

Reimbursement Recommendation

Asciminib (Scemblix)

Indication: Adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase

Sponsor: Novartis Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Scemblix?

Canada's Drug Agency (CDA-AMC) recommends that Scemblix be reimbursed by public drug plans for the treatment of adults with newly diagnosed Philadelphia chromosome (Ph)-positive (which happens when a person has a changed chromosome called the Ph) chronic myeloid leukemia (CML) (a cancer of the bone marrow and blood cells) in the chronic phase (CP) (when the disease is present but usually progresses slowly and causes few or no symptoms) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Scemblix should only be covered to treat adults with newly diagnosed Ph-positive CML who are in the CP, have a good performance status, and do not have T315I or V299L mutations.

What Are the Conditions for Reimbursement?

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

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that patients treated with Scemblix had higher rates of major molecular response (an important marker of treatment response that guides treatment success in CML) than patients treated with imatinib. The evidence was insufficient to draw definitive conclusions on how Scemblix compares to nilotinib, dasatinib, or bosutinib.
- Scemblix addresses some unmet patient needs as it improves molecular responses, has manageable side effects, and offers an additional treatment option with a convenient oral route of administration.
- Based on public list prices, Scemblix is not considered cost-effective at a willingness-to-pay threshold of \$50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to currently reimbursed alternatives. A price reduction is therefore required.

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 Ph chromosome.

Summary

In 2019, the incidence rate of CML in Canada was 2.3 per 100,000 population.

Unmet Needs in CML

Some patients must discontinue their currently available tyrosine kinase inhibitor (TKI) therapy because of side effects or because their disease no longer responds to the therapy. Treatment intolerance is a main reason for treatment discontinuation across all lines of therapy, often leading to further toxicity with alternative TKIs. There is a need for more tolerable treatment options that support long-term adherence and effective disease control.

How Much Does Scemblix Cost?

Treatment with Scemblix is expected to cost approximately \$4,760 per patient per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that asciminib be reimbursed for adults with newly diagnosed Ph-positive CML in the CP only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT) (ASC4FIRST; N = 405) demonstrated that treatment with asciminib resulted in clinical benefit in adults with newly diagnosed Ph-positive CML in the CP. The ASC4FIRST trial demonstrated that, compared with investigator-selected tyrosine kinase inhibitors (IS-TKIs) (imatinib, nilotinib, dasatinib, or bosutinib), both overall and within the imatinib stratum, asciminib resulted in statistically significant and clinically meaningful improvements in the primary analyses of major molecular response (MMR) at week 48. The MMR rate at 48 weeks was 67.7% (95% confidence interval [CI], 60.72 to 74.07) in the asciminib group and 49.02% (95% CI, 41.97 to 56.10) in the IS-TKI group, a difference of 18.88% (95% CI, 9.59 to 28.17). Within the imatinib stratum, the MMR rate at 48 weeks was 69.31% (95% CI, 59.34 to 78.10) in the asciminib group and 40.20% (95% CI, 30.61 to 50.37) in the imatinib group, a difference of 29.55% (95% CI, 16.91 to 42.18). Clinically meaningful improvements in favour of asciminib were further demonstrated in the key secondary analyses of MMR at 96 weeks compared to IS-TKIs, both overall and within the imatinib stratum. In addition, pERC noted that the analyses of outcomes compared to second-generation TKIs were descriptive in nature and were considered supportive evidence. The impact of asciminib on health-related quality of life (HRQoL) compared to IS-TKIs was very uncertain due to the open-label design of the trial and the large amount of missing data. pERC considered asciminib to have a manageable safety profile, with fewer serious adverse events (AEs) and fewer AEs leading to treatment discontinuation compared to imatinib, second-generation TKIs, and IS-TKIs overall.

Patients identified a need for effective treatment options that improve HRQoL and symptom control with reduced side effects, and that offer an additional and convenient treatment option. pERC concluded that, compared to IS-TKIs overall and within the imatinib stratum, asciminib met some patient needs because it improves molecular responses, has manageable side effects, and offers an additional treatment option with a convenient oral route of administration; however, the benefits of asciminib relative to second-generation TKIs remained uncertain. Due to limitations in the evidence, the impact of asciminib on HRQoL was inconclusive.

Using the sponsor-submitted price for asciminib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) considered most appropriate by pERC for asciminib was \$276,985 per QALY gained compared with all TKIs. The cost-effectiveness of asciminib is highly uncertain due to the immaturity of the clinical effectiveness data, particularly for survival outcomes, and the modelling assumptions underpinning the projected long-term survival benefit. pERC noted that in the CDA-AMC base case, virtually all (99.9%) of the modelled survival benefit occurs beyond the trial's 96-week follow-up and is driven entirely by structural assumptions rather than observed data. The analysis considered appropriate by pERC adopted a shorter time horizon to mitigate the influence of unsupported long-term assumptions, which

provided a more credible estimate in the context of substantial uncertainty as it reduces the extrapolation period and aligns more closely with the clinical trial evidence. At this ICER, asciminib is not cost-effective at a \$50,000 per QALY gained willingness-to-pay threshold for adults with newly diagnosed Ph-positive CML in the CP. A price reduction 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 be reimbursed in adults who meet the following criteria: 1.1. have newly diagnosed Ph-positive CML in the CP.	Evidence from the ASC4FIRST trial showed that treatment with asciminib compared with IS-TKIs, both overall and within the imatinib stratum, resulted in clinical benefit in patients with these characteristics.	—
2. Patients should have a good performance status.	Patients with an ECOG PS of 0 or 1 were included in the ASC4FIRST trial.	Patients with an ECOG PS of 2 or greater may be treated at the discretion of their clinician.
3. Patients must not have any of the following criteria: 3.1. long QT syndrome 3.2. evidence of T315I or V299L mutations at any prior assessment.	The ASC4FIRST trial excluded patients with long QT syndrome and T315I or V299L mutations.	—
Renewal		
4. Assessment for renewal should be based on all of the following: 4.1. hematologic, cytogenetic (if a bone marrow aspiration is performed), and molecular response by RT-PCR 3 to 6 months after treatment initiation 4.2. blood counts and molecular response by RT-PCR every 3 to 6 months thereafter 4.3. a toxicity profile that is acceptable to the patient and clinician.	Patients in the ASC4FIRST trial were assessed for molecular response every 4 weeks until week 12 and then every 12 weeks until end of study treatment. According to the clinical experts, patients in clinical practice are also assessed every 12 weeks in line with the ELN 2020 recommendations.	Although pERC agreed with the clinical experts that the ELN 2020 recommendations ^a regarding treatment failure are appropriate for this patient population, they noted that the decision for discontinuation should take a patient-centred approach, based on clinical judgment and patient preferences.
Prescribing		
5. Treatment should be prescribed by clinicians with expertise and experience in treating CML.	This criterion will ensure that asciminib is prescribed for appropriate patients and that adverse effects are managed in an optimal and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price	The ICER for asciminib is \$276,985 per QALY gained compared with all TKIs. This analysis mitigated the influence of unsupported long-term survival assumptions by shortening the model time horizon. Based on this scenario, price reductions in excess of 30% will be required for asciminib to achieve an ICER below \$50,000 per QALY gained compared to all TKIs.	—

