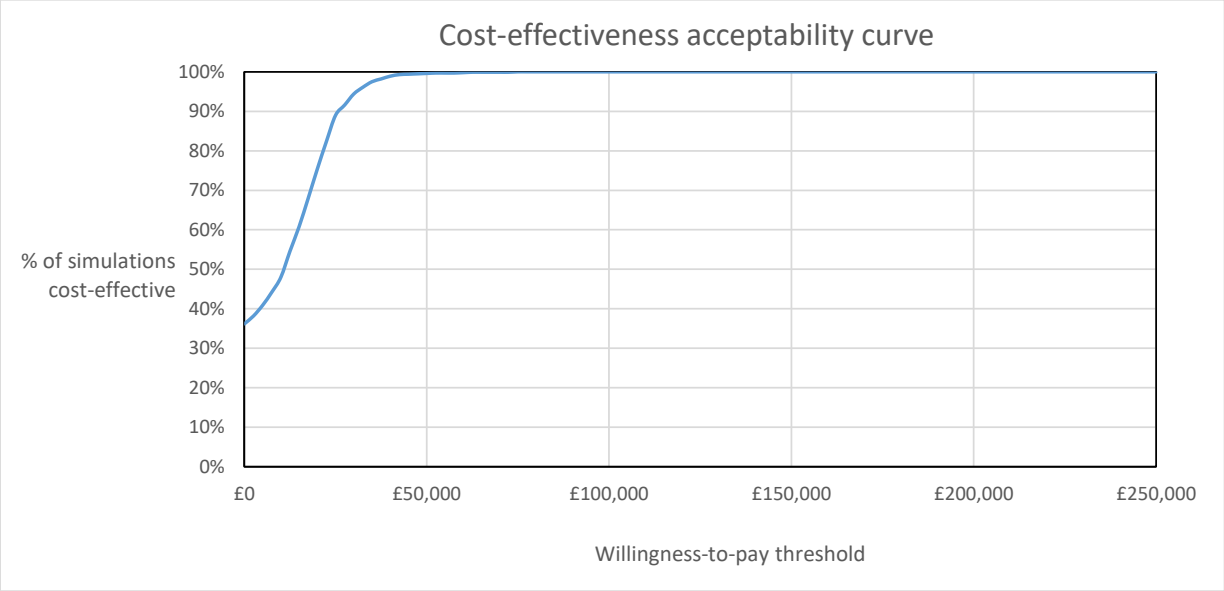


Figure 12: Cost-effectiveness acceptability curve – asciminib (PAS price) vs nilotinib



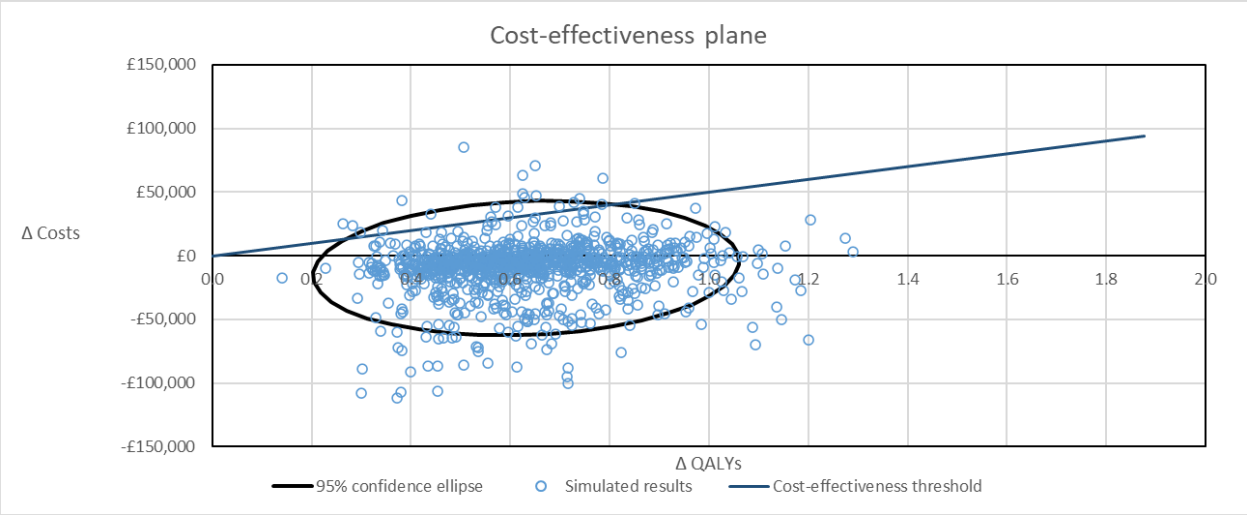
Abbreviations: PAS, Patient Access Scheme.

Asciminib vs dasatinib

Figure 13: Cost-effectiveness plane – asciminib (list price) vs dasatinib

Abbreviations: QALYs, quality-adjusted life years.

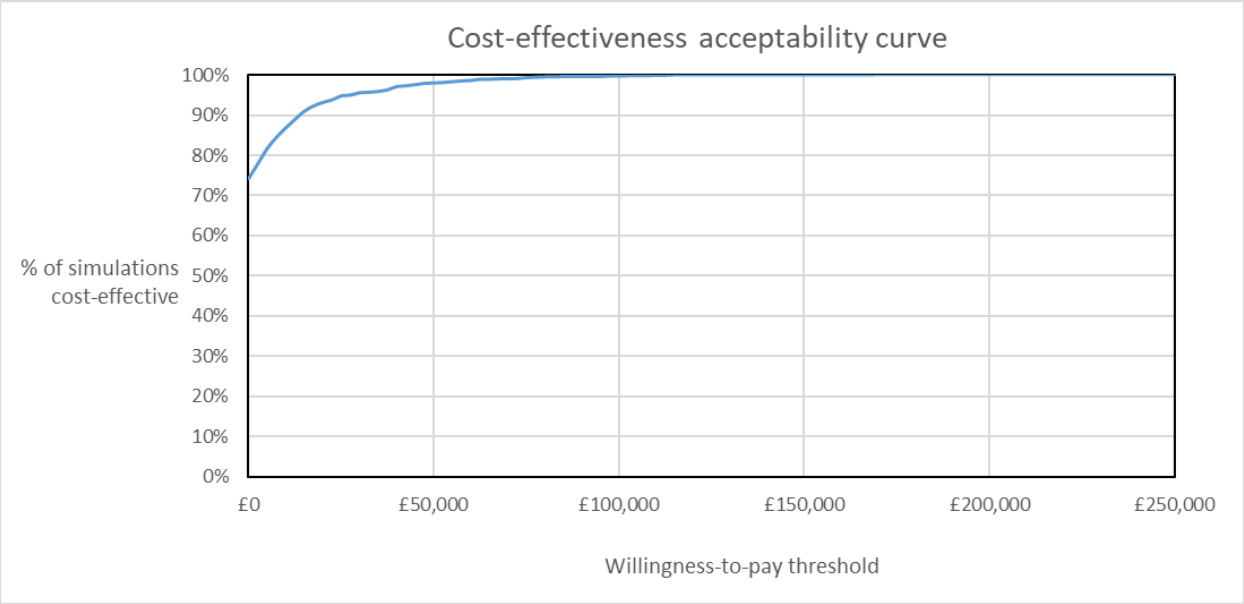
Figure 14: Cost-effectiveness plane – asciminib (PAS price) vs dasatinib



Abbreviations: QALYs, quality-adjusted life years.

Figure 15: Cost-effectiveness acceptability curve – asciminib (list price) vs dasatinib

Figure 16: Cost-effectiveness acceptability curve – asciminib (PAS price) vs dasatinib



Abbreviations: PAS, Patient Access Scheme.

One-way sensitivity analysis

Asciminib vs bosutinib

Table 12: One-way sensitivity analysis - asciminib (list price) vs bosutinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
RDI - asciminib	[redacted]	[redacted]
Mean OS from discontinuation of third-line treatment - bosutinib	[redacted]	[redacted]
Proportion on bosutinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Mean OS from discontinuation of third-line treatment - asciminib	[redacted]	[redacted]
Proportion on nilotinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
ASCEMBL, mean values, CP, on treatment	[redacted]	[redacted]
RDI - bosutinib	[redacted]	[redacted]
Patient characteristics by comparator - bosutinib - age	[redacted]	[redacted]
TTD Survival parameters - asciminib from ASCEMBL - vs bosutinib - loglogistic - bosutinib dummy	[redacted]	[redacted]
ASCEMBL, mean values, CP, off treatment	[redacted]	[redacted]

Abbreviations: CP, chronic phase; ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 17: Tornado diagram - asciminib (list price) vs bosutinib

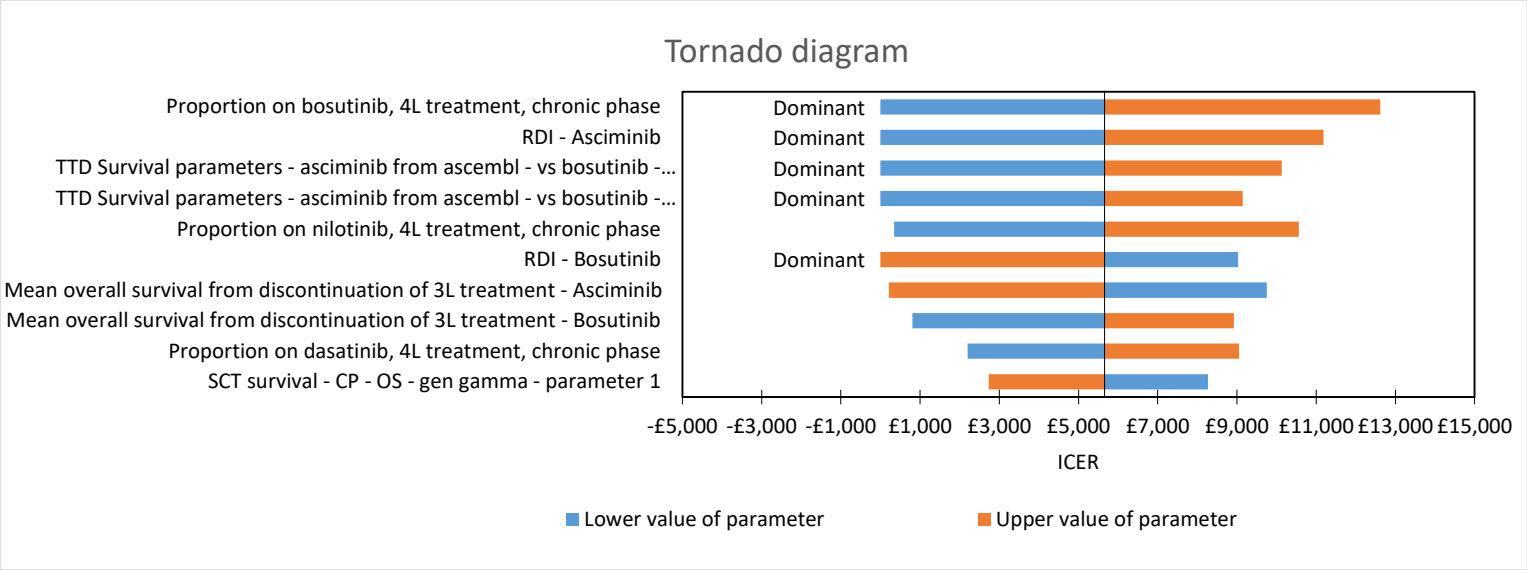
Abbreviations: 3L, third-line; 4L, fourth line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity; TTD, time to discontinuation.

Table 13: One-way sensitivity analysis - asciminib (PAS price) vs bosutinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Proportion on bosutinib, fourth-line treatment, chronic phase	Dominant	£12,621
RDI – asciminib	Dominant	£11,187
TTD survival parameters - asciminib from ASCEMBL - vs bosutinib - loglogistic - bosutinib dummy	Dominant	£10,133
TTD survival parameters - asciminib from ASCEMBL - vs bosutinib - loglogistic - parameter 1	Dominant	£9,142
Proportion on nilotinib, fourth-line treatment, chronic phase	£345	£10,558
RDI - bosutinib	£9,029	Dominant
Mean OS from discontinuation of third-line treatment - asciminib	£9,755	£214
Mean OS from discontinuation of third-line treatment - bosutinib	£809	£8,925
Proportion on dasatinib, fourth-line treatment, chronic phase	£2,200	£9,052
SCT survival - CP - OS - gen gamma - parameter 1	£8,267	£2,732

Abbreviations: CP, chronic phase; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, Patient Access Scheme; RDI, relative dose intensity; SCT, stem cell transplant; TTD, time to discontinuation.

Figure 18: Tornado diagram - asciminib (PAS price) vs bosutinib



Abbreviations: 3L, third-line; 4L, fourth line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; TTD, time to discontinuation.

Asciminib vs ponatinib

Table 14: One-way sensitivity analysis - asciminib (list price) vs ponatinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
RDI - ponatinib	[redacted]	[redacted]
Median treatment duration - ponatinib	[redacted]	[redacted]
Proportion on ponatinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
RDI - asciminib	[redacted]	[redacted]
Mean OS from discontinuation of third-line treatment - ponatinib	[redacted]	[redacted]
TTD survival parameters - asciminib vs ponatinib - exponential - parameter 1	[redacted]	[redacted]
Proportion on bosutinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Proportion on nilotinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Proportion on dasatinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Patient characteristics by comparator - ponatinib - age	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 19: Tornado diagram - asciminib (list price) vs ponatinib

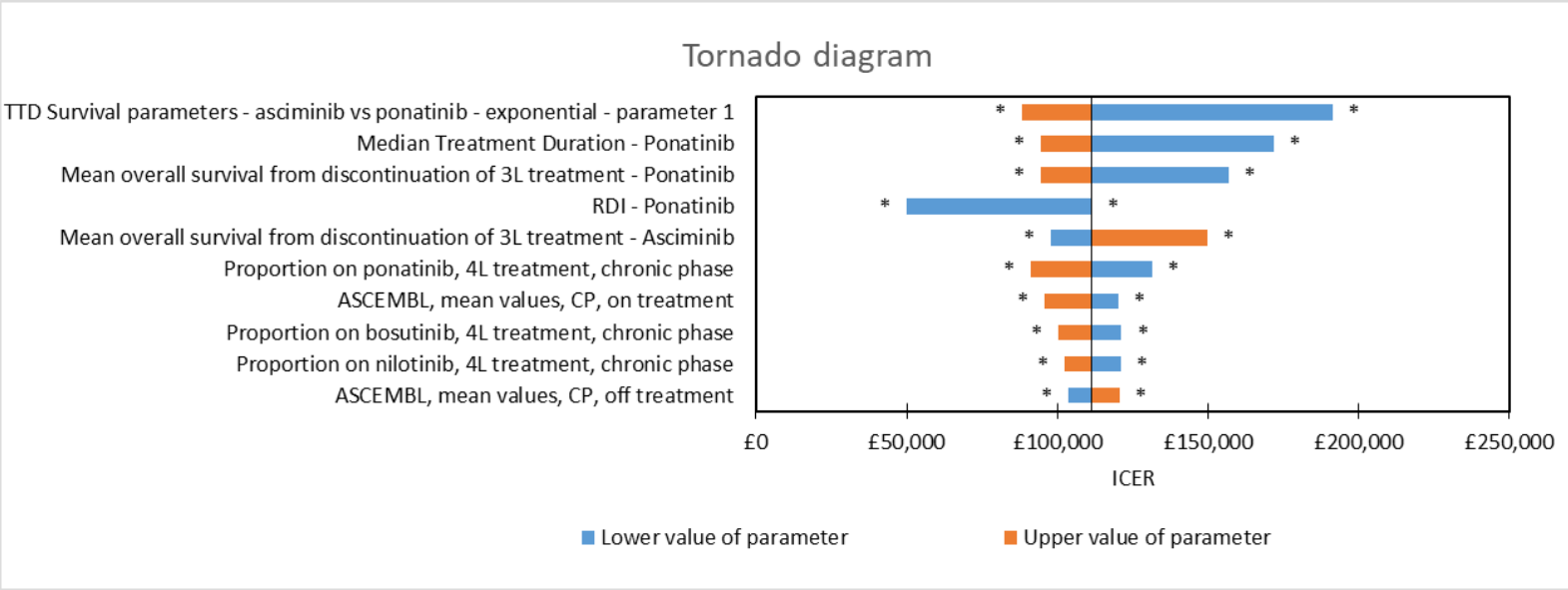
*Southwest quadrant results.
Abbreviations: 3L, third-line; 4L, fourth-line; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity; TTD, time to discontinuation.

Table 15: One-way sensitivity analysis - asciminib (PAS price) vs ponatinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
TTD survival parameters - asciminib vs ponatinib - exponential - parameter 1	£191,566	£88,446
Median treatment duration - ponatinib	£171,875	£94,671
Mean OS from discontinuation of third-line treatment - ponatinib	£156,751	£94,548
RDI - ponatinib	£50,185	£111,470
Mean OS from discontinuation of third-line treatment - asciminib	£97,851	£149,764
Proportion on ponatinib, fourth-line treatment, chronic phase	£131,577	£91,363
ASCEMBL, mean values, CP, on treatment	£120,242	£95,782
Proportion on bosutinib, fourth-line treatment, chronic phase	£121,331	£100,426
Proportion on nilotinib, fourth-line treatment, chronic phase	£121,112	£102,390
ASCEMBL, mean values, CP, off treatment	£103,520	£120,743

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 20: Tornado diagram - asciminib (PAS price) vs ponatinib



*Southwest quadrant results.
Abbreviations: 3L, third-line; 4L, fourth-line; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity; TTD, time to discontinuation.

Asciminib vs nilotinib

Table 16: One-way sensitivity analysis - asciminib (list price) vs nilotinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Mean OS from discontinuation of third-line treatment - asciminib	[redacted]	[redacted]
RDI - asciminib	[redacted]	[redacted]
Proportion on bosutinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Mean OS from discontinuation of third-line treatment - nilotinib	[redacted]	[redacted]
Median treatment duration - nilotinib	[redacted]	[redacted]
Proportion on ponatinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Proportion on dasatinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
ASCEMBL, mean values, CP, on treatment	[redacted]	[redacted]
ASCEMBL, mean values, CP, off treatment	[redacted]	[redacted]
Proportion on nilotinib, fourth-line treatment, chronic phase	[redacted]	[redacted]

Abbreviations: CP, chronic phase; ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity.

