Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2482

asciminib 20mg and 40mg film-coated tablets (Scemblix®)

Novartis Pharmaceuticals UK Ltd

07 October 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process

asciminib (Scemblix®) is accepted for use within NHSScotland.

Indication under review: for the 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), and without a known T315I mutation.

In an open-label, phase III study, asciminib was associated with significantly higher major molecular response rates than another TKI in patients with Ph+ CML-CP who had received at least two previous TKIs and did not have a T315I mutation.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the 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), and without a known T315I mutation.[1, 2]

Dosing Information

The recommended dose of asciminib is 80mg daily, taken orally either as 80mg once daily at approximately the same time each day or as 40mg twice daily at approximately 12-hour intervals. Tablets should be taken orally, swallowed whole, without food and food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib. Treatment with asciminib should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

The summary of product characteristics (SPC) provides dose modifications for the management of adverse reactions.

Treatment with asciminib should be initiated by a physician knowledgeable in the diagnosis and treatment of patients with chronic myeloid leukaemia.[1, 2]

Product availability date

31 July 2022

Asciminib received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 11 January 2022. The indication was for the treatment of adult patients with Ph+ CML-CP without a T315I mutation who have been previously treated with two or more TKIs.[3]

Asciminib meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Asciminib is an oral inhibitor of BCR-ABL1 tyrosine kinase. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket, known as a STAMP inhibitor. This differs to other available TKIs and offers the potential to maintain activity against most ABL1 kinase domain mutations that cause resistance to other TKIs.[1, 2, 4]

The evidence comes from one randomised, open-label, phase III study (ASCEMBL) which compared asciminib with bosutinib in adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) who had been previously treated with two or more TKIs and had no known T315I or V299L mutations. Eligible patients had either treatment failure (lack of efficacy as defined by the 2013 European LeukemiaNet recommendations for receiving a second line TKI) or intolerance to their most recent TKI. Patients had BCR-ABL1 transcript levels on the international scale (BCR-ABL1^{IS}) ≥1% (and, ≥0.1% for those with intolerance). Eligible patients were randomised in a ratio of 2:1 to receive asciminib (40mg orally twice daily without food, n=157) or

bosutinib (500mg orally once daily with food, n=76). The asciminib dose could not be increased but the bosutinib dose could be increased to 600mg daily for patients with no ≥ grade 3 adverse event (AE) who had not achieved a complete haematological response by week 8 or a complete cytogenetic response by week 12. Following a protocol amendment, patients who discontinued treatment with bosutinib only due to a lack of efficacy were allowed to crossover to asciminib. Treatment was to continue for up to 96 weeks after the last patient's first dose or 48 weeks after the last patients switched to asciminib whichever is longer. Randomisation was stratified according to major cytogenetic response at baseline.[4]

The primary outcome was major molecular response at week 24 defined as BCR-ABL1^{IS} of ≤0.1% with no treatment failure before week 24. Analysis was performed in the full analysis set which included all randomised patients. A hierarchical statistical testing strategy was applied for the primary and key secondary outcome (major molecular response at week 96). Other secondary outcomes included major molecular response rate and complete cytogenetic response at scheduled time-points, time to treatment failure, progression-free survival (PFS) and overall survival (OS). Since they were not controlled for multiplicity, results reported were considered descriptive only and non-inferential (no p-values reported).[4, 5]

At the time of the primary analysis (data cut-off 25 May 2020), after a median duration of follow-up of 14.9 months, there was a significantly higher rate of major molecular response at week 24 in the asciminib group compared with the bosutinib group. In an updated analyses (data cut-off 6 October 2021), after median follow-up of 2.3 years, major molecular response at week 96 (key secondary outcome) was significantly higher with asciminib compared with bosutinib. Details are presented in Table 1.

