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Reimbursement Recommendation

Momelotinib (Ojjaara)

Indication: For the treatment of splenomegaly and/or disease-related symptoms, in adult patients with intermediate or high-risk primary myelofibrosis (MF), post polycythemia vera myelofibrosis or post essential thrombocythemia MF who have moderate to severe anemia.

Sponsor: GlaxoSmithKline Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Ojjaara?

Canada's Drug Agency (CDA-AMC) recommends that Ojjaara be reimbursed by public drug plans for the treatment of adult patients with intermediate or high-risk primary myelofibrosis (MF), post–polycythemia vera MF, or post–essential thrombocythemia MF who have moderate to severe anemia.

Which Patients Are Eligible for Coverage?

Ojjaara should only be covered to treat splenomegaly and/or disease-related symptoms in adult patients with intermediate or high-risk primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF, who have an enlarged spleen that is palpable in physical examination and at least 5 cm below the rib cage margin, moderate to severe anemia, and good performance status.

What Are the Conditions for Reimbursement?

Ojjaara should only be reimbursed if it is prescribed by specialists in treating MF and the cost of Ojjaara does not exceed the drug program cost of treatment with the least costly Janus kinase inhibitor (JAKi) reimbursed for the treatment of adults with MF.

Why Did CDA-AMC Make This Recommendation?

- Evidence from the SIMPLIFY-1 and MOMENTUM trials demonstrated that Ojjaara increases transfusion independence and may improve splenic response rate (SRR) and reduce disease-related symptoms compared to ruxolitinib and danazol.
- Based on the CDA-AMC assessment of the health economic evidence, Ojjaara does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Ojjaara compared with the least costly JAKi reimbursed for MF.
- Ojjaara met some patient needs by likely reducing transfusion requirements and symptom burden of MF.
- Based on public list prices, Ojjaara is estimated to cost the public drug plans approximately $11 million over the next 3 years.

Summary

Additional Information

What Is MF?

MF is a rare, chronic, and progressive bone marrow disorder characterized by bone marrow fibrosis, bone marrow failure, systemic inflammation, and an enlarged spleen. It can develop as primary MF or as secondary forms following essential thrombocythemia or polycythemia vera. The incidence of primary MF in Canada is estimated at 0.80 per 100,000 person-years, with approximately 200 new cases diagnosed annually.

Unmet Needs in MF

Patients with MF need treatments that provide more durable responses, better management of anemia, and potential modification of disease progression.

How Much Does Ojjaara Cost?

Treatment with Ojjaara is expected to cost approximately $6,464 per patient per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that momelotinib be reimbursed for the treatment of splenomegaly and/or disease-related symptoms, in adult patients with intermediate or high-risk MF, post–polycythemia vera MF, or post–essential thrombocythemia MF who have moderate to severe anemia, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One randomized, double-blind, active-controlled, phase III trial (the SIMPLIFY-1 trial, N = 432) in patients with MF who had not previously received JAKi therapy demonstrated that 24 weeks of treatment with momelotinib resulted in an increase in the number of patients who were transfusion independent, compared to ruxolitinib (difference of 18.0% of patients; 95% confidence interval [CI], 9.0% to 26.0%). In a subpopulation of patients in the SIMPLIFY-1 trial with anemia (hemoglobin < 100 g/L, n = 180), the rate of transfusion independence was 46.5% for patients treated with momelotinib and 26.6% for patients treated with ruxolitinib, corresponding to a difference of 20% (95% CI, 5% to 34%). Further, 1 randomized, double-blind, active-controlled, phase III trial (the MOMENTUM trial, N = 195) in patients with MF with anemia (hemoglobin < 100 g/L) and prior exposure to a JAKi demonstrated that 24 weeks of treatment with momelotinib may have resulted in an increase in the number of patients who were transfusion independent, compared to treatment with danazol (difference of 11.0% of patients; 95% CI, –0.8% to 22.8%). In addition, evidence from the MOMENTUM trial demonstrated that treatment with momelotinib was also likely to increase the SRR (treatment difference in the proportion of responders = 19.4%; 95% CI, 11.0% to 27.8%) and reduce disease-related symptoms as measured by the total symptom score (TSS) on the MF Symptom Assessment Form (MFSAF) (treatment difference in the proportion of responders = 15.67%; 95% CI, 5.5% to 25.8%), compared to treatment with danazol.

Patient input identified the following needs for new treatments for MF: fewer and less severe side effects, improved quality of life with reduced symptom burden, delayed disease progression, and a reduction in transfusions and transfusion dependency. pERC concluded that momelotinib met some of these needs, as it likely reduces transfusion requirements and may reduce the symptom burden of MF.

At the sponsor-submitted price for momelotinib and publicly listed prices for all relevant comparators, momelotinib was more costly than some relevant comparators used in the treatment of adults with MF. Given the limitations and uncertainty associated with the long-term comparative efficacy of momelotinib to relevant comparators, there is insufficient evidence to justify a price premium over the least expensive JAKi reimbursed for the treatment of adults with MF.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Momelotinib should be initiated in adult patients, with or without prior treatment experience with a JAKi, who have primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF, who meet all of the following criteria: 1.1. high-risk or intermediate-2 risk MF defined by the DIPSS, or intermediate-1 risk associated with symptomatic splenomegaly and/or hepatomegaly 1.2. palpable splenomegaly of at least 5 cm 1.3. moderate to severe anemia, defined by a hemoglobin level less than 100 g/L.	Evidence from the SIMPLIFY-1 and MOMENTUM trials demonstrated that treatment with momelotinib has a beneficial effect compared to danazol and ruxolitinib, respectively, in adults with high-risk or intermediate-2 risk primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF with splenomegaly, who were symptomatic and had anemia. Further, patients included in the SIMPIFY-1 trial did not have prior treatment with a JAKi and patients included in the MOMENTUM trial were required to have been previously treated with a JAKi for at least 90 days, or at least 28 days with an RBC transfusion requirement of at least 4 units in 8 weeks or grade 3 or 4 hematological AEs. As such, there was evidence of a treatment benefit with momelotinib regardless of JAKi exposure.	The DIPSS and DIPSS-plus were used to assess MF risk status in the SIMPLIFY-1 and MOMENTUM trials, respectively. As such, either can be used for the assessment of risk status to inform patient eligibility for treatment with momelotinib.
2. Patients must have good performance status.	In the SIMPLIFY-1 and MOMENTUM trials, patients were required to have an ECOG performance status score of 0 to 2.	—
Renewal		
3. Patients should be assessed for a response to treatment with momelotinib every 3 to 6 months.	Evidence of a response to treatment was demonstrated following 24 weeks of treatment with momelotinib in the SIMPLIFY-1 and MOMENTUM trials.	Response to treatment refers to an observed clinical benefit as determined by the treating clinician. This may include a reduction in transfusion requirements, a reduction in splenic volume, or an improvement in symptoms of MF.
Discontinuation		
4. Treatment with momelotinib should be discontinued upon occurrence of any of the following: 4.1. response to treatment has not been demonstrated after 6 months of treatment 4.2. disease progression 4.3. development of serious adverse events or unacceptable toxicity.	In the SIMPLIFY-1 and MOMENTUM trials, momelotinib was discontinued due to disease progression, splenic progression, or unacceptable toxicity.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Momelotinib should be prescribed under the care of a clinician with expertise in treating and managing MF.	This is meant to ensure that momelotinib is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. The price of momelotinib should be negotiated so that it does not exceed the drug program cost of treatment with the least costly JAKi reimbursed for the treatment of MF.	There is insufficient evidence to justify a price premium for momelotinib over the least costly JAKi reimbursed for MF.	—

DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; JAKi = Janus kinase inhibitor; MF = myelofibrosis; RBC = red blood cell.

