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CADTH Reimbursement Recommendation

Asciminib (Scemblix)

Indication: For the treatment of adult patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with 2 or more tyrosine kinase inhibitors

Sponsor: Novartis Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Scemblix?

CADTH recommends that Scemblix should be reimbursed by public drug plans for the treatment of Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Scemblix should only be covered to treat adults with Ph+ CML who are in chronic phase (CP) with treatment failure on or intolerance to 2 or more prior tyrosine kinase inhibitor (TKI) therapies and have no evidence of *T315I* or *V299L* mutations.

What Are the Conditions for Reimbursement?

Scemblix should only be reimbursed if prescribed by clinicians with expertise and experience in treating CML and if the cost of Scemblix is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Scemblix had higher rates of major molecular response, a marker of treatment response that predicts long-term survival, than patients treated with bosutinib.
- Scemblix meets patient needs that include improve survival, maintain or improve health-related quality of life, and have fewer side effects than other available treatments.
- Based on CADTH's assessment of the health economic evidence, Scemblix does not represent good value to the health care system at the public list price. Therefore, a price reduction is needed.
- Based on public list prices, Scemblix is estimated to cost the public drug plans approximately $13.3 million over 3 years.

Additional Information

What Is CML?

CML is a cancer of the bone marrow and blood cells that is commonly caused by an abnormal chromosome known as the Philadelphia chromosome. In 2018, the incidence rate of CML in Canada was 2.0 per 100,000 population.

Unmet Needs in CML

Some patients must discontinue their TKI therapy because of side effects or because their disease no longer responds to the therapy. This occurs in approximately one-third of patients in the first line of therapy. There are limited treatment options for patients who have received 2 or more prior TKI therapies, and 1 of the options has serious safety concerns (ponatinib).

How Much Does Scemblix Cost?

At the public list price, treatment with Scemblix is expected to cost approximately $170 per day ($62,092 per year).

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that asciminib be reimbursed for the treatment of adult patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with 2 or more tyrosine kinase inhibitors (TKIs) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

There is evidence from 1 randomized controlled trial that shows treatment with asciminib has added clinical benefit for patients with Ph+ CML in CP previously treated with 2 or more TKIs. The ASCEMBL trial (N = 233) demonstrated that, compared with bosutinib, 24 weeks of treatment with asciminib was associated with a statistically significant and clinically meaningful improvement in major molecular response (MMR). The MMR rate at 24 weeks, which was the primary end point, was 25.48% (95% confidence interval [CI], 18.87% to 33.04%) in the asciminib group and 13.16% (95% CI, 6.49% to 22.87%) in the bosutinib group, with a difference of 12.24% (95% CI, 2.19% to 22.30%; P = 0.029). MMR rate results at 48 weeks and complete cytogenic response (CCyR) at 24 and 48 weeks were supportive of the primary end point. Although the data for progression-free survival (PFS) and overall survival (OS) were immature at the available data cut-off dates, pERC noted that improved MMR is associated with improved long-term survival outcomes with currently available TKIs. The results suggest that treatment with asciminib may lead to improved health-related quality of life (HRQoL) compared with bosutinib, but conclusions could not be drawn about HRQoL because the EQ visual analogue scale (VAS) was an exploratory outcome in the ASCEMBL trial and subject to potential bias because of the open-label nature of the trial and missing data at post-baseline assessments. Despite these limitations, the results suggest that HRQoL may be maintained or improved over time with asciminib. The adverse event (AE) profiles suggest that asciminib is better tolerated than bosutinib, with 21.1% of the bosutinib group discontinuing treatment because of an AE versus 5.8% of the asciminib group. Considering all the evidence, pERC concluded that asciminib better met some of the needs identified by patients than bosutinib because it improves MMR rate, may maintain or improve HRQoL, and has fewer side effects.