Table 1: Results for the primary and secondary outcomes in the full analysis set of ASCEMBL[1, 2, 4-6]

	Asciminib (n=157)	**Bosutinib (n=76)**	**Adjusted difference (95% CI), p-value**
Primary outcome			
Major molecular response rate at week 24	25% (40/157)	13% (10/76)	12% (2.2% to 22%), p=0.029
Key secondary outcome			
Major molecular response rate at week 96	38% (59/157)	16% (12/76)	22% (11% to 33%), p=0.001
Other secondary outcomes			
Patients maintaining major molecular response, KM estimate at week 72	97%	93%	
Complete cytogenetic response rate at week 24	41% (42/103)	24% (15/62)	17% (3.6% to 31%)
Complete cytogenetic response rate at week 96	40% (41/103)	16% (10/62)	24% (10% to 37%)
Median time to treatment failure (96 week analysis), months	24	6	

CI=confidence interval; KM=kaplan-Meier; complete cytogenetic response=no Philadelphia chromosome metaphases in bone marrow with a minimum of 20 metaphases examined.

PFS and OS were also secondary outcomes but the data at 24 weeks and 48 weeks were immature with few patients experiencing an event. At the latest analysis (cut-off date 6 October 2021), the 2-year, Kaplan Meier estimates for PFS rates were 94% in the asciminib group and 91% in the bosutinib group and for OS rates were 97% and 99% respectively.[6]

Patient-reported outcomes were assessed as exploratory outcomes including MD Anderson Symptom Inventory (MDASI)-CML questionnaire and EuroQol-5D-5L, which found small improvements from baseline in both treatment groups with minimal difference between the groups. At week 24, according to the Patient Global Impression of Change (PGIC), a higher proportion of asciminib compared with bosutinib patients were very much improved (17% versus 8.0%) or much improved (32% versus 18%) and there were small numerical improvements in percentage work time missed, work impairment and activity impairment and a small overall difference favouring asciminib over bosutinib in the Work Productivity and Activity Impairment-CML questionnaire.[5] However results should be interpreted with caution due to the open-label study design.

The submitting company performed unanchored matching adjusted indirect comparisons (MAICs) of asciminib (using individual patient data from ASCEMBL) with ponatinib (using a phase II single-arm study, n=270), nilotinib (using a retrospective cohort, n=39) and dasatinib (using a retrospective cohort, n=34) in patients with CML-CP where ≥75% of patients had prior experience with two or more TKIs and who had no T315I mutation. Time to treatment discontinuation (TTD) was the outcome assessed and was used to extrapolate into OS in the economic analysis. However, since TTD was not reported in the studies, the median duration of study treatment was used as a proxy. Patients from the ASCEMBL study were matched for available characteristics from the comparator study and the corresponding median TTD for asciminib was estimated. The MAIC results found that following matching with ponatinib, the median TTD for ponatinib was longer than for asciminib. Following separate matching with nilotinib and dasatinib, the median TTD was not reached for asciminib compared with 11 months for nilotinib and 14 months for dasatinib.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

At the time of the primary analysis (data cut-off 25 May 2020), after a median follow-up of 14.9 months, the median duration of treatment was 43.3 weeks with asciminib and 29.2 weeks with bosutinib. Any treatment-emergent AE was reported by 90% (140/156) of patients in the asciminib group and 96% (73/76) in the bosutinib group and these were considered treatment-related in 63% and 88% respectively. In the asciminib and bosutinib groups respectively, patients reporting a grade 3 or higher AE were 51% versus 61%, patients with a reported serious AE were 13% versus 18%, patients with a dose reduction due to treatment emergent AEs were 21% versus 42%, the proportion of AEs that led to dose interruptions were 38% versus 57% and patients discontinuing therapy due to an AE was 5.8% versus 21%.[4, 5]

At the 25 May 2020 data cut-off, the most frequently reported treatment-emergent AEs of any grade in the asciminib group versus the bosutinib group were: thrombocytopenia, including decreased platelet count (29% versus 18%), neutropenia, including decreased neutrophil count

and febrile neutropenia (22% versus 21%), headache (16% versus 13%), diarrhoea (12% versus 71%), hypertension (12% versus 3.9%), nausea (12% versus 46%), fatigue (10% versus 9.2%), anaemia (9.6% versus 7.9%), nasopharyngitis (9.6% versus 2.6%), arthralgia (9.0% versus 1.3%), rash (7.1% versus 24%) and vomiting (7.1% versus 26%), increased alanine aminotransferase (3.8% versus 28%) and aspartate aminotransferase (3.8% versus 21%). Results from the 96 weeks analysis were similar.[7]