Figure 21: Tornado diagram - asciminib (list price) vs nilotinib

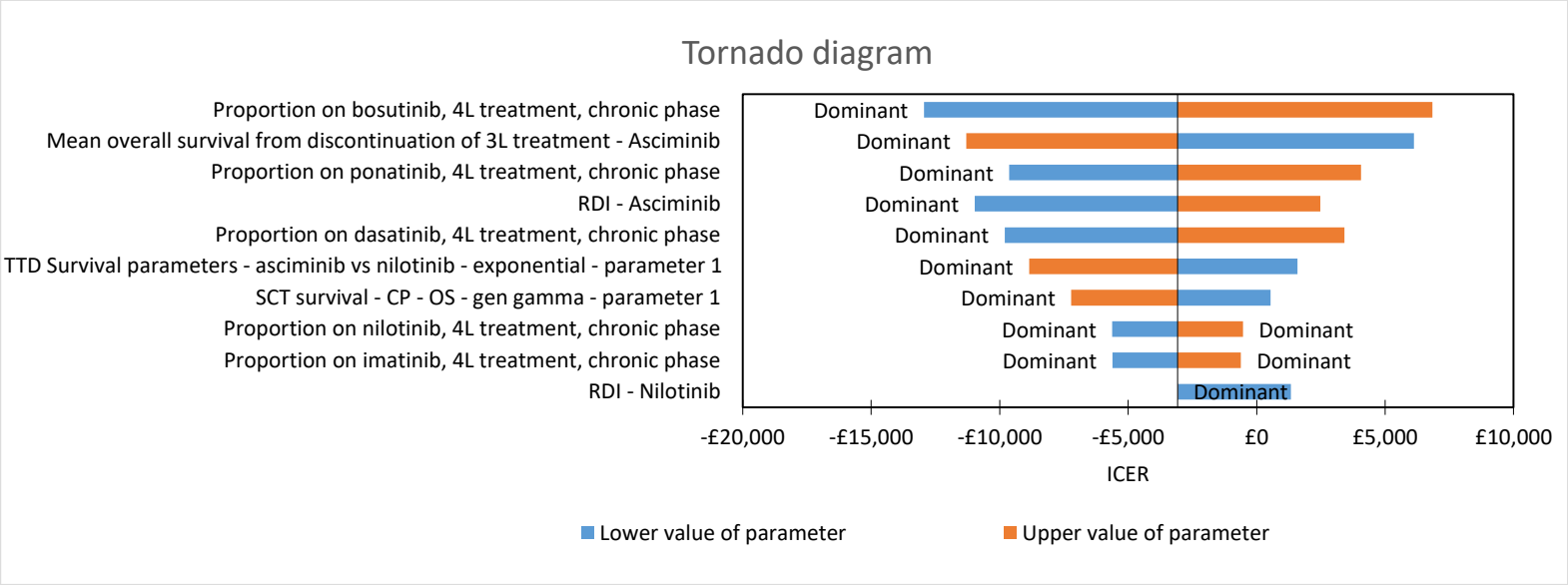
Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity.

Table 17: One-way sensitivity analysis - asciminib (PAS price) vs nilotinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Proportion on bosutinib, fourth-line treatment, chronic phase	–£12,947	£6,835
Mean OS from discontinuation of third-line treatment - asciminib	£6,124	–£11,296
Proportion on ponatinib, fourth-line treatment, chronic phase	–£9,627	£4,066
RDI - asciminib	–£10,973	£2,482
Proportion on dasatinib, fourth-line treatment, chronic phase	–£9,806	£3,418
TTD survival parameters - asciminib vs nilotinib - exponential - parameter 1	£1,588	–£8,855
SCT survival - CP - OS - gen gamma - parameter 1	£545	–£7,220
Proportion on nilotinib, fourth-line treatment, chronic phase	–£5,628	–£531
Proportion on imatinib, fourth-line treatment, chronic phase	–£5,608	–£618
RDI - nilotinib	£1,338	–£3,079

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; SCT, stem cell transplant; TTD, time to discontinuation.

Figure 22: Tornado diagram - asciminib (PAS price) vs nilotinib



Abbreviations: 3L, third-line; 4L, fourth-line; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, Patient Access Scheme; RDI, relative dose intensity; SCT, stem cell transplant; TTD, time to discontinuation.

Asciminib vs dasatinib

Table 18: One-way sensitivity analysis - asciminib (list price) vs dasatinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Mean OS from discontinuation of third-line treatment - dasatinib	[redacted]	[redacted]
Mean OS from discontinuation of third-line treatment - asciminib	[redacted]	[redacted]
RDI - asciminib	[redacted]	[redacted]
Proportion on bosutinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Median treatment duration - dasatinib	[redacted]	[redacted]
Proportion on nilotinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
Proportion on ponatinib, fourth-line treatment, chronic phase	[redacted]	[redacted]
TTD survival parameters - asciminib vs dasatinib - exponential - parameter 1	[redacted]	[redacted]
ASCEMBL, mean values, CP, on treatment	[redacted]	[redacted]
RDI - dasatinib	[redacted]	[redacted]

Abbreviations: CP, chronic phase; ICER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 23: Tornado diagram - asciminib (list price) vs dasatinib

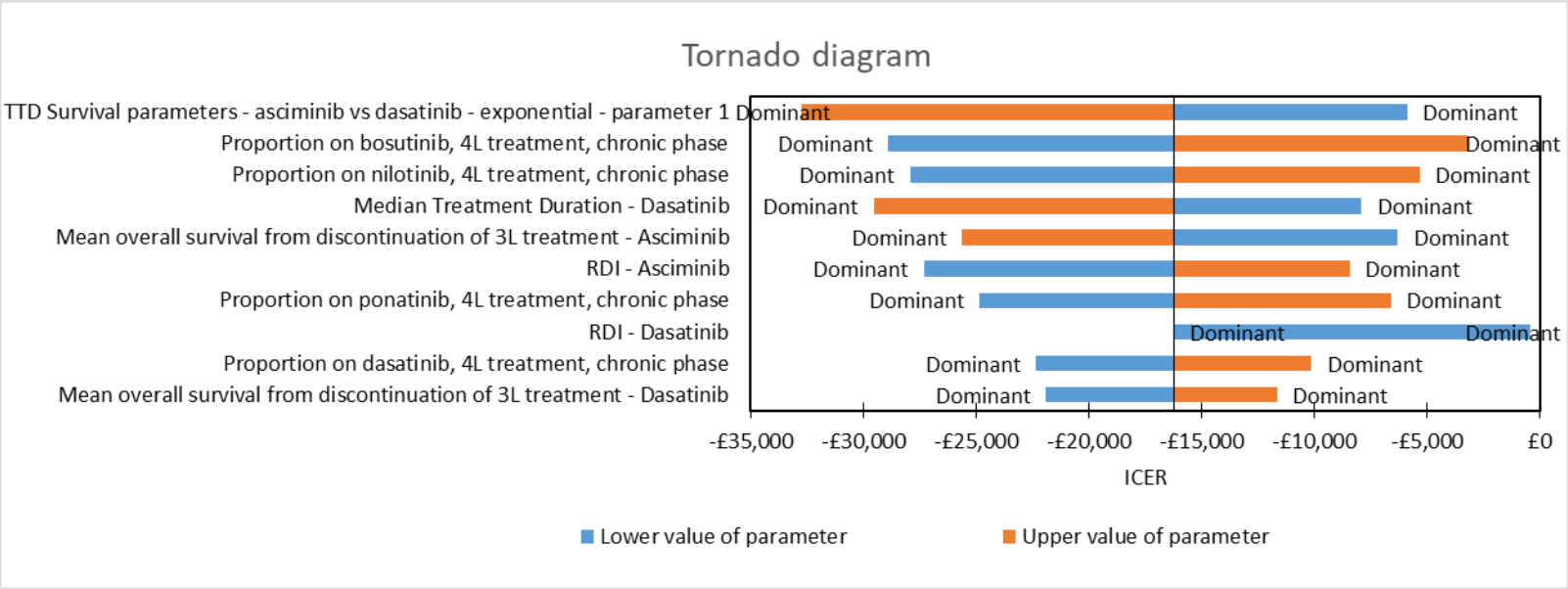
Abbreviations: 3L, third-line; 4L, fourth-line; CP, chronic phase; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity; TTD, time to discontinuation.

Table 19: One-way sensitivity analysis - asciminib (PAS price) vs dasatinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
TTD survival parameters - asciminib vs dasatinib - exponential - parameter 1	–£5,875	–£32,771
Proportion on bosutinib, fourth-line treatment, chronic phase	–£28,927	–£3,193
Proportion on nilotinib, fourth-line treatment, chronic phase	–£27,937	–£5,319
Median treatment duration - dasatinib	–£7,919	–£29,545
Mean OS from discontinuation of third-line treatment - asciminib	–£6,291	–£25,622
RDI - asciminib	–£27,322	–£8,428
Proportion on ponatinib, fourth-line treatment, chronic phase	–£24,865	–£6,617
RDI - dasatinib	–£407	–£16,238
Proportion on dasatinib, fourth-line treatment, chronic phase	–£22,340	–£10,135
Mean OS from discontinuation of third-line treatment - dasatinib	–£21,912	–£11,674

Abbreviations: CER, incremental cost-effectiveness ratio; OS, overall survival; RDI, relative dose intensity; TTD, time to discontinuation.

Figure 24: Tornado diagram - asciminib (PAS price) vs dasatinib



Abbreviations: 3L, third-line; 4L, fourth-line; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; RDI, relative dose intensity; TTD, time to discontinuation.

Scenario analysis

Asciminib vs bosutinib

Table 20: Scenario results – asciminib (list price) vs bosutinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	1.33	[redacted]	0%
5 years survival post third-line discontinuation	[redacted]	1.46	[redacted]	–7%
3.5 years survival post third-line discontinuation	[redacted]	1.55	[redacted]	–13%
10 years survival post third-line discontinuation	[redacted]	1.17	[redacted]	11%
12 years survival post third-line discontinuation	[redacted]	1.07	[redacted]	19%
Discount rates zero	[redacted]	2.20	[redacted]	1%
Discount rates 5%	[redacted]	1.12	[redacted]	0%
Mean time in AP 12 months	[redacted]	1.54	[redacted]	–13%
Mean time in AP 8 months	[redacted]	1.56	[redacted]	–13%
Mean time in BP 8 months	[redacted]	1.55	[redacted]	–14%
Mean time in BP 4 months	[redacted]	1.56	[redacted]	–12%
Proportion undergoing SCT at third-line discontinuation 12%	[redacted]	1.34	[redacted]	0%
Proportion undergoing SCT at third-line discontinuation 4%	[redacted]	1.34	[redacted]	1%
Proportion undergoing SCT at start of AP 40%	[redacted]	1.28	[redacted]	0%
Proportion undergoing SCT at start of AP 10%	[redacted]	1.36	[redacted]	0%
Proportion undergoing SCT at start of BP 40%	[redacted]	1.30	[redacted]	1%
Proportion undergoing SCT at start of BP 10%	[redacted]	1.35	[redacted]	–1%
HSUV by treatment arm	[redacted]	1.41	[redacted]	–5%
HSUV by treatment status & arm	[redacted]	1.45	[redacted]	–8%
HSUV from Szabo 2010 (22)	[redacted]	1.43	[redacted]	–7%
Exponential survival for TTD for asciminib & bosutinib	[redacted]	0.87	[redacted]	4%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Weibull survival for TTD for asciminib & bosutinib	[redacted]	1.16	[redacted]	–2%
Gompertz survival for TTD for asciminib & bosutinib	[redacted]	2.88	[redacted]	–7%
Log-normal survival for TTD for asciminib & bosutinib	[redacted]	1.46	[redacted]	–2%
Gamma survival for TTD for asciminib & bosutinib	[redacted]	1.07	[redacted]	–1%
Generalized Gamma survival for TTD for asciminib & bosutinib	[redacted]	1.84	[redacted]	–13%

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCT, stem cell transplant; TTD, time to discontinuation.

Table 21: Scenario results – asciminib (PAS price) vs bosutinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	£7,549	1.33	£5,659	0%
5 years survival post third-line discontinuation	£9,999	1.46	£6,859	21%
3.5 years survival post third-line discontinuation	£12,471	1.55	£8,035	42%
10 years survival post third-line discontinuation	£4,738	1.17	£4,061	–28%
12 years survival post third-line discontinuation	£2,930	1.07	£2,738	–52%
Discount rates zero	£38,270	2.20	£17,435	208%
Discount rates 5%	£500	1.12	£448	–92%
Mean time in AP 12 months	£12,080	1.54	£7,824	38%
Mean time in AP 8 months	£12,862	1.56	£8,244	46%
Mean time in BP 8 months	£11,276	1.55	£7,290	29%
Mean time in BP 4 months	£13,672	1.56	£8,778	55%
Proportion undergoing SCT at third-line discontinuation 12%	£7,829	1.34	£5,861	4%
Proportion undergoing SCT at third-line discontinuation 4%	£8,423	1.34	£6,289	11%
Proportion undergoing SCT at start of AP 40%	£3,542	1.28	£2,774	–51%
Proportion undergoing SCT at start of AP 10%	£9,552	1.36	£7,011	24%
Proportion undergoing SCT at start of BP 40%	£5,852	1.30	£4,516	–20%
Proportion undergoing SCT at start of BP 10%	£8,398	1.35	£6,206	10%
HSUV by treatment arm	£7,549	1.41	£5,369	–5%
HSUV by treatment status & arm	£7,549	1.45	£5,222	–8%
HSUV from Szabo 2010 (22)	£7,549	1.43	£5,289	–7%
Exponential survival for TTD for asciminib & bosutinib	£9,931	0.87	£11,462	103%
Weibull survival for TTD for asciminib & bosutinib	£13,912	1.16	£12,006	112%
Gompertz survival for TTD for asciminib & bosutinib	£14,759	2.88	£5,117	–10%
Log-normal survival for TTD for asciminib & bosutinib	£8,899	1.46	£6,081	7%
Gamma survival for TTD for asciminib & bosutinib	£12,643	1.07	£11,854	109%

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Generalized Gamma survival for TTD for asciminib & bosutinib	£36,563	1.84	£19,890	252%

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCT, stem cell transplant; TTD, time to discontinuation.

Asciminib vs ponatinib

Table 22: Scenario results – asciminib (list price) vs ponatinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	–0.55	[redacted]	0%
5 years survival post third-line discontinuation	[redacted]	–0.60	[redacted]	40%
3.5 years survival post third-line discontinuation	[redacted]	–0.64	[redacted]	68%
10 years survival post third-line discontinuation	[redacted]	–0.48	[redacted]	–66%
12 years survival post third-line discontinuation	[redacted]	–0.44	[redacted]	–
Discount rates zero	[redacted]	–0.88	[redacted]	–24%
Discount rates 5%	[redacted]	–0.46	[redacted]	13%
Mean time in AP 12 months	[redacted]	–0.63	[redacted]	64%
Mean time in AP 8 months	[redacted]	–0.64	[redacted]	72%
Mean time in BP 8 months	[redacted]	–0.63	[redacted]	58%
Mean time in BP 4 months	[redacted]	–0.64	[redacted]	78%
Proportion undergoing SCT at third-line discontinuation 12%	[redacted]	–0.55	[redacted]	–7%
Proportion undergoing SCT at third-line discontinuation 4%	[redacted]	–0.55	[redacted]	–22%
Proportion undergoing SCT at start of AP 40%	[redacted]	–0.52	[redacted]	1%
Proportion undergoing SCT at start of AP 10%	[redacted]	–0.56	[redacted]	–1%
Proportion undergoing SCT at start of BP 40%	[redacted]	–0.53	[redacted]	3%
Proportion undergoing SCT at start of BP 10%	[redacted]	–0.56	[redacted]	–1%
HSUV by treatment arm	[redacted]	–0.44	[redacted]	25%
HSUV by treatment status & arm	[redacted]	–0.44	[redacted]	24%
HSUV from Szabo 2010 (22)	[redacted]	–0.60	[redacted]	–9%

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCT, stem cell transplant.

Table 23: Scenario results – asciminib (PAS price) vs ponatinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	–£61,154	–0.55	£111,470	0%
5 years survival post third-line discontinuation	–£70,294	–0.60	£117,437	5%
3.5 years survival post third-line discontinuation	–£77,593	–0.64	£121,768	9%
10 years survival post third-line discontinuation	–£48,990	–0.48	£102,060	–8%
12 years survival post third-line discontinuation	–£41,951	–0.44	£95,340	–14%
Discount rates zero	–£68,422	–0.88	£77,879	–30%
Discount rates 5%	–£59,025	–0.46	£127,980	15%
Mean time in AP 12 months	–£76,608	–0.63	£120,849	8%
Mean time in AP 8 months	–£78,587	–0.64	£122,684	10%
Mean time in BP 8 months	–£75,441	–0.63	£118,811	7%
Mean time in BP 4 months	–£79,763	–0.64	£124,725	12%
Proportion undergoing SCT at third-line discontinuation 12%	–£59,920	–0.55	£109,244	–2%
Proportion undergoing SCT at third-line discontinuation 4%	–£57,323	–0.55	£104,548	–6%
Proportion undergoing SCT at start of AP 40%	–£60,544	–0.52	£115,675	4%
Proportion undergoing SCT at start of AP 10%	–£61,459	–0.56	£109,510	–2%
Proportion undergoing SCT at start of BP 40%	–£61,102	–0.53	£114,873	3%
Proportion undergoing SCT at start of BP 10%	–£61,180	–0.56	£109,846	–1%
HSUV by treatment arm	–£61,154	–0.44	£139,775	25%
HSUV by treatment status & arm	–£61,154	–0.44	£137,803	24%
HSUV from Szabo 2010 (22)	–£61,154	–0.60	£101,223	–9%

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SCT, stem cell transplant.