Using the sponsor-submitted price for asciminib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for asciminib was $207,406 per quality-adjusted life-year (QALY) compared with bosutinib. At this ICER, asciminib is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adults with CML-CP who have prior experience with 2 or more TKIs. A reduction in price of at least 26% is required for asciminib to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with asciminib should only be reimbursed in adult patients with Ph+ CML in CP with treatment failure on or intolerance to 2 or more prior TKI therapies.	Evidence from the ASCEMBL trial showed that asciminib had a clinical benefit in patients with these characteristics.	Intolerance to prior TKI therapies should be assessed by the treating physician as outlined in the ELN 2020 recommendations.
2. Patients must not have any of the following: 2.1. AP or BP CML 2.2. evidence of *T315I* or *V299L* mutations at any prior assessment.	There is no evidence to support a benefit of asciminib in patients with these characteristics as they were excluded from the ASCEMBL trial.	—
Renewal		
3. Assessment for renewal should be based on all of the following: 3.1. hematologic, cytogenetic (if a bone marrow aspiration is performed), and molecular response by RT-PCR 3 to 6 months after treatment initiation 3.2. blood counts and molecular response by RT-PCR every 3 to 6 months thereafter 3.3. a toxicity profile that is acceptable to the patient and clinician.	Patients in the ASCEMBL trial were assessed for molecular response every 12 weeks following the primary efficacy end point evaluation at week 24. According to the clinical experts, patients in clinical practice are also assessed every 12 weeks.	Although pERC agreed with the clinical experts that the ELN 2020 recommendations regarding treatment failure are appropriate for this patient population, they noted that the decision for discontinuation should be left up to the clinical judgment of the treating physician together with the patient.
Prescribing		
4. Treatment should be prescribed by clinicians with expertise and experience in treating CML.	This will ensure that adverse effects are managed in an optimized and timely manner.	—
5. Asciminib may be prescribed at a dosage of 40 mg twice daily or 80 mg once daily.	Although the ASCEMBL trial only included the 40 mg twice daily dosage of asciminib, pERC agreed with the clinical experts that either of the Health Canada–approved dosages (40 mg twice daily or 80 mg once daily) may be used.	—
Pricing		
6. A reduction in price.	The ICER for asciminib is $207,406 per QALY gained when compared with bosutinib. A price reduction of at least 26% would be	—

Reimbursement condition	Reason	Implementation guidance
	required for asciminib to be able to achieve an ICER of $50,000 per QALY compared to bosutinib.	
Feasibility of adoption		
7. The feasibility of adoption of asciminib must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukemia; CP = chronic phase; ELN = European LeukemiaNet; pERC = CADTH pCODR Expert Review Committee; Ph+ = Philadelphia chromosome positive; RT-PCR = real-time polymerase chain reaction; TKI = tyrosine kinase inhibitor.

Discussion Points

- One of the key limitations of the ASCEMBL trial results was the lack of long-term data. The trial is ongoing; the MMR rate at 96 weeks will be assessed at a later data cut-off, which will provide more information on the durability of treatment response with asciminib.
- pERC acknowledged that MMR is a well-established surrogate for long-term survival outcomes and a marker of treatment response used to monitor disease control in clinical practice.
- The efficacy and safety of asciminib versus relevant comparators other than bosutinib are unknown due to the severe limitations of the indirect treatment comparisons (ITCs) of asciminib versus ponatinib, dasatinib, and nilotinib. In the 3 unanchored matching-adjusted indirect comparisons (MAICs), there was a high risk of bias from residual confounding and the effective sample sizes for the comparisons were very small.
- pERC discussed that patients with experience from previous TKI therapies value the minimization of side effects and acknowledged that, based on the ASCEMBL trial evidence and input from patients, asciminib appears to have a more tolerable safety profile.
- pERC discussed that patients who have received 2 prior TKI therapies and have cardiovascular risk factors may not be candidates for treatment with ponatinib and that asciminib provides an additional treatment option in this setting.
- Although patients in the ASCEMBL trial had not received bosutinib as 1 of their prior TKI therapies, pERC agreed with the clinical experts that asciminib should be effective in patients who have failed, or who are intolerant to, 2 or more TKIs that include bosutinib because of the similarities in mechanism of action between bosutinib and the other non-asciminib TKIs. Therefore, pERC noted that patients who received bosutinib as 1 of their prior TKI therapies should be considered for reimbursement of asciminib.
- The sponsor's submitted cost-utility analysis suggested that asciminib would be cost-saving compared with bosutinib, due to the reduced costs of subsequent therapies (particularly ponatinib). This finding was based on an assumption about ponatinib dosing (the frequency of use of a 45 mg daily versus 15 mg daily dosage) that was not supported by sources within the literature or experts consulted by CADTH. The cost-effectiveness of asciminib is highly sensitive to assumptions about subsequent therapy.

Background

CML is a clonal bone marrow stem cell disorder that results in the unregulated growth of myeloid precursor cells and the production of excessive neutrophils, eosinophils, and basophils in the bone marrow. Blood and bone marrow cells in patients with CML usually contain a characteristic chromosomal abnormality, known as the Philadelphia chromosome (Ph), resulting from a balanced translocation between chromosomes 9 and 22. The gene product of this *BCR-ABL* translocation is a tyrosine kinase that is constitutively active, resulting in the continuous activation of other cell cycle regulatory proteins and unrestrained bone marrow proliferation. In 2018, the incidence rate of CML across all ages and sexes in Canada, excluding Quebec, ranged from 510 cases in 2011 to 585 cases in 2018, which corresponded to an incidence rate of 2.0 per 100,000 population.