Discussion Points

- **Place in therapy:** pERC noted that MF is a rare disease with limited treatment options, high symptom burden, and high resource use. Overall, the evidence demonstrated that momelotinib may be a treatment option for patients with MF, particularly for patients in whom anemia is the most challenging symptom rather than splenomegaly or constitutional symptoms, or when treatment with ruxolitinib leads to significant anemia. pERC also noted that it is unclear if momelotinib offers an advantage in SRR over existing therapies or offers better symptom resolution compared to ruxolitinib in patients who are treatment-naive. Therefore, the use of momelotinib or other available therapies is anticipated to be based on therapeutic needs and an overall symptom assessment.
- **GRADE certainty of evidence:** The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of certainty of evidence for efficacy outcomes ranged from moderate to high certainty in the SIMPLIFY-1 trial, very low to moderate certainty in the SIMPLIFY-2 trial, and low to moderate certainty in the MOMENTUM trial. Although the transfusion independence response rate in the MOMENTUM trial was a secondary end point that was not controlled for multiplicity, the overall evidence from the 3 trials was supportive of a treatment benefit for momelotinib relative to ruxolitinib, best available treatment (BAT), and danazol for this outcome. Further, in the MOMENTUM trial, which specifically enrolled patients with anemia who had experience with JAKi treatment, momelotinib likely improved splenomegaly and reduced symptoms of MF compared to danazol. In the SIMPLIFY-1 trial, which enrolled patients not previously treated with a JAKi, there was likely no difference in the SRR for patients treated with momelotinib compared to ruxolitinib.
- **Risk status:** pERC discussed the evidence for patients with intermediate-1 MF. In the MOMENTUM trial, about 5% of patients in both treatment groups had intermediate-1 MF. In the SIMPLIFY-1 trial, the proportion of patients with intermediate-1 MF at baseline was 21% and 20% for the momelotinib and ruxolitinib groups, respectively; in the SIMPLIFY-2 trial, 22% and 31% of patients in the momelotinib and BAT groups, respectively, had intermediate-1 MF at baseline. pERC also noted that

patients with intermediate-1 MF were required to have symptomatic splenomegaly or hepatomegaly to be eligible for the SIMPLIFY-1 and SIMPLIFY-2 trials. In the absence of a subgroup analysis by risk status, pERC noted that it is challenging to determine the benefit in patients with intermediate-1 MF; however, given the benefit observed in transfusion independence in the overall population, it was considered reasonable to consider momelotinib for patients with intermediate-1 MF with anemia. Further, pERC noted that the results do not suggest an added benefit relative to ruxolitinib or BAT in terms of SRR in the SIMPLIFY-1 and SIMPLIFY-2 trials.

- **Gaps in the evidence:** pERC discussed the lack of evidence comparing momelotinib to ruxolitinib with an erythropoietin stimulating agent (ESA) for the treatment of MF with anemia as a notable gap in the evidence. For reference, ESAs were prohibited in the SIMPLIFY-1 and MOMENTUM trials, and only 3.8% of patients randomized to BAT in the SIMPLIFY-2 trial were treated with an ESA.
- **Relevance of the SIMPLIFY-2 trial**: Patients enrolled in the SIMPLIFY-2 trial were not required to have anemia; however, the mean hemoglobin level at baseline was 94 to 95 g/L. In the SIMPLIFY-2 trial, momelotinib likely resulted in an increase in the number of patients who were transfusion independent compared to BAT; however, the clinical relevance of the increase was uncertain. Also, when compared to BAT, momelotinib may result in an increase in the number of patients who are considered responders based on TSS, but the evidence is very uncertain about the effect of momelotinib on SRR.
- **Long-term evidence:** pERC discussed the long-term evidence for momelotinib based on a long-term, open-label extension of the SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM trials. pERC noted that the studies suggest that more than two-thirds of patients experienced sustained efficacy with momelotinib beyond 24 weeks, as it may provide ongoing benefits in terms of transfusion independence, splenic response, and symptom relief; however, data were only available up to 24 weeks in the open-label phase (48 weeks of treatment total), which may not be long enough to observe important safety and efficacy outcomes.
- **Survival and progression:** pERC was unable to conclude whether treatment with momelotinib delayed disease progression in patients with MF, which was identified as important by patients. Although overall survival (OS) and leukemia-free survival were evaluated in the MOMENTUM trial, the end points were exploratory and only available up to week 24, which was considered an insufficient duration of time to assess these outcomes. Based on the results that were available, there was no difference in OS between momelotinib and ruxolitinib (in the SIMPLIFY-1 trial) and danazol (in the MOMENTUM trial).
- **Relevance of fedratinib as a comparator:** The sponsor submitted a deviation request to exclude fedratinib as a comparator in the pharmacoeconomic analysis. The reasons provided to justify this exclusion were the lack of available data in the literature to inform a direct or indirect treatment comparison between fedratinib and ruxolitinib and the absence of evidence of a difference in efficacy between the 2 treatments. The sponsor also claimed that fedratinib has a higher drug acquisition cost than ruxolitinib, meaning that the exclusion of fedratinib would not have a meaningful effect on the cost-effectiveness analysis. CDA-AMC accepted this request and excluded fedratinib from

the economic analysis. Accordingly, the cost-effectiveness of momelotinib compared to fedratinib is unknown, and there is insufficient evidence to justify a higher price for momelotinib than for fedratinib in patients with MF who have anemia.

Background

MF is a rare, chronic, and progressive bone marrow disorder categorized as a Philadelphia chromosome–negative myeloproliferative neoplasm (MPN). Characterized by the excessive production of reticulin and collagen fibres, MF leads to bone marrow fibrosis, bone marrow failure, systemic inflammation, and splenomegaly. MF can develop as primary myelofibrosis (PMF) or as secondary forms following essential thrombocythemia or polycythemia vera. PMF is the most aggressive type and has the potential to progress into acute myeloid leukemia (AML). The incidence of primary MF in Canada is estimated at 0.80 per 100,000 person-years, with approximately 200 new cases diagnosed annually, accounting for 1% of all hematological malignancies. Key clinical manifestations of MF include severe anemia, thrombocytopenia, marked hepatosplenomegaly, and constitutional symptoms such as fatigue, night sweats, and unintentional weight loss. Current treatment options primarily include JAKis like ruxolitinib, which are aimed at reducing splenomegaly and managing symptoms. However, unmet needs remain, especially for patients who experiences disease progression after JAKi therapy.

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of momelotinib, administered orally at a dosage of 200 mg once daily, in the treatment of disease-related splenomegaly or symptoms, and anemia in adult patients with primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF who are either JAKi naive or have been previously treated with a JAKi. Momelotinib — which also inhibits *ACVR1* — may provide additional benefits, particularly in managing anemia, by restoring iron homeostasis and reducing the need for red blood cell (RBC) transfusions. Momelotinib has not been previously reviewed by CDA-AMC.

Momelotinib has been approved by Health Canada for the treatment of splenomegaly and/or disease-related symptoms, in adult patients with intermediate or high-risk primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF who have moderate to severe anemia. Momelotinib is a JAKi that inhibits wild-type JAK1 and JAK2 and mutant JAK2. It is available as 100 mg, 150 mg, and 200 mg oral tablets, and the dosage recommended in the product monograph is 200 mg taken orally once daily.