The most common treatment-related AEs in the asciminib group were thrombocytopenia (20%), neutropenia (15%), headache (9.0%) and nausea (6.4%) and in the bosutinib group were diarrhoea (70%), nausea (38%), increased alanine aminotransferase (28%), vomiting (24%), rash (20%) and increased aspartate aminotransferase (18%).[4]

There were three deaths during the treatment period: two in the asciminib group and one in the bosutinib group. In the asciminib group, these were due to arterial embolism and ischaemic stroke and were considered possibly or probably not related to study treatment. In the bosutinib group, one patients died due to septic shock, which was considered to be related to study treatment.[4]

Summary of clinical effectiveness issues

Chronic myeloid leukaemia (CML) is a malignant clonal disorder of haematopoietic stem cells. The majority of patients with CML have an abnormal chromosome known as the Philadelphia chromosome which transforms normal haematopoietic cells into malignant cells producing tyrosine kinase resulting in uncontrolled cell proliferation. There are three phases of CML: chronic phase, accelerated phase and blast phase. In the chronic phase, the disease is developing slowly and is most stable and patients generally have minimal symptoms, including fatigue, abdominal discomfort, weight loss, night sweats and fever. The aims of treatment are to produce a complete haematological response, early molecular response, complete cytogenetic response, major molecular response, and deep molecular response. Treatment can control the disease, allowing patients to remain in remission for many years. Patients who respond to treatment in the chronic phase generally have a good prognosis with a 10-year survival rate of approximately 85%, almost similar to life expectancy in the normal population.

First-line treatment of CML in the chronic phase is usually with the first generation TKI, imatinib, which is well tolerated and is associated with survival rates after 8-years of follow-up of 85% to 90%. Mutations to BCR-ABL1 gene can result in resistance to imatinib. Second generation TKIs, nilotinib, dasatinib and bosutinib may be used in patients who do not respond, stop responding or do not tolerate imatinib. They may also be used first-line in certain patients (including those with higher risk or those wanting to have children when a rapid molecular response is desirable). Ponatinib is a third generation TKI which is also effective against mutant variants of the BCR-ABL gene including the T315I mutation. There are no recommendations for standard of care at third and later lines of therapy and choice of further TKIs is determined by previous therapy, mutations and co-morbidities. Allogenic stem cell transplant (allo-SCT) is the only potential cure for CML. However, it is associated with morbidity and mortality and is therefore limited to use in patients who are fit and have suitable donors.[8-10] Asciminib meets SMC orphan criteria.

Clinical experts consulted by SMC considered that asciminib fills an unmet need offering an additional treatment for patients intolerant or refractory to other TKIs. They consider asciminib to be a therapeutic advancement in this setting as it has a mechanism distinct from other available TKIs and a different safety profile.

Key strengths

- Asciminib is an alternative TKI for the treatment of CML. It has a novel mechanism of action, the first in class STAMP inhibitor, which may offer the potential to maintain activity against ABL1 kinase domain mutations that cause resistance to other TKIs.
- The randomised, phase III ASCEMBL study provides direct evidence of the efficacy and safety of asciminib compared with a relevant comparator for later lines of CML therapy, the TKI bosutinib.
- In ASCEMBL, there were significantly higher major molecular response rates at weeks 24 and 96 (assessed as primary and key secondary outcomes) in patients treated with asciminib compared with bosutinib; response rates were approximately doubled at both 24 and 96 weeks suggesting a clinically meaningful improvement for patients.
- The treatment effect of asciminib appeared generally consistent across subgroups including when used in the third, fourth, or fifth line of treatment.

Key uncertainties

- The ASCEMBL study is ongoing. Available results are for the surrogate outcome of major molecular response at weeks 24 and 96. Although statistically significant, the major molecular response rate for asciminib at week 24 (25%) was lower than had been anticipated according to the sample size calculation (35%).
- Trial results are only for surrogate markers. Results for longer term, clinically relevant outcomes are awaited. Future results of PFS and overall survival may be confounded by patients who crossover from bosutinib to asciminib.[4]
- There are no direct data comparing asciminib with nilotinib, dasatinib and ponatinib and the company performed unanchored MAICs to adjust the asciminib results for the comparator study populations. However, limitations in the MAICs, including the quality of the available studies for the comparators, the unanchored methods and the use of treatment duration as a proxy for TTD, affect the robustness of the results. The small patients numbers, limited matching and differing durations of follow-up and heterogeneity in inclusion of patients with mutations (particularly in the ponatinib study where 24% of patients had a T315I mutation) were also considered important limitations which made the MAIC results highly uncertain.