The majority of patients (> 95%) with CML are in CP at diagnosis. Approximately one-third of patients treated with the first-generation TKI imatinib discontinue therapy either because of intolerance of side effects or loss of response due to drug resistance. The second-generation TKIs dasatinib, nilotinib, and bosutinib have a much smaller spectrum of resistance mutations, but all are susceptible to the *T315I* mutation. Ponatinib is a third-generation TKI with activity against wild-type and mutant *BCR-ABL*; however, it is associated with serious toxicity, including cardiovascular, cerebrovascular, and peripheral vascular events.

Health Canada has approved asciminib for the treatment of adult patients with Ph+ CML-CP previously treated with 2 or more TKIs. Asciminib is a potent inhibitor of *ABL/BCR-ABL1* tyrosine kinase with a novel mode of action. It is available as 20 mg and 40 mg oral tablets; the dosage recommended in the product monograph is 80 mg once daily or 40 mg twice daily.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 phase III randomized controlled trial in patients with Ph+ CML-CP who received at least 2 prior TKI therapies
- a review of 1 phase I open-label study in patients with Ph+ CML-CP who received at least 2 prior TKI therapies
- a review of 1 sponsor-submitted ITC report comparing asciminib with other treatments used for patients with CML-CP who have received at least 2 prior TKI therapies
- patients' perspectives gathered by 2 patient groups: Chronic Myelogenous Leukemia Society of Canada and the Lymphoma and Leukemia Society of Canada (LLSC) and Canadian CML Network
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with Ph+ CML-CP
- input from 2 clinician groups, including Ontario Health – Cancer Care Ontario (OH-CCO) and a peer group of hematologists from across Canada who are involved in treating CML patients

- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient group submissions were received: 1 from the Chronic Myelogenous Leukemia Society of Canada and 1 from the LLSC and Canadian CML Network. The Chronic Myelogenous Leukemia Society of Canada gathered information from 10 patients with CML and their caregivers through remote surveys and interviews conducted between January and February 2022. The LLSC and Canadian CML Network conducted a collaborative anonymous online survey for patients with CML between November 30, 2021, and January 3, 2022. A total of 16 participants responded to this survey, of which 11 were patients with CML and 5 were a caregiver, friend, or family member of a patient with CML.

According to the submission from the Chronic Myelogenous Leukemia Society of Canada, most patients do not feel sick when they are diagnosed with CML-CP, but are overwhelmed and physically and emotionally drained due to financial stress associated with the cost of treatment and frequent appointments and testing. Family members also suffer because the family routine changes significantly and caregivers and/or spouses become more responsible for household management. In both submissions, patients described numerous side effects to the various TKIs, such as fatigue, muscle cramps or pain, rash, joint pain, headaches, fluid retention, and serious cardiovascular problems. It was clear that side effects seriously impact patients' quality of life. Those who responded to the LLSC and Canadian CML Network survey indicated that their daily life was affected through moderate impacts on the following: ability to exercise, ability to work, mental health, ability to concentrate, ability to travel, personal image, and ability to continue daily activities. Similarly, respondents indicated moderate impacts of the following: stress, anxiety, and/or worry; difficulty sleeping; loss of sexual desire; finances; interruption of life goals and/or accomplishments; and depression.

Patients identified extended survival, improved quality of life, minimization of side effects, and a return to normal life as important. The majority of patients treated with asciminib rated a positive impact of this treatment on their ability to perform daily activities. All respondents with experience with asciminib treatment agreed (11%) or strongly agreed (89%) that asciminib improved HRQoL, and all would recommend this treatment to other patients diagnosed with CML.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts with experience in the diagnosis and management of CML highlighted the need for more treatment options to be made available for patients who have received 2 or more prior TKIs. Ponatinib has been shown to be effective in this setting but has serious safety concerns; patients with cardiovascular risk factors will be contraindicated and have limited options available. Asciminib would likely become the preferred treatment used in the third line. The clinical experts noted that the end point of MMR is a clinically useful measure of response, and that treatment discontinuation should be assessed according to

European LeukemiaNet (ELN) guidelines for treatment failure or the inability of the patient to tolerate treatment.