Sources of Information Used by the Committee

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

- a review of 3 phase III randomized controlled trials (RCTs) (2 double-blind and 1 open-label) in adult patients with PMF or secondary MF (post–polycythemia vera and post–essential thrombocythemia MF), who are JAKi naive or have been treated with a JAKi, and 3 long-term extension studies

- patients' perspectives gathered by 2 patient groups: a joint input by the Leukemia and Lymphoma Society of Canada (LLSC) and the Canadian Myeloproliferative Neoplasm Network (CMPNN), and Heal Canada
- input from public drug plans and cancer agencies that participate in the Reimbursement Review process
- 2 clinical specialists with expertise diagnosing and treating patients with MF
- input from 2 clinician group(s): a joint input from LLSC and the Canadian MPN Clinician Group, and Ontario Health – Cancer Care Ontario (OH-CCO)'s hematology cancer disease site drug advisory committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

LLSC and the CMPNN jointly provided patient input for this review, sourcing information from 3 online surveys conducted between March 2024 and May 2024, with a total of 73 respondents. Heal Canada also provided input for this review, sourcing information mainly from surveys and interviews. These surveys from both inputs gathered insights from patients with MF and their caregivers, focusing on their lived experiences and specific interactions with the drug under review, momelotinib. MF profoundly impacts patients and their families, affecting physical, emotional, and financial aspects of daily life. Many patients reported relying heavily on caregiver support, which placed significant burdens on both parties. Key outcomes important to patients included the management of fatigue, anemia, and spleen size, with a particular emphasis on reducing symptom burden, improving quality of life, and decreasing the need for blood transfusions. Notably, 73% of respondents with experience using momelotinib felt it improved their quality of life.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

Clinical experts consulted for this submission identified significant unmet needs in the current treatment landscape for MF. While existing JAKis like ruxolitinib and fedratinib effectively address symptoms such as splenomegaly and constitutional symptoms, they do not modify the underlying disease or delay its progression. Additionally, hematopoietic stem cell transplant, the only potentially curative treatment, is viable for fewer than 10% of patients due to its high morbidity and mortality. Experts emphasized the need for therapies that provide more durable responses, better management of anemia, and potential modification of disease progression.

Regarding the place of momelotinib in therapy, experts suggested that it could be an important option for patients with MF who require JAKi therapy and also have clinically significant anemia. Momelotinib would be particularly beneficial for patients who are naive to JAKis or those who have developed anemia or

intolerance on existing JAKi therapy. The experts noted that it could be used in first-line settings and as a second-line or third-line treatment for patients with clinically relevant anemia and MPN symptoms. However, the experts noted that momelotinib might be less suitable for patients whose primary issue is symptomatic splenomegaly in the context of ruxolitinib resistance or intolerance.

Based on the input provided by the clinical experts, the patient population most likely to benefit from momelotinib includes those with MF who are JAKi naive with splenomegaly or MPN symptoms and clinically relevant anemia, as well as those experiencing anemia or intolerance on other JAKi therapies. Patients whose main issue is splenomegaly without accompanying anemia or MPN symptoms may be less likely to benefit.

Experts recommended assessing the response to momelotinib through patient-reported outcomes, physical examinations (including spleen size), and anemia parameters such as hemoglobin levels and transfusion frequency. They suggested that responses should be evaluated approximately every 3 months, with a clinically meaningful response being indicated by subjective improvements, reduced spleen size, and improved anemia metrics. Treatment discontinuation should be considered if there is no response after about 6 months, a loss of a prior response, or grade 3 adverse events (AEs) that do not resolve with dose modification.

Finally, experts advised that momelotinib should be prescribed and monitored by hematologists or oncologists with expertise in MF, ideally in hospital outpatient clinics or specialty settings where appropriate expertise is available. Regional access to such specialists should be considered when prescribing momelotinib.

Clinician Group Input

Clinician group input on the review of momelotinib was provided by 15 clinicians from LLSC and the Canadian MPN Clinician Group, as well as OH-CCO’s drug advisory committee. Both clinician groups emphasized the significant unmet need for effective treatments to manage anemia in MF, aligning with the clinical experts consulted for this submission, who also identified anemia management as a critical challenge. While both the clinician groups and the CDA-AMC clinical experts recognized the potential of momelotinib to benefit patients with MF-associated anemia, the clinician groups noted that momelotinib lacks evidence on the reduction in the risk of progression to acute leukemia. The clinician groups highlighted that momelotinib's response assessment in clinical practice should include improvements in hemoglobin, reductions in transfusions, and stable disease or improvement in symptom burden, which are also consistent with the views of the CDA-AMC clinical experts. These clinician groups believe that momelotinib could be relevant to clinical practice, especially for patients who struggle with anemia and transfusion dependence, although they also caution that it does not address all aspects of disease progression.

Drug Program Input

Input was obtained from the drug programs that participate in the Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for momelotinib:

- considerations for initiation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- potential need for a provisional funding algorithm.

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Would use of momelotinib be limited to patients with anemia due to myelofibrosis?	The clinical experts indicated that the use of momelotinib would likely be prioritized for patients with myelofibrosis who are anemic or borderline anemic. The clinical experts highlighted the importance of carefully considering the threshold for anemia, particularly for patients with mild anemia (hemoglobin levels between 100 g/L and 120 g/L). Momelotinib could be particularly beneficial in cases where treatment with ruxolitinib has led to anemia. pERC agreed with the experts, but noted that the evidence for patients with anemia was limited to those with moderate to severe anemia (hemoglobin levels less than or equal to 100 g/L).
Generalizability	
At the time of funding, should patients receiving alternative therapies (e.g., ruxolitinib, fedratinib, hydroxyurea) be eligible to switch to momelotinib?	The experts indicated that momelotinib should be available as an upfront treatment, including as a second-line option after initial treatment with other therapies. The experts noted that patients currently receiving alternative therapies, such as ruxolitinib or fedratinib, could be eligible to switch to momelotinib, especially if they develop anemia. However, the switch might be more appropriate in cases where splenomegaly is not the primary concern, and anemia is the predominant issue. pERC agreed with the experts, noting that consideration for switching to momelotinib should be due to anemia as the main symptom.
Funding algorithm	
Is there evidence for downstream treatment options following progression on momelotinib?	The experts indicated that while there is no direct evidence for downstream treatment options following progression on momelotinib, other JAK inhibitors like fedratinib may be considered as a subsequent line of therapy for patients with myelofibrosis for whom ruxolitinib is contraindicated or for patients who cannot tolerate ruxolitinib. The experts indicated that momelotinib could be used as a first-line treatment, with fedratinib as a potential second-line option. In cases where the primary concern is anemia rather than splenomegaly, momelotinib might be more suitable in third-line settings. However, the experts acknowledged that the evidence is limited, and treatment decisions should be individualized based on patient response and specific clinical scenarios. pERC acknowledged that treatment decisions are individualized based on the symptomatic treatment needs. However, pERC noted that treatment options

Implementation issues	Response
	following progression on ruxolitinib are limited, and that no evidence was identified for the use of fedratinib following progression on momelotinib.

JAK = Janus kinase; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Note that the sponsor's application was filed on a pre–Notice of Compliance (NOC) basis. The clinical and economic evidence included herein was based on the indication that was initially submitted to Health Canada and CDA-AMC, which was for the treatment of disease-related splenomegaly or symptoms, and anemia in adult patients with primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF who are JAKi naive or have been treated with a JAKi.

Clinical Evidence

Systematic Review

Description of Studies

Three pivotal RCTs were included in the sponsor's submission to assess the efficacy and safety of momelotinib for MF in adults. The SIMPLIFY-1 trial (N = 432) was a phase III, double-blind, multicentre study that compared momelotinib with ruxolitinib in patients who were JAKi naive with primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF. The primary end point was SRR at week 24, defined as 35% or greater reduction in spleen volume from baseline. Secondary outcomes included the TSS response rate (defined as the proportion of patients with a ≥ 50% reduction from baseline in symptom burden) and transfusion independence (defined as the proportion of patients who do not require any RBC transfusions for a period of 12 weeks while maintaining hemoglobin levels ≥ 8 g/dL). The SIMPLIFY-2 trial (N = 156) was a phase III, open-label, multicentre study that evaluated the efficacy of momelotinib versus BAT (where 88.5% of patients received ruxolitinib as the BAT of choice) in patients with MF who were previously treated with ruxolitinib but had either an inadequate response or experienced intolerance. The primary end point was SRR at week 24, with secondary outcomes including TSS response rate and OS. The MOMENTUM trial (N = 195) was a phase III, double-blind, multicentre study that focused on patients with symptomatic and anemic MF who had received prior JAKi therapy. The trial compared momelotinib with danazol, with the primary end point being the TSS response rate at week 24. Secondary outcomes included SRR, transfusion independence, and OS.