Despite the uncertainties, the clinical case is considered acceptable.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of asciminib, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- CML is a form of leukaemia which mainly occurs in middle-aged and older patients. Symptoms vary with the stage of disease and can include fatigue, pain, frequent infections, abdominal discomfort, and fever. The physical and mental impact of CML and its treatment can reduce the quality of life for patients, families and carers. This is particularly relevant for the small number of patients who have been treated with at least two previous TKIs and have limited further treatment options.
- In patients with CML in the chronic phase, TKI treatment can fail due to resistance or intolerance. In patients who have already received at least two TKIs, subsequent treatment options are limited. There is a high unmet need for further effective treatment options for patients who may otherwise require an allo-SCT which carries a high risk of morbidity and mortality.
- Asciminib is a TKI with a novel mechanism of action which has been associated with improved response rates. The availability of another effective medicine, with a reasonable safety profile, may provide a life-changing treatment for these patients. It may allow treatment to be personalised to the individual patient and any relevant co-morbidities, providing reassurance on optimal long-term management. This may have substantial physical and mental health benefits for patients, allowing them to live normal lives and continue or resume work.
- The different mode of action may result in fewer off-target adverse events with asciminib and PACE participants highlighted experience which demonstrated improved tolerability compared with other possible TKIs.
- Asciminib treatment delivery is similar to other TKIs and no additional healthcare resource use is expected.

Additional Patient and Carer Involvement

We received patient group submissions from Leukaemia Care and the Chronic Myeloid Leukaemia Support Group, both organisations are registered charities. Leukaemia Care has received 14.3% pharmaceutical company funding in the past two years, including from the submitting company. The Chronic Myeloid Leukaemia Support Group has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing asciminib with bosutinib, ponatinib, nilotinib and dasatinib for the third line, or later, treatment of Ph+ CML-CP. This was wider than the granted licence indication, which included an additional restriction requiring patients to have no known T315I mutation. While this discrepancy introduced some uncertainty into the economic case, it was not felt sufficient to prevent a robust review of asciminib as it would be used in Scottish practice.

To compare treatments, the company developed a partitioned survival model, which was run for a duration of 50 years using monthly cycles. The model contained 5 states, which were chronic phase (CP) on index TKI treatment, CP on subsequent treatment, acute phase (AP), blast phase (BP) and death. Within the submission the phrase 'index treatment' referred to the first use of asciminib or the comparator in the patients treatment pathway, taking place at third line or later. Additionally, the model allowed for patients to undergo allo-SCT. Patients could receive allo-SCT at the discontinuation of the index treatment, upon progression to AP or upon progression to BP.

Occupancy of the CP on index treatment state for the comparison between asciminib and bosutinib was informed by patient level data taken from the ASCEMBL study.[4] A log-normal parametric curve was fitted to the observed study TTD data to project out into the future. The occupancy of the CP on index treatment state for the other comparators was informed by the results of an indirect comparison. From that, only median durations of treatments could be extracted which the company treated as a proxy for median TTD. This necessitated that exponential parametric functions be used to model those survival curves, appropriately parametrised so that the median modelled TTD matched that estimated from the indirect comparison.

Data on the length of occupancy of the subsequent health states within the main model was limited. As a result, the company assumed that the mean duration of occupancy of those states matched estimates drawn from the literature, regardless of treatment received at index stage. These durations were estimated as 68 months in the CP subsequent treatment state, 10 months in the AP state and 6 months in the BP state. This meant that after the discontinuation of index treatment, a patient was expected to live for 7 years, on average. Again, exponential functions were used to create estimates of state occupancy across time.