Clinician Group Input

Clinician group input on the review of asciminib for the treatment of adult patients with Ph+ CML in CP previously treated with 2 or more TKIs was received from 2 groups: OH-CCO Hematology Drug Advisory Committee (2 clinicians) and a peer group of hematologists from across Canada who are involved in treating CML patients (14 clinicians). The clinician groups both highlighted that patients with CML who are the least suitable for treatment with asciminib would be those in accelerated phase or blast crisis. The peer group emphasized that a well-tolerated treatment is likely to have high adherence, which is correlated with positive efficacy outcomes.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation questions	Response
Relevant comparators	
The ASCEMBL trial compared asciminib with bosutinib, which is an appropriate comparator. Other potential comparators include ponatinib, dasatinib, and nilotinib. In 1 jurisdiction, bosutinib is not funded in the fourth-line setting.	Despite the absence of direct comparisons with ponatinib, dasatinib, and nilotinib, and the limitations of the sponsor-submitted ITC, pERC noted that asciminib can also be given in place of ponatinib, dasatinib, and nilotinib to patients with Ph+ CML-CP who have received at least 2 prior TKI therapies.
Considerations for initiation of therapy	
Should patients in AP or BC be eligible? The funding request for asciminib is specifically for patients with CML-CP. Bosutinib and ponatinib received reimbursement recommendations for CML in CP, AP, or BC.	The clinical experts noted that there is a phase I trial in which these patients were included; however, this trial was a dose-finding trial, and these patients were not included in the ASCEMBL trial. Patients with AP and BC CML represent a small percentage of overall patients, and because of this they are unlikely to be studied in a randomized trial. Although the requested reimbursement population and Health Canada–approved indication do not include this population, 1 of the 2 clinical experts indicated that, considering the lack of options for this patient population, asciminib should be made available to this group. pERC agreed that there is insufficient evidence to support the use of asciminib in AP or BC CML. Therefore, pERC was of the opinion that patients with AP or BC CML should not be eligible for asciminib treatment.
Should patients with a *T315I* or *V299L* mutation be eligible for asciminib and, if so, would treatment with 2 prior TKIs be required?	The requested reimbursement population and Health Canada–approved indication do not include patients with a *T315I* or *V299L* mutation. The FDA has approved treatment of these patients with a higher dose. The clinical experts noted that if asciminib were to be made available for patients with *T315I* or *V299L* mutations, it would be reasonable to require 2 prior TKIs, with an exception made for patients with risk factors for vascular complications (i.e., not fit for ponatinib). pERC clarified that treatment with the higher dosage of asciminib (200 mg twice daily) is outside the scope of this review. pERC discussed that there was insufficient evidence to inform the use of asciminib in

Implementation questions	Response
	patients with *T315I* or *V299L* mutations because these patients were excluded from the ASCEMBL trial.
It is noted that the FDA approved dosing for asciminib in patients with the *T315I* mutation and CML is 200 mg twice daily.	pERC noted that the recommended dosages for the indication under review are 40 mg twice daily or 80 mg once daily; the 200 mg twice daily dosage is out of scope for this review.
Considerations for discontinuation of therapy	
Should treatment failure, and therefore discontinuation, be informed by ELN 2020 recommendations for treatment of CML?	The clinical experts indicated that the ELN 2020 recommendations are appropriate for this patient population. pERC agreed with the clinical experts but considered it appropriate to leave the decision for discontinuation up to the clinical judgment of the treating physician.
Consideration for prescribing of therapy	
Asciminib 40 mg twice daily by mouth. Tablets will be available in 20 mg and 40 mg strength in blister packs of 10 blisters per card (6 cards per carton). Pricing is nonlinear with dose.	pERC considered this statement in their deliberations.
Generalizability	
In the event of a positive funding recommendation, should patients receiving alternative TKI (third line or later) be eligible to switch to asciminib when funding becomes available?	According to the clinical experts, for patients to be switched from 1 therapy to another, either treatment intolerance or treatment failure must be met. pERC agreed with the clinical experts.
Funding algorithm	
Drug may change the place in therapy of comparator drugs.	pERC agreed with this statement. As noted in the response to the first question in this table, pERC noted that asciminib can be given in place of ponatinib, dasatinib, and nilotinib to patients with Ph+ CML-CP who have received at least 2 prior TKI therapies. pERC discussed that the optimal sequencing of therapies after the use of 2 prior TKI therapies is unclear.
What is the place in therapy for asciminib relative to the other TKIs (e.g., bosutinib, ponatinib)?	The clinical experts stated that asciminib should be used in the same manner that was used in the ASCEMBL trial, which is consistent with the submitted indication (i.e., CML patients in CP that have received at least 2 prior TKIs). They noted that this includes patients that have received bosutinib as 1 of the 2 prior TKIs. pERC agreed with the clinical experts.
The ASCEMBL trial allowed patients who failed bosutinib to switch to asciminib but the efficacy data on the switch was not included in the trial publication. Should sequencing between asciminib and bosutinib be funded?	Patients who have failed bosutinib were not included in the ASCEMBL trial, which limits the ability of the clinical experts to conclude with certainty that asciminib is effective in these patients. However, the clinical experts felt that, given the similarities in mechanism of action between bosutinib and the other non-asciminib TKIs, asciminib should be effective in patients who have failed or who are intolerant to 2 or more TKIs, including bosutinib. As such, the clinical experts were of the opinion that sequencing between asciminib and bosutinib should be funded. pERC agreed with the clinical experts.

Implementation questions	Response
Care provision issues	
Asciminib is associated with potential drug-drug, drug-food, and drug-herb interactions requiring assessment or management, which will increase use of pharmacy resources.	pERC agreed with this statement and considered it in their deliberations.
System and economic issues	
There is confidential pricing for bosutinib, ponatinib, and nilotinib. Imatinib and dasatinib are available as generics.	pERC considered this statement in their deliberations.