CML = chronic myeloid leukemia; CP = chronic phase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ELN = European LeukemiaNet; ICER = incremental cost-effectiveness ratio; IS-TKI = investigator-selected tyrosine kinase inhibitors; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Ph = Philadelphia chromosome; QALY = quality-adjusted life-year; RT-PCR = real-time polymerase chain reaction; TKI = tyrosine kinase inhibitor.

^aHochhaus A, Baccarani M, Silver RT, et al. *European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia*. *Leukemia*. 2020;34:966 to 84.

Discussion Points

- Unmet need:** pERC noted that CML is a type of blood cancer typically diagnosed in the CP. The committee acknowledged input from patient and clinician groups, highlighting that current therapies include *BCR-ABL* TKIs — imatinib as a first-line option and second-generation TKIs, such as dasatinib, nilotinib, or bosutinib, used in both first- and second-line settings. The clinical experts consulted by CDA-AMC noted that most patients remain dependent on long-term (often lifelong) TKI therapy and the use of second-generation TKIs may be limited by serious and sometimes irreversible AEs, including severe organ dysfunction. The clinician group input highlighted that treatment intolerance is a main reason for treatment discontinuation across all lines of therapy, often leading to further toxicity with alternative TKIs. The committee concluded that there is a need for more tolerable treatment options that support long-term adherence and effective disease control.
- Efficacy outcomes:** The committee noted that, compared to treatment with IS-TKIs, both overall and within the imatinib stratum, asciminib resulted in statistically significant and clinically meaningful improvements in MMR rates at 48 and 96 weeks, supported by a “high” level of certainty per the CDA-AMC Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment. pERC agreed with the clinical experts consulted by CDA-AMC that molecular responses provide an established and objective measure of efficacy for guiding treatment selection and monitoring patients with CML. The results for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) instrument were rated as being of “very low” certainty using GRADE. HRQoL outcomes were identified as important to patients and clinicians in achieving treatment goals. Weighing the uncertainty in the patient-reported outcomes against the meaningful improvements in molecular response, pERC concluded that the available evidence meets patient needs, recognizing that early and sustained molecular responses are associated with better disease control and may allow for treatment-free remission in some patients.

pERC noted that no head-to-head comparison was available comparing asciminib with any individual second-generation TKI. Comparative results in the second-generation stratum (nilotinib, dasatinib, or bosutinib) were descriptive in nature, without formal hypothesis testing or adjustment for multiple comparisons. Comparisons between asciminib and second-generation TKIs showed inconsistent results, with some outcomes (e.g., MMR rate at 96 weeks) suggesting a trend toward clinically meaningful benefit, while others (including MMR rate at 48 weeks) suggested little to no difference, thereby reducing certainty in the evidence. Overall, pERC concluded that the comparative evidence was insufficient to draw definitive conclusions on the relative efficacy of asciminib versus second-generation TKIs.

- **AEs:** pERC discussed patients' desire for treatments with fewer adverse effects and noted that grade 3 or greater AEs, serious AEs, and AEs leading to treatment discontinuation occurred less frequently in patients receiving asciminib compared to those receiving imatinib, second-generation TKIs, and IS-TKIs overall. The most common AEs in the asciminib group were COVID-19, diarrhea, headache, muscle pain, and fatigue. The most common AEs of special interest were myelosuppression and gastrointestinal toxicity, all of which were reported less frequently in patients receiving asciminib. The committee agreed with the clinical experts consulted by CDA-AMC that, overall, asciminib's safety profile appeared manageable. However, the committee discussed that the generalizability of the comparative harms results versus IS-TKIs was limited due to dosing based on product monographs rather than patient-adjusted dosing used in clinical practice in Canada, lack of stratification by individual second-generation TKIs, and limited follow-up duration.
- **Economic considerations:** pERC identified substantial uncertainty in the analysis of cost-effectiveness of asciminib due to the immaturity of the clinical effectiveness data, particularly for survival outcomes, and the modelling assumptions underpinning the projected long-term survival benefit. pERC considered that the CDA-AMC base case likely overestimates the benefit of asciminib, as virtually all (99.9%) of the modelled overall survival benefit occurs beyond the trial's 96-week follow-up and is driven entirely by structural model assumptions rather than observed data. In the ASC4FIRST trial, only 5 deaths were reported at 96 weeks, providing limited evidence to support long-term survival extrapolation. Given these uncertainties, pERC considered a scenario using a shorter time horizon to reduce the influence of the extrapolation period and provide a more credible estimate of cost-effectiveness. This scenario mitigates the influence of unsupported long-term survival assumptions, resulting in an ICER of \$276,985 per QALY gained compared with all TKIs. pERC concluded that this scenario better reflects the available clinical evidence as it relies less on how the trial data are extrapolated over the lifetime time horizon.

Background

CML is a type of blood cancer in which certain white blood cells (i.e., granulocytes) grow and multiply in an uncontrolled manner (i.e., proliferation). This is the result of a change in the genes in which parts of 2 chromosomes (9 and 22) swap places (i.e., reciprocal translocation) and create the Ph, which leads to the

formation of the *BCR::ABL1* fusion gene, which produces a tyrosine kinase enzyme that is constantly active. This abnormal enzyme continuously sends signals (i.e., cell cycle pathways) that push bone marrow cells to keep dividing, leading to excessive growth (i.e., myeloid cell proliferation).

CML accounts for approximately 15% to 20% of all adult cases of leukemia. The incidence rate of CML across all ages and sexes in Canada (excluding Quebec) ranged from 400 to 665 cases from 2009 to 2019, respectively. This corresponds to an incidence rate of 2.3 per 100,000 population in 2019. The 20-year prevalence rate in 2018 in Canada (excluding Quebec) was higher in males (17.1 per 100,000) than in females (13.3 per 100,000). The 20-year prevalence of CML across all ages and sexes in Canada (excluding Quebec) ranged from 3,785 cases in 2015 to 4,325 cases in 2018. This corresponds to a 20-year prevalence rate of 15.2 per 100,000 population in 2018. It is estimated that about 90% to 95% of patients with CML are in CP at diagnosis, which usually manifests as leukocytosis and immature myeloid cells in the blood.