Asciminib vs nilotinib

Table 24: Scenario results – asciminib (list price) vs nilotinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	0.91	[redacted]	0%
5 years survival post third-line discontinuation	[redacted]	0.98	[redacted]	8%
3.5 years survival post third-line discontinuation	[redacted]	1.03	[redacted]	14%
10 years survival post third-line discontinuation	[redacted]	0.81	[redacted]	–14%
12 years survival post third-line discontinuation	[redacted]	0.76	[redacted]	–23%
Discount rates zero	[redacted]	1.35	[redacted]	–5%
Discount rates 5%	[redacted]	0.79	[redacted]	3%
Mean time in AP 12 months	[redacted]	1.03	[redacted]	13%
Mean time in AP 8 months	[redacted]	1.04	[redacted]	14%
Mean time in BP 8 months	[redacted]	1.03	[redacted]	13%
Mean time in BP 4 months	[redacted]	1.03	[redacted]	14%
Proportion undergoing SCT at third-line discontinuation 12%	[redacted]	0.91	[redacted]	–2%
Proportion undergoing SCT at third-line discontinuation 4%	[redacted]	0.91	[redacted]	–6%
Proportion undergoing SCT at start of AP 40%	[redacted]	0.87	[redacted]	0%
Proportion undergoing SCT at start of AP 10%	[redacted]	0.93	[redacted]	0%
Proportion undergoing SCT at start of BP 40%	[redacted]	0.88	[redacted]	1%
Proportion undergoing SCT at start of BP 10%	[redacted]	0.92	[redacted]	0%
HSUV by treatment arm	[redacted]	0.97	[redacted]	–6%
HSUV by treatment status & arm	[redacted]	1.02	[redacted]	–11%
HSUV from Szabo 2010 (22)	[redacted]	0.99	[redacted]	–8%

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCT, stem cell transplant.

Table 25: Scenario results – asciminib (PAS price) vs nilotinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	–£2,803	0.91	Dominant	–
5 years survival post third-line discontinuation	£6,413	0.98	£6,553	–
3.5 years survival post third-line discontinuation	£13,533	1.03	£13,118	–
10 years survival post third-line discontinuation	–£15,588	0.81	Dominant	–
12 years survival post third-line discontinuation	–£23,158	0.76	Dominant	–
Discount rates zero	£13,868	1.35	£10,270	–
Discount rates 5%	–£6,260	0.79	Dominant	–
Mean time in AP 12 months	£13,047	1.03	£12,704	–
Mean time in AP 8 months	£14,022	1.04	£13,531	–
Mean time in BP 8 months	£12,904	1.03	£12,548	–
Mean time in BP 4 months	£14,169	1.03	£13,691	–
Proportion undergoing SCT at third-line discontinuation 12%	–£3,969	0.91	Dominant	–
Proportion undergoing SCT at third-line discontinuation 4%	–£6,416	0.91	Dominant	–
Proportion undergoing SCT at start of AP 40%	–£5,336	0.87	Dominant	–
Proportion undergoing SCT at start of AP 10%	–£1,537	0.93	Dominant	–
Proportion undergoing SCT at start of BP 40%	–£4,079	0.88	Dominant	–
Proportion undergoing SCT at start of BP 10%	–£2,165	0.92	Dominant	–
HSUV by treatment arm	–£2,803	0.97	Dominant	–
HSUV by treatment status & arm	–£2,803	1.02	Dominant	–
HSUV from Szabo 2010 (22)	£56,527	0.99	£56,981	–

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SCT, stem cell transplant.

Asciminib vs dasatinib

Table 26: Scenario results – asciminib (list price) vs dasatinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	0.61	[redacted]	0%
5 years survival post third-line discontinuation	[redacted]	0.66	[redacted]	–1%
3.5 years survival post third-line discontinuation	[redacted]	0.70	[redacted]	–2%
10 years survival post third-line discontinuation	[redacted]	0.54	[redacted]	1%
12 years survival post third-line discontinuation	[redacted]	0.50	[redacted]	2%
Discount rates zero	[redacted]	0.94	[redacted]	–7%
Discount rates 5%	[redacted]	0.53	[redacted]	4%
Mean time in AP 12 months	[redacted]	0.70	[redacted]	–2%
Mean time in AP 8 months	[redacted]	0.71	[redacted]	–2%
Mean time in BP 8 months	[redacted]	0.70	[redacted]	–3%
Mean time in BP 4 months	[redacted]	0.70	[redacted]	–1%
Proportion undergoing SCT at third-line discontinuation 12%	[redacted]	0.61	[redacted]	–1%
Proportion undergoing SCT at third-line discontinuation 4%	[redacted]	0.61	[redacted]	–3%
Proportion undergoing SCT at start of AP 40%	[redacted]	0.59	[redacted]	1%
Proportion undergoing SCT at start of AP 10%	[redacted]	0.63	[redacted]	–1%
Proportion undergoing SCT at start of BP 40%	[redacted]	0.60	[redacted]	2%
Proportion undergoing SCT at start of BP 10%	[redacted]	0.62	[redacted]	–1%
HSUV by treatment arm	[redacted]	0.68	[redacted]	–10%
HSUV by treatment status & arm	[redacted]	0.73	[redacted]	–15%
HSUV from Szabo 2010 (22)	[redacted]	0.67	[redacted]	–9%

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCT, stem cell transplant; TTD, time to discontinuation.

Table 27: Scenario results – asciminib (PAS price) vs dasatinib

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base–case ICER
Base–case	–£9,970	0.61	Dominant	–
5 years survival post third-line discontinuation	–£6,698	0.66	Dominant	–
3.5 years survival post third-line discontinuation	–£4,359	0.70	Dominant	–
10 years survival post third-line discontinuation	–£14,767	0.54	Dominant	–
12 years survival post third-line discontinuation	–£17,657	0.50	Dominant	–
Discount rates zero	£3,008	0.94	£3,217	–
Discount rates 5%	–£12,728	0.53	Dominant	–
Mean time in AP 12 months	–£4,835	0.70	Dominant	–
Mean time in AP 8 months	–£3,879	0.71	Dominant	–
Mean time in BP 8 months	–£5,272	0.70	Dominant	–
Mean time in BP 4 months	–£3,436	0.70	Dominant	–
Proportion undergoing SCT at third-line discontinuation 12%	–£10,457	0.61	Dominant	–
Proportion undergoing SCT at third-line discontinuation 4%	–£11,479	0.61	Dominant	–
Proportion undergoing SCT at start of AP 40%	–£11,508	0.59	Dominant	–
Proportion undergoing SCT at start of AP 10%	–£9,201	0.63	Dominant	–
Proportion undergoing SCT at start of BP 40%	–£10,642	0.60	Dominant	–
Proportion undergoing SCT at start of BP 10%	–£9,634	0.62	Dominant	–
HSUV by treatment arm	–£9,970	0.68	Dominant	–
HSUV by treatment status & arm	–£9,970	0.73	Dominant	–
HSUV from Szabo 2010 (22)	–£9,970	0.67	Dominant	–

Abbreviations: AP, accelerated phase; BP, blast phase; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SCT, stem cell transplant.

Appendix D: Analysis of HMRN fourth-line overall survival

Table 28: Survival models fitted to the pseudo-patient data generated from the KM curve for OS at fourth line TKI therapy in HMRN

Survival model	Scale parameter	Shape parameter	AIC
Exponential	[redacted]		90.49536
Weibull	[redacted]	[redacted]	92.21005
Gomperz	[redacted]	[redacted]	91.8484
Loglogistic	[redacted]	[redacted]	91.91644
Lognormal	[redacted]	[redacted]	91.23765

Abbreviations: AIC, Akaike's Information Criterion; HMRN, haematological malignancy research network; KM, Kaplan-Meier; OS, overall survival; TKI, tyrosine kinase inhibitor.

Figure 25: KM survival curve and survival models fitted to pseudo patient data on OS at fourth line in HMRN

Abbreviations: HMRN, haematological malignancy research network; KM, Kaplan-Meier; OS, overall survival.

Appendix E: Anchored MAIC comparison between ASCEMBL and HMRN TTD and response

As previously described, we considered the clinical study data included in the matched adjusted indirect comparison (MAIC) analyses of the original submission to be superior to comparing with data in the Haematological Malignancy Research Network (HMRN) dataset due to the observational nature of the latter (findings of the clinical study MAICs were presented in Appendix I as part of submission materials). For example, sample size was larger (albeit the difference was marginal in the case of dasatinib and nilotinib) and patient selection criteria are likely to be more robust in a clinical trial setting.

However, at the request of the Evidence Review Group (ERG), additional analyses were undertaken to perform an anchored MAIC using ASCEMBL and HMRN data, with bosutinib as the common comparator. The findings of anchored MAIC comparisons between asciminib, dasatinib, and nilotinib for time-to-discontinuation (TTD), and major molecular response (MMR) by 6 months, are presented here. For ponatinib, patient data were only available for [redacted] patients from the HMRN dataset, and this was considered too small a sample size to enable a reliable comparison to be made. Therefore, no comparison was made with ponatinib. The ASCEMBL trial remains the most robust comparison of outcomes between asciminib and bosutinib, and further comparison with outcomes for bosutinib based on data from HMRN are not presented here.

These analyses took a similar approach to the original MAIC analyses (e.g. estimation of weights using the method of moments to match patients for their characteristics), with the key difference being that an anchored comparison was possible via the common comparator, bosutinib, in both studies. Anchoring allows adjustment for unobserved differences in patient characteristics or clinical practice that may differ between ASCEMBL and HMRN and is recommended, where possible, when undertaking MAIC (10). A MAIC was considered more appropriate than a conventional Bucher comparison without population-adjustment, as this approach can reduce bias in the relative treatment effect that may occur due to differences in characteristics between the datasets.

In the base case analysis, matching was undertaken to generate a set of weights for patients in ASCEMBL which aligned the mean values for patient baseline characteristics in ASCEMBL with those for the bosutinib treatment group in HMRN. A sensitivity analysis was also undertaken to reflect the potential differences in patient characteristics across treatment groups in HMRN. In the sensitivity analysis, weighting was undertaken to align aggregate patient characteristics for ASCEMBL with those for either the bosutinib or the relevant comparator arm (nilotinib or dasatinib). The choice of arm was determined by the aggregate values considered likely to generate the least favourable outcomes for patients in ASCEMBL. These were older age, higher proportion of males, and higher proportion resistant to previous tyrosine kinase inhibitor (TKI) therapy.

Patient baseline characteristics

An analysis of patients with chronic myeloid leukaemia (CML) in HMRN was commissioned by Novartis (23). The report on the results of that analysis provided data on TTD and MMR for patients according to line of therapy and TKI treatment. Data were provided for the subgroup of patients without the T315I mutation. In addition to summary data, Kaplan-Meier (KM) curves were reported for TTD. The report provided baseline characteristics by treatment group only up to and including third-line therapies. This is likely due to the smaller numbers of patients receiving fourth-line or later treatment. The baseline characteristics reported for the HMRN dataset, including for third-line patients, were median age, proportion of patients who were male and female, reason for switching prior TKI, and T315I mutation status (Table 29).

Table 29: Baseline characteristics for third-line patients in HMRN compared with ASCEMBL

Treatment group	Total number of patients	Mean / median age (years)	Sex		Reason for switching TKI			T315I mutation, n (%)
			Male, n (%)	Female, n (%)	Resistance, n (%)	Intolerance, n (%)	Other, n (%)	
ASCEMBL								
Asciminib	157	51.0 [redacted]	82 (52.2)	75 (47.8)	95 (60.5)	59 (37.6)	3 (1.9)	3 (1.9)
Bosutinib	76	51.0 [redacted]	31 (40.8)	45 (59.2)	54 (71.1)	22 (28.9)	0 (0)	2 (2.6)[†]
HMRN								
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†]One patient each with T315I mutation or V299L mutation; [‡]Median only.
Abbreviations: HMRN, haematological malignancy research network; TKI, tyrosine kinase inhibitor.

The ASCEMBL patients were [redacted] than patients receiving bosutinib, dasatinib or nilotinib in the HMRN dataset, and there was a [redacted] proportion of male patients in ASCEMBL than in the nilotinib group. However, the [redacted] between the two studies. Across treatment groups within HMRN, patient characteristics were broadly similar for the reason for switching TKI. There were some notable differences for the nilotinib group compared to bosutinib and dasatinib; patients were [redacted]. In light of the modest patient numbers, this probably arose through chance.

Study reported outcome data for TTD and MMR

For TTD, data from HMRN were available for the subgroup of third-line patients without T315I mutation, and therefore a comparison was possible for patients in the subgroup of no T315I mutation from both studies. Patients with the V299L mutation were also excluded as part of the pre-specified criteria for the ASCEMBL trial, and thus the single ASCEMBL patient in the bosutinib treatment arm with this mutation was also excluded from the analysis. Data were reported as median values with confidence intervals (CIs) and KM curves.

A summary of the unadjusted outcome findings from each study for TTD, and MMR by 6 months, are presented in Table 30. It was noted that TTD was [redacted]), but it is unclear what factors contributed to such a large difference in the findings, without being able to examine individual patient data from HMRN. Similarly, the proportion of patients experiencing MMR by 6 months was [redacted] compared with bosutinib from HMRN [redacted] The explanation for this difference is not entirely apparent, although it may again be linked with the factors described above.

Table 30: Third-line TTD and MMR from HMRN vs all ASCEMBL patients, excluding patients with T315I mutation

Treatment group	Number at risk	Median TTD months (95% CI)	Number of patients	MMR by 6 months, n (%)
ASCEMBL				
Asciminib	154	[redacted]	[redacted]	[redacted]
Bosutinib	74	[redacted]	[redacted]	[redacted]
HMRN				
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]	[redacted]
Nilotinib	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HMRN, haematological malignancy research network; [redacted]; MMR, major molecular response; TTD, time to discontinuation.

MAIC results for TTD, ASCEMBL vs HMRN

Pseudo-individual patient level data (IPD) were created for HMRN patients from the KM curves for third-line treatment by regimen, for patients without the T315I mutation (Figure 79 of the HMRN report (23)). The data were digitised and converted to pseudo-IPD using the Guyot et al. 2012 algorithm (24) and accompanying published code for R software. Numbers at risk were available from the KM figure, and median TTD, along with number of TTD events by treatment, were extracted from the tables in the HMRN report (Table 6 of the HMRN report (23)).

Hazard ratios (HRs) were first calculated for each treatment pair (asciminib vs bosutinib and either dasatinib or nilotinib vs bosutinib) by study, and then compared using the log HR and associated variance, before converting back to the natural scale to report the HR for asciminib vs comparator. Adjusted analysis was undertaken after matching the mean patient characteristics in ASCEMBL to the bosutinib treatment group in HMRN (base case). In sensitivity analysis, matching was undertaken to mean patient characteristics of either the bosutinib treatment group, or the relevant comparator treatment group (whichever was considered to have the least favourable characteristics. Note that for the comparison between asciminib and dasatinib, the two scenarios are identical).

Data for mean age were not available by treatment from HMRN, therefore, as the median and mean values were likely to be similar, matching was conducted under the assumption that mean and median age were the same across treatment groups in HMRN.

Asciminib versus dasatinib, TTD

For the comparison between asciminib and dasatinib, effective sample size (ESS) reduced the original sample size in ASCEMBL by almost [redacted] but the sample was still sufficiently powered to consider the results stable. The baseline characteristics for the bosutinib treatment group were considered less favourable than for the dasatinib treatment group. Consequently, matching of baseline characteristics in the sensitivity analysis was identical to the base case, and results are unchanged between scenarios (Table 31).

Table 31: Comparison of baseline characteristics – Asciminib (ASCEMBL) vs dasatinib (HMRN), pre- and post-matching

Treatment group	N/ESS	Mean/median age, years	Sex		Reason for switching TKI		
			Male, %	Female, %	Resistance, %	Intolerance, %	Other, %
Dasatinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib unadjusted (ASCEMBL)	154	51.0 / [redacted]	52.2	47.8	60.5	37.6	1.9
Bosutinib unadjusted (ASCEMBL)	74	51.0 / [redacted]	30.8	59.2	71.1	28.9	0
Asciminib and bosutinib after matching, base case and sensitivity analysis (ASCEMBL)‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

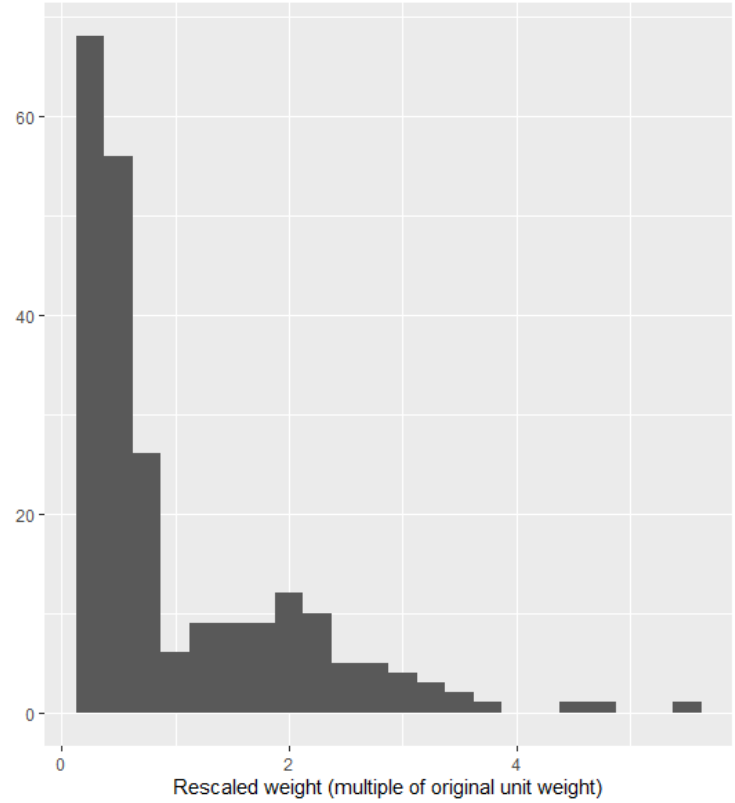
Base case = matching to BOS arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the BOS and DAS groups in HMRN

†Median only; ‡ASCEMBL was matched to identical values for patient characteristics in the two scenario analyses when comparing with dasatinib, and hence the results are the same

Abbreviations: BOS, bosutinib; DAS, dasatinib; ESS, effective sample size; HMRN, haematological malignancy research network; TKI, tyrosine kinase inhibitor.

All patients had re-scaled weights less than 6.0 with only one patient received a re-scaled weighting greater than 5.0, so findings were not unduly influenced by any individual patient. Re-scaled weights ranged from a minimum of 0.13 to a maximum of 5.53, with a median of 0.52 and mean of 1.00. The distribution of re-scaled weights is presented in the histogram in Figure 26. Note that the same weights are applied to each patient in the ASCEMBL trial based on patient characteristic data alone and were independent of the patient's outcome. Thus, patients in ASCEMBL received the same weights for the analysis of TTD, and MMR by 6 months, conditional on the HMRN treatment group selected as comparator.