AP = accelerated phase; BC = blast crisis; CML = chronic myeloid leukemia; CP = chronic phase; ELN = European LeukemiaNet; ITC = indirect treatment comparison; TKI = tyrosine kinase inhibitor.

Clinical Evidence

Description of Studies

ASCEMBL (N = 233) is a phase III, open-label, randomized study of asciminib that compared with bosutinib in patients with CML-CP who had received 2 or more TKIs and experienced treatment failure or intolerance to the most recent TKI. The primary objective of ASCEMBL was to determine the efficacy of asciminib (40 mg twice daily) compared with bosutinib (500 mg daily) in achieving MMR at the 24-week time point. HRQoL, OS, PFS, and CCyR were secondary end points in the trial. Patients were treated until treatment failure or intolerance. Patients in the bosutinib group were permitted to switch to asciminib if they experienced treatment failure. The end of study was defined as 96 weeks after the last patient received their first dose or up to 48 weeks after the last patient switched from bosutinib to asciminib. Patients had to have a European Cooperative Oncology Group (ECOG) performance status of 0 to 2; patients with known presence of *T315I* or *V299L* mutation were excluded.

The mean age in both groups was 51.0 years with a slightly higher proportion of men in the asciminib group (52.2%) compared with the bosutinib group (40.8%). The mean time since initial diagnosis of CML was 6.2 (standard deviation [SD] = 5.75) years in the asciminib group and 7.0 (SD = 5.63) years in the bosutinib group. There were 28.0% and 27.6% of patients in major cytogenetic response at baseline according to bone marrow aspirate measurements in the asciminib and bosutinib groups, respectively; however, bone marrow aspirate measurements were missing at baseline for 22.3% of the asciminib group and 11.8% of the bosutinib group. Patients with any mutation were balanced at baseline with 12.7% in the asciminib group and 13.2% in the bosutinib group. A similar number of patients had received between 2 and 3 lines of prior TKI therapy in each treatment group, although there was a higher proportion of patients who had received only 2 prior TKI therapies in the asciminib group (52.2%) compared with the bosutinib group (39.5%). The reasons for discontinuation of the previous TKI were imbalanced across the treatment groups, with a higher proportion of patients in the asciminib group discontinuing due to lack of efficacy.

Efficacy Results

Health-Related Quality of Life

The baseline mean EQ VAS score was 71.3 (SD = 21.71) in the asciminib group and 74.2 (SD = 18.79) in the bosutinib group (higher scores indicate better HRQoL). Mean change from baseline at week 24 was 7.5 (SD = 23.36) in the asciminib group (n = 106) and 0.5 (SD = 17.87) in the bosutinib group (n = 38); this outcome was not tested statistically.

Overall Survival and Progression-Free Survival

OS and PFS outcomes were immature at the time of primary analysis (May 25, 2020; mean duration of follow-up 15.6 months) and at the updated data cut-off (January 1, 2021; mean duration of follow-up 23.0 months). At the primary analysis, 2.5% of patients in the asciminib group and 1.3% of patients in the bosutinib group had experienced a survival event, and 4.5% of patients in the asciminib group and 6.6% of patients in the bosutinib group had experienced a progression event. These results were unchanged at the updated data cut-off.

Mean Molecular Response

MMR at the 24-week time point was the primary end point of the ASCEMBL trial. At the primary analysis, the MMR rate at 24 weeks in the asciminib group was 25.48% (95% CI, 18.87% to 33.04%); in the bosutinib group, it was 13.16% (95% CI, 6.49% to 22.87%). The primary end point was based on a common risk stratification of major cytogenetic response (MCyR) versus no MCyR at baseline; the difference in MMR rate based on common risk difference was 12.24% (95% CI, 2.19% to 22.30%) with a P value of 0.029. At the updated data cut-off, the MMR rate at 48 weeks was 26.11% (95% CI, 19.44% to 33.72%) in the asciminib group and 11.84% (95% CI, 5.56% to 21.29%) in the bosutinib group; the difference in response rate based on common risk difference was 16.09% (95% CI, 5.69% to 26.49%; not tested statistically).

Complete Cytogenic Response

The CCyR at 24 weeks in the asciminib group was 40.78% (95% CI, 31.20% to 50.90%); in the bosutinib group it was 24.19% (95% CI, 14.22% to 36.74%). Assessed by common risk stratification of MCyR versus no MCyR at baseline, the difference in response rate based on common risk difference was 17.30% (95% CI, 3.62% to 30.99%). At the updated data cut-off, the difference in response rate at 48 weeks based on common risk difference was 19.05% (95% CI, 4.87% to 33.24%). This analysis was not adjusted for multiplicity.