There are a variety of goals of treatment, and these can vary depending on the experts asked and the patients themselves, according to the clinical experts; these include survival, molecular response of varying depths, symptom control and quality of life, treatment-free remission, and freedom from side effects. The mainstay of treatment for CML in the CP are first-generation (imatinib), second-generation (dasatinib, nilotinib, and bosutinib), and third-generation (ponatinib) TKIs that target this abnormal *BCR::ABL1* kinase. Presently, first- and second-generation TKIs are recommended for first-line therapy of CML in the CP. In the case of treatment failure or intolerance, the recommendation is to switch to a previously unused first-, second-, or third-generation TKI. Asciminib inhibits the *ABL1* kinase activity of the *BCR::ABL1* fusion protein by specifically targeting the *ABL* myristoyl pocket. Asciminib has been previously reviewed by CDA-AMC and received a positive recommendation on August 5, 2022, for the treatment of adults with Ph-positive CML in the CP previously treated with 2 or more TKIs.

Asciminib has been approved by Health Canada for adults with Ph-positive CML in the CP who are newly diagnosed or who have previously received 1 or more TKIs. Asciminib is a third-generation TKI that is available as an orally administered tablet and the dosage recommended in the product monograph is 80 mg daily, either as a single dose or 40 mg twice daily.

Sources of Information Used by the Committee

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

- a review of 1 phase III, open-label RCT in adults with newly diagnosed Ph-positive CML in the CP
- patients' perspectives gathered by 4 patient groups, the CML Society of Canada, Heal Canada, and a joint submission from the Canadian CML Network and the Leukemia & Lymphoma Society of Canada
- input from the public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with CML

- input from 2 clinician groups, the Canadian CML Physicians Interest Group and the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

Four organizations provided input: the CML Society of Canada, Heal Canada, and a joint submission from the Canadian CML Network and the Leukemia & Lymphoma Society of Canada. Input was gathered from a total of 126 patients using surveys and interviews.

Patient respondents described the significant physical and emotional burden of CML, including stress, fatigue, pain, and sleep disturbances, which impact their daily activities, work, and social lives. Patients also noted the challenges of finding an effective treatment with minimal side effects and expressed a desire to someday be able to discontinue their treatment while maintaining remission.

Patient respondents with experience using asciminib across the patient group inputs received by CDA-AMC consistently described asciminib as easier to use and less disruptive to daily life compared to other TKIs. Many reported improved blood counts, reduced fatigue, improved mental health, and an overall enhanced quality of life. These respondents also reported a range of side effects, including coldlike symptoms; bone, joint, and muscle pain; brain fog; fatigue; headache; low blood cell counts; and skin rash. Despite these effects, the patient advocacy groups emphasized asciminib's ability to improve quality of life in terms of performing daily routines in personal and work life.

With respect to outcomes of importance, patients prioritized symptom control, reduced side effects, enhanced quality of life, and treatment convenience.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts noted that newer drugs have not been able to improve survival. Although the vast majority of patients who have disease that is managed properly and are able to adhere to therapy do well, there are patients whose disease does not respond or becomes refractory to therapy, according to clinical experts. Nonadherence occurs due to a variety of reasons, including side effects that are not being addressed, patient age, and beliefs. The clinical experts also added that although newer drugs may not have the same side effects as older drugs, they come with their own set of unique side effects. The experts noted that the more advanced the disease is, or the more advanced the disease becomes, the harder it is to control. They emphasized the importance of having many treatment options available to patients, with the ultimate goal of having the best response possible with the fewest side effects possible.

One clinical expert noted that asciminib and other second-generation drugs may have better efficacy in patients with high Sokal risk scores (a score to assess prognosis and severity of disease); another

consideration that determines choice of treatment is comorbidities. This clinical expert noted that some clinicians may prescribe asciminib in the first line for patients with multiple comorbidities and those with high-risk features (i.e., who are part of the high-risk group on any prognostic score model; the most commonly used tool being the European Treatment and Outcome Study long-term survival (ELTS) and Sokal). The experts noted that if treatment-free remission is not the goal it is unclear how aggressive one needs to be considering that survival is more or less the same with all TKIs. In situations in which treatment-free remission is the goal, it is typically achieved with faster-acting, more potent drugs, and this in turn can lead to cost savings. The experts noted that if patients are to receive a treatment for the rest of their life, they likely prefer the treatment with the least symptoms.

The clinical experts noted that at this time there is insufficient evidence to conclusively predict which patients might have disease that responds better to asciminib than to the other available TKIs, adding that the patients most in need of intervention are those with multiple comorbidities that can make it difficult to receive other TKIs. The clinical experts noted that the objective outcome is a reduction of the mutated *BCR::ABL1* gene and that improvement in this molecular marker may have an important impact on patients' mental health; they also noted that molecular response has been used as an end point in clinical trials (in addition to quality of life and freedom from symptoms), which for some patients is a very important outcome.

The clinical experts indicated that reasons for discontinuation would include disease progression or resistance, serious adverse effects that cannot be controlled, or if a deep response allowing for treatment-free remission is achieved and maintained. Other reasons for discontinuation could include a switch in drug therapy because of toxicity or a stem cell transplant (if necessary).

The clinical expert highlighted the importance of having CML experts or hematologists in consultation with CML experts diagnosing and monitoring the disease due to its rarity and the expense of the drugs involved.

Clinician Group Input

Two clinician groups (the Canadian CML Physicians Interest Group and the Ontario Health [Cancer Care Ontario] Hematology Cancer Drug Advisory Committee), including 45 physicians, provided input.

There were no obvious areas of disagreement between the clinical experts and the clinician groups.

The clinician groups agreed with the clinical experts that improving survival and molecular responses, maintaining or improving HRQoL, providing the opportunity for treatment-free remission, and minimizing harms are all treatment goals in CML.