Figure 26: Histogram of rescaled weights – matching asciminib (ASCEMBL) vs dasatinib (HMRN) based on common comparator arm characteristics (bosutinib), base case and sensitivity analysis



Abbreviations: HMRN, haematological malignancy research network.

Table 32 presents the findings of the unadjusted and adjusted KM estimates for each treatment group. The lower limit of the 95% CI for TTD for asciminib lengthened slightly when the population-adjustment was made, [redacted] months. The rescaled patient numbers report the sum of the number of patients after weighting. By definition, these sum to the original sample size of 228. However, the sum of the rescaled weights in each arm of the ASCEMBL data can differ from the number of patients in each

arm. The ESS allows for the reduction in statistical power that occurs due to the differential weighting of observations, which results in greater sensitivity of aggregate statistics to patients with higher weights. The value estimates the size of an unweighted sample of equivalent power. Note that the sum of the adjusted patient numbers at risk reported in Table 32 is not the same as the ESS, as these are based on different calculations.

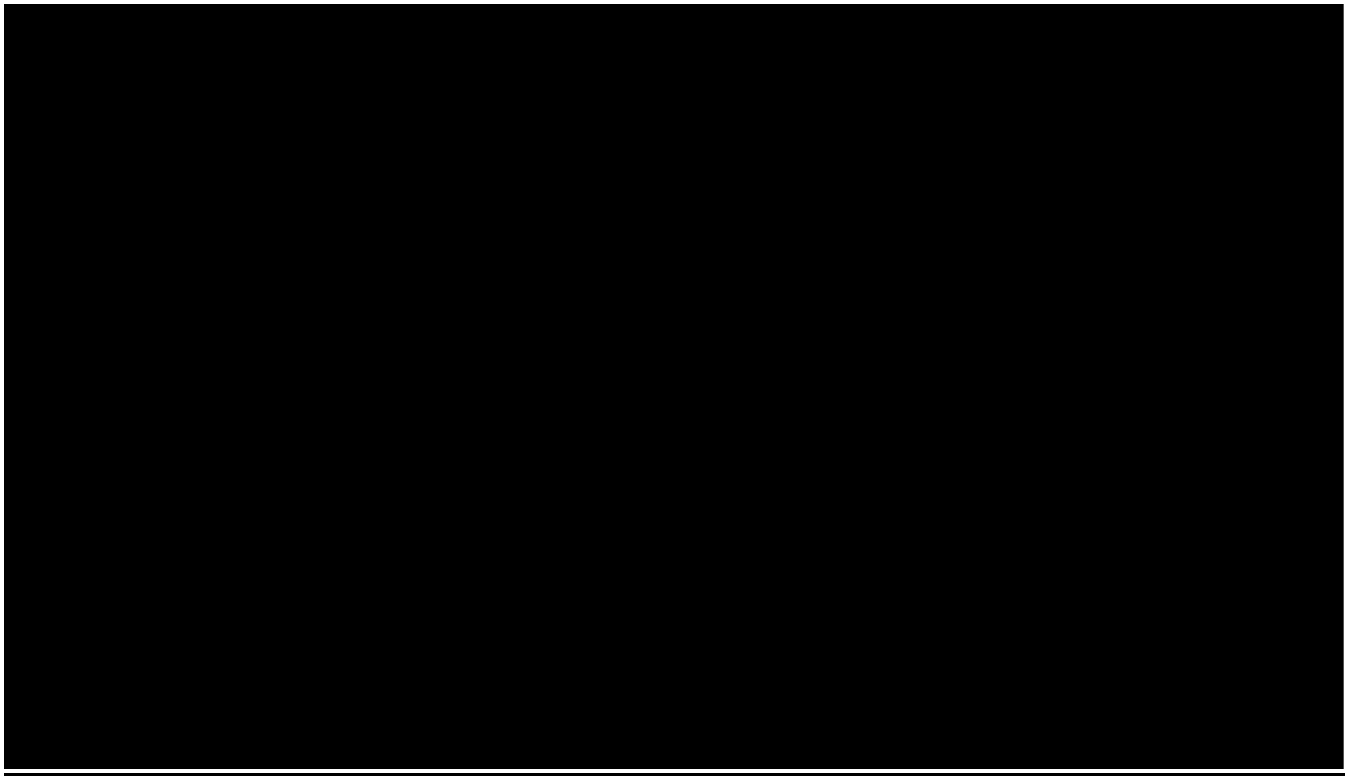
Table 32: KM summary of TTD – Asciminib (ASCEMBL) vs dasatinib (HMRN)

Treatment (study)	Numbers at risk/re-scaled numbers at risk	Events/re-scaled weighted events	Median TTD months (95% CI)
Dasatinib (HMRN)	[redacted]	[redacted]	[redacted]
Bosutinib (HMRN)	[redacted]	[redacted]	[redacted]
Asciminib unadjusted (ASCEMBL)	154	[redacted]	[redacted]
Bosutinib unadjusted (ASCEMBL)	74	[redacted]	[redacted]
Asciminib adjusted, base case and sensitivity analysis (ASCEMBL)†	[redacted]	[redacted]	[redacted]
Bosutinib adjusted, base case and sensitivity analysis (ASCEMBL)†	[redacted]	[redacted]	[redacted]

Base case = matching to bosutinib arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to tyrosine kinase inhibitor amongst the bosutinib and dasatinib groups in HMRN
†ASCEMBL was matched to identical values for patient characteristics in the two scenario analyses when comparing with dasatinib, and hence the results are the same
Abbreviations: CI, confidence interval; HMRN, haematological malignancy research network; KM, Kaplan-Meier; [redacted]; TTD, time to discontinuation.

The KM curves for each treatment from both the unadjusted and weighted patient data are presented in Figure 27.

Figure 27: Time to treatment discontinuation for unadjusted and population-matched asciminib (ASCEMBL) vs dasatinib (HMRN) and common comparator arm (bosutinib) – base case and sensitivity analysis



Abbreviations: adj, adjusted; ASC, asciminib; BOS, bosutinib; DAS, dasatinib; HMRN, haematological malignancy research network; unadj, unadjusted.

The HR estimates for the direct comparison of asciminib vs bosutinib from ASCEMBL patient data were [redacted] of asciminib in both unadjusted and weighted analyses, with patients experiencing [redacted] discontinuation compared with bosutinib [redacted], Table 33). Using the Bucher method to make an indirect treatment comparison between unadjusted HRs for asciminib vs bosutinib and dasatinib vs bosutinib, the results were also [redacted] of asciminib.

When applying the weighting, the [redacted], as the 95% CI is wider than in the unweighted analysis, likely due to the reduced ESS. However, the point estimate [redacted] and pointed to [redacted]

Table 33: HR summary for TTD – Asciminib (ASCEMBL) vs dasatinib (HMRN)

Treatment comparison	Model	N/ESS for ASCEMBL	HR for TTD (95% CI)
Direct comparisons			
Asciminib vs bosutinib	Unweighted comparison from ASCEMBL	228	[redacted]
Asciminib vs bosutinib	Weighted HR matching, base case and sensitivity analysis‡	[redacted]	[redacted]
Dasatinib vs bosutinib	Unweighted comparison from HMRN dataset	[redacted]	[redacted]
Indirect comparisons			
Asciminib vs dasatinib	Unweighted comparison	[redacted]	[redacted]
Asciminib vs dasatinib	Weighted HR matching, base case and sensitivity analysis‡	[redacted]	[redacted]

Base case = matching to bosutinib arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to tyrosine kinase inhibitor amongst the bosutinib and dasatinib groups in HMRN

†Findings that are significantly in favour of asciminib; ‡ASCEMBL was matched to identical values for patient characteristics in the two scenario analyses when comparing with dasatinib, and hence the results are the same.

Abbreviations: CI, confidence interval; ESS, effective sample size; HMRN, haematological malignancy research network; HR, hazard ratio; TTD, time to discontinuation.

Asciminib versus nilotinib, TTD

For the comparison between asciminib and nilotinib, the ESS was similarly reduced to around [redacted] of the original population in ASCEMBL in the matching to HMRN bosutinib characteristics analysis. However, it was [redacted] in sensitivity analysis, with the ESS at around [redacted] of the original sample size in ASCEMBL. This suggests limited overlap between patient characteristics in the patients enrolled, and is easily seen when comparing the median age of [redacted] years in ASCEMBL vs matching to [redacted] years in the HMRN data, and the proportion of males across the combined treatment arms in ASCEMBL of [redacted] vs [redacted] in the HMRN data (Table 34).

Table 34: Comparison of baseline characteristics – Asciminib (ASCEMBL) vs nilotinib (HMRN), pre- and post-matching

Treatment group	N/ESS	Mean / median age, years	Sex		Reason for switching TKI		
			Male (%)	Female (%)	Resistance (%)	Intolerance (%)	Other (%)
Nilotinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib (HMRN)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib unadjusted (ASCEMBL)	154	51.0 / 52.0	52.2	47.8	60.5	37.6	1.9
Bosutinib unadjusted (ASCEMBL)	74	51.0 / 52.0	40.8	59.2	71.1	28.9	0
Asciminib and bosutinib after matching, base case (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib and bosutinib after matching, Sensitivity analysis (ASCEMBL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

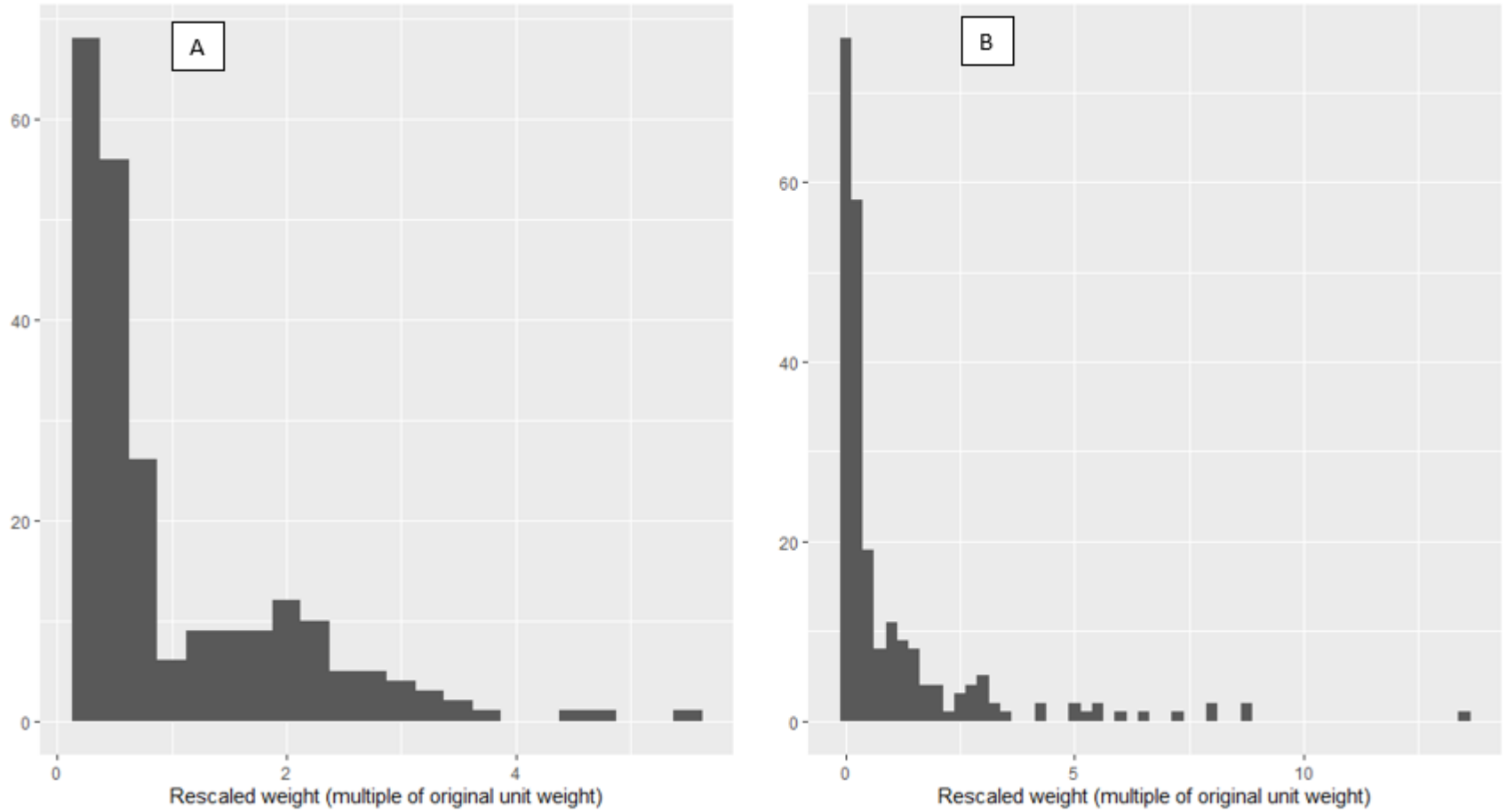
Base case = matching to BOS arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the bosutinib and dasatinib groups in HMRN
†Median only.
Abbreviations: ESS, effective sample size; HMRN, haematological malignancy research network; TKI, tyrosine kinase inhibitor.

Matching to the HMRN characteristics of the common comparator, bosutinib, the weights for the adjusted asciminib vs bosutinib comparison in ASCEMBL are identical to those used for adjusting the ASCEMBL data prior to comparing with dasatinib in the

previous section. Therefore, only three patients received re-scaled weights greater than 4, with weights ranging between a minimum of 0.13 to a maximum of 5.53, with median value of 0.52 and mean 1.00 (Figure 28A).

In contrast, Figure 28B presents re-scaled weights from the sensitivity analysis, and shows a wider spread of weights (note the differing scale on the x-axis between Figure A and B). Consequently, some patients have a large influence on the findings due to the large allocated weighting they receive. Weights in the sensitivity analysis ranged between 0.007 and 13.62, with a median of 0.26 and mean of 1.00; the difference in this range of weights is reflected in the smaller ESS for this scenario. As noted previously, because weights are estimated for patients in the ASCEMBL trial based on characteristics only, the same weights are applied to patients for both TTD, and MMR by 6 months, when matching for the same characteristics.

Figure 28: Histograms of rescaled weights



A: Histogram matching asciminib (ASCEMBL) vs nilotinib (HMRN) based on common comparator arm characteristics (bosutinib)

B: Histogram matching asciminib (ASCEMBL) vs nilotinib (HMRN) based on "worst case" characteristics from the nilotinib vs bosutinib comparison in HMRN

Abbreviations: HMRN, haematological malignancy research network.

Table 35 presents the findings of the unadjusted and adjusted KM estimates for each treatment group. The lower limit of the 95% CI for TTD for asciminib increased slightly from [redacted] when the population adjustment was matching bosutinib characteristics from HMRN. The opposite was true when matching in the sensitivity analysis.

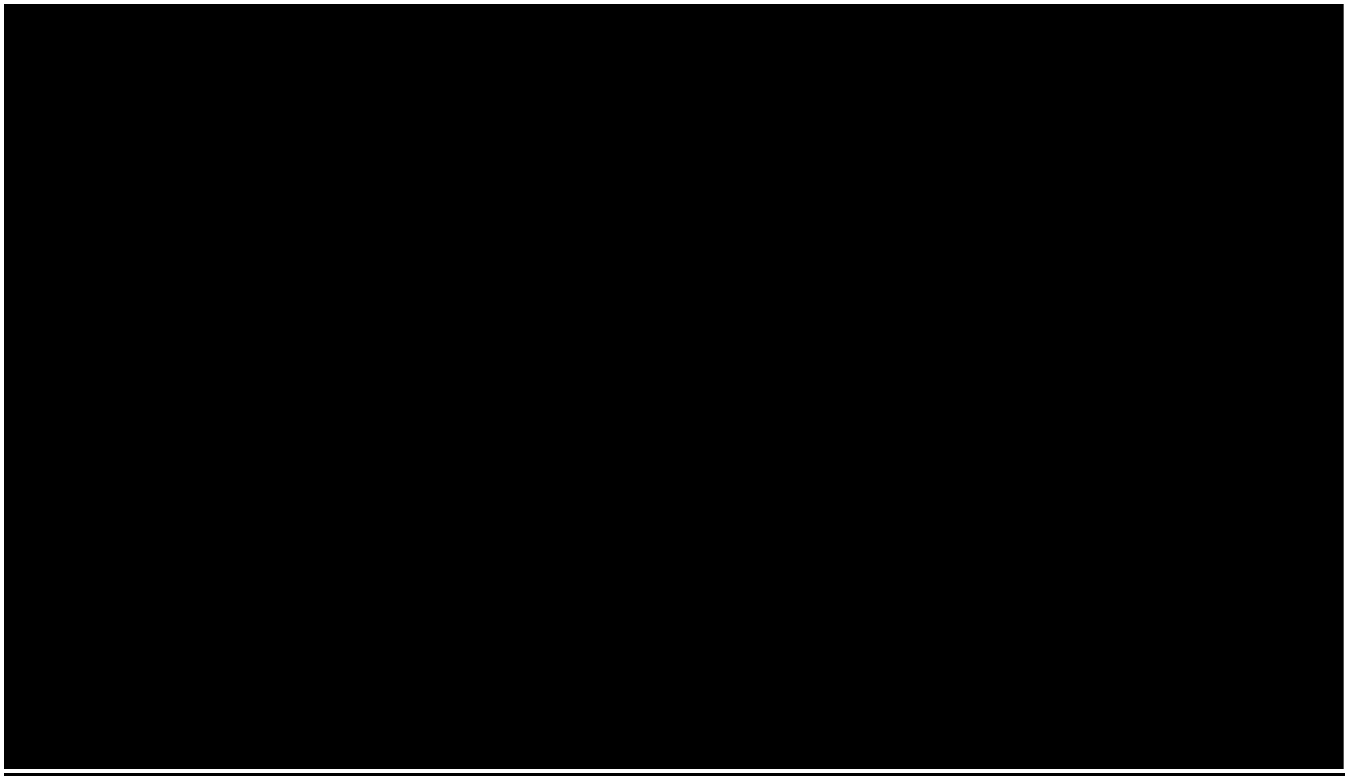
Table 35: KM summary of TTD – Asciminib (ASCEMBL) vs nilotinib (HMRN)