Survival within the allo-SCT sub-model was based upon digitised Kaplan Meier curves from Niederweiser et al (2021), to which log-normal curves were fitted.[11]

Each health state within the model was attributed a utility value in order to capture health related quality of life. Values for the two CP states were derived from EQ-5D questionnaires completed by participants of the ASCEMBL study.

Medicine costs included in the model covered acquisition costs for index treatments as well as subsequent therapy lines, administration costs (where relevant) and AE costs. Further, each state was attributed a monthly cost built up from a large selection of resource categories. The cost of allo-SCT was estimated £109,279. Costs of kinase domain mutation testing were included,

although not until after patients had exited from the CP stage. During CP, patients are likely to be tested equally regardless of whether treated with asciminib or a comparator, and so that exclusion was viewed as reasonable.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. PAS discounts are in place for bosutinib, ponatinib, nilotinib and dasatinib, and these were included in the results used for decision-making by using estimates of the comparator PAS price.

SMC is unable to present the results provided by the company which used an estimates of the PAS prices for bosutinib, ponatinib and dasatinib due to commercial confidentiality and competition law issues. Nilotinib is manufactured by the submitting company, which would allow for the PAS discount to be included, however it has not been presented in order to maintain consistency across the comparators.

Table 2: Base-case pairwise results (PAS discount on asciminib only)

Comparison Asciminib vs …	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Bosutinib	1,486	1.81	1.53	971
Ponatinib	–136,958	-0.66	-0.54	253,878*
Nilotinib	21,629	0.96	0.90	24,120
Dasatinib	–1,064	0.70	0.60	Dominant

*In the south-west quadrant of cost-effectiveness plane, as a result of estimated incremental cost and health outcomes reductions

Abbreviations: *LYG = Life years gained, QALYs = quality adjusted life years, ICER = incremental cost-effectiveness ratio*

In addition to the base case, the company also provided a variety of scenario analyses exploring areas of uncertainty. A selection of alternative scenarios are presented below.

Table 3: Scenario analysis (PAS discount on asciminib only)

Scenario description	Base case description	ICER (£)			
		Bos.	Pon.	Nil.	Das.
Five years survival post index TKI discontinuation	Seven years survival post index TKI discontinuation	5,161	236,366*	24,986	£1,098
Three and a half years survival post third-line discontinuation		8,228	224,395*	25,191	£2,614
Mean time in AP 12 months	Mean time in AP 10 months	906	253,276*	24,008	Domin't
Mean time in AP 8 months		1,040	254,485*	24,232	Domin't
Mean time in BP 8 months	Mean time in AP 6 months	539	252,387*	23,715	Domin't
Mean time in BP 4 months		1,418	255,404*	24,536	Domin't
CP utility differs across treatment arms but consistent across on index/subsequent treatment states	CP utility values equal across treatment arms but differ across on index treatment/subsequent treatment states	934	324,312*	22,750	Domin't
CP utility differs across treatment arms and		905	315,622*	21,457	Domin't

index/subsequent treatment states					
Exponential survival for TTD	Log-normal survival for TTD	Domin't	N/A	N/A	N/A
Weibull survival for TTD		2,070	N/A	N/A	N/A
Gompertz survival for TTD		3,973	N/A	N/A	N/A
Log-logistic survival for TTD		Domin't	N/A	N/A	N/A
Gamma survival for TTD		955	N/A	N/A	N/A
Generalised Gamma survival for TTD		14,059	N/A	N/A	N/A

*In the south-west quadrant of cost-effectiveness plane, as a result of estimated incremental cost and health outcomes reductions

Abbreviations: *Bos., bosutinib; Pon., ponatinib; Nil., nilatonib; Das., dasatinib; AP, accelerated phase; BP, blast phase; CP, chronic phase; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTD, time to discontinuation; Domin't, asciminib dominant over comparator.*

The strengths of the economic case were assessed as being:

- The model structure appeared to be robust and consistent with other medicines reviewed by SMC in the clinical area.
- The treatment most likely to be replaced remains a source of uncertainty, however, the analysis covered the most likely candidates.