Drug Program Input

The clinical experts consulted for this review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation Issue	Response
Relevant comparators	
The ASC4FIRST trial compared asciminib with standard of care TKIs — imatinib, nilotinib, dasatinib, or bosutinib. Bosutinib is currently only funded for patients previously treated with a TKI. Imatinib is a full benefit in some jurisdictions. Ponatinib is available after 2 or more TKIs or for T315I mutation–positive disease.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
The funding request and Health Canada–approved indication for asciminib is specifically for patients with CML in the CP. Imatinib, nilotinib, dasatinib, and bosutinib are funded for CML in the CP, AP, or BC. Should patients in AP or BC be eligible for asciminib?	The clinical experts noted that asciminib should be considered a viable treatment option for these patients when it is deemed the most appropriate choice for an individual patient, particularly given the precedent of using other drugs in this setting. However, the experts also note that it is unclear whether asciminib would be more effective than any other treatment currently used for this patient population due to the lack of evidence in this specific population. The ASC4FIRST trial did not include data on the AP and BC phases of CML. pERC discussed that there was insufficient evidence to inform the use of asciminib in patients in the AP or BC phases of CML. This aligns with the committee’s conclusions regarding AP and BC in its previous positive conditional recommendation for asciminib for patients with Ph-positive CML in the CP who have been treated with 2 or more TKIs. However, pERC acknowledged that in the 5th edition of the 2022 WHO classification for CML,^a AP is no longer considered an independent phase in the biological continuum of CML but instead is regarded as “high-risk CP.” The rationale for the WHO’s reclassification was that progression to AP has decreased with TKI treatment, and high-risk features at diagnosis associated with CP progression and resistance to TKIs are considered more relevant factors. The committee felt that it would be reasonable to generalize the results from the ASC4FIRST trial to patients with increased risk of progression in the CP of CML. Features associated with increased risk of progression in the CP of CML according to the 2022 WHO classification are as follows. Concerning features at diagnosis (any of the following): • high ELTS score (a measure predicting long-term survival) • 10% to 19% blasts in bone marrow or peripheral blood (the finding of lymphoblasts in peripheral blood or bone marrow [even if < 10%] is consistent with blast phase disease) • 20% or more basophils in peripheral blood • additional clonal cytogenetic abnormalities in Ph-positive cells (e.g., second Ph, –7, isochromosome 17q, complex karyotype, 3q26.2 rearrangements)

Implementation Issue	Response
	- clusters of small megakaryocytes (including micromegakaryocytes) with increased reticulin or collagen fibrosis. Concerning features emerging during treatment (any of the following): - failure to experience complete hematologic response to the first TKI - resistance to 2 sequential TKIs, excluding known causes like specific kinase domain mutations - new chromosomal abnormalities that develop during treatment - compound mutations in the <i>BCR::ABL1</i> gene while receiving TKI therapy.
Patients were aged > 18 years and had an ECOG PS score of 0 to 1. Can patients with an ECOG PS score of 2 or greater receive treatment with asciminib?	pERC agreed with the clinical experts that it would be reasonable to generalize the results of the ASC4FIRST trial to patients with an ECOG PS score of 2 or greater. pERC noted that for the majority of patients, performance status would likely be impacted by comorbidities and not CML itself.
Can asciminib be given again to patients who experienced relapsed while off therapy?	pERC agreed with the clinical experts that in the absence of data to guide a firm recommendation, it may be reasonable to resume treatment again with asciminib in patients who lose complete molecular response or experience relapse while off therapy, based on current practice with other TKIs in this setting.
Ponatinib is considered for patients who are T315I mutation positive. Should patients with a T315I mutation be eligible for asciminib?	The ASC4FIRST trial excluded patients with T315I mutations. The clinical experts noted that patients with a T315I mutation should not be excluded from receiving asciminib. The clinical experts noted that there is evidence (a phase I study) to support asciminib's activity in advanced lines in patients with T315I mutations; the experts felt there is no biological rationale to assume that first-line treatment with asciminib for CML in the CP in patients with T315I mutations would not have similar activity. One clinical expert added that having an alternative to ponatinib would be welcomed, as it has some concerning long-term side effects (e.g., vascular and metabolic toxicities), and patients with T315I mutations have a poor prognosis. pERC discussed that there was insufficient evidence to inform the use of asciminib in patients with T315I mutations because these patients were excluded from the ASC4FIRST trial.
Considerations for prescribing of therapy	
The recommended total daily dose is 80 mg, which can be taken orally either as 80 mg once daily at approximately the same time each day, or as 40 mg twice daily at approximately 12-hour intervals.	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
In the event of a positive funding recommendation, should patients receiving an alternative TKI be eligible to switch to asciminib when funding becomes available?	pERC agreed with the clinical experts that switching a patient from 1 therapy to another should be supported by a valid clinical rationale, such as treatment intolerance or treatment failure. If a patient's disease is responding well to a first-line TKI and tolerating it, that treatment should be continued.

Implementation Issue	Response
Funding algorithm	
Asciminib may change the place in therapy of comparator drugs.	This is a comment from the drug programs to inform pERC deliberations.
This is a complex therapeutic space with multiple lines of therapy, subpopulations, and competing products. Under what clinical circumstances would asciminib be used over existing first-line drugs?	The clinical experts consulted by CDA-AMC agreed that asciminib constitutes another effective treatment option for patients in the first line. However, while it showed benefit compared to imatinib, its comparison to second-generation TKIs was less certain; no head-to-head comparison against individual second-generation TKIs was available and the comparison against the mix of second-generation TKIs in the ASC4FIRST trial was not adjusted for multiple comparisons. It was unclear whether the safety differences between asciminib and second-generation TKIs were driven by a specific TKI within that group. The clinicians noted that while asciminib's adverse event profile appeared manageable overall, its long-term safety was unknown. The choice to use asciminib in the first line would be a patient-centred choice based on patient and disease-specific characteristics and preferences. One clinical expert consulted by CDA-AMC noted that, given the available evidence on the efficacy and safety of asciminib, it may not be selected as a first-line treatment over existing treatment options. The other clinical expert noted that asciminib may be a preferred option in the first line in patients with multiple comorbidities (e.g., pulmonary hypertension, cardiovascular disease, bleeding) who may not be able to tolerate other TKIs. This expert also noted that asciminib's safety profile (less pulmonary and/or vascular toxicity) may make it a preferable option for patients with high-risk features (i.e., those considered high risk on any prognostic score model; the most commonly used tools being the ELTS and Sokal). pERC acknowledged the clinical experts' responses and concluded that the choice to use asciminib in the first line would be a patient-centred choice based on patient and disease-specific characteristics and preferences.
Care provision issues	
Asciminib is associated with potential drug-drug, drug-food, and drug-herb interactions.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
There is confidential pricing for bosutinib, and nilotinib, dasatinib, and imatinib are available as generics.	This is a comment from the drug programs to inform pERC deliberations.

AP = accelerated phase; BP = blast phase; BC = blast crisis; CDA-AMC = Canada's Drug Agency; CML = chronic myeloid leukemia; CP = chronic phase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ELTS = European Treatment and Outcome Study long-term survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Ph = Philadelphia chromosome; TKI = tyrosine kinase inhibitor.