Treatment (study)	Numbers at risk/re-scaled numbers at risk	Events	Median TTD months (95% CI)
Nilotinib (HMRN)	[redacted]	[redacted]	[redacted]
Bosutinib (HMRN)	[redacted]	[redacted]	[redacted]
Asciminib unadjusted (ASCEMBL)	154	[redacted]	[redacted]
Bosutinib unadjusted (ASCEMBL)	74	[redacted]	[redacted]
Asciminib adjusted, base case (ASCEMBL)	[redacted]	[redacted]	[redacted]
Bosutinib adjusted, base case (ASCEMBL)	[redacted]	[redacted]	[redacted]
Asciminib adjusted, sensitivity analysis (ASCEMBL)	[redacted]	[redacted]	[redacted]
Bosutinib adjusted, sensitivity analysis (ASCEMBL)	[redacted]	[redacted]	[redacted]

Base case = matching to BOS arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the bosutinib and dasatinib groups in HMRN.
Abbreviations: CI, confidence interval; HMRN, haematological malignancy research network; KM, Kaplan-Meier [redacted]; TTD, time to discontinuation

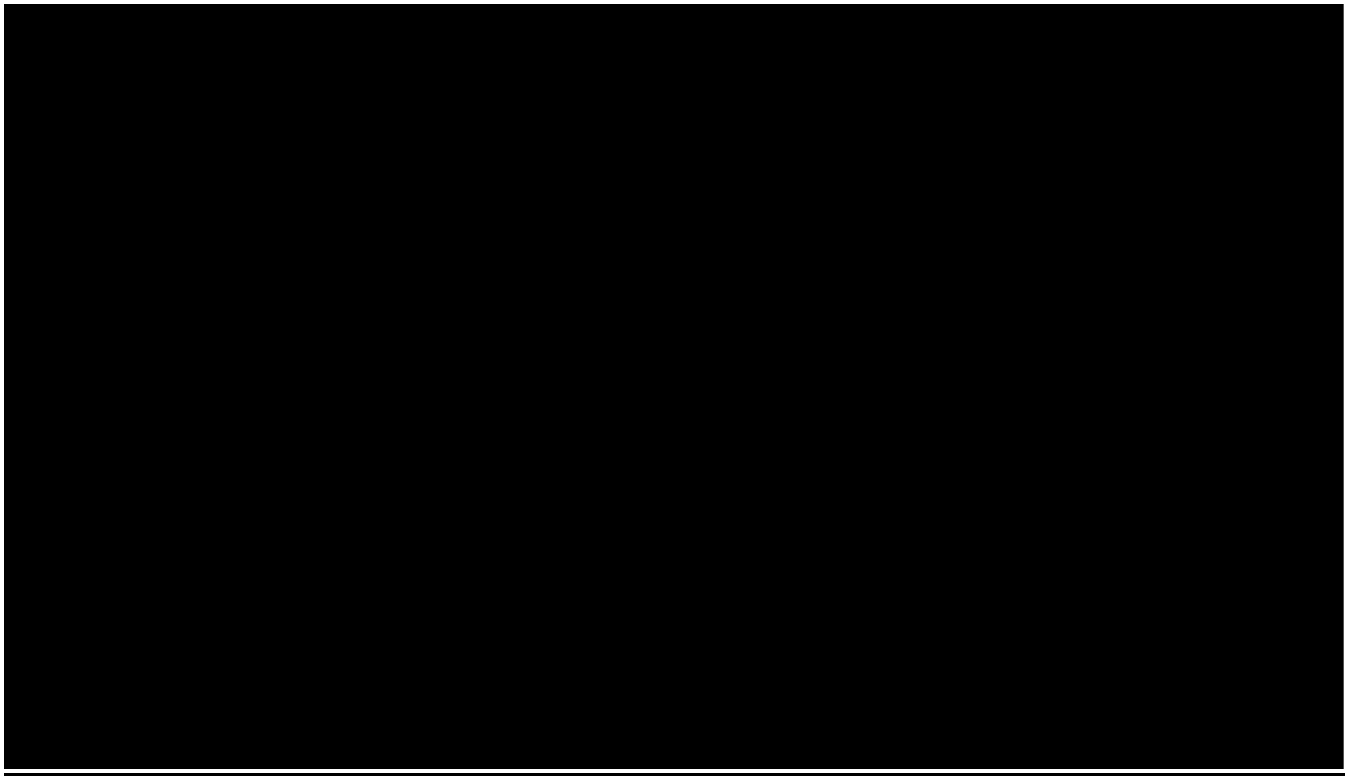
The KM curves for each treatment from both the unadjusted and weighted patient data are presented in Figure 29 (base case) and Figure 30 (sensitivity analysis).

Figure 29: Time to treatment discontinuation for unadjusted and population-matched asciminib (ASCEMBL) vs nilotinib (HMRN) and common comparator arm (bosutinib) – base case



Abbreviations: adj, adjusted; ASC, asciminib; BOS, bosutinib; NIL, nilotinib; unadj, unadjusted.

Figure 30: Time to treatment discontinuation for unadjusted and population-matched asciminib (ASCEMBL) vs nilotinib (HMRN) and common comparator arm (bosutinib) – sensitivity analysis



Abbreviations: adj, adjusted; ASC, asciminib; BOS, bosutinib; NIL, nilotinib; unadj, unadjusted.

The HR estimates for asciminib vs bosutinib were [redacted] of asciminib in both the unweighted and weighted analyses, with patients experiencing a [redacted] of discontinuation compared with bosutinib (95% CI for the HR [redacted], Table 33). The only exception was where the ESS was severely reduced from the original sample size (228 vs 53.6), thus resulting in greater uncertainty in the estimate (wider 95% CI). In the comparison of asciminib vs nilotinib for both unadjusted and weighted analyses, the results were also [redacted] of asciminib. For the sensitivity analysis where the ESS is reduced to [redacted], the risk of

discontinuation for asciminib compared with nilotinib is [redacted] however this estimate is not considered to be reliable, given the small ESS. In addition, there is obvious violation of proportional hazards assumption in the comparison between nilotinib and bosutinib (KM curves in HMRN dataset cross, Figure 29). This may be another consequence of the small sample sizes in both groups. Royston and Parmar 2014 noted that even when non-proportional hazards are present, the HR obtained is some type of average over event times (25). As such, a HR resulting from a study where non-proportional hazards have been detected still represents a form of average treatment effect over the study period. Hence the HRs for asciminib remain informative regarding the [redacted] for asciminib compared with nilotinib within the observed follow-up.

Table 36: HR summary for TTD – Asciminib (ASCEMBL) vs nilotinib (HMRN)

Treatment comparison	Model	N/ESS for ASCEMBL	HR for TTD (95% CI)
Direct comparisons			
Asciminib vs bosutinib	Unweighted comparison from ASCEMBL	228	[redacted]
Asciminib vs bosutinib	Weighted HR matching, base case	[redacted]	[redacted]
Asciminib vs bosutinib	Weighted HR matching, sensitivity analysis	[redacted]	[redacted]
Nilotinib vs bosutinib	Unweighted comparison from HMRN dataset	[redacted]	[redacted]
Indirect comparisons			
Asciminib vs nilotinib	Unweighted comparison	[redacted]	[redacted]
Asciminib vs nilotinib	Weighted HR matching, base case	[redacted]	[redacted]
Asciminib vs nilotinib	Weighted HR matching, sensitivity analysis	[redacted]	[redacted]

Scenario 1 = matching to bosutinib arm from HMRN; Scenario 2 = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the bosutinib and dasatinib groups in HMRN.
[†]Findings that are significantly in favour of asciminib.
Base case = matching to BOS arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the BOS and DAS groups in HMRN
Abbreviations: CI, confidence interval; ESS, effective sample size; HMRN, haematological malignancy research network; HR, hazard ratio; TTD, time to discontinuation.

MAIC results for MMR by 6 months, ASCEMBL vs HMRN

To compare MMR by 6 months between asciminib and comparators, odds ratios (ORs) were first calculated for each treatment pair (asciminib vs bosutinib and either nilotinib or dasatinib vs bosutinib) by study and then compared using the log OR and associated variance, before converting back to the natural scale to report the OR for asciminib vs comparator. The characteristics of the patient populations providing data on MMR in HMRN were identical to those providing data on TTD. Consequently, analysis of MMR is presented following application of the same weights as those applied in the analysis of TTD. Again, a base case analysis is presented with a match to the bosutinib treatment group in HMRN. Sensitivity analysis is presented in which the treatment group (either bosutinib or the relevant comparator TKI) is selected according to baseline characteristics considered least favourable for achieving MMR (older age, male sex and resistance to previous TKI).

Asciminib versus dasatinib, MMR by 6 months

When indirectly comparing asciminib with dasatinib in the MAIC, the baseline characteristics pre- and post-matching are as previously described in Table 31, and the individual patient weights for patients enrolled in ASCEMBL remain as shown in Figure 26.

The OR estimates for MMR are summarised in Table 37. For the comparison of asciminib vs bosutinib directly from ASCEMBL data only (the first comparison made in the anchored MAIC process), the data were [redacted] in both unadjusted and weighted analysis when matched in the base case, with patients experiencing [redacted] of experiencing MMR by 6 months as compared with bosutinib (95% CI for the OR [redacted], Table 37). However, it is noticeable that the OR [redacted] when the weighting is applied, due to an [redacted] in the proportion of patients experiencing an event in the bosutinib arm combined with a [redacted] in the number of events for the asciminib arm.

When asciminib and dasatinib were indirectly compared in both unadjusted and population-adjusted comparisons, there was [redacted] between the odds of experiencing MMR by 6 months (the 95% CI [redacted], the point at which the [redacted]). The confidence interval was particularly wide in the unadjusted comparison, most likely due to the low number of patients from the HMRN dataset. As with the TTD scenarios, for the comparison between asciminib and dasatinib, the matching scenarios include an identical set of baseline characteristics, and therefore the OR results are also identical between the base case and sensitivity analysis.

Table 37: OR summary for MMR by 6 months – Asciminib (ASCEMBL) vs dasatinib (HMRN)

Treatment comparison	Model	N/ESS for ASCEMBL	OR for MMR by 6 months (95% CI)
Direct comparisons			
Asciminib	Unweighted comparison from ASCEMBL dataset	154	[redacted]
Bosutinib		74	
Asciminib	Weighted OR matching, ASCEMBL, base case and sensitivity analysis‡	[redacted]	[redacted]
Bosutinib			
Dasatinib	Unweighted comparison from HMRN dataset	[redacted]	[redacted]
Bosutinib		[redacted]	
Indirect comparisons			
Asciminib	Unweighted Bucher comparison	228	[redacted]
Dasatinib			
Asciminib	Weighted HR matching, base case and sensitivity analysis‡	[redacted]	[redacted]
Dasatinib			

Base case = matching to bosutinib arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the bosutinib and dasatinib groups in HMRN.
†Findings that are significantly in favour of asciminib; ‡ASCEMBL was matched to identical values for patient characteristics in the two scenario analyses when comparing with dasatinib, and hence the results are the same.
Abbreviations: CI, confidence interval; ESS, effective sample size; HMRN, haematological malignancy research network; HR, hazards ratio; MMR, major molecular response; OR, odds ratio; TKI tyrosine kinase inhibitor.

Asciminib versus nilotinib, MMR by 6 months

When indirectly comparing asciminib with nilotinib for the comparison of MMR by 6 months, the baseline characteristics pre- and post-matching are as presented in Table 34, and the individual patient weights applied to patients enrolled in ASCEMBL are shown in Figure 28.

The OR estimates for MMR in the comparison of asciminib vs bosutinib using the ASCEMBL patient data only [redacted] of asciminib in both unadjusted and weighted analysis when matched in the base case, with patients experiencing [redacted] of MMR by 6 months as compared with bosutinib (95% CI for the OR [redacted], Table 38).

When asciminib and nilotinib were indirectly compared in both unadjusted and population-adjusted comparisons, there [redacted] between the odds of experiencing MMR by 6 months (the 95% [redacted] the point at which the [redacted]) and confidence intervals were very wide for all asciminib vs nilotinib comparisons. The point estimate is in favour of [redacted] with asciminib compared with nilotinib.

Table 38: OR summary for MMR by 6 months – Asciminib (ASCEMBL) vs nilotinib (HMRN)

Treatment comparison	Model	N/ESS for ASCEMBL	OR for MMR by 6 months (95% CI)
Direct comparisons			
Asciminib	Unweighted comparison from ASCEMBL dataset	154	[redacted]
Bosutinib		74	
Asciminib	Weighted OR matching, ASCEMBL, base case	[redacted]	[redacted]
Bosutinib			
Asciminib	Weighted OR matching, ASCEMBL, sensitivity analysis	[redacted]	[redacted]
Bosutinib			
Nilotinib	Unweighted comparison from HMRN dataset	[redacted]	[redacted]
Bosutinib		[redacted]	
Indirect comparisons			
Asciminib	Unweighted Bucher comparison	228	[redacted]
Nilotinib			
Asciminib	Weighted HR matching, base case	[redacted]	[redacted]
Nilotinib			
Asciminib	Weighted HR matching, sensitivity analysis	[redacted]	[redacted]
Nilotinib			

Base case = matching to bosutinib arm from HMRN; sensitivity analysis = matching to the oldest age, greatest proportion male and greatest proportion resistant to TKI amongst the bosutinib and dasatinib groups in HMRN

[†]Findings that are significantly in favour of asciminib.

Abbreviations: CI, confidence interval; ESS, effective sample size; HMRN, haematological malignancy research network; HR, hazards ratio; MMR, major molecular response; OR, odds ratio; TKI tyrosine kinase inhibitor.

Conclusion

The company has undertaken a MAIC of asciminib compared with HMRN data for dasatinib and nilotinib, following a request from the ERG. The availability of data on MMR and TTD for patients recei102ving bosutinib, dasatinib and nilotinib at third line in HMRN allowed a comparison with asciminib anchored on the common bosutinib treatment. The findings of the MAIC for TTD and MMR by 6 months were [redacted] with the findings of the unanchored MAIC included as part of the original submission, which used the clinical trial comparator data identified in the SLR. The current analyses demonstrated that [redacted] TTD compared with dasatinib/nilotinib. With regard to MMR by 6 months, whilst unadjusted comparisons showed a [redacted] MMR for asciminib compared with dasatinib and nilotinib, differences were [redacted] after adjustment. Inevitably, matching reduced the statistical power to detect a difference between asciminib and nilotinib or dasatinib. A comparison with ponatinib was not possible due to the very low number of ponatinib patients reported ([redacted] at third-line with reported baseline characteristics; [redacted] at fourth-line but no reported baseline characteristics).

The anchored MAIC with HMRN is subject to a number of limitations, not least that assignment to treatment in HMRN is not random, and the number of patients at third line was small. In addition, follow-up times differed between the studies, with median TTD for bosutinib in HRMN being similar to maximum follow-up from ASCEMBL. For these reasons the company chose to base the comparison of effectiveness of asciminib with nilotinib, dasatinib and ponatinib on the best available clinical study for each comparator.

Despite these limitations, the additional analysis supports the results from the comparison with clinical studies, with the benefit that the HMRN dataset provided KM curves for TTD from which pseudo-IPD could be recreated. The analyses reported that asciminib demonstrates [redacted] compared to both dasatinib and nilotinib.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm on 14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating chronic myeloid leukaemia after two or more tyrosine kinase inhibitors and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Mhairi Copland
2. Name of organisation	Royal College of Pathologists/BSH/Royal College of Physicians
3. Job title or position	Professor of Haematology and Honorary Consultant, University of Glasgow
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic myeloid leukaemia? ☐ A specialist in the clinical evidence base for chronic myeloid leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No discosures.

8. What is the main aim of treatment for chronic myeloid leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in chronic myeloid leukaemia after two or more tyrosine kinase inhibitors?	
11. How is chronic myeloid leukaemia after two or more tyrosine kinase inhibitors currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s), dasatinib, nilotinib, bosutinib and ponatinib since the publication of NICE technology appraisal guidance [TA425, TA401 and TA451]?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	

Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 2: Concerns with the ASCEMBL trial	The ERG have expressed concerns about the bias and quality of the ASCEMBL clinical trial, and identified a number of issues with design/baseline variables. Study drug allocation was done centrally, so I think there is a low risk of bias. However, there do look to be modest imbalances in some of the baseline variables in the ASCEMBL data. For example, there were more women in the asciminib arm, and on a sub-analysis, women appeared to have a superior response to asciminib. There were also fewer patients in CCyR in the bosutinib arm at study entry which may have favoured asciminib. A higher proportion of patients on the bosutinib arm entered the trial after 3 or more lines of therapy. However, not of these baseline variables were statistically significant. Patients were well matched for age and ECOG performance status. In my opinion, the time since diagnosis of CML was similar between the two arms.