Baseline characteristics across the studies showed a population predominantly comprising patients with intermediate-2 or high-risk MF. Across the 3 trials, more than half of the patients were male, the majority were white, and the mean age ranged from 64 years to 71 years across treatment groups. Specifically, in the SIMPLIFY-1 trial, 56.5% of patients were male and 43.5% were female, with 9.2% of patients identifying as Asian, 0.9% as Black, 82.6% as white, and 7.9% as other or not reported. In the SIMPLIFY-2 trial, 59.6% of patients were male and 40.4% female, with 3.8% identifying as Black, 81.4% identifying as white, and 14.7% as other or not reported. In the MOMENTUM trial, 63.1% of patients were male and 36.9% were female, with 9.2% identifying as Asian, 2.1% as Black, 80.5% as white, and 6.2% as other. With the exception of anemia-

related characteristics in the MOMENTUM trial, in which only patients with a hemoglobin level of less than 10 g/dL where included, the rest of the baseline characteristics were relatively consistent across the 3 trials, with relatively balanced demographic and clinical characteristics between treatment arms.

Efficacy Results

In the SIMPLIFY-1 trial, 66.5% of patients treated with momelotinib experienced transfusion independence at week 24, compared to 49.3% in the ruxolitinib group, with a proportion difference of 0.18 (95% CI, 0.09 to 0.26). In the SIMPLIFY-2 trial, 43.3% of patients in the momelotinib group experienced transfusion independence compared with 21.2% in the BAT group, with a proportion difference of 0.23 (95% CI, 0.09 to 0.37). In the MOMENTUM study, 30.8% of patients treated with momelotinib experienced transfusion independence at week 24, compared to 20.0% in the danazol group (proportion difference = 10.99%; 95% CI, −0.80% to 22.77%), with an adjusted proportion difference noninferiority test that targeted 80% retention of the effect of danazol at 14.77% (95%CI, 3.13% to 26.41%; P = 0.0064).

The mean rate of RBC transfusions at week 24 in the SIMPLIFY-1 trial was 0.5 units per patient-month in the momelotinib group versus 1.0 unit in the ruxolitinib group, with a transfusion rate ratio of 0.28 (95% CI, 0.19 to 0.43). In the SIMPLIFY-2 trial, the mean transfusion rate was 1.6 units in the momelotinib group compared to 1.8 units in the BAT group (transfusion rate ratio = 0.80; 95% CI, 0.49 to 1.31). In the MOMENTUM trial, patients in the momelotinib group received a mean 6.6 units compared with a mean 10.9 units in the danazol group, with a treatment difference of −5.66 units (95% CI, −10.65 to −0.68).

In the SIMPLIFY-1 trial, 26.5% of patients in the momelotinib group achieved a splenic response at week 24, compared to 29.5% in the ruxolitinib group. Momelotinib met the noninferiority criterion with an adjusted proportion difference (targeting 60% retention of the effect of ruxolitinib) of 0.09 (95% CI, 0.02 to 0.16; P = 0.014), but it did not demonstrate superiority (proportion difference = −0.03; 95% CI, −0.12 to 0.05; P = 0.45). In the SIMPLIFY-2 trial, the SRR was 6.7% in the momelotinib group and 5.8% in the BAT group (proportion difference = 0.01; 95% CI, −0.09 to 0.10; P = 0.90). In the MOMENTUM trial, the SRR was 23.1% in the momelotinib group versus 3.1% in the danazol group (proportion difference = 19.37%; 95% CI, 10.96% to 27.77%; P = 0.001).

In the SIMPLIFY-1 trial, 28.4% of patients in the momelotinib group experienced a TSS response at week 24, compared to 42.2% in the ruxolitinib group (proportion difference = −14.0%; 95% CI, −23.0% to −5.0%; P = 0.9985). A noninferiority test that targeted 67% retention of ruxolitinib failed the predefined noninferiority margin where the lower bound of the 2-sided 95% CI should be greater than 0. Specifically, the adjusted proportion difference noninferiority testing was 0.00 (95% CI, –0.08 to 0.08; P = 0.98). In the SIMPLIFY-2 trial, 26.2% of patients in the momelotinib group experienced TSS response compared to 5.9% in the BAT group, with a proportion difference of 0.20 (95% CI, 0.09 to 0.32). In the MOMENTUM study, 24.6% of patients in the momelotinib group experienced TSS response compared to 9.2% in the danazol group, with a proportion difference of 15.67% (95% CI, 5.54% to 25.81%; P = 0.0095).

Harms Results

Across the trials, most patients treated with momelotinib experienced at least 1 AE. In the SIMPLIFY-1 trial, 92.5% of patients in the momelotinib group experienced at least 1 AE compared to 95.4% in the ruxolitinib group. In the SIMPLIFY-2 trial, the rates were 97.1% in the momelotinib group and 88.5% in the BAT group. For the MOMENTUM study, 93.8% of patients in the momelotinib group reported at least 1 AE compared to 95.4% in the danazol group. Thrombocytopenia and anemia were commonly reported AEs across these trials. In the SIMPLIFY-1 trial, thrombocytopenia occurred in 18.7% of patients taking momelotinib and 29.2% of patients taking ruxolitinib, while anemia was reported in 14.5% of patients taking momelotinib and 37.5% of patients taking ruxolitinib. In the SIMPLIFY-2 trial, thrombocytopenia was observed in 10.6% of patients taking momelotinib and 5.8% of patients receiving BAT, and anemia was reported in 13.5% of patients taking momelotinib compared to 17.3% in the BAT group. In the MOMENTUM study, thrombocytopenia was seen in 22.3% of patients taking momelotinib versus 10.8% of patients taking danazol, while anemia was observed in 7.7% of patients taking momelotinib and 6.2% of patients taking danazol.

Grade 3 or 4 AEs were observed in all treatment groups across all studies. In the SIMPLIFY-1 trial, 34.6% of patients taking momelotinib experienced grade 3 or 4 AEs compared to 43.5% in the ruxolitinib group. In the SIMPLIFY-2 trial, 54.8% of patients in the momelotinib group had grade 3 or 4 AEs versus 42.3% in the BAT group. In the MOMENTUM trial, 48.5% of patients in the momelotinib group reported grade 3 or 4 AEs compared to 63.1% in the danazol group. Thrombocytopenia and anemia were the most common grade 3 or 4 AEs. In the SIMPLIFY-1 trial, thrombocytopenia was reported in 7.0% of patients taking momelotinib and 4.6% of patients taking ruxolitinib, while anemia was reported in 6.1% of patients taking momelotinib and 22.7% of patients taking ruxolitinib. In the SIMPLIFY-2 trial, thrombocytopenia was observed in 10.6% of patients taking momelotinib versus 5.8% of patients receiving BAT, and anemia was reported in 13.5% of patients taking momelotinib compared to 17.3% in the BAT group. In the MOMENTUM trial, thrombocytopenia was seen in 16.9% of patients in the momelotinib group and 7.7% of patients in the danazol group, while anemia was reported in 7.7% of patients in the momelotinib group and 6.2% of patients in the danazol group.

Serious adverse events (SAEs) were frequent across the trials. In the SIMPLIFY-1 trial, 22.9% of patients in the momelotinib group experienced at least 1 SAE compared to 18.1% in the ruxolitinib group. In the SIMPLIFY-2 trial, 35.6% of patients in the momelotinib group had at least 1 SAE versus 23.1% in the BAT group. In the MOMENTUM trial, 34.6% of patients in the momelotinib group reported at least 1 SAE compared to 40.0% in the danazol group. Common SAEs included anemia, pneumonia, and sepsis. In the SIMPLIFY-1 trial, anemia was observed in 1.9% of patients in the momelotinib group and 3.7% of patients in the ruxolitinib group, and pneumonia was reported in 1.9% of patients in the momelotinib group and 1.4% of patients in the ruxolitinib group. In the SIMPLIFY-2 trial, sepsis was observed in 2.9% of patients in the momelotinib group, while no cases were reported in the BAT group. In the MOMENTUM trial, anemia was seen in 3.8% of patients in the momelotinib group versus 4.6% in the danazol group, and pneumonia was reported in 2.3% of patients in the momelotinib group and 9.2% of patients in the danazol group.