Duration of Response

At the time of primary analysis, 5.6% of the 54 patients receiving asciminib who had gained an MMR at any time went on to lose their response compared with 0% of the 14 patients receiving bosutinib who had gained a response at any time. At the updated data cut-off, these values were 3.2% and 5.6%, respectively.

At the time of primary analysis, 2.3% of the 44 patients receiving asciminib who had gained a CCyR at any time had gone on to lose their response compared with 5.3% of the 19 patients receiving bosutinib who had gained a response at any time. At the updated data cut-off, these values were 2.0% and 4.5%, respectively.

Time to Response

At the time of primary analysis, the mean time to first MMR in the 54 patients receiving asciminib who had achieved an MMR at any time was 19.0 weeks (SD = 14.40) and 22.8 weeks (SD = 18.37) for the 14 patients receiving bosutinib who had gained a response at any time. At the updated data cut-off, these values were 24.7 weeks (SD = 21.71) and 31.1 weeks (SD = 25.81), respectively.

At the time of primary analysis, the mean time to first CCyR in the 44 patients receiving asciminib who had achieved an MMR at any time was 25.4 weeks (SD = 5.09) and 29.0 weeks (SD = 11.50) for the 19 patients receiving bosutinib who had gained a response at any time. At the updated data cut-off, these values were 29.1 weeks (SD = 13.47) and 31.6 weeks (SD = 12.60), respectively.

Harms Results

At the time of primary analysis, the majority of patients in both treatment groups had experienced at least 1 treatment-emergent AE: 89.7% in the asciminib group and 96.1% in the bosutinib group. The most common AEs in the asciminib group were thrombocytopenia (22.4% versus 13.2% in the bosutinib group), neutropenia (17.9% versus 17.1% in the bosutinib group), and headache (16.0% versus 13.2% in the bosutinib group). The most common AEs in the bosutinib group were diarrhea (71.1% versus 11.5% in the asciminib group), nausea (46.1% versus 11.5% in the asciminib group), and increased alanine aminotransferase (27.6% versus 3.8% in the asciminib group). Serious AEs occurred in 13.5% of patients in the asciminib group and 18.4% of patients in the bosutinib group, with none occurring in more than 1 patient, other than pyrexia. Withdrawal from study treatment due to AEs occurred in 5.8% of patients in the asciminib group and 21.1% of patients in the bosutinib group. The AE that most commonly resulted in withdrawal in the asciminib group was thrombocytopenia (1.9% versus 1.3% in the bosutinib group); in the bosutinib group, it was increased alanine aminotransferase (5.3% versus zero in the asciminib group). Deaths occurred in 2.6% of patients in the asciminib group and 1.3% of patients in the bosutinib group. The largest differences in notable harms between the study treatments were in hepatotoxicity (8.3% of patients in the asciminib group reported AEs compared with 30.3% of patients in the bosutinib group) and gastrointestinal toxicity (31.4% of patients in the asciminib group reported AEs compared with 78.9% of patients in the bosutinib group). Pancreatic toxicity was similar between the treatment groups with 8.3% of patients in the asciminib group reporting AEs compared with 9.2% of patients in the bosutinib group.

Critical Appraisal

The primary end point of the ASCEMBL trial was stratified based on MCyR at baseline; however, there was an imbalance within the patients in MCyR at baseline and proportionally more patients in the asciminib group were in CCyR than in the bosutinib group, potentially biasing the study results in favour of asciminib. There was also a substantial number of patients with missing MCyR data at baseline, resulting in 15.9% of asciminib patients and 14.5% of bosutinib patients assigned to the incorrect stratum. A sensitivity analysis was conducted to correct for this using *BCR-ABL1* ratio as a proxy for cytogenetic response, the results of which are consistent with the primary analysis. Formal statistical testing was only conducted on the primary end point, and none of the other analyses aside from the primary end point analysis were controlled for multiplicity (including MMR at 48 weeks). There were slight differences in baseline characteristics of important prognostic factors with

proportionally more patients in the bosutinib group having received higher numbers of prior TKIs and having discontinued their prior TKI due to resistance, suggesting bias in favour of asciminib. However, logistic regression adjusting for these factors found similar results with the primary analysis.

According to clinical experts consulted by CADTH, the demographic and disease characteristics of the ASCEMBL population were reflective of the Canadian population with CML-CP after 2 or more prior TKIs; however, patients with *T315I* or *V299L* mutations were excluded from the trial population, which affects the generalizability to this group of patients. The dosage of asciminib in the ASCEMBL trial (40 mg twice daily) represents only 1 of the anticipated Health Canada–approved dosages (40 mg twice daily and 80 mg once daily). It is unclear if the ASCEMBL evidence is generalizable to a dosage of 80 mg once daily. All outcomes evaluated in the trial and considered in this review (MMR, CCyR, OS, PFS, HRQoL) were clinically relevant, important to patients, and are used in clinical practice. The duration of follow-up was sufficient for assessment of the primary outcome of MMR and secondary outcomes of CCyR and HRQoL; however, conclusions regarding longer-term outcomes of PFS and OS cannot be drawn given the immaturity of the data. Subgroup analysis was not powered to detect treatment differences in patients who experienced treatment failure on their most recent TKI compared with treatment intolerance, line of therapy, disease severity at baseline, or mutational status, and there was no test for subgroup differences. Nevertheless, the clinical experts consulted for this review felt that the results were generalizable across strata for all these subgroups.