*Khoury JD, Solary E, Abia O, et al. *The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms*. Leukemia. 2022;36:1703-19.

Clinical Evidence

Systematic Review

Description of Studies

The available evidence for this review of asciminib includes 1 ongoing open-label RCT (ASC4FIRST) that compared asciminib to IS-TKIs overall and within the imatinib and second-generation TKIs (i.e., dasatinib, bosutinib, and nilotinib) strata in adults with newly diagnosed Ph-positive CML in the CP. There were 405 patients with CML in the CP who were randomized, 1:1, to asciminib or 1 of the other IS-TKIs, with imatinib being received by up to half of the patients in this control group. Randomization was stratified by ELTS score (low, intermediate, or high risk) and by IS-TKI before randomization (including imatinib and second-generation TKIs). The ASC4FIRST trial is ongoing, with an expected follow-up of 5 years, and the latest report submitted by the sponsor provided results up to 96 weeks. The coprimary outcome was the comparison of asciminib versus IS-TKI MMR rate at 48 weeks, and the other coprimary outcome compared asciminib to imatinib, in what was referred to as the imatinib stratum. The study was to be declared positive if it met either of the 2 primary objectives. Key secondary end points compared the efficacy of asciminib versus IS-TKIs overall and versus imatinib based on the proportion of participants with MMR at week 96. Time to discontinuation of study treatment due to AEs for asciminib versus second-generation TKIs was designated a secondary outcome. The overall safety objective was to characterize the safety and tolerability profile of asciminib compared to IS-TKIs and second-generation TKIs.

There was no indirect treatment comparison or studies addressing gaps submitted for this review.

Patients in the imatinib stratum were older than patients in the second-generation stratum. The median age of patients in the imatinib stratum was 56 years (range, 21 to 79 years) in the asciminib group and 54.5 years (range, 20 to 86 years) in the control group, and in the second-generation stratum was 43 years (range, 18 to 76 years) in the asciminib group and 43 years (range, 19 to 83 years) in the control group. The majority of patients (55%) had a Framingham risk score of “low” across all groups; however, the percentage of patients who were considered low risk was lower in the imatinib stratum (40%) than in the second-generation TKI stratum (69%). The majority of patients (61%) had an ELTS score of “low,” and this was consistent across strata.

Efficacy Results

Overall Survival

At the week 96 analysis, at a median follow-up time of [REDACTED] months, there were [REDACTED] patients ([REDACTED]) who died during the survival follow-up in the asciminib group and [REDACTED] patients ([REDACTED]) who died in the IS-TKI group. No deaths were reported on treatment. The [REDACTED] deaths in the asciminib group were due to [REDACTED] and complications from [REDACTED]. In the IS-TKI group, deaths occurred due to [REDACTED].

Major Molecular Response

The ASC4FIRST trial met both primary end points. At 48 weeks, within the full analysis set, there were 136 patients (67.7%) in the asciminib group and 100 patients (49.0%) in the IS-TKI group who experienced MMR, for a between-group difference of 18.88% (95% CI, 9.59% to 28.17%; $P < 0.001$). In the imatinib stratum, there were 70 patients (69.3%) in the asciminib group and 41 patients (40.2%) in the imatinib group who experienced MMR, for a between-group difference of 29.55% (95% CI, 16.91% to 42.18%; $P < 0.001$). The results of the other secondary end point, MMR at week 48 in the second-generation TKI full analysis set, showed that there were 66 patients (66%) in the asciminib group and 59 patients (58%) in the second-generation TKI group who experienced MMR, for a between-group difference of 8.17% (95% CI, -5.14% to 21.47%).

The ASC4FIRST trial met both key secondary end points. At 96 weeks, there were 149 patients (74.1%) in the asciminib group and 106 patients (52.0%) in the IS-TKI group who experienced MMR, for a between-group difference of 22.42% (95% CI, 13.55%, 31.29%; $P < 0.001$). In the imatinib stratum, there were 77 patients (76.2%) in the asciminib group and 48 patients (47.1%) in the imatinib group who experienced MMR, for a between-group difference of 29.68% (95% CI, 17.57%, 41.79%; $P < 0.001$). The results of the other secondary end point, MMR at week 96 in the second-generation TKI full analysis set, showed that there were 72 patients (72.0%) in the asciminib group and 58 patients (56.9%) in the second-generation TKI group who experienced MMR, for a between-group difference of 15.14% (2.32%, 27.95%).

Sensitivity Analysis

Within the full analysis set, the sensitivity analysis (in which patients who had missing polymerase chain reaction [PCR] evaluations were considered nonresponders) conducted in the ASC4FIRST trial for the rate of MMR at week 48 showed consistency with the primary results, and this was also the case within the imatinib stratum and within the second-generation TKI stratum. There were no participants missing their MMR assessment at week 96; therefore, the results of the sensitivity analysis of MMR rate at week 96, without imputation of data for participants who had missing *BCR::ABL1* transcript evaluations, were identical to the main analysis results. Within the imatinib stratum, there were no participants missing their week 96 MMR assessment; therefore, the results of the sensitivity analyses of MMR rate at week 96 without imputation (treatment difference of [REDACTED]) were identical to the main analysis.