Discontinuations due to AEs were relatively common. In the SIMPLIFY-1 trial, 12.6% of patients in the momelotinib group discontinued treatment due to AEs compared to 5.6% in the ruxolitinib group. In the

SIMPLIFY-2 trial, discontinuation rates were 21.2% in the momelotinib group versus 1.9% in the BAT group. In the MOMENTUM trial, 17.7% of patients in the momelotinib group discontinued treatment compared to 23.1% in the danazol group. Thrombocytopenia was a key reason for discontinuation, especially in the SIMPLIFY-2 trial, where it led to treatment cessation in 4.8% of patients treated with momelotinib (and was not reported in the BAT group). In the MOMENTUM trial, thrombocytopenia caused discontinuation in 0.8% of patients in the momelotinib group versus 3.1% of patients in the danazol group.

Mortality rates varied across the studies. In the SIMPLIFY-1 trial, 3.7% of patients taking momelotinib died compared to 2.8% of patients taking ruxolitinib. In the SIMPLIFY-2 trial, mortality was 7.7% in the momelotinib group and 9.6% in the BAT group. In the MOMENTUM trial, 29.2% of patients in the momelotinib group died compared to 30.8% in the danazol group. In the SIMPLIFY-1 trial, most deaths in the momelotinib group were due to treatment-emergent adverse events (TEAEs) unrelated to disease progression, while in the MOMENTUM trial, a notable number of deaths were linked to TEAEs in both the momelotinib and danazol groups.

Notable harms included peripheral neuropathy, reported in 10.3% of patients taking momelotinib in the SIMPLIFY-1 trial and 11.5% in the SIMPLIFY-2 trial, with fewer cases in the comparator groups (5.6% in the ruxolitinib group and not reported in the BAT group). In the MOMENTUM trial, infections were prevalent, affecting 33.8% of patients taking momelotinib and 35.4% of those taking danazol. Other significant AEs in the MOMENTUM trial included hemorrhage (21.5% in the momelotinib group versus 18.5% in the danazol group), malignancies (5.4% in the momelotinib group versus 9.2% in the danazol group), thromboembolism (3.8% in the momelotinib group versus 9.2% in the danazol group), and transformation to AML (3.1% in the momelotinib group versus 4.6% in the danazol group).

Critical Appraisal

The studies included in this review were generally well designed, with RCTs and active comparator arms, which strengthened their internal validity. The SIMPLIFY-1 and MOMENTUM trials were double-blind studies, while the SIMPLIFY-2 trial was open-label, increasing the potential for bias, particularly in subjective outcomes like TSS. The studies used robust randomization and allocation concealment methods, with noninferiority to be met if the lower 95% CI did not go below the null. This margin was established based on prior evidence, which was supported by clinical experts. However, there was limited clinical rationale provided for the threshold used to determine the comparator efficacy preservation. The open-label design of the SIMPLIFY-2 trial introduced a risk of bias in favour of momelotinib, especially for patient-reported outcomes. A significant limitation across all studies was the high rate of treatment discontinuation, which was particularly imbalanced in the MOMENTUM trial, in which more patients discontinued treatment in the danazol group than in the momelotinib group. Additionally, the lack of adjustment for type I error (multiple testing) in several efficacy outcomes further complicated the interpretation of these results, particularly in the SIMPLIFY-2 trial, in which the primary objectives were not met, rendering subsequent analyses nominal and unadjusted.

The external validity of the studies is supported by their attempt to capture a representative population of patients with MF, including those who are JAKi naive, JAKi experienced, and anemic. The baseline

characteristics of the study populations were consistent with those seen in clinical practice in Canada, according to clinical experts. However, the studies have limitations in generalizability due to the lack of comparisons against certain relevant treatments, such as fedratinib or hydroxyurea, particularly in the Canadian context. The use of danazol in the MOMENTUM trial, which is uncommon in Canadian practice, further limits the applicability of the results. Additionally, the short 24-week duration of the studies is insufficient to assess long-term outcomes such as survival and disease progression, which are critical in MF management. The high rates of treatment discontinuation also limit the generalizability of the findings to patients who are likely to remain on therapy, potentially skewing results toward those who respond well to treatment. Lastly, the absence of established minimum important differences (MIDs) for key outcomes diminishes the ability to interpret the clinical significance of the differences observed between momelotinib and comparators.

GRADE Summary of Findings and Certainty of the Evidence

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 patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Transfusion independence response rate (follow-up: week 24)
- Rate of RBC transfusion (follow-up: week 24)
- SRR (follow-up: week 24)
- TSS response rate (follow-up: week 24)
- SAEs (follow-up: week 24)

Table 3: Summary of Findings for Momelotinib Versus Ruxolitinib for Patients With Myelofibrosis Who Are Treatment Naive

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Ruxolitinib	Momelotinib	Difference		
Blood transfusion							
Transfusion independence response rate Follow-up: Week 24	432 (1 RCT)	NR	49.3 per 100	66.5 per 100 (59.8 to 72.8 per 100)	18.0 more per 100 (9.0 to 26.0 more)	High[a,b]	Momelotinib results in an increase in the number of patients who are transfusion independent compared to ruxolitinib. The clinical relevance of the increase is uncertain.
Rate of RBC transfusion, mean units per month Follow-up: Week 24	432 (1 RCT)	Rate ratio = 0.28 (0.19 to 0.43)	1.0	0.5 (SD = 1.27)	NR	High[b,c]	Momelotinib results in a decrease in amount of blood transfusion units per month when compared to ruxolitinib. The clinical relevance of the decrease is uncertain.
Splenic response (a spleen volume reduction of ≥ 35% from baseline at the week 24 assessment as measured by MRI or CT scans)							
Splenic response rate Follow-up: Week 24	432 (1 RCT)	NR	29.5 per 100	26.5 per 100 (20.74 to 32.94 per 100)	3 less per 100 (12.0 less to 5.0 more)	Moderate[d]	Momelotinib likely results in little to no difference in splenic response rate when compared to ruxolitinib.
Symptoms response (a ≥ 50% reduction in TSS at week 24 vs. baseline as measured by the modified MPN-SAF)							
TSS response rate Follow-up: Week 24	432 (1 RCT)	NR	42.2 per 100	28.4 per 100 (22.45 to 35.03 per 100)	14.0 less per 100 (23.0 to 5.0 less)	High[a,b]	Momelotinib results in a decrease in number of patients who are responders based on TSS compared to ruxolitinib. The clinical relevance of the decrease is uncertain.
Harms							
SAEs Follow-up: Week 24	432 (1 RCT)	NR	18.2 per 100	22.9 per 100 (NR)	5 more per 100 (3 less to 12 more)	Low[b,e]	Momelotinib may result in an increase in the proportion of patients who experience ≥ 1 SAE compared with ruxolitinib. The clinical importance of the increase is uncertain.

CDA-AMC = Canada's Drug Agency; CI = confidence interval; NR = not reported; MID = minimal important difference; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; RBC = red blood cell; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; TSS = total symptom score; 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 table footnotes.

[a]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a CI that excludes the null suggest benefit, as judged by the CDA-AMC review team.

[b]End point not adjusted for multiple testing; thus, it should be used as supportive evidence.