	The study was not blinded. This would be extremely challenging as asciminib is taken twice daily fasting, and bosutinib once daily with food, so I don't believe this would be feasible. There is the potential for biased decision making with regards to time to discontinuation (TTD). Crossover for specific criteria from bosutinib to asciminib, but not vice versa was allowed within the trial. In addition, both patients and physicians, if allocated asciminib, as it is a new drug, may have been biased to continue with this for longer. However, I think the risk of this is small, as the criteria for cross-over were very strict, and only in the latter part of the trial. Overall, I think there were small imbalances within the baseline characteristics of the patients recruited to the trial, there was a low risk of bias in the randomisation process, and there is a small risk of physician/patient -introduced bias in the TTD.
Key issue 3: Lack of evidence on survival outcomes	The reported ASCEMBL data is still very immature (48 weeks). Due the nature of CML and the good responses with reduction in progression to advanced phase disease with TKIs (even in patients not achieving optimal responses), the lack of a difference in survival at 48 weeks is not surprising. Indeed, in the comparative studies done to date, e.g. DASISION (dasatinib versus imatinib), ENESTnd (nilotinib versus imatinib) and BFORE (bosutinib versus imatinib), while faster and deeper molecular and cytogenetic responses were seen with the second generation TKIs compared to imatinib, there wasn't a significant difference in PFS or OS. ASCEMBL is quite novel in that it is a randomised study in the third line setting, and such a trial hasn't been performed for the other TKIs, so this data isn't available. Therefore, while survival data is always important to have, I don't think survival outcomes are appropriate when considering the differences in effectiveness between the TKIs.
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	The company do not provide evidence that TTD is a marker of long-term survival. However, given the nature of CML when treated with TKIs, as discussed in relation to issue 3 above, survival is no longer an appropriate endpoint when considering different TKIs. TTD takes into account stopping treatment for both lack of efficacy and poor tolerability. In the third and subsequent line of therapy setting, these patients

	have very limited other therapeutic options. Whilst not ideal, on reflection, I think that TTD is probably a reasonable and pragmatic measure of efficacy, and may be considered a surrogate for survival.
Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	The MAIC data have been used as there are no other clinical trials comparing different second and third generation TKIs in this setting. In addition, when single arm studies have been done in a similar setting, second and subsequent lines of therapy), the inclusion criteria may have been different as may the primary and secondary endpoints, making comparisons difficult. In addition, the second line studies with e.g. nilotinib and dasatinib were performed 15 years ago when cytogenetics was the most common method for monitoring response, whereas now we are much more focussed on deeper molecular responses – MMR and better. While the model is imperfect, given how the treatment of CML has evolved with the introduction of individual drugs over a number of years, with no head-to-head comparison in later lines of therapy until ASCEMBL, I think it is a reasonable alternative.
Key issue 6: The model structure is subject to considerable uncertainty	I am not an expert in modelling, so. My comments are limited. The company's model is based on TTD, rather than response (e.g. CCyR) or survival. A response-based model was used for the technology appraisal for ponatinib (TA451). With regards to using TTD as the model parameter in the cumulative survival model. TTD is probably a good surrogate here. Patients have limited additional treatment options, so while not having a good response (e.g. not in CCyR), the treatment may be maintaining them in haematological response, and stopping them from progressing to a more advanced phase of disease, so the patients are deriving benefit from the drug. With regards to response as an endpoint (e.g.CCyR or MMR) in the surrogate survival model, patients do lose responses, and may or may not switch treatment at that point, as there isn't an alternative more appropriate therapy. This may not be picked up with this model if a patient obtains a response and then loses it. I think both models have some advantages and some limitations. These are already acknowledged by the ERG from previous technology appraisals for TKIs in CML.

Key issue 7: Removal of retreatment	A small proportion of patients will be re-treated with a TKI they have received previously. Whilst this is uncommon, it can happen with intolerance, where the least intolerant drug is used. In addition, it may be that a patient has a suboptimal response to a second/third generation TKI and is switched to try and obtain a deeper level of response, but is then intolerant to the next line of therapy, and as a compromise, returns to the prior line of therapy. I think re-treatment needs to remain an option in later lines of therapy.
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	I am not an expert in modelling, and cannot comment on this specific point. I note from Table 21 that there is little difference in the projected survival outcomes whether or not log-normal or log-logistic is used.
Key issue 9: Duration of post-discontinuation survival	The post discontinuation survival is subject to substantial uncertainty. The company has assumed 7 years to align with previous appraisals. This seems a very modest figure. Whilst median OS of 14-19 years, as suggested by the ERG on the extrapolated ponatinib data from PACE seems very optimistic, because CML treatment is moving so quickly, we simply don't have this data.
Key issue 10: Use of Neiderwieser 2021 for stem-cell transplant survival	The paper from Niederweiser et al, incorporates patients with accelerated and blast phase CML from 1990-2018; so pre- and post TKI introduction, and doesn't include chronic phase. There is a recent Swedish Registry study of 118 chronic phase CML patients who underwent alloSCT from 2002-2017 by Lubking et al which focuses on chronic phase and is in the TKI era (Lubking et al, Bone Marrow Transplantation 2019;54:1764-74.
Key issue 11: Age-adjusted utilities	I'm sorry I can't comment on this point.
Key issue 12: Comparator dosing	Comparator dosing is unlikely to be 100% of starting dose for each drug. For example, with ponatinib on achievement of CCyR or MMR, the dose is reduced and maintained at 15mg daily.

	For nilotinib, dasatinib and bosutinib, a significant minority of patients will not be on full dose. The majority of available data will also be in the first line setting, and not for later lines of therapy. Dependent on tablet pricing, this may or may not reduce the comparator cost. There may also be wastage of tablets if patients need to change the dose due to side effects. There are a number of recent/ongoing trials of dose adaptation/modification which may provide information about comparator dosing (reviewed in Copland, *Current Hematologic Malignancy Reports* 2019;14:337-345; table 2.
Are there any important issues that have been missed in ERG report?	I didn't see additional issues to address.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Asciminib has demonstrated superiority in a phase 3 clinical trial versus bosutinib in the third line setting for treatment of CP-CML.

Asciminib has a favourable safety profile compared with other available second and third generation TKIs.

The management and molecular monitoring of patients on asciminib is the same as for existing, approved TKIs.

Asciminib would offer a new and well-tolerated treatment approach for many patients failing existing TKIs or who were unsuitable for existing TKIs due to co-morbidities.

The ASCEMBL trial is a comparative study of asciminib versus bosutinib. Similar comparative studies were not available for the other TKIs in the second or subsequent lines of therapy. This gives confidence to the results seen with asciminib in comparison to other TKIs.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Clinical expert statement and technical engagement response form

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

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Deadline for comments by **5pm on 14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating chronic myeloid leukaemia after two or more tyrosine kinase inhibitors and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dragana Milojkovic
2. Name of organisation	NCRI study group Chair for CML/RCPath
3. Job title or position	Professor of Practice, Consultant Haematologist , Imperial College NHS Trust
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic myeloid leukaemia? ☒ A specialist in the clinical evidence base for chronic myeloid leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

8. What is the main aim of treatment for chronic myeloid leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Part 1 (Q8- 24) has previously been completed and submitted with Professor Mhairi Copland. In the recent meeting with NICE , it was agreed that the Part 1 section did not need to be completed again.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in chronic myeloid leukaemia after two or more tyrosine kinase inhibitors?	
11. How is chronic myeloid leukaemia after two or more tyrosine kinase inhibitors currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s), dasatinib, nilotinib, bosutinib and ponatinib since the publication of NICE technology appraisal guidance [TA425, TA401 and TA451]?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	

Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 2: Concerns with the ASCEMBL trial	No concerns. A comment that the number of intolerant patients compared with resistant patients on TKI, the number of prior lines of treatment, and the number of BCR-ABL1 kinase mutations, were slightly balanced in favour of the asciminib arm. No previous TKI study has ever been blinded.
Key issue 3: Lack of evidence on survival outcomes	The follow up is not prolonged, however from all previous TKI studies we are aware that achievement of CCYR is a surrogate marker of survival, and after achieving this milestone , responses are fairly durable.
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	Reasonable, as while patients remain on treatment, this implies that they are responding and tolerating treatment. Treatment discontinuation is as a result of treatment failure, and at this point patients are facing very limited options, and likely an allogeneic stem-cell transplant, which has its own economic considerations, leaving aside the toxicity and morbidity of an allogeneic transplant procedure. I agree that CCyR and MMR are more traditional intermediate end-points.

Clinical expert statement

Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	Comments noted. 'Limited or incomplete reporting of outcomes (only MMR, CCyR and TTD)'- many TKI studies are focused on CCyR as a surrogate marker of survival (and indeed in the NCCN guidelines this is the goal of therapy), and MMR to reflect Event-free survival. A cumulative survival model seems acceptable.
Key issue 6: The model structure is subject to considerable uncertainty	No additional comment
Key issue 7: Removal of retreatment	'The company's approach to modelling subsequent treatments uses the same basket of treatments regardless of the primary treatment received. This implicitly allows retreatment with the primary treatment. This is inconsistent with clinical practice.' In real-world practice, patients can be re-treated with their previous treatment in the intolerant setting- frequently patients experience even worse side-effects after switching TKI and can revert back to their previous treatment. Therefore, this is consistent with clinical practice.
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	No additional comment

Key issue 9: Duration of post-discontinuation survival	7 years seems reasonable for a resistant patient, but I note the ERG concerns that this is a conservative estimate after the analysis of the PACE clinical trial. The long-term outcome of patients on ponatinib, particularly in an ageing population is of concern, particularly due to a high rate of vascular occlusive events on ponatinib. 'The HMRN data reports that 58.8% of fourth-line patients are alive at 5 years.' If this includes patients who are intolerant , then the survival will be higher, as they have a biologically different disease- in all studies the outcome of intolerant patients is higher, as they encounter a TKI that they able to take on a daily basis.
Key issue 10: Use of Neiderwieser 2021 for stem-cell transplant survival	References found on page 97 of the ERG document. Neiderwieser *Bone Marrow Transplantation* **volume 56**, pages2834–2841 (2021) Blast crisis patients ; (n = 96) or accelerated phase (n = 51) transplanted between 1990 and 2018. ≥CP2 (n = 70), in AP (n = 40) or in BC (n = 37). ALL OF THESE PATIENTS WERE IN ADVANCED PHASE TO BEGIN WITH – THE CHRONIC PHASE HERE (CP2) IS A RETURN TO CHRONIC PHASE AFTER TREATMENT. THIS IS NOT THE SAME AS DE NOVO CHRONIC PHASE AND CANNOT BE USED AS A COMPARISON. SO THERE WILL BE LITTLE DIFFERENCE BETWEEN CP2 AND AP AS THEY ARE BOTH PROGRESSIONS, BUT CP2 HAS A LOWER BLAST COUNT PRE TRANSPLANT. ALL REFERENCES FOR RETURN TO CHRONIC PHASE AFTER ADVANCED PHASE TREATMENT SHOULD BE 'CP2' TO AVOID CONFUSION. The Jabbour reference cited does not mention transplant, only predictive factors for response (67). Jabbour E, Kantarjian H, O'Brien S, Shan J, Garcia-Manero G, Wierda W, et al. Predictive factors for outcome and response in patients treated with second-generation tyrosine kinase inhibitors for chronic myeloid leukemia in chronic phase after imatinib failure. Blood 2011;117:1822-7. 10.1182/blood-2010-07-293977. However, it is generally accepted that transplant in CP1 , has a better outcome then transplant in AP and blast crisis remains very challenging, with the worst outcome and prognosis.
Key issue 11: Age-adjusted utilities	Comment on this point in the ERG document is missing . In any case, there are a number of side-effects of TKI therapy that are more pronounced with age: pleural and pericardial effusions and arterial occlusive

	evets. Asciminib appears to be reasonably well tolerated in patients with underlying cardio-pulmonary co-morbidities.
Key issue 12: Comparator dosing	The doses of nilotinib and dasatinib are likely to be approaching 100%. Ponatinib is not easily tolerated , and due to the high arterio-occlusive events, the recommendation is to try to reduce the dose as soon as a durable response is achieved. However, even on low doses of ponatinib, MI and CVA can occur. The OPTIC study is the more informative on step-wise dose reduction, but it has to be emphasised that the age of patients in the OPTIC study was much lower than in PACE and patients with CV morbidity were more excluded, which does not reflect the real -world patient population accurately.
Are there any important issues that have been missed in ERG report?	Comment on the ERG report: 'Ponatinib is currently the only NICE recommended TKI for patients with a T315I mutation, and the relative effectiveness of ponatinib and asciminib in these patients is uncertain.' THE EFFICACY OF PONATINIB WITH THE T315I MUTATION IS ROBUST, FOLLOWNG DATA FROM THE PACE AND OPTIC STUDIES. Further, evidence on survival outcomes of CML patients receiving SCT would be informative. The ERG is, however, unaware of any such evidence. 'the results suggests that patients may stay on ponatinib for longer than asciminib' – PONATINIB CAN BE GIVEN SECOND LINE IN CASE OF A T315I MUTATION. SECOND LINE THERAPY IS ALWAYS MORE EFFECTIVE THAN THRID LINE THERAPY (ON AVERAGE 50% CCYR IN COMPARISON TO 10-30% FOR THIRD LINE)

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Asciminib is of clinical benefit to patients who have failed two prior TKIs and the results validate the targeting of the myristoyl site.
- Asciminib has a favourable tolerability profile.
- By targeting the myristoyl binding pocket, there is no 'off BCR-ABL target' signalling, and other pathways traditionally implicated in side-effects of TKI therapy, such as inhibition of c-kit and pdgfr does not occur.
- Asciminib does not appear to have a cardio-vascular toxicity signal (MI/CVA/ PAOD), unlike other TKIs
- Patients who fail 2 lines of previous TKI therapy present a significant therapeutic challenge and are often facing an allogeneic stem cell transplant as the next therapeutic approach. This necessitates a well tolerated and effective third line treatment, and asciminib is desirable to meet these expectations.

Thank you for your time.

Your privacy

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Patient expert statement

Leukaemia (chronic myeloid) - asciminib (after 2 tyrosine kinase inhibitors) [ID3813]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Gerard Graham Dickinson**
2. Are you (please tick all that apply):	**X**☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Chronic Myeloid Leukaemia Support Group
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ **X** I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **x** other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **X** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was first diagnosed in April 2013 at the age of 58 having been fit and healthy in adult life and with a new born son recently arrived. Indeed, I initially put the symptoms of excessive fatigue and poor sleep down to the arrival of our son and the inevitable sleepless nights that followed. Wrongly as it transpired. This son, Alex, was the first of 3 children that I had in my later marriage. I had been married previously in early adulthood and have 3 children from that relationship, all now in their 30's and indeed one who has 2 children making me a grandfather as well as father of 3 young children, current ages, 9, 7 and 5. We are a close family. At the time of my diagnosis, I was the Managing Partner of the London office of a major law firm, having founded the London Office in 2008. By 2013, I managed 150 people in London and following my return to

	work after an initial absence of 5 months in 2013, that number had grown to 250 as the result of a merger with another law firm that I managed to fruition. While regularly attending on my treating medical team at the Hammersmith Hospital and receiving treatment in the form of Imatinib, I managed to return to full-time work although I did reduce some of my managerial responsibilities. During the initial years following diagnosis in 2013, as mentioned, my wife and I had 2 further children, in 2014 and 2017. For the first 2 years, my treatment with Imatinib progressed well and I had little by way of symptomology or adverse effects. However, by late 2015, blood tests showed that the impact of the drug was waning , compounded by the discovery of theT315I mutation in the BCR::ABL1 gene that I also had. I underwent tests for a possible bone marrow transplant and one of my brothers is apparently a close match should such a transplant be the solution. Before proceeding to that stage however, I agreed with my consultant to try other potential drug therapies and, after a couple of other trials , eventually found that Ponatinib appeared to work well and tests demonstrated that, even with my T315I mutation, results were good and with minimal side effects. I was able to continue my domestic and work life well. By late 2017 that situation changed for the worse again. I again started to be very unwell and testing showed that the Ponatinib was no longer assisting.

	At this point, with no other drug therapy available, my consultant discussed with me the inevitability of moving to the bone marrow transplant option. In considering this option, she explained the treatment in detail, the necessary pre- transplant treatment, immediate post-operative potential outcomes and risk factors and then, if successful, likely long term implications. As she has since advised me, the worst outcome of transplant is that there is a risk of dying as a result, the risk being of the order of 25-30% for a person in their 60s. These discussions highlighted that, if I survived, in reality I would be unable to continue to work at anything like my then level as a senior lawyer acting for a wide range of key clients of the business; I would be unable to manage operational functions of a multi-office UK firm and indeed, international firm and would inevitably have serious restrictions on my domestic life, especially around my very young children. In short, the reality to be faced was an end to my career, to my role leading a major international business and with severe impact on my domestic life with my wife and young family. Not an attractive prospect. Recognising these varied impacts, my consultant did flag to me a new, very early stage, drug trial that was available in a limited number of locations around the world but not in the UK. She explained that this new, unnamed drug manufactured by Novartis, was specifically designed for patients with my particular T315I abnormality. I asked if she could make enquiries and let me know if any options were available. 24 hours later, she called to explain that the nearest trial centre was located in a specialist CML unit at Hopital St Louis in Paris. She knew the doctor conducting the trial who agreed that if I could attend for tests and assessment, then they would consider accepting me on to the trial programme.

	My own consultant, Professor Jane Apperley, explained that , if accepted, this would require very regular attendance in Paris involving both expense, some claimable, but in particular a heavy time commitment. I was in the fortunate position of having reasonably good French language skills and , perhaps most importantly , fellow Partners in my Law firm who were prepared to allow me to have the 2 days a week time off to enable my attendance. In short, I was in a lucky position and one not readily available to other patients in the UK who might not be able to take such advantage. I duly attended for tests in Paris and was deemed to be a suitable candidate for admission to the trial and, once approved by Novartis, became one of approximately 250 participants. This programme began in October 2017. For the first 6 months I attended weekly in Paris, 2 days off work each time. This then moved to monthly for another year and finally every 3 months. I was prescribed a high dose of what we now know to be Asciminib, 320mg per day. The improvement in my condition was immediate. Having been unwell in the preceding 3 months with symptoms of gross fatigue, sweats and general weakness, I soon felt much stronger, energised and sleeping well.

	Initial symptoms by way of side effects, that have continued to the present day, were dry and itchy skin and loss of body hair. Any exposure to sun would result in skin sensitivity but nothing more than requiring good sun cream care and general moisturising for my skin, and continuing to date. My regular trips and assessments were very positive and indeed, I made friends with other similar patients on the trial. All reported the same positive reaction to Asciminib with good improvement in their condition. I maintained a daily activity log/ dietary chart throughout the trial. In addition I would occasionally report back to Prof Apperley, though she was updated from Paris direct. The really hard part was the travel and it was frustrating that there was no opportunity to be trialling this drug in the UK. Moreover, I very much felt that I was in something of a "selfish" position. How come I could benefit so much from this drug trial when many others back home couldn't; just because I had a good job with very understanding colleagues and the financial ability to manage the expense of weekly trips to Paris. Unfortunately, the arrival of Covid-19 in March 2020 changed everything. I was not allowed to travel by the French authorities and hence my participation in the trial had to stop. Fortunately, both my doctor running the Paris trial and Professor Apperley, were able to persuade Novartis, that, while I would no longer be part of the trial, I should continue to receive Asciminb. Novartis kindly agreed that I should do so and I continue to receive the drug on "compassionate use " terms. It is frustrating , indeed disconcerting, to see that phrase on the label of every box of tablets ! It is now effectively 5 years since I began my treatment with Asciminib. More than twice the time during which I was prescribed a variety of then established drugs, none of which worked for longer than 2 years. My condition is stable; all of my blood results are good and there no signs of any relapse or deterioration.