The weaknesses of the economic case were assessed as being:

- The economic modelling was reliant upon the results of the MAIC in order to compare asciminib with ponatinib, nilotinib and dasatinib. As detailed within the clinical section, the results of the MAIC were classed as highly uncertain due to the evidence included and the methods employed. This had important knock on implications for the economic results.
- The modelling approach for time to discontinuation of index treatment used for the comparators included in the MAIC was somewhat simplistic, due to data limitations. This was a source of uncertainty and alternative assumptions were not extensively explored in sensitivity analysis.
- The occupancy of health states subsequent to the CP on index treatment state was also modelled very simplistically. However, this approach did appear to be consistent with other submissions in the clinical area and changes in mean duration of occupancy had limited impacts upon economics results.

The Committee considered the benefits of asciminib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as asciminib is an orphan/ orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted asciminib for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The British Society of Haematology published "A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia" in July 2020.[8] This recommends imatinib as the first-line treatment for the majority of adults and children with CML presenting in chronic phase. A second generation TKI can be considered for patients with a high or intermediate EUTOS Long-Term Survival or Sokal score and for patients who wish to explore treatment discontinuation at an early stage for example female patients who want to become pregnant. Co-morbidities should be assessed to help in the choice of second generation TKI. In patients with documented treatment failure in first-line therapy, change to an alternative TKI should be considered. The choice of second-line therapy in resistant patients is initially guided by BCR-ABL1 kinase domain mutational analysis. Dose escalation to imatinib 600mg daily is reasonable for patients with a suboptimal response meeting the ELN warning criteria and with good tolerance of the standard dose. In the absence of specific mutations the patients pre-existing co-morbidities and the known side effect profiles of the second generation TKIs should inform the treatment choice. Allogeneic SCT should be considered for CML patients in chronic phase who are resistant to at least one second generation TKI, though a trial of a third generation TKI is reasonable prior to committing to transplantation. Some patients with intolerance to multiple TKIs may justifiably proceed to fourth-line therapy. The guideline also provides some recommendations for discontinuing TKI therapy for certain patients only who have been on an approved TKI therapy for at least 3 years (but preferably 5 years).

The European Leukemia Network published "European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia" in March 2020.[10] This guideline notes that there is no comparative evidence in the third line setting and beyond, and that treatment should be guided by the sensitivity profile of the BCR-ABLI mutation where possible. The use of ponatinib, a third generation TKI, after failure of two or more second generation TKIs is the only treatment licensed in this setting and has been found to be efficacious in the treatment of patients with the T315I mutation. In addition, the guideline recommends the use of ponatinib where no mutation exists as long as there are no cardiovascular risk factors present.

The European Society for Medical oncology (ESMO) published guidelines titled "Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up" in 2017.[10] These guidelines offer the following recommendations for patients with resistant and refractory disease:

- Mutational analysis is required in patients who are failing imatinib or second generation TKIs, or those who progress to advanced or blast phase.

- Options are imatinib, nilotinib, dasatinib, bosutinib or ponatinib. Ponatinib should be considered the agent of choice in patients with the T315I mutation, and in instances where other TKIs are not indicated

- Allogeneic stem cell transplantation remains an important therapeutic option for patients in CML-CP who fail two or more TKIs or who are potentially harbouring the T315I mutation (after a trial of ponatinib therapy).

National institute for health and care excellence (NICE) published Technology appraisal guidance for dasatinib, nilotinib, imatinib for imatinib resistant or intolerant CML in December 2016.[12] These guidelines recommend the following treatments in the second line and beyond for patients with CML-CP:

- Dasatinib and nilotinib: recommended for adult patients with CP or AP Ph+ CML-CP who cannot have imatinib or are imatinib-resistant

- High-dose imatinib (600 mg in the chronic phase) is not recommended for treating Ph+ CML-CP in adults whose disease is imatinib-resistant.

These guidelines predate the availability of asciminib.

Additional information: comparators

Bosutinib, nilotinib, dasatinib and ponatinib.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
asciminib	40mg orally twice daily or 80mg once daily	49,144

Costs from MIMS online on 29 September 2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 14 patients eligible for treatment with asciminib in year 1 rising to 16 in year 5. The uptake rate was estimated to be 12% in year 1 (2 patients) and 66% in year 5 (11 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 August 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for

comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.