[c]Results for absolute between-group difference with 95% CI for the full study population were not available. Furthermore, no MID was identified and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects. Therefore, the null was used in relation to the relative treatment effect. Did not rate down for imprecision; a relative treatment effect larger than the null and a CI that excludes the null suggest benefit, as judged by the CDA-AMC review team.

[d]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down 1 level for serious imprecision as the lower bound of the CI suggests harm and the upper bound of the 95% CI suggests benefit and/or little to no difference.

[e]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects. Rated down 2 levels for very serious imprecision, as the lower bound of the CI suggests benefit and the upper bound of the 95% CI suggests harm.

Source: Data on File, 2021 (SIMPLIFY-1 CSR); GSK Data on File, 2021 (SIMPLIFY-2 CSR); GSK Data on File, 2023 (MOMENTUM CSR).

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

Table 4: Summary of Findings for Momelotinib Versus Best Available Treatment for Patients With Myelofibrosis Who Are JAKi Experienced

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Best available treatment	Momelotinib	Difference		
Blood transfusion							
Transfusion independence response rate Follow-up: Week 24	156 (1 RCT)	NR	21.2 per 100	43.3 per 100 (33.59 to 53.35 per 100)	23.0 more per 100 (9.0 to 37.0 more)	Moderate[a,b]	Momelotinib likely results in an increase in the number of patients who are transfusion independent compared to best available treatment. The clinical relevance of the increase is uncertain.
Rate of RBC transfusion, mean units per month Follow-up: Week 24	156 (1 RCT)	Rate ratio = 0.80 (0.49 to 1.31)	1.8	1.6 (SD = 2.09)	NR	Low[b,c]	Momelotinib may result in a decrease in amount of blood transfusion units per month when compared to best available treatment. The clinical relevance of the increase is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Best available treatment	Momelotinib	Difference		
Splenic response (a spleen volume reduction of ≥ 35% from baseline at the week 24 assessment as measured by MRI or CT scans)							
Splenic response rate Follow-up: Week 24	156 (1 RCT)	NR	5.8 per 100	6.7 per 100 (2.75 to 13.38 per 100)	1 more per 100 (9 less to 10.0 more)	Very low[d]	The evidence is very uncertain about the effect of momelotinib on splenic response rate when compared to best available treatment.
Symptoms response (a ≥ 50% reduction in TSS at week 24 vs. baseline as measured by the modified MPN-SAF)							
TSS response rate Follow-up: Week 24	156 (1 RCT)	NR	5.9 per 100	26.2 per 100 (18.04 to 35.80 per 100)	20.0 more per 100 9 to 32 more)	Low[b,e]	Momelotinib may result in an increase in number of patients who are responders based on TSS compared to best available treatment. The clinical relevance of the increase is uncertain.
Harms							
SAEs Follow-up: Week 24	156 (1 RCT)	NR	23.1 per 100	35.6 per 100 (NR)	13 more per 100 (2 less to 27 more)	Low[b,f]	Momelotinib may result in an increase in the proportion of patients who experience ≥ 1 SAE compared with ruxolitinib. The clinical importance of the increase is uncertain.

CDA -AMC = Canada's Drug Agency; CI = confidence interval; MID = minimal important difference; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; NR = not reported; RBC = red blood cell; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; TSS = total symptom score; vs. = versus.

[a]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a CI that excludes the null suggest benefit as judged by the CDA-AMC review team. Rated down 1 level for serious risk of bias due to missing data and the lack of washout period.

[b]End point not adjusted for multiple testing; thus, it should be used as supportive evidence.

[c]Results for absolute between-group difference with 95% CI for the full study population were not available. Furthermore, no MID was identified and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects Rated down 2 levels for very serious imprecision as the lower bound of the CI suggests comparative harm and the upper bound of the 95% CI suggests comparative benefit.

[d]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down 2 levels for very serious imprecision as the lower bound of the 95% CI suggests serious harm and the upper bound of the 95% CI suggest serious benefit. Rated down 1 level for serious risk of bias due to missing data and lack of washout period.

[e]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down 2 levels for very serious risk of bias due to open-label design in a subjective outcome, missing data, and lack of washout period.

[f]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects. Rated down 2 levels for very serious imprecision, as the lower bound of the CI suggests benefit and the upper bound of the 95% CI suggests harm.

Source: Data on File, 2021 (SIMPLIFY-1 CSR); GSK Data on File, 2021 (SIMPLIFY-2 CSR); GSK Data on File, 2023 (MOMENTUM CSR).

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

Table 5: Summary of Findings for Momelotinib Versus Danazol for Patients With Myelofibrosis and Anemia Who Are JAKi Experienced

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Danazol	Momelotinib	Difference		
Blood transfusion							
Transfusion independence response rate Follow-up: Week 24	195 (1 RCT)	NR	20.0 per 100	30.8 per 100 (22.98 to 39.46)	10.99 more per 100 (0.8 less to 22.77 more per 100)	Low[a,b]	Momelotinib may result in an increase in the number of patients who are transfusion independent compared to danazol. The clinical relevance of the increase is uncertain.
Number of RBC whole blood units transferred, mean Follow-up: Week 24	195 (1 RCT)	NR	10.9	6.6 (SD = 8.41)	−5.66 (−10.65 to −0.68)	Moderate[b,c]	Momelotinib likely results in a decrease in amount of blood transfusion units when compared to danazol. The clinical relevance of the decrease is uncertain.
Splenic response (a spleen volume reduction of ≥ 35% from baseline at the week 24 assessment as measured by MRI or CT scans)							
Splenic response rate Follow-up: Week 24	195 (1 RCT)	NR	3.1 per 100	23.1 per 100 (16.14 to 31.28)	19.37 more per 100 (10.96 to 27.77 more)	Moderate[d]	Momelotinib likely results in an increase in splenic response rate when compared to danazol. The clinical relevance of the increase is uncertain.
Symptoms response (a ≥ 50% reduction in TSS at week 24 vs. baseline as measured by MFSAF)							
Total symptom score response rate Follow-up: Week 24	195 (1 RCT)	NR	9.2 per 100	24.6 per 100 (17.49 to 32.94 per 100)	15.67 more per 100 (5.54 to 25.81 more)	Moderate[d]	Momelotinib likely results in an increase in number of patients who are responders based on total symptom score compared to Danazol. The clinical relevance of the decrease is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Danazol	Momelotinib	Difference		
Harms							
SAEs Follow-up: Week 24	195 (1 RCT)	NR	40 per 100	34.6 per 100 (NR)	5 less per 100 (20 less to 9 more)	Low[b,e]	Momelotinib may result in a decrease in the proportion of patients who experience ≥ 1 SAE compared with ruxolitinib. The clinical importance of the increase is uncertain.

CDA -AMC = Canada's Drug Agency; CI = confidence interval; MID = minimal important difference; MFSAF = Myelofibrosis Symptom Assessment Form; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; NR = not reported; RBC = red blood cell; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; TSS = total symptom score; vs. = versus.

[a]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down 1 level for serious imprecision as the lower bound of the 95% CI suggests minimal harm and/or no difference and the upper bound of the 95% CI suggest benefit. Rated down 1 level for serious risk of bias due to missing data.

[b]End point not adjusted for multiple testing; thus, it should be used as supportive evidence.

[c]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects, therefore the null was used. Rated down 1 level for serious risk of bias due to the large and imbalanced number of treatment discontinuation and the lack of data imputation methods for this outcome.

[d]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Did not rate down due to imprecision. Rated down 1 level for serious risk of bias due to the large and imbalanced number of treatment discontinuations.

[e]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects. Rated down 2 levels for very serious imprecision as the lower bound of the CI suggests benefit and the upper bound of the 95% CI suggests harm.

Source: Data on File, 2021 (SIMPLIFY-1 CSR); GSK Data on File, 2021 (SIMPLIFY-2 CSR); GSK Data on File, 2023 (MOMENTUM CSR).

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

Long-Term Extension Studies

This section summarizes 3 open-label extension studies: the SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM studies.