	For the last 5 years, my wife and young children have had the benefit of a pretty normal life with their father, much more so than in the early years after diagnosis in 2013. Equally importantly, I have continued to work full time and positively in my law firm, although no longer as Managing Partner. Despite my age, I have no plans to retire any time soon and as and when that decision comes around, I will be much happier doing so in a controlled manner benefitting both my family commitments and all of my staff in the business. In short, but for the good fortune that I had in having this trial available in 2017, the good fortune of being in a position where I could actively commit to and participate in it, I would have had to give up work, undergo a bone marrow transplant and take my chances of the outcome both in my personal, family and work life. As I would regularly say while in Paris to the medical team there, if only other UK residents with my condition could have the benefit of such treatment with Asciminib.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The care and treatment that I have received in the NHS has been outstanding but as commented above, none of the drug therapies available have lasted for longer than 2 years in my case , compounded as it is with the T cell mutation. Having continued to receive Asciminb post covid for the last 2 years on a compassionate basis, combined with the excellent care from my treating team at the Hammersmith, I have benefitted greatly in being able to lead a normal life both domestically and at work and without financial burden on society or other NHS services.

10. Is there an unmet need for patients with this condition?	Absolutely. This condition can be treated without the need for expensive, high risk, invasive surgery and without prejudicing the capacity for normal life and work. On a personal basis, I have continued to work , very successfully, employing several hundred colleagues in comparison with the draconian alternative of transplant surgery with all of the accompanying risk factors and inevitable cessation of work and major disruption to family life.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	I take my meds twice a day, with no disruption to my daily lifestyle/ diet. I blood test regularly but other than that, am able to get on with my life with little in the way of side effects/ symptomology. Family and colleagues don't even notice that I am undergoing trial treatment as it works and works simply and well. Other than my quarterly blood tests and check with my consultant, I need no other medical scrutiny, not even at GP level.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	None.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so,	Anyone could benefit from this drug treatment. Easy to use, minimal inconvenience and with hardly any side effects.

please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Perhaps the rhetorical question that I regularly asked the team in Paris comes to mind…. If only other UK residents could benefit from Asciminib.
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope	

(particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?”] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- A simple, effective drug still working well 5 years later
- Enables a full and normal life/ work
- Asciminib v transplant/ invasive surgery….so much better for patient outcomes and relieving pressures on the NHS
- easily monitored with minimal impact on health care professionals

• why should I be the one to benefit simply because I had the means and resources to participate in this drug trial overseas. I am so grateful that I could do so.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm on 14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 2: Concerns with the ASCEMBL trial	No	It is extremely difficult to blind patients to which treatment they are on when treatments require different fasting mechanisms. Whether or not the difference in populations have led to bias in the results should be determined by subgroup analyses for statistically significant difference and not assumed.
Key issue 3: Lack of evidence on survival outcomes	No	This appraisal should not be disadvantaged by the nature of CML as a chronic illness and the impact of this on ascertaining overall survival. We urge the committee to use an appropriate measure for efficacy in this population.
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	No	See comments above r.e. key issue 3.
Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	No	No comments
Key issue 6: The model structure is subject to considerable uncertainty	No	No comments

Key issue 7: Removal of retreatment	No	No comments
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	No	No comments
Key issue 9: Duration of post-discontinuation survival	No	No comments
Key issue 10: Use of Neiderwieser 2021 for stem-cell transplant survival	No	No comments
Key issue 11: Age-adjusted utilities	No	No comments
Key issue 12: Comparator dosing	No	No comments

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 2: Concerns with the ASCEMBL trial	Yes/No	Our experts have no concerns. A comment that the number of intolerant patients compared with resistant patients on TKI, the number of prior lines of treatment, and the number of BCR-ABL1 kinase mutations, were slightly balanced in favour of the asciminib arm. No previous TKI study has ever been blinded.
Key issue 3: Lack of evidence on survival outcomes	Yes/No	The follow up is not prolonged, however from all previous TKI studies we are aware that achievement of CCYR is a surrogate marker of survival, and after achieving this milestone, responses are durable.
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	Yes/No	Reasonable, as while patients remain on treatment, this implies that they are responding and tolerating treatment. Treatment discontinuation is as a result of treatment failure, and at this point patients are facing very limited options, and likely an allogeneic stem-cell transplant, which has its own economic considerations, leaving aside the toxicity and morbidity of an allogeneic transplant procedure. In general however, it is agreed that CCyR and MMR are more traditional intermediate endpoints.
Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	Yes/No	Comments noted. **'Limited or incomplete reporting of outcomes (only MMR,**

		CCyR and TTD)'- many TKI studies are focused on CCyR as a surrogate marker of survival (and indeed in the NCCN guidelines this is the goal of therapy), and MMR to reflect Event-free survival. A cumulative survival model seems acceptable.
Key issue 6: The model structure is subject to considerable uncertainty	Yes/No	No additional comment
Key issue 7: Removal of retreatment	Yes/No	**'The company's approach to modelling subsequent treatments use the same basket of treatments regardless of the primary treatment received. This implicitly allows retreatment with the primary treatment. Our experts note that this is inconsistent with clinical practice.'** In real-world practice, patients can be re-treated with their previous treatment in the intolerant setting- frequently patients experience even worse side-effects after switching TKI and can revert to their previous treatment. Therefore, this is consistent with clinical practice.
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	Yes/No	No additional comment
Key issue 9: Duration of post-discontinuation survival	Yes/No	Our experts believe that 7 years seems reasonable for a resistant patient but note the ERG concerns that this is a conservative estimate after the analysis of the PACE clinical trial. The long-term outcome of patients on ponatinib, particularly in an ageing population, is of concern, particularly due to a high rate of vascular occlusive events on ponatinib. **'The HMRN data reports that 58.8% of fourth-line patients are alive at 5 years.'** If this

		includes patients who are intolerant, then the survival will be higher, as they have a biologically different disease- in all studies the outcome of intolerant patients is higher, as they encounter a TKI that they able to take daily. The chance of achieving CCyR in a truly resistant patient third line in most studies is 10-30%.
Key issue 10: Use of Neiderwieser 2021 for stem-cell transplant survival	Yes/No	References found on page 97 of the ERG document. Neiderwieser ***Bone Marrow Transplantation*** **volume 56**, pages 2834–2841 (2021) Blast crisis patients; (n = 96) or accelerated phase (n = 51) transplanted between 1990 and 2018. ≥CP2 (n = 70), in AP (n = 40) or in BC (n = 37). Importantly these patients were in advanced phase to begin with – the chronic phase here (CP2) is a return to chronic phase after treatment for blast crisis. This is not the same as *de novo* chronic phase and cannot be used as a comparison for CP1. There will be little difference between CP2 and AP as they are both evaluation after disease progression, but CP2 has a lower blast count pre transplant. All references for return to chronic phase after advanced phase treatment should be 'CP2' to avoid confusion. The Jabbour reference cited does not mention transplant, only predictive factors for response (67). Jabbour E, Kantarjian H, O'Brien S, Shan J, Garcia-Manero G, Wierda W, et al. Predictive factors for outcome and response in patients treated with second-generation tyrosine kinase inhibitors for chronic myeloid leukemia in chronic phase after imatinib failure. Blood 2011;117:1822-7. 10.1182/blood-2010-07-293977. However, it is generally accepted that transplant in CP1 , has a better outcome then transplant in AP. Blast crisis remains very challenging, with the worst outcome and prognosis.
Key issue 11: Age-adjusted utilities	Yes/No	There are a number of side-effects of TKI therapy that are more pronounced with age: pleural and pericardial effusions and arterial occlusive

		evets. Asciminib appears to be reasonably well tolerated in patients with underlying cardio-pulmonary co- morbidities.
Key issue 12: Comparator dosing	Yes/No	The doses of nilotinib and dasatinib are likely to be approaching 100%. Ponatinib is not easily tolerated, and due to the high arterio-occlusive events, the recommendation is to try to reduce the dose as soon as a durable response is achieved. However, even on low doses of ponatinib, MI and CVA can occur. The OPTIC study is the more informative on step-wise dose reduction, but it has to be emphasised that the age of patients in the OPTIC study was much lower than in PACE and patients with CV morbidity were more excluded, which does not reflect the real -world patient population accurately.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: General	General	Yes/No	**Ponatinib is currently the only NICE recommended TKI for patients with a T315I mutation, and the relative effectiveness of ponatinib and asciminib in these patients is uncertain.'** The efficacy of ponatinib with the T315I mutation is robust, following data from the PACE and OPTIC studies**.** **'Further, evidence on survival outcomes of CML patients receiving SCT would be informative. The ERG is, however, unaware of any such evidence.'** There is international data from the German CML study group, and IBMTR. **'The results suggests that patients may stay on ponatinib for longer than asciminib'** – ponatinib can be given second line in case of a T315I mutation. Second line therapy is always more effective than third line therapy (on average 50% CCyr in comparison to 10-30% for third line treatment).
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Single Technology Appraisal (STA)

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors (corrected) [ID3813]

ERG addendum: review of company's response to technical engagement

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

Date 6th May 2022

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Declared competing interests of the authors

None

Rider on responsibility for report

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

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Overview

This addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional evidence provided by the company in their responses to the technical engagement issues which emerged from the ERG report.

The technical engagement covered 11 key issues for consideration (see Table 1). The company's technical engagement response resolved several issues outlined in the ERG's critique, either through the provision of additional evidence or acceptance of the ERG's judgement on aspects of the economic modelling. Specifically, issues 2, 7, 8, 10, 11 and 12 are now considered by the ERG to be resolved. Further, the ERG wishes to highlight that it also considers issue 1 resolved. This issue concerned the evidence supporting the effectiveness and cost-effectiveness of asciminib in the T315L subgroup. This issue was not discussed in the company's technical engagement response. The company have, however, made it clear that reimbursement is not sought for patients with the T315I mutation. Concerns outlined in the ERG's critique regarding the absence of evidence in this population are therefore no longer relevant.

The company's responses to each of the issues are discussed in Section 0. Section 3 presents an overview of the company's revised base-case and the updated ERG base-case.

Table 1 Summary of company's Technical Engagement response

Issue	Resolved
Key issue 2: Concerns with the ASCEMBL trial	Resolved
Key issue 3: Lack of evidence on survival outcomes	Resolved (some uncertainty remaining)
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	Unresolved
Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	Unresolved
Key issue 6: The model structure is subject to considerable uncertainty	Unresolved
Key issue 7: Removal of retreatment	Resolved (some uncertainty remaining)
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	Resolved
Key issue 9: Duration of post-discontinuation survival	Unresolved
Key issue 10: Use of Niederwieser 2021 for stem-cell transplant survival	Resolved (some uncertainty remaining)
Key issue 11: Age-adjusted utilities	Resolved
Key issue 12: Comparator dosing	Resolved

2 Description and critique of additional evidence

2.1 Issue 2: Concerns with the ASCEMBL trial

The ERG thanks the company for performing the requested regression analyses to investigate the possible impact of baseline imbalance in ASCEMBL on trial outcomes. We agree that the analyses presented show that the impact of asciminib on major molecular response (MMR) is robust to baseline imbalances, and so is not likely to be biased. While analyses were only provided for MMR we consider it reasonable to assume that other outcomes are also robust to any baseline imbalances.

The ERG notes that some concerns around the ASCEMBL trial being unblinded remain. In particular, that time to treatment discontinuation (TTD) might potentially be influenced by knowledge of which treatment was received, which could have led to biased results. The ERG agrees that blinding the trial would not have been feasible, but notes that the potential for biased results is a concern in any unblinded trial. The ERG accepts the view expressed elsewhere in the engagement process (by Prof. Copland) that the risk of bias in TTD is likely to be small.

2.2 Issue 3: Lack of evidence on survival outcomes

The ERG notes that we raised this issue in our report to highlight the difficulties in assessing the long-term clinical and economic impact of asciminib in the absence of survival data. As stated in our report, we understand that mature survival data will not be available for ASCEMBL, and the limitations of using survival data in CML. We agree with the limitations described elsewhere in the engagement (e.g. by Prof. Milojkovic) and that Complete cytogenetic response (CCyR) should represent a reasonable surrogate for good survival (Prof. Copland).

The company states that: Overall survival (OS) was [redacted] and [redacted] in the asciminib and bosutinib arms, respectively; and PFS was [redacted] and [redacted] in the asciminib and bosutinib arms, respectively. The ERG notes that there is therefore no evidence to suggest that asciminib might be inferior to bosutinib.

2.3 Issue 4: Use of time to treatment discontinuation to inform the economic analysis

A key area of uncertainty identified by the ERG relates to the model structure adopted in the company's economic analysis and its reliance on TTD as an indicator of clinical effectiveness. The company in support of this approach emphasises providing new indirect evidence on the surrogate value of TTD, citing three publishes studies in non-small cell lung cancer and in renal cell carcinoma. The company also reiterates the advantages of the cumulative survival approach highlighting the simplicity and transparency of the approach.

As previously outlined the ERG acknowledges that the advantages of the cumulative survival approach and the precedent set out in previous technology appraisals. The new evidence provided by the company, however, only partially addresses concerns raised by the ERG and importantly does not provide direct evidence on the surrogate value of TTD in CML population. The ERG does not think that evidence linking TTD to survival in other conditions (small cell lung cancer and renal cell carcinoma) can be safely assumed to apply to CML. The surrogate value of TTD, therefore, remains highly uncertain. Further, the company's response does not address concerns raised regarding the value of TTD as a measure of clinical benefit. While TTD is likely to be indicative of treatment failure and loss of response, it is also likely to be determined by a range of other factors. Consequently, TTD is likely confounded as a measure of clinical benefit, limiting the reliability of using TTD as a clinical endpoint and the reliability of cross-study comparisons.

The ERG position, therefore, remains unchanged and remains in favour of the response-based approach previously adopted in TA451 (ponatinib). The ERG acknowledges that this remains a finely balanced decision, but the two principal advantages of this approach remain: i) That response is an objective and widely accepted measure of clinical benefit in CML, and ii) That evidence supports the surrogate value of response in a CML population. The ERG base case, therefore, continues to use the response-based model, though selected scenarios are also explored using the cumulative survival approach.

We may be able to respond further once additional MAIC analyses have been supplied.

2.4 Issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis

The ERG notes that we will provide a full response to this issue once additional MAIC analyses have been supplied.

The company provided further information on why trials were excluded from Matching-Adjusted Indirect Comparisons (MAIC) analyses. The ERG accepts these explanations, and agrees that small size of the trials, and other issues, would mean they would not be appropriate for use in MAIC analyses. The ERG therefore accepts that the trials used by the company in their MAIC analyses are likely to be the only trials for which a robust MAIC could be performed. We note that this means that the MAICs have only one trial per comparator treatment, and so the robustness of the MAICs to different trials and their varying characteristics cannot be assessed.

The company has not provided any new evidence on some areas of this issue; namely, the limited set of variables adjusted for, and the limited outcome reporting. The ERG's concerns in these areas remain, as set out in our report, unless subsequent MAIC analyses provide new information.

The company provided some further data for MAICs of TTD (Tables 2 and 3 of their technical engagement submission). We note that this makes interpretation of the MAIC analyses clearer, and more clearly demonstrates that TTD with asciminib appears [redacted] to nilotinib and dasatinib, but [redacted] to ponatinib. We reiterate our concerns with using TTD in the MAIC analyses, because of the potential for subjective grounds for discontinuation, and that reasons for discontinuation may not be consistent across trials.

2.5 Issue 7: Removal of retreatment

The ERG's base-case analysis revised the distribution of subsequent treatments to remove the possibility of retreatment with the primary TKI treatment (third-line treatment). This scenario was motivated by data from the Haematological Malignancy Research Network (HRMN) network, which demonstrates that retreatment occurs in [redacted] of patients, and clinical advice that suggested that retreatment with the same TKI is increasingly uncommon in clinical practice. The company response notes comment from the patient group as well cited evidence from the HRMN that retreatment does occur in practice. The company, however, acknowledges that retreatment is likely to be less common than reflected in the company base-case assumptions. The company, therefore, considers that the true proportion of patients retreated in a fourth-line setting and beyond will fall somewhere between the company's estimates and zero.

The ERG considers the position outlined by the company to be an accurate summation of clinical practice. As indicated by responses to TE received from clinical experts and Leukaemia Care, it is clear that some patients are retreated with previously received TKI's. The ERG, however, considers, that on balance the ERG's scenario better reflects current practice given the relative minority of patients retreated and the difficulties with accurately estimating the true proportion of patients retreated. Therefore, while the company is correct in summation that the proportion of patients retreated is likely to fall between the company's estimates and zero, the ERG considers that this figure will be closer to the ERG's modelled assumptions. Note the company base case has been revised to align with ERG's base case.

2.6 Issue 8: Use of log-logistic to extrapolate time to treatment discontinuation

The company's original base-case model used a log-normal distribution to model TTD (bosutinib comparison only). In the ERG critique, it was noted that the log-logistic model provides a similar statistical fit and aligns better with the clinical opinion elicited by the company. In their TE response, the company acknowledges the arguments put forward by the ERG and update their base case to align with the ERG. Both the ERG and the company acknowledge that this issue has minimal impact on the ICER. The ERG considers this issue resolved.

2.7 Issue 9: Duration of post-discontinuation survival

The original company base case utilised a 7-year post-discontinuation mean survival, which was based on survival estimates from Kantarjian *et al.*[1] used in TA401[2] and clinical expert opinion. The ERG highlighted substantive concerns with the Kantarjian *et al.*[1] data and considered the survival estimates used by the company to be pessimistic. Extrapolated evidence from the more up-to-date PACE trial suggested survival ranged from 14 to 19 years from the commencement of third-line therapy. Moreover, evidence reported in by the HMRN shows median survival in this population is [redacted] The ERG's original base case retained the 7 years but presented exploratory scenarios which included mean post-discontinuation survival of 10.1 and 14.6 years, based on PACE.

In response to TE, the company digitised the HMRN data, which consisted of 8 years of follow-up of patients in the 4th line setting, and fitted survival models to the data. The results ranged between [redacted] and [redacted] years. The company, however, considered these predictions to be overly optimistic and retained the 7-year post-discontinuation survival in the base case.