Subgroup Analysis

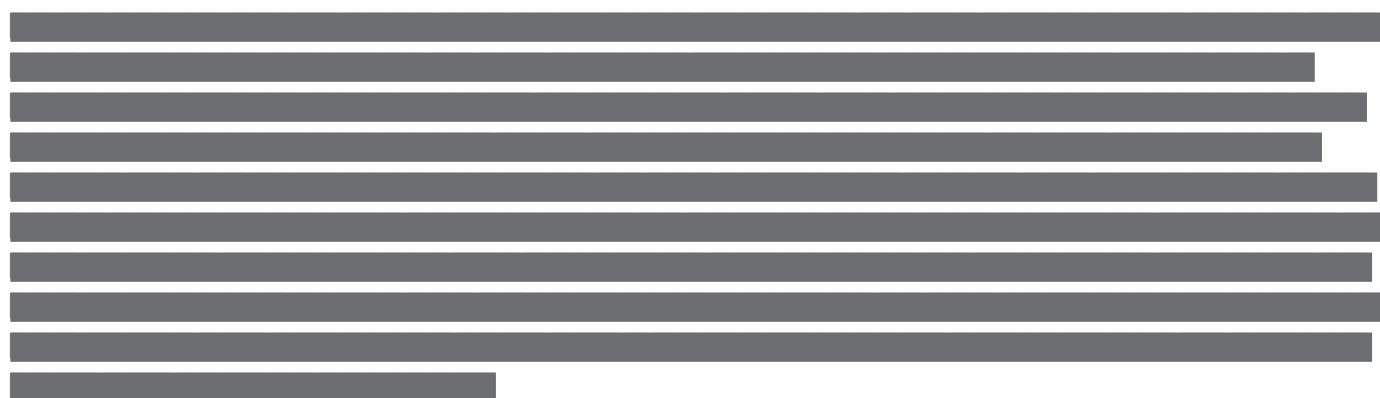
The subgroup analyses for the primary end point in the full analysis set were performed based on demographics as well as ELTS scores. At 96 weeks, the results for the number of patients experiencing MMR were reported for patients with low ELTS scores at randomization (risk difference between groups of 15.5%; 95% CI, 4.6% to 26.5%; $N = 247$), intermediate scores (risk difference between groups of 31.0%; 95% CI, 13.5% to 48.5%; $N = 113$) and high scores (risk difference between groups of 38.1%; 95% CI, 11.6%, 64.7%; $N = 45$). The results were similar when ELTS scores were based on case report form data. There were no tests for interaction reported.

Duration of MMR

By the week 96 assessment, [REDACTED] patients in the asciminib group and [REDACTED] patients in the IS-TKI group had experienced MMR at least once, [REDACTED] patients [REDACTED] in the asciminib group [REDACTED] patients [REDACTED] in the IS-TKI group had subsequently experienced a loss of MMR. Among the [REDACTED] patients who experienced a loss of MMR in the asciminib group, [REDACTED] had confirmed loss of MMR and subsequently discontinued treatment, while [REDACTED] patient interrupted their dose (patient decision) and subsequently discontinued treatment due to a protocol deviation. Among the [REDACTED] patients who experienced a loss of response in the IS-TKI group, [REDACTED] had confirmed loss of MMR and subsequently discontinued treatment, while [REDACTED] patient discontinued treatment due to an AE and had a *BCR::ABL1* level greater than 1% at week 48 at the early discontinuation visit. The Kaplan-Meier estimated probability of patients experiencing MMR maintenance for at least 96 weeks [REDACTED] ([REDACTED]) in the asciminib group and [REDACTED] ([REDACTED]) in the IS-TKI group.

Molecular Response With a 2 Log or Greater Reduction in *BCR::ABL1* Transcripts

At 48 weeks there were 175 patients (87.1%) in the asciminib group and 148 patients (72.5%) in the IS-TKI group who experienced molecular response with a 2 log or greater reduction in *BCR::ABL1* transcripts (MR2) for a between-group difference of [REDACTED]. In the stratum of patients who received imatinib, there were 85 patients (84.2%) in the asciminib group and 63 patients (61.7%) in the imatinib group who experienced MR2, for a between-group difference of [REDACTED]. In the second-generation TKI stratum, there were 90 patients (90.0%) in the asciminib group and 85 patients (83.3%) in the second-generation TKI group who experienced MR2, for a between-group difference [REDACTED].



Molecular Response With a 4 Log or Greater Reduction in *BCR::ABL1* Transcripts

At 48 weeks, there were 78 patients (38.8%) in the asciminib group and 40 patients (20.6%) in the IS-TKI group who experienced molecular response with a 4 log or greater reduction in *BCR::ABL1* transcripts (MR4), for a between-group difference of 18.38% [REDACTED]. In the imatinib stratum, there were 43 patients (42.6%) in the asciminib group and 15 patients (14.7%) in the imatinib group who experienced MR4, for a between-group difference of 28.22% [REDACTED]. In the second-generation TKI stratum, there were 35 patients (35.0%) in the asciminib group and 27 patients

(26.5%) in the second-generation TKI group who experienced MR4, for a between-group difference of 7.54% [redacted].

At 96 weeks, there were 98 patients (48.8%) in the asciminib group and 56 patients (27.5%) in the IS-TKI group who experienced an MR4, for a between-group difference of [redacted]. In the imatinib stratum, there were 53 patients (52.5%) in the asciminib group and 24 patients (23.5%) in the second-generation TKI group who experienced MR4, for a between-group difference of [redacted]. In the second-generation stratum, there were 45 patients (45.0%) in the asciminib group and 32 patients (31.4%) in the second-generation TKI group who experienced an MR4, for a between-group difference of [redacted].

Molecular Response With a 4.5 Log or Greater Reduction in *BCR::ABL1* Transcripts

At 48 weeks there were 34 patients (16.9%) in the asciminib group and 18 patients (8.8%) in the IS-TKI group who experienced a molecular response with a 4.5 log or greater reduction in *BCR::ABL1* transcripts (MR4.5), for a between-group difference of 8.20% (95% CI, 1.78% to 14.62%). In the imatinib stratum, 18 patients (17.8%) in the asciminib group and 5 patients (4.9%) in the imatinib group experienced an MR4.5, for a between-group difference of 13.13% (95% CI, 4.69% to 21.56%). In the second-generation stratum, there were 16 patients (16.0%) in the asciminib group and 13 patients (12.8%) in the second-generation TKI group who experienced MR4.5, for a between-group difference of 3.24% (95% CI, -6.34% to 12.83%).

At 96 weeks, there were 62 patients (30.9%) in the asciminib group and 36 patients (17.7%) in the IS-TKI group who experienced an MR4.5, for a between-group difference of 13.26% [redacted]. In the imatinib stratum, there were 36 patients (35.6%) in the asciminib group and 12 patients (11.8%) in the imatinib group who experienced an MR4.5, for a between-group difference of 24.03% ([redacted]). In the second-generation TKI stratum, there were 26 patients (26.0%) in the asciminib group and 24 patients (23.5%) in the second-generation TKI group who experienced an MR4.5, for a between-group difference of 2.45% ([redacted]).

Time to First MMR

Within the full analysis set, the probability of experiencing MMR by week 48 was numerically higher in the asciminib arm (66.5%; 95% CI, 59.5 to 72.6) than in the IS-TKI arm (46.3%; 95% CI, 39.2 to 53.0). Within the imatinib stratum, the probability of experiencing MMR by week 48 was numerically higher in the asciminib arm (69.1%; 95% CI, 58.8 to 77.2) than in the IS-TKI arm (38.0%; 95% CI, 28.5 to 47.5). Within second-generation TKI stratum, the probability of experiencing MMR by week 48 was numerically higher in the asciminib arm (64.0%; 95% CI, 53.7 to 72.6) than in the IS-TKI arm (54.5%; 95% CI, 44.2 to 63.6).