Indirect Comparisons

Description of Studies

One MAIC report was submitted by the sponsor and is included in this report. In the absence of direct comparative evidence from trials, the aim of each MAIC was to compare the efficacy (response rate [MMR and CCyR] and time to treatment discontinuation) of asciminib versus ponatinib, nilotinib, and dasatinib in CML-CP patients who have received at least 2 prior TKIs. To identify evidence for relevant comparators, a systematic literature review was conducted to identify evidence from interventional and observational studies. Given the availability of individual patient data from the index trial ASCEMBL, the sponsor aimed to adjust for between-study differences in the distribution of prognostic factors and treatment effect modifiers. The sponsor consulted with an expert clinician to identify which characteristics should be adjusted for in the analysis and their relative importance. For response comparisons, the ponatinib single-arm, phase II study (PACE; N = 203); nilotinib and dasatinib single-centre, prospective cohort study (N = 26; 6 of which received nilotinib); and dasatinib single-centre, retrospective medical record review (N = 24) were used.

Efficacy Results

In the comparison of MMR rate and CCyR rate at both 6 and 12 months in the weighted sample of patients from ASCEMBL compared with the PACE trial (ponatinib), [redacted]

The comparison of efficacy end points was only available for CCyR at both 6 and 12 months in the weighted sample of patients from ASCEMBL compared with patients treated with dasatinib or nilotinib. [redacted]

The comparison of efficacy end points was only available for MMR at 6 months in the weighted sample of patients from ASCEMBL compared with patients treated with dasatinib. [redacted]

Critical Appraisal

The sponsor submitted 1 MAIC report that included comparisons of interest for asciminib versus ponatinib, dasatinib, and nilotinib. The choice to conduct an unanchored MAIC was justified considering the lack of a common comparator. There were important differences in the design of the comparator studies which limit the ability to draw conclusions about the efficacy of asciminib compared with the other treatments. ASCEMBL was a randomized phase III interventional trial, whereas comparator trials included observational trials. These are prone to unique biases (e.g., selection bias, confounding) compared with those collected from prospective interventional studies (such as randomized controlled trials and single-arm trials) that cannot be controlled for using MAIC methods.

An important limitation, inherent to all MAIC analyses, is that all prognostic factors should ideally be adjusted between index and comparator trials to eliminate as much bias from the comparison as possible. This includes both measured and unmeasured characteristics and, thus, it can never be fully accounted for. The list of characteristics provided by the sponsor that were adjusted for were not informed by a systematic review of literature or clinical expert identification; rather, they were chosen because they were included in the comparator trials and could be reliably calculated for patients in the ASCEMBL trial. In addition, all identified prognostic factors could not be matched because of non-convergence and concerns for effective sample size.

The effective sample size for most comparisons was very small, which resulted in very wide CIs that precluded the ability to draw conclusions from the data. For nilotinib specifically, the only available trial that included response data was a retrospective trial of 26 patients, of which only 6 received nilotinib while the other 20 received dasatinib, although the issue of small effective sample size is present for all comparisons. As such, the efficacy of asciminib versus the chosen comparators for response cannot be compared.

Other Relevant Evidence

Description of Studies

The sponsor submitted a phase I, multi-centre, open-label study. The primary objective was to determine the maximum tolerated dose and/or recommended dose for expansion of asciminib single agent or in combination with other drugs. Among the 317 enrolled patients, 30 patients without the *T315I* mutation were treated with the 40 mg twice daily dosage and 17 were treated with the 80 mg once daily dosage.

Efficacy Results

MMR results were consistent with the pivotal trial. Patients receiving asciminib 40 mg twice daily had an MMR rate of 16% at 24 weeks, while patients receiving asciminib at 80 mg daily had an MMR rate of 28.6% at 24 weeks.

Harms Results

All patients in the 40 mg twice daily (n = 30) and 80 mg daily (n = 17) groups had AEs. Serious AEs were found among 11 (36.7%) and 8 (47.1%) patients taking 40 mg twice daily and 80

mg daily, respectively. AEs leading to dose adjustment or interruption were observed among 14 (46.7%) and 10 (58.8%) patients taking 40 mg daily and 80 mg daily dosages, respectively. The notable harms included myelosuppression (36.7% and 41.2%), pancreatic toxicity (53.3% and 29.4%), hepatotoxicity (including laboratory terms) (16.7% and 17.6%), gastrointestinal AEs (70.0% and 52.9%), and cardiac failure (6.7% and 17.6%) for all grades in asciminib 40 mg twice daily and 80 mg once daily arms, respectively. The safety profile was similar to that in the pivotal trial.