Description of Studies

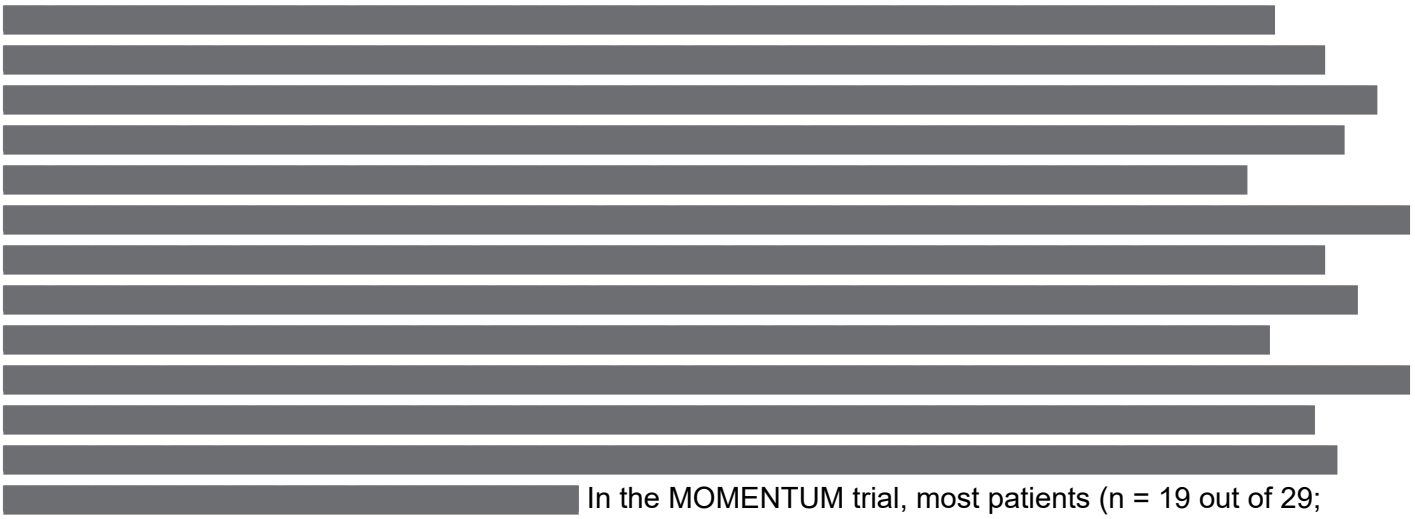
The open-label, long-term extension of the SIMPLIFY-1 trial evaluated the open-label treatment with momelotinib for up to 216 weeks after the randomized, double-blinded phase (i.e., through week 240). The open-label extension of the SIMPLIFY-2 trial evaluated the open-label treatment with momelotinib for up to 204 weeks after the randomized treatment phase (i.e., through week 228). All patients who completed the 24-week randomized treatment phase in the SIMPLIFY-1 and SIMPLIFY-2 trials were eligible to participate in the extended treatment phases.

The open-label extension of the MOMENTUM trial evaluated the open-label treatment with momelotinib for up to 180 weeks (i.e., through week 204) and danazol up to 24 weeks after the randomized, double-blinded phase of the MOMENTUM trial. Patients who completed the 24-week randomized treatment phase in the MOMENTUM trial and discontinued treatment early due to splenic progression, or discontinued treatment early for other reasons but completed scheduled assessments through week 24, had the option to continue momelotinib.

The total median duration of follow-up (combined randomized and open-label extension phases) was 35.3 months (range, 0.4 to 59.3) in the SIMPLIFY-1 trial and 28.2 months (range, 0.3 to 50.4) in the SIMPLIFY-2 trial. In the open-label extension phase of the SIMPLIFY-1 trial, the majority of patients in the continuing momelotinib (40.4%) and switching to momelotinib (48.7%) treatment groups had high-risk MF per the International Prognostic Scoring System criteria and a positive *JAK2V617F* mutation status (58.5% and 64.0% in the continuing momelotinib and switching to momelotinib treatment groups, respectively) at baseline. The proportion of patients with hemoglobin levels below 10 g/dL was higher in the switch to momelotinib group (56.3%) than in the continuing momelotinib group (37.4%).

In the SIMPLIFY-2 trial, the majority of patients in the continuing momelotinib group (64.1%) and switch to momelotinib treatment group (55.0%) had intermediate-2 risk MF per the Dynamic International Prognostic Scoring System (DIPSS) criteria, and more than 60% of patients in both treatment groups had a positive *JAK2V617F* mutation status (60.9% versus 72.5% in the continuing momelotinib and switching to momelotinib groups, respectively). Further, a numerically larger proportion of patients in the continuing momelotinib group (57.8%) were transfusion dependent than those in the switch to momelotinib group (50.0%). The proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 was higher in the continuing momelotinib group (64.1%) than in the switch to the momelotinib group (47.5%). Further, a numerically smaller proportion of patients in the continuing momelotinib group (4.7%) had an ECOG performance status score of 2 than in the switch to momelotinib group (15.0%). While there were no patients with an ECOG performance status score of 3 in the continuing momelotinib group, 5% of patients in the switch to momelotinib group had an ECOG performance status score of 3. The proportion of patients with hemoglobin levels below 8 g/dL was higher in the continuing momelotinib group (28.1%) than in the switch to momelotinib group (7.5%).

Efficacy Results



In the MOMENTUM trial, most patients (n = 19 out of 29; 79.2%) in the continuing momelotinib group and 50.0% of patients (n = 1 out of 2) in the switch from danazol to momelotinib group who were responders at week 24 were also classified as responders at week 48. Of patients who were nonresponders at week 24 in the continuing to momelotinib group (n = 43) and switch from danazol to momelotinib group (n = 28), 23.3% and 10.7% were classified as responders at week 48, respectively.

In the MOMENTUM trial, a majority of patients who were transfusion independent responders at week 24 were also transfusion independent responders at week 48, including 88.2% of patients (n = 30 out of 34) in the continuing momelotinib treatment group and 80.0% (n = 8 out of 10) in the switch to momelotinib treatment group. A majority of patients with a 50% or greater reduction from baseline TSS as measured by the MFSAF at week 24 were classified as responders at week 48, including 72.0% (n = 18 out of 25) in the continuing momelotinib treatment group and all patients (n = 5 out of 5; 100%) in the switch to momelotinib treatment group.

Harms Results

In the SIMPLIFY-1 trial, the overall frequencies of TEAEs (89.8% versus 78.4%), were numerically higher in patients who switched from ruxolitinib to momelotinib than those who continued momelotinib following 24 weeks of treatment with momelotinib in the open-label extension phase. Similar trends were observed for the most common grade 3 or 4 AEs (37.6% versus 27.5%), SAEs (23.4% versus 15.8%), and TEAEs leading to treatment discontinuation (14.7% versus 8.8%), with numerically higher proportions for patients who switched from ruxolitinib to momelotinib than those who continued momelotinib. The most commonly reported AEs — occurring in at least 10% of patients — were diarrhea, thrombocytopenia, anemia, fatigue, nausea, and cough, in both groups. The most common AEs leading to treatment discontinuation were thrombocytopenia, fatigue, and peripheral sensory neuropathy (no events in the continuing momelotinib group and relatively few [2.0% to 2.5%] in the switch from ruxolitinib to momelotinib group). Among the continuing momelotinib and switch from ruxolitinib to momelotinib groups, the following AEs of special interest (AESIs) were reported: peripheral neuropathy (5.3% versus 7.6%), nonhematological AEs (77.2%

versus 87.3%), cataracts (4.7% versus 3.6%), and first dose effects (NR versus 2.0%). Regarding deaths due to TEAEs not related to disease progression, 10.5% of deaths occurred in the continuing momelotinib group and 8.6% in the switch from ruxolitinib to momelotinib group.