The ERG considers there to be substantive uncertainty regarding the duration of post-discontinuation survival and notes that clinical opinion on this issue is somewhat divided with Prof. Copland suggesting that 7 years is somewhat pessimistic, while Prof. Milojkovic considered the figure reasonable. There, however, are two sources of evidence (HMRN and PACE) that seem to support a longer period of post-discontinuation survival. Further, there is a significant overlap in predicted OS from these sources of evidence. Given this balance of evidence, the ERG favours using 10.6 years to model post-discontinuation survival. This figure lies in the overlap of predicted OS from both sources of evidence and is the most conservative extrapolation based on OS evidence form the PACE trial.

2.8 Issue 10: Use of Niederwieser 2021 for stem-cell transplant survival

Aligning with previous TA's the company's original base-case analysis used Jabbour et al. to model outcomes in patients receiving stem cell transplant (SCT). The ERG noted in its critique that Jabbour et al. is relatively old and reports on reports on relatively few patients (n = 47). The ERG considered a more recent and larger study (n = 147 Niederwieser *et al*.[3] study to be a superior source of evidence. The company agreed that Niederwieser *et al.*[3] represents a superior source to inform SCT outcome and updated their base-case analysis accordingly.

As part of the Niederwieser *et al.*[3] study, differences in survival outcomes according to whether patients receive SCT in the chronic phase (CP), accelerated phase (AP) or blast phase (BP) are explored. The study finds no difference in outcomes for patients in the CP and AP but poorer outcomes for patients who receive SCT in the BP phase. Motivated by these finding the company have updated their base case to reflect this evidence, such that outcomes for patients receiving SCT in

the CP and AP are assumed to be the same, while inferior outcomes are assumed in the BP. This updates assumption in both the company and ERG base case where outcomes were assumed equivalent in the AP and BP, with superior outcomes assumed in the CP.

The ERG considers this update to the company's base assumptions plausible in light of the evidence in Niederwieser *et al.*[3] but notes that the absence of evidence of difference is not necessarily indicative of there being no difference in outcomes. Further, the ERG considers it to be clinically plausible that outcomes will be inferior in patients with more advanced disease. The ERG, therefore, does not update its base case to align with the company. The ERG considers these issues largely resolved though uncertainty remains regarding the pooling of outcomes for AP patients.

2.9 Issue 11: Age adjustment

The company's base case used an additive approach to age adjust utilities. The ERG, however, suggested that more typically a multiplicative approach is adopted to age adjust utilities. The company in their TE response acknowledges that alternative methods can be used to adjust alternatives and considers that both approaches are appropriate. The company, however, further highlights that the new methods guide explicitly recommends a multiplicative approach and therefore the company updates their base case to use the multiplicative approach favoured by the ERG. The ERG considers this issue resolved.

2.10 Issue 12: Comparator dosing

The original scenario presented by the ERG was a simple reduction in the dose intensity of ponatinib from 45mg to 15mg after 1 year in the cumulative survival model. In the surrogate survival model, the scenario assumed all individuals with a CCyR, PCyR and CHR receive 15mg, those without a response receive 30mg, which again occur at 1 year. The company presented an alternative scenario which includes: i) the price of 30mg is the same as 45mg; ii) patients achieving a MCyR are assumed to move to 15 mg doses and the cost is halved; iii) patients in CP not achieving a MCyR, and all patients in the accelerated and blast phase were assumed to have a 45mg/30mg dose as there is no difference in price.

The ERG considers the company's approach presented during TE to be superior alternative to the ERG's simple scenario and this has been adopted in the updated ERG base case. The scenario used in the updated ERG base case assumes dose reductions occur at 12 months. The ERG considers this issue resolved, though acknowledges that uncertainty remains regarding the timing of dose reductions.

3 Results

3.1 Company analysis

3.1.1 Modelling assumptions

In response to the issues noted in the ERG Report, and following the technical engagement teleconference, the company updated their base case cost-effectiveness analyses. The following ERG-preferred assumptions are incorporated within the company's revised model:

- Correction of errors identified by the ERG;
- Issue 7: Removal of retreatment;
- Issue 8: Use of log-logistic to extrapolate time to treatment;
- Issue 10: Use of Niederwieser 2021 for stem-cell transplant survival (this includes both using the survival data and the grouping of clinical outcomes for patients in the AP with CP);
- Issue 11: Age-adjusted utilities.

In addition, the following have been altered in the company's revised model:

- Issue 12: Comparator dosing
- An additional error was identified in the model, whereby the cost of nilotinib was not being applied correctly

The company maintain their original position on the following assumptions:

- Issue 9: Duration of post-discontinuation survival

The ERG also notes that in response to TE, the company reiterated the strengths of using the cumulative survival model but did not explicitly express preference for its use over the surrogate survival model in the updated company base case. The company's updated base case results in response to TE are presented for the cumulative survival model only. The ERG, however, prefers the surrogate survival model but appreciates both are subject to considerable uncertainty (see Section 2.4).

3.1.2 Results

The results of the updated company base-case are presented in Table 2. These results exclude the confidential PAS discounts for bosutinib, ponatinib, nilotinib and Dasatinib. The ERG understands the confidential PAS for nilotinib could be included as the manufacturer of asciminib is also the manufacturer of nilotinib. However, for consistency the results presented below include the asciminib

PAS only. Results with the PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix separate to this report.

Table 2 Company base-case results: deterministic pairwise analysis (Asciminib PAS only)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)
Asciminib vs bosutinib					
Bosutinib	[redacted]	6.26	–	–	–
Asciminib	[redacted]	7.59	£7,549	1.33	£5,659
Asciminib vs dasatinib					
Dasatinib	[redacted]	5.98	–	–	–
Asciminib	[redacted]	6.59	–£9,970	0.61	Dominant
Asciminib vs nilotinib					
Nilotinib	[redacted]	5.76	–	–	–
Asciminib	[redacted]	6.67	–£2,803	0.91	Dominant
Asciminib vs ponatinib					
Ponatinib	[redacted]	6.83	–	–	–
Asciminib	[redacted]	6.28	–£61,154	–0.55	£111,470

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

3.2 ERG analysis

Table 3 presents the results of the updated ERG base-case following the resolution of a number of the issues discussed in the company's TE response. The ERG's updated analysis retains the same assumptions as in the base-case presented in the ERG Report with the exception of two differences:

1) The inclusion of the error correction as identified and amended by the company.
2) The inclusion of the company's preferred approach to modelling the dosing intensity of ponatinib (Issue 12).

One issue that the ERG has retained for consistency with the original ERG preferred base case is the grouping of AP outcomes with BP outcomes. However, as mentioned in Section 2.8, the updated company-preferred base case includes the grouping of AP outcomes with CP outcomes to align with Niederweiser 2021 study. The discrepancy of whether AP outcomes are similar to CP or BP remains an area of uncertainty however, the ERG does not have a strong opinion regarding this issue.

In addition to the base case analysis, the ERG also presents scenario analysis to explore concerns regarding the validity of the of the non-randomised comparisons used to inform the model. This scenario assumes equivalence between asciminib and ponatinib; and equivalence between bosutinib, nilotinib and dasatinib. Scenario analysing using the cumulative survival approach is also presented

in Table 4. This scenario explores uncertainty in the post-discontinuation survival updating the 7 years assumed previously to 10.1 years. This has been included as the post-discontinuation survival assumption does not impact the surrogate survival model (ERG-preferred approach) but does impact the cumulative survival model (company-presented approach).

Table 3 ERG exploratory scenarios

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Change from company-preferred base case
Updated ERG preferred base case						
Asciminib vs bosutinib						
Bosutinib	[redacted]	6.12	-	-	-	
Asciminib	[redacted]	7.20	[redacted]	1.07	**Dominant**	n/a
Asciminib vs dasatinib						
Dasatinib	[redacted]	5.94	-	-	-	
Asciminib	[redacted]	8.13	[redacted]	2.18	**30,538**	n/a
Asciminib vs Nilotinib						
Nilotinib	[redacted]	5.85	-	-	-	
Asciminib	[redacted]	8.14	[redacted]	2.29	**27,016**	n/a
Asciminib vs ponatinib						
Ponatinib	[redacted]	6.93	-	-	-	
Asciminib	[redacted]	6.75	[redacted]	-0.18	**240,186***	128,716
Exploratory analysis: Updated ERG preferred base case assuming equivalence						
Asciminib vs bosutinib						

Bosutinib	n/a	n/a	-	-	-	
Asciminib	n/a	n/a	n/a	n/a	n/a	n/a
Asciminib vs dasatinib						
Dasatinib	[redacted]	6.14		-	-	
Asciminib	[redacted]	7.20	[redacted]	1.06	**Dominant**	n/a
Asciminib vs Nilotinib						
Nilotinib	[redacted]	6.08		-	-	
Asciminib	[redacted]	7.20	[redacted]	1.12	**1,576**	n/a
Asciminib vs ponatinib						
Ponatinib	[redacted]	7.16		-	-	
Asciminib	[redacted]	7.20	[redacted]	0.04	**Dominant**	n/a
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; quality-adjusted life-years. *ICER falls in the south-west quadrant of the cost-effectiveness plane						

Table 4 Company revised base case + ERG preferred assumption of post-discontinuation survival of 10.1 years

Technologies	**Total costs (£)**	**Total QALYs**	**Incr. costs (£)**	**Incr. QALYs**	**ICER vs baseline (£/QALY)**	**Change from company-preferred base case**
Asciminib vs bosutinib						
Bosutinib	[redacted]	7.22		-	-	-

Asciminib	[redacted]	8.38	[redacted]	1.16	**3,998**	-1,661
Asciminib vs dasatinib						
Dasatinib	[redacted]	6.99		-	-	-
Asciminib	[redacted]	7.53	[redacted]	0.54	**Dominant**	n/a
Asciminib vs Nilotinib						
Nilotinib	[redacted]	6.79		-	-	-
Asciminib	[redacted]	7.60	[redacted]	0.81	**Dominant**	n/a
Asciminib vs ponatinib						
Ponatinib	[redacted]	7.74		-	-	-
Asciminib	[redacted]	7.26	[redacted]	-0.48	**101,733***	-9,737

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

*ICER falls in the south-west quadrant of the cost-effectiveness plane

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Single Technology Appraisal (STA)

Asciminib for chronic myeloid leukaemia after two or more tyrosine kinase inhibitors [ID3813]

ERG addendum: review of company's response to technical engagement - additional MAIC analyses

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Overview

This second addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional Matched Indirect Adjusted Comparison (MAIC) analyses comparing the ASCEMBL trial to HMRN data, as provided by the company in their responses to the technical engagement issues which emerged from the ERG report.

The technical engagement covered 11 key issues for consideration. For completeness we repeat our summary of our position here (see Table 1). This document provides the ERG's critique of the supplied MAIC analyses and their impact on Issues 4 and 5 of the technical engagement response. For our position on all other issues, please see our response of 25 March.

The ERG critique of the new MAIC analyses is presented in Section 2. Its impact on Issues 4 and 5 of the technical engagement are summarised in Section 3.

Table 1 Summary of company's Technical Engagement response

Issue	Resolved
Key issue 2: Concerns with the ASCEMBL trial	Resolved
Key issue 3: Lack of evidence on survival outcomes	Resolved (some uncertainty remaining)
Key issue 4: Use of time to treatment discontinuation to inform the economic analysis	Unresolved
Key issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis	Unresolved
Key issue 6: The model structure is subject to considerable uncertainty	Unresolved
Key issue 7: Removal of retreatment	Resolved (some uncertainty remaining)
Key issue 8: Use of log-logistic to extrapolate time to treatment discontinuation	Resolved
Key issue 9: Duration of post-discontinuation survival	Unresolved
Key issue 10: Use of Niederwieser 2021 for stem-cell transplant survival	Resolved (some uncertainty remaining)
Key issue 11: Age-adjusted utilities	Resolved
Key issue 12: Comparator dosing	Resolved

2 Critique of additional MAIC analyses

2.1 Methodology and general comments

The company have supplied a set of MAIC analyses comparing asciminib and bosutinib in the ASCEMBL trial to dasatinib, nilotinib and bosutinib in the HMRN data. No MAIC for ponatinib was performed due to the limited number of patients who received it. The ERG agrees that a MAIC of ponatinib was not feasible.

No additional analyses were provided for the MAICs comparing ASCEMBL to other clinical trials. The ERG's various concerns with those analyses, such as uncertainty around the choice of variables adjusted for, (see the ERG report) remain.

MAICs were performed for TTD and MMR outcomes. The ERG reiterates our concerns with using TTD in MAIC analysis, due to potentially very different patient circumstances, availability of other treatments, and reasons for discontinuation between ASCMEBL and the HRMN data, which cannot be easily adjusted for.

The company performed an anchored analysis, anchoring the analysis against bosutinib. The ERG agrees that, in general, an anchored analysis is preferable, to account for factors that could not be adjusted for. However, both MMR and TTD were [redacted] for bosutinib in ASCEMBL when compared to HMRN. The reasons for this difference are unclear, and the difference is very influential on the results of any anchored analysis. If this difference applies only to the bosutinib arm of ASCEMBL, and not equally to the asciminib arm, then all anchored analyses could be substantially biased. The ERG therefore considers that both anchored and unanchored analyses should be considered.

The ERG considers that the methods used for the MAIC analyses were reasonable. The variables adjusted for were not explicitly stated but appear to be those reported for the HMRN data (age, sex, reason for switching TKI). This is a reasonable set of variables, but there may remain other important factors which could not be adjusted for, including MCyR and PCyR at baseline, and ECOG status. After adjustment the ASCEMBL data represents a reasonable match to the bosutinib, dasatinib and nilotinib data in HMRN. The weighting suggests that no individual patient gets undue weight in the analysis. The effective sample size for ASCEMBL is approximately [redacted], indicating limited overlap, but still represents a reasonable sample size for analysis.

2.2 Results of MAIC of TTD

As fewer than half of patients on asciminib in ASCEMBL had discontinued treatment the median TTD had not been reached. this was unchanged after MAIC adjustment, so assessing how median

TTD compares to other treatment is not feasible. The median TTD for bosutinib was larger unaltered by adjustment, at [redacted] This is [redacted] than in the HMRN data: [redacted]. The reasons for this discrepancy are unclear, but highlight the difficulty in comparing TTD across data sets.

Examining the Kaplan-Meier curves (Figures 27 and 29 of technical engagement submission) for TTD suggests that asciminib has a [redacted] TTD profile to dasatinib before adjustment, and perhaps [redacted] after adjustment. Asciminib appears [redacted] to nilotinib in both cases. The ERG notes that this is an unanchored assessment.

In the anchored analysis, the hazard ratio for asciminib compared to dasatinib [redacted] asciminib: [redacted], although it does not quite reach statistical significance. The ERG notes the substantial inconsistency with an unanchored assessment; a consequence of the poor TTD of bosutinib in ASCEMBL. The results are similar for the comparison with nilotinib; [redacted] asciminib: [redacted], but not statistically significant.

2.3 Results of MAIC of MMR

In the unanchored MAIC of asciminib compared to dasatinib the results [redacted] asciminib but with a wide confidence interval (OR at 6 months [redacted]). In the anchored analysis results [redacted] dasatinib, but also with a wide confidence interval ([redacted]).

In both anchored and unanchored MAICs of asciminib compared to nilotinib results [redacted], but were not statistically significant (e.g. for anchored analysis: OR at 6 months [redacted])

Given the wide confidence intervals observed, the ERG concludes that there is no evidence to clearly suggest [redacted] in terms of MMR.

2.4 Conclusions

The ERG notes several concerns raised by the presented MAIC analyses. They illustrate our continued concerns with the robustness of using TTD as a measure of efficacy. Differences between naïve, unanchored and anchored analyses of TTD, and their inconsistency with results for MMR, suggest that are serious possible problems with the robustness of TTD in this assessment. The ERG suggests that this may be because very different patient circumstances and reasons for discontinuing treatment across studies mean that comparing TTD across studies is unreliable.

The ERG thinks that MAIC analyses of objective response data (MMR and CCyR) are the most appropriate means of comparing asciminib to other treatments not used in ASCEMBL. We conclude

that the MAIC analyses against HMRN show no clear evidence of any difference between asciminib and dasatinib or nilotinib. This is consistent with the limited MAIC analyses previously performed by the company, as discussed in the ERG report.

3 Impact of new MAICs on technical engagement

3.1 Issue 4: Use of time to treatment discontinuation to inform the economic analysis

For our full response on this issue please refer to our document of 25 March.

As discussed in Section 2, the MAIC analysis highlight further concerns with the robustness of using TTD as a measure of efficacy. The ERG position, therefore, remains unchanged and remains in favour of the response-based approach previously adopted in TA451 (ponatinib).

3.2 Issue 5: Limitations of the matched adjusted indirect comparison (MAIC) analysis

The company provided further information on why trials were excluded from Matching-Adjusted Indirect Comparisons (MAIC) analyses. The ERG accepts these explanations, and agrees that small size of the trials, and other issues, would mean they would not be appropriate for use in MAIC analyses. The ERG therefore accepts that the trials used by the company in their MAIC analyses are likely to be the only trials for which a robust MAIC could be performed. We note that this means that the MAICs have only one trial per comparator treatment, and so the robustness of the MAICs to different trials and their varying characteristics cannot be assessed.

The company has not provided any new evidence for the MAIC analyses comparing ASCEMBL to other trials; namely, the limited set of variables adjusted for, and the limited outcome reporting. The ERG notes that reporting of MAIC analyses for MMR and CCyR was incomplete, with no discussion of variable adjusted for, no reporting of confidence intervals, and no estimation of odds ratios. The ERG's concerns about the validity of these analyses remain, as set out in our report.

The company provided some further data for MAICs of TTD (Tables 2 and 3 of their technical engagement submission). We note that this makes interpretation of the MAIC analyses clearer, and more clearly demonstrates that TTD with asciminib appears [redacted] to nilotinib and dasatinib, but [redacted] to ponatinib. We reiterate our concerns with using TTD in the MAIC analyses, because of the potential for subjective grounds for discontinuation, and that reasons for discontinuation may not be consistent across trials.

The MAIC analyses using the HMRN data are discussed in Section 2 above. This further highlighted the ERG's concerns with using TTD as a measure of response, given the substantial difference between results in ASCEMBL and HRMN, and the consequent large differences between anchored

and unanchored MAIC analyses. The ERG considers the MAIC of MMR to be more robust, and notes this showed [redacted] in MMR rates between asciminib and dasatinib and nilotinib.

The ERG concludes that there remains [redacted] between asciminib and dasatinib, nilotinib or ponatinib. Most of the ERG's concerns regarding the robustness and completeness of all indirect comparisons remain unresolved.