Critical Appraisal

There are several internal validity concerns that limit the certainty of conclusions that can be drawn. The primary concern is that there was no control group and no adjustment for known prognostic factors or effect modifiers, thus causal conclusions cannot be established, and the findings are at high risk of confounding. Since the trial was open label, there is a risk that common subjective harms may have been over-reported. Although the inclusion and exclusion criteria are clear, some details of the participant disposition are limited (i.e., number screened versus randomized). There was no hypothesis testing in the trial. The small sample size may negatively affect the reliability of the findings. The patients were not randomized, and there is a possibility of selection bias because it is not clear whether the patients were consecutively enrolled.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adults (≥ 18 years) with CML-CP with prior experience with 2 or more TKIs. Aligns with reimbursement request.
Treatment	Asciminib
Submitted price	Asciminib, 40 mg: $85.00 per tablet Asciminib, 20 mg: $63.00 per tablet
Treatment cost	Average annual cost: $62,092
Comparators	• Bosutinib • Ponatinib • Nilotinib • Dasatinib • Allogenic stem cell transplantation
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years

Component	Description
Time horizon	Lifetime (40 years)
Key data source	ASCEMBL trial
Key limitations	• The comparative effectiveness of asciminib is uncertain for all comparators. The CADTH Clinical Review found insufficient evidence to draw conclusions about comparative OS for asciminib compared with bosutinib in the ASCEMBL trial. The comparative efficacy evidence for all other comparators was derived from highly uncertain indirect evidence, and no conclusions could be drawn. The sponsor's base case relied heavily on long-term extrapolations of benefit and a lack of treatment waning that were not supported by trial evidence and clinical experts felt to be overly optimistic. • The sponsor estimated OS based on MMR, the ASCEMBL trial's primary outcome, using a method that lacked face validity and was highly uncertain. Although the clinical experts agreed that MMR is correlated to OS, the data that was used to establish the surrogacy relationship appeared to violate the proportional hazard assumption and did not fit well to the parametric survival function that was used to estimate long-term OS. • The cost of subsequent treatments was likely overestimated. The sponsor assumed a full dose for all subsequent therapies. Clinical experts consulted by CADTH suggested that this assumption was unrealistic and does not match clinical practice or guidelines published in the literature. • Other methodological limitations were identified by the CADTH review: lack of time-to-discontinuation and OS data for some comparator treatments, the sponsor's choice of a partitioned survival model contributed additional uncertainty due to a lack of mature OS and PFS data, the model produced inconsistent estimates of asciminib effectiveness depending on the choice of comparator therapy, and the choice of subsequent treatment was independent of third-line treatment, which lacked face validity.
CADTH reanalysis results	• CADTH made the following revisions to address the identified limitations: corrected public listed price for dasatinib and reduced dosing intensity for dasatinib, nilotinib, and ponatinib as subsequent treatments. • In the CADTH base case, asciminib was associated with an ICER of $207,406 (incremental costs = $121,148; incremental QALYs = 0.58) compared with bosutinib. CADTH was not able to estimate a base-case ICER for asciminib vs. other comparators because of uncertain comparative efficacy evidence. A price reduction of at least 26% would be needed for asciminib to be cost-effective compared with bosutinib at a willingness-to-pay threshold of $50,000 per QALY.

CML = chronic myeloid leukemia; CP = chronic phase; ICER = incremental cost-effectiveness ratio; PSM = partitioned survival model; QALY = quality-adjusted life-year; TKI = tyrosine kinase inhibitor.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- the model lacked transparency and flexibility
- relative dose intensities were inconsistent and did not reflect clinical practice or the published literature
- market shares and market capture were underestimated for some comparators
- subsequent treatment costs were not included and inappropriately modelled
- the Non-Insured Health Benefits (NIHB) population was double counted
- comparator costs were uncertain due to variation across jurisdictions.

CADTH reanalysis included updating relative dose intensities or doses, altering the initial market shares of the comparators and increasing uptake of asciminib in years 2 and 3, and removing NIHB clients who were double counted in the sponsor's analysis. With these changes, CADTH reanalyses indicated that the reimbursement of asciminib for the third-line or later treatment of adults with Ph+ CML-CP without the *T315I* mutation would be associated

with a budgetary increase of $3,597,276 in year 1, $4,327,522 in year 2, and $5,342,178 in year 3, for a 3-year total incremental cost of $13,266,975. CADTH was unable to appropriately address uncertainties around subsequent therapies.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: June 8, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None