In the full analysis set, time to first MMR was numerically higher in the asciminib arm than in the IS-TKI arm (median time to first MMR = 24.3 versus 36.4 weeks, respectively). In the imatinib stratum, MMR was experienced numerically faster in the asciminib arm than in the IS-TKI arm (median time to first MMR = 24.1 versus 48.6 weeks, respectively). In the second-generation TKI stratum, MMR was experienced numerically faster in the asciminib arm than in the IS-TKI arm (median time to first MMR = 24.3 versus 36.1 weeks, respectively).

Health-Related Quality of Life

HRQoL was reported as ordinal categorical data for the EORTC QLQ-C30 and the EORTC QLQ Chronic Myeloid Leukemia 24 (CML24) symptom burden. A large number of participants (approximately [REDACTED]) in both groups had missing baseline assessments. There was a large amount of missing data in the asciminib ([REDACTED] with missing data at week 48 and week 96, respectively) and IS-TKI groups ([REDACTED] with missing data at week 48 and week 96, respectively) for the EORTC QLQ-C30 global health status/QoL. There was a similar amount of missing data for the EORTC-CML24 symptom burden ([REDACTED]). At week 96, for EORTC QLQ-C30 global health status/QoL, the number of patients who were “very much better” for asciminib versus IS-TKIs was [REDACTED] patients ([REDACTED]) versus [REDACTED] patients ([REDACTED]), respectively, and “very much worse” was [REDACTED] patients ([REDACTED]) versus [REDACTED] patients ([REDACTED]), respectively. At week 96, for EORTC QLQ-C30 global health status/QoL, [REDACTED] patients in the asciminib group and [REDACTED] in the IS-TKI group had a moderate to high worsening, defined as a score that decreased by more than [REDACTED] points from baseline. For EORTC-CML24 symptom burden, the number of patients who were “very much better,” in the asciminib versus IS-TKI groups, was [REDACTED] patients [REDACTED] versus 0, respectively, and “very much worse,” [REDACTED] patients [REDACTED] versus [REDACTED] patients [REDACTED].

Health Care Resource Utilization

After 96 weeks, [REDACTED] patients [REDACTED] in the asciminib group and [REDACTED] patients [REDACTED] in the IS-TKI group had used at least 1 health care resource. The most common resource used was hospitalization ([REDACTED] patients [REDACTED] in the asciminib group and [REDACTED] patients [REDACTED] in the IS-TKI group).

Harms Results

Adverse Events

AEs were reported in 191 patients (96%) in the asciminib group and 197 patients (98%) in the IS-TKI group at 96 weeks. A grade 3 or higher AE occurred in 89 patients (45%) in the asciminib group compared to 110 patients (55%) in the IS-TKI group at 96 weeks. [REDACTED] in the asciminib group and 42 patients (22%) in the IS-TKI group, and diarrhea, occurring in 35 patients (18%) in the asciminib group and 56 patients (28%) in the IS-TKI group.

Serious Adverse Events

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Withdrawals Due to Adverse Events

AEs leading to treatment discontinuation occurred in 10 patients (5%) in the asciminib group and 26 patients (13%) in the IS-TKI group after 96 weeks of treatment.

The secondary end point, time to discontinuation of study treatment due to AEs for asciminib versus second-generation TKIs, was tested at week 96 and was met. The results of the cause-specific hazard analysis showed that the risk of study treatment discontinuation due to AEs was lower in the asciminib group than in the second-generation TKI group (hazard ratio = 0.463; 95% CI, 0.215 to 0.997; P = 0.0246).

Mortality



Notable Harms

The notable harms prioritized by the clinical experts were acute pancreatitis and the category of ischemic cardiac and central nervous system (CNS) events. After 96 weeks, there were [REDACTED] in each of the asciminib and IS-TKI groups who had an event of acute pancreatitis and there were [REDACTED] in the asciminib group and [REDACTED] patients [REDACTED] in the IS-TKI group who had an AE that fell under the broad category of ischemic heart and CNS conditions.

Other notable harms included myelosuppression, which occurred in [REDACTED] patients [REDACTED] in the asciminib group and [REDACTED] patients [REDACTED] in the IS-TKI group; gastrointestinal toxicity, which occurred in [REDACTED] patients [REDACTED] in the asciminib group and [REDACTED] patients [REDACTED] in the IS-TKI group; and clinical hepatotoxicity, which occurred in [REDACTED] patients [REDACTED] in the asciminib group and [REDACTED] patients [REDACTED] in the IS-TKI group.

Critical Appraisal

- The open-label design of the ASC4FIRST trial may bias the assessment of outcomes, particularly patient-reported outcomes such as HRQoL. The evidence was very uncertain about the effect of asciminib on HRQoL compared to an IS-TKI due to the open-label design and large amount of missing data. Fewer patients in the asciminib group discontinued treatment early compared to those in the IS-TKI group, and this may have biased the assessment of outcomes, most notably harms outcomes due to the differences in exposure. MMR (48 and 96 weeks) and time to discontinuation of study treatment due to AEs were adjusted for multiple testing; however, several other important outcomes, such as HRQoL and other molecular response, were not adjusted for multiplicity and are considered to provide supportive evidence.
- ASC4FIRST is an ongoing trial, and the current follow-up of 96 weeks is not of sufficient duration to assess key clinical outcomes such as overall survival, long-term molecular responses, and harms.
- The clinical experts noted that the dosages of the comparators may not reflect dosages in routine clinical practice, where patients would be carefully up-titrated to minimize the risk of side effects, which, according to the clinical experts, may have inflated the occurrence of harms in the IS-TKI

group. The results from the ASC4FIRST trial were not stratified by second-generation TKI, though the clinical experts noted that the occurrence and specific harms of interest are different between second-generation TKIs.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

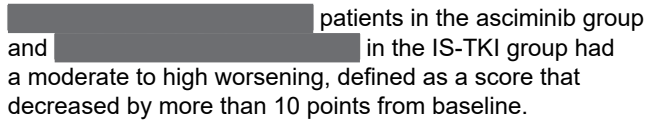
When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. For the MMR outcome, the threshold for a clinically important between-group effect was estimated by the clinical experts to be 10% to 15%, and for MR2 it was estimated to be 5% to 10%. Due to the significant amount of missing baseline data (about 40%) for patient-reported outcomes, change from baseline data were not interpretable. In addition, the 95% CIs for the change from baseline scores in each group, as well as the between-group difference with its associated 95% CI, were lacking. For harms outcomes, the clinical experts estimated that a 10% between-group difference would be clinically meaningful.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from the patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- patients experiencing MMR at week 48
- patients experiencing MR2 at week 48
- change in EORTC QLQ-C30 global health status/QoL score from baseline
- harms: patients experiencing acute pancreatitis (clinical) or ischemia (cardiac and/or CNS).