In the SIMPLIFY-2 trial, the overall frequencies of TEAEs (100% versus 93.8%), grade 3 or 4 AEs (55.0% versus 28.1%), SAEs (27.5% versus 20.3%), TEAEs leading to treatment discontinuation (37.5% versus 7.8%), and AEs leading to treatment interruption and/or dose reduction (19.2% versus 16.3%) were numerically higher in patients who switched from BAT to momelotinib than those who continued momelotinib, respectively. The most commonly reported AEs occurring in at least 15% of patients were cough and diarrhea in patients who continued momelotinib in the extended treatment phase; and asthenia, pyrexia, diarrhea, thrombocytopenia, cough, and anemia in patients who switched from BAT to momelotinib. The most commonly reported SAEs occurring in at least 5% of patients were anemia, pyrexia, and confusional state in patients who switched from BAT to momelotinib. No patient in the continuing momelotinib group experienced any of these SAEs. The most common AEs leading to treatment discontinuation were thrombocytopenia, diarrhea, and headache (no events in the continuing momelotinib group and 5.0% to 7.5% in the switch from BAT to momelotinib group). Among the continuing momelotinib and switch from BAT to momelotinib groups, the following AESIs were reported: peripheral neuropathy (10.9% versus 20.0%), nonhematological AEs (98.4% versus 100%), cataracts (1.6% versus 0%), and first dose effects (NR versus 7.5%). Deaths due to TEAEs not related to disease progression were reported in 21.9% of patients who continued treatment with momelotinib and 7.5% of patients who switched from BAT to momelotinib treatment.

In MOMENTUM, following 24 weeks of treatment with momelotinib in the open-label treatment phase, the overall frequencies of TEAEs (89.2% versus 85.4%), grade 3 or higher TEAEs (51.6% versus 48.8%), and serious TEAEs (32.3% versus 29.3%) were numerically slightly higher in patients who continued momelotinib than those who switched from danazol to momelotinib. The most commonly reported AEs — occurring in at least 10% of patients — were diarrhea, thrombocytopenia, pyrexia, asthenia, and anemia in patients who continued momelotinib, and thrombocytopenia and diarrhea in those who switched from danazol to momelotinib. The most commonly reported SAEs — occurring in at least 2% of patients — were urinary tract infection, acute kidney injury, febrile neutropenia, and squamous cell carcinoma of the skin in patients who continued momelotinib, and acute kidney injury and urinary tract infection in those who switched from danazol to momelotinib. The most common AEs leading to treatment discontinuation were anemia, AML, and transformation to AML (no events in the continuing momelotinib group for AML and transformation to AML, or in the switch from danazol to momelotinib group for anemia). No deaths due to TEAEs not related to disease progression were reported in any of the treatment groups.

Critical Appraisal

Internal Validity

The open-label extension phase design of the SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM trials may have biased the reporting of some end points because awareness of the study treatment received may have influenced the perception of improvement and/or harms by patients and clinicians, particularly for outcomes that are subjective in measurement and interpretation (e.g., TSS response rate and subjective

AEs). In the open-label extension phases, all patients were taking momelotinib. As such, there was no relevant randomized comparison group (i.e., for any active comparator of interest), which precludes causal conclusions. In terms of protocol deviations, for the SIMPLIFY-2 trial, the proportion of patients with at least 1 important protocol violation was higher in the continuing to momelotinib treatment group (20.3%) than in the switch to momelotinib treatment group (10.0%) in the extended treatment phase. No information on protocol deviation for the open-label extension phase of the MOMENTUM study was reported separately; as such, any risk of bias due to deviations from the intended interventions is uncertain. The results are reflective of patients who were able to tolerate and stay on momelotinib (in the continuing momelotinib group). No information on missing data imputations were reported for the open-label extension phase in the SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM clinical study reports provided by the sponsors. In the SIMPLIFY-1 and SIMPLIFY-2 trials, the number of patients who discontinued treatment before week 24 of the open-label treatment phase were higher among those who switched from ruxolitinib to momelotinib or BAT to momelotinib treatment group than in the continuing momelotinib treatment group. The main reason behind this imbalance in both groups was due to AEs. This may potentially bias the safety results as patients who were still continuing the open-label extension phase had better tolerability of momelotinib than those who had discontinued.

External Validity

Since the patients who took part in the open-label extension phases were originally from the pivotal trials and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label extension phases for all 3 studies. The trials included both patients who were transfusion dependent and independent, which is generalizable to more patients.

Indirect Comparisons

None submitted.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor submitted 2 retrospective analyses and 1 interim result of an ongoing extended access study to address gaps related to long-term survival by baseline transfusion independence status. These studies were not included in the Clinical Review Report, as they provided supplementary evidence rather than addressing specific gaps in the evidence.

Economic Evidence

Cost and Cost-Effectiveness

Table 6: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with PMF, PPV-MF, or PET-MF who are JAKi naive or who have been treated with a JAKi.
Treatment	Momelotinib
Dose regimen	200 mg daily
Submitted price	$230.86 per tablet
Submitted treatment cost	$6,464.11 per 28-day cycle
Comparators	JAKi-naive: ruxolitinib JAKi-experienced: BAT
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (33 years)
Key data sources	The SIMPLIFY-1 and SIMPLIFY-2 trials were used to inform efficacy and safety data for the JAKi-naive and JAKi-experienced populations, respectively. The MOMENTUM trial was also used to identify relevant adverse events.
Key limitations	• The long-term effectiveness of momelotinib is uncertain. The results observed at 24 months were assumed to persist for the remainder of a patient's lifetime (up to 33 years), and no treatment waning effect was considered. The vast majority of incremental QALYs were estimated beyond 24 months, and cost-effectiveness is therefore highly sensitive to this assumption. • The pharmacoeconomic model may not accurately reflect the use of subsequent therapy for JAKi-experienced patients after they progress on momelotinib. Input from clinical experts consulted by CDA-AMC suggested that patients may continue to receive JAKi therapy beyond progression if no alternative therapy is available. The submitted model assumed that patients would discontinue JAKi therapy following progression on momelotinib. This assumption led to a reduced incremental cost that favoured the cost-effectiveness of momelotinib. • The model considered transfusion status but did not consider splenic response or other symptomatic outcomes that are used in treatment decision-making, according to clinical expert input. The model therefore may not fully reflect how treatment discontinuation decisions would be made in clinical practice.
CDA-AMC reanalysis results	• CDA-AMC conducted a reanalysis in which patients who received momelotinib as primary therapy could receive subsequent therapy with ruxolitinib as a component of BAT. • In JAKi-naive patients, the ICER for momelotinib relative to ruxolitinib was $245,628 per QALY gained (incremental cost = $23,841; incremental QALYs = 0.097). • In JAKi-experienced patients, the ICER for momelotinib relative to BAT was $327,295 per QALY gained (incremental cost = $30,087; incremental QALYs = 0.092). • Based on an assumption that 15% of eligible patients are JAKi naive and the remaining 85% are JAKi experienced, a price reduction of 27% would be required for momelotinib to be considered cost--

Component	Description
	effective at a willingness to pay threshold of $50,000 per QALY gained when considering a blended population.

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PET = post–essential thrombocytopenia myelofibrosis; PMF = primary myelofibrosis; PPV-MF = post–polycythemia vera myelofibrosis; QALY = quality-adjusted life-year.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the number of patients eligible for treatment is uncertain and the estimated market uptake of momelotinib is uncertain. The CDA-AMC reanalysis was conducted using the eligible adult population and market uptake estimates anticipated to be more reflective of Canadian clinical practice. The CDA-AMC reanalysis suggests that reimbursing momelotinib for the treatment of disease-related splenomegaly or symptoms and anemia in adult patients with primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF who are JAKi naive or have been treated with a JAKi is expected to be $10,966,008 (year 1: $1,394,787; year 2: $3,946,755; year 3: $5,624,465). The estimated budget impact is sensitive to the number of patients who receive momelotinib.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, 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.

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