[Table 3](#) presents the GRADE summary of findings for asciminib versus IS-TKIs for patients with newly diagnosed or previously treated Ph-positive CML in the CP.

Table 3: Summary of Findings for Asciminib vs. IS-TKIs for Patients With CML in the CP

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Investigator-selected TKI	Asciminib 80 mg	Difference		
MMR							
Proportion of patients who experienced MMR at week 48 (primary outcome)	N = 405 (1 RCT)	NR	49 per 100	68 per 100 (61 to 74 per 100)	19 more per 100 (10 more to 28 more)	High ^a	Asciminib results in a clinically important increase in the proportion of patients who experience MMR compared to IS-TKIs.
Molecular response ^b							
MR2 rate at scheduled data collection time points Week 48	N = 405 (1 RCT)	NR	73 per 100	87 per 100		High ^a	Asciminib results in a clinically important increase in the number of patients who experience MR2 when compared to IS-TKIs.
HRQoL ^b							
Change in EORTC QLQ-C30 global health status/QoL scale score from baseline Follow-up: 96 weeks	N = 123 (1 RCT)	NR	 patients in the asciminib group and  in the IS-TKI group had a moderate to high worsening, defined as a score that decreased by more than 10 points from baseline.			Very low ^c	The evidence is very uncertain about the effect of asciminib on HRQoL when compared to IS-TKIs.
Harms (safety set ^d)							
Acute pancreatitis Follow-up: 96 weeks	N = 401 (1 RCT)	NR				Low ^e	Asciminib may result in little to no difference in acute pancreatitis compared to IS-TKIs. The clinical importance of the effect is unclear.
Ischemic heart and CNS conditions Follow-up: 96 weeks	N = 401 (1 RCT)	NR				Low ^e	Asciminib may result in little to no difference in acute ischemic heart and CNS conditions compared to IS-TKIs after 96 weeks of treatment. The clinical

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Investigator-selected TKI	Asciminib 80 mg	Difference		
							importance of the effect is unclear.

CDA-AMC = Canada's Drug Agency; CI = confidence interval; CNS = central nervous system; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL = health-related quality of life; IS-TKI = investigator-selected tyrosine kinase inhibitor; MID = minimal important difference; MMR = major molecular response; MR2 = molecular response with a 2 log or greater reduction in *BCR::ABL1* transcripts; NR = not reported; RCT = randomized controlled trial; TKI = tyrosine kinase inhibitor; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the following footnotes.

^aThe clinical experts consulted by CDA-AMC identified a clinically meaningful between-group difference of 10% to 15% for MMR and 5% to 10% for MR2.

^bThese outcomes were not adjusted for multiplicity.

^cThe level of evidence was rated down 3 levels for extremely serious risk of bias due to the open-label nature of the study and the subjective nature of the outcome (rated down once), as well as the missing outcomes data (65% missing outcomes data in the asciminib group and 74% missing outcomes data in the IS-TKI group) (rated down twice). The level of evidence was rated down 1 level for serious imprecision. As a large proportion of participants were missing baseline data (about 40% in both arms), change from baseline EORTC QLQ-C30 global health status/QoL scale scores are not interpretable. The 95% CIs intervals for the change from baseline scores in each group as well as the between-group difference with its associated 95% CI were lacking.

^dThe safety set comprises all participants who receive at least 1 dose of any study treatment. Participants were analyzed according to the actual study treatment received, and actual treatment received is defined as the randomized treatment if the participant took at least 1 dose of that treatment, or the first treatment received if the randomized treatment was never received.

^eThe CDA-AMC review team did not rate down for risk of bias, as, according to the CDA-AMC review team's judgment, the potential risk of bias arising from the open-label study design was unlikely to impact adverse events such as acute pancreatitis and ischemic heart and CNS conditions. The clinical experts suggested an MID of 10%, which was used to assess certainty. The level of evidence was rated down 2 levels for very serious imprecision due to the low number of events in each group.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted by the sponsor.

Economic Evidence

Economic Evaluation and Budget Impact

- Asciminib is available as 20 mg and 40 mg tablets. At the submitted prices of \$63.00 per 20 mg tablet and \$85.00 per 40 mg tablet, the 28-day cost of asciminib is expected to be \$4,760 per patient, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from the ASC4FIRST trial, which compared asciminib with all TKIs. Evidence submitted by the sponsor indicates that asciminib is likely to increase the number of patients experiencing MMR and deep molecular response compared with all TKIs among patients with newly diagnosed Ph-positive CML in the CP. The impact of asciminib on OS could not be assessed because of immature data.
- The results of the CDA-AMC base case suggest:
 - Asciminib is predicted to be associated with higher costs to the health care system than all TKIs (incremental costs = \$273,995), primarily driven by increased costs associated with drug acquisition.
 - Asciminib is predicted to be associated with a gain of 3.48 life-years compared to all TKIs and may result in a gain of 2.91 QALYs compared to all TKIs.
 - The ICER for asciminib compared to all TKIs was \$94,270 per QALY gained. The estimated ICER for asciminib versus all TKIs was highly sensitive to assumptions about long-term efficacy and OS. Approximately 99% of the incremental health benefit of asciminib compared to all TKIs was gained in the extrapolated period. In the absence of long-term comparative evidence, the predicted QALY gain for patients receiving asciminib is highly uncertain and may be overestimated.
 - The results of the CDA-AMC base case are highly uncertain and likely overestimate the benefit of asciminib. The model contains structural design choices that could not be modified and bias the results in favour of asciminib. Moreover, there is no long-term evidence to support the magnitude of OS benefit assumed by the sponsor. As such, the cost-effectiveness of asciminib is expected to lie between the CDA-AMC base case (ICER = \$94,270 per QALY gained) and the scenario assuming a shorter time horizon (ICER = \$276,985 per QALY gained).
- CDA-AMC estimates that the budget impact of reimbursing asciminib for the treatment of adults with newly diagnosed Ph-positive CML in the CP who are initiating first-line therapy will be approximately

\$18 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$43 million on asciminib over this period. The actual budget impact of reimbursing asciminib will depend on the percentage of patients covered by public drug plans and subsequent therapies.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice Chair), Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney

Meeting date: August 13, 2025

Regrets: Six expert committee members did not attend.

Conflicts of interest: None



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