Reimbursement Recommendation

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(Draft)

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.

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC pCODR 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 primary myelofibrosis (MF), post polycythemia vera MF or post essential thrombocythemia MF who have moderate to severe anemia, only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

One randomized, double-blind, active-controlled, phase III trial (SIMPLIFY-1, N = 432) in patients with MF who had not previously received a JAKi therapy demonstrated that 24 weeks of treatment with momelotinib results in an increase in the number of patients who are transfusion independent compared to ruxolitinib (difference of 18.0% patients; 95% CI, 9.0% to 26.0%). In a subpopulation of patients in SIMPLIFY-1 with anemia (Hgb < 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, one randomized, double-blind, active-controlled, phase III trial (MOMENTUM, N = 195) in patients with MF with anemia (Hgb < 100 g/L) and prior exposure to a JAK inhibitor (JAKi) demonstrated that 24 weeks of treatment with momelotinib may have resulted in an increase in the number of patients who are transfusion independent compared to treatment with danazol (difference of 11.0% 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 splenic response rate (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, 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 myelofibrosis. 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 myelofibrosis.

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 the following criteria: 1.1. high-risk or intermediate-2 risk MF defined by the Dynamic International Prognostic Scoring System (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 Hgb level less than 100 g/L	Evidence from SIMPLIFY-1 and MOMENTUM 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 SIMPIFY-1 did not have prior treatment with a JAKi and patients included in MOMENTUM were required to have been previously treated with a JAKi for at least 90 days, or at least 28 days with 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 the DIPSS-plus were used to assess MF risk status in SIMPLIFY-1 and MOMENTUM, 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 SIMPLIFY-1 and MOMENTUM, patients were required to have an ECOG performance status 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 SIMPLIFY-1 and MOMENTUM.	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 SIMPLIFY-1 and MOMENTUM, momelotinib was discontinued due to disease progression, splenic progression, or unacceptable toxicity.	–
Prescribing		
5. Momelotinib should be prescribed under the care of a clinician with expertise in treating and managing myelofibrosis.	This is meant to ensure that momelotinib is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
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 myelofibrosis.	There is insufficient evidence to justify a price premium for momelotinib over the least costly JAKi reimbursed for myelofibrosis.	

DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; Hgb = hemoglobin; 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 where 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 is unclear if momelotinib offers an advantage in SRR over existing therapies or offers better symptom resolution compared to ruxolitinib in treatment-naïve patients. 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 GRADE assessment of certainty of evidence for efficacy outcomes ranged from moderate to high certainty in SIMPLIFY-1, very low to moderate in SIMPLIFY-2, and low to moderate in MOMENTUM. Although the transfusion independence response rate in MOMENTUM was a secondary endpoint that was not controlled for multiplicity, the overall evidence from the 3 trials was supportive of a treatment benefit for momelotinib relative to ruxolitinib, BAT, and danazol for this outcome. Further, in MOMENTUM, which specifically enrolled patients with anemia who had experience with JAKi treatment, momelotinib likely improves splenomegaly and reduces symptoms of MF compared to danazol. In SIMPLIFY-1 which enrolled patients not previously been 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 MOMENTUM, about 5% of patients in both treatment groups had intermediate-MF. In SIMPLIFY-1, the proportion of patients with intermediate-1 MF at baseline was 21% and 20% for the momelotinib and ruxolitinib groups, respectively, and in SIMPLIFY-2, 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 SIMPLIFY-1 and SIMPLIFY-2. In the absence of a subgroup analysis by risk status, pERC noted it is challenging to determine the benefit in patients with intermediate-1; 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 SIMPLIFY-1 and SIMPLIFY-2.
- **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 SIMPLIFY-1 and MOMENTUM and only 3.8% of patients randomized to BAT in SIMPLIFY-2 were treated with an ESA.
- **Relevance of SIMPLIFY-2**: Patients enrolled in SIMPLIFY-2 were not required to have anemia; however, the mean Hgb level at baseline was 94 to 95 g/L. In SIMPLIFY-2, momelotinib likely results in an increase in the number of patients who are transfusion independent compared to Best Available Treatment (BAT); however, the clinical relevance of the increase is uncertain. Also, when compared to BAT, momelotinib may result in an increase in number of patients who are responders based on total symptoms score, 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 SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM. pERC noted that the studies suggest that over two-thirds of patients achieved 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 myelofibrosis, which was identified as important by patients. Although overall survival and leukemia-free survival were evaluated in MOMENTUM, the endpoints 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 (SIMPLIFY-1) and danazol (MOMENTUM).
- **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 two 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 MF patients with anemia.

Background

Myelofibrosis (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 fibers, 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 (ET) or polycythemia vera (PV). 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 JAK inhibitors like ruxolitinib, which are aimed at reducing splenomegaly and managing symptoms. However, unmet needs remain, especially for patients who progress after JAK inhibitor 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 myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis who are either JAK inhibitor-naïve or have been previously treated with a JAK inhibitor. Momelotinib, which also inhibits Activin A receptor type 1 (ACVR1), may provide additional benefits, particularly in managing anemia, by restoring iron homeostasis and reducing the need for red blood cell 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 myelofibrosis (MF), post polycythemia vera myelofibrosis or post essential thrombocythemia MF who have moderate to severe anemia. Momelotinib is a JAK inhibitor that inhibits wild type Janus Kinase 1 and 2 (JAK1/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 three Phase 3 RCTs (two double-blind and one open-label) in adult patients with PMF or secondary MF (post-PV and post-ET MF), who are JAKi naïve or have been treated with a JAKi; and three long-term extension studies.
- patients' perspectives gathered by two patient groups: a joint input by the Leukemia & 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
- two clinical specialists with expertise diagnosing and treating patients with myelofibrosis
- input from two clinician group(s), [a joint input from the Leukemia Lymphoma Society of Canada (LLSC) and the Canadian MPN Clinician Group, and Ontario Health (Cancer Care Ontario) Hematology Cancer disease site Drug Advisory Committee (OH-CCO's Drug Advisory Committee)]
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

The Leukemia & Lymphoma Society of Canada (LLSC) and The Canadian MPN Network (CMPNN) jointly provided patient input for this review, sourcing information from three online surveys conducted between March 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 myelofibrosis and their caregivers, focusing on their lived experiences and specific

interactions with the drug under review, momelotinib. Myelofibrosis 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 include 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 myelofibrosis. While existing JAK inhibitors 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 transplantation (HSCT), 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 myelofibrosis who require JAK inhibitor therapy and also have clinically significant anemia. Momelotinib would be particularly beneficial for JAK inhibitor-naïve patients or those who have developed anemia or intolerance on existing JAK inhibitor therapy. The experts noted that it could be used in first-line settings and as a second- or third-line treatment for patients with clinically relevant anemia and myeloproliferative neoplasm (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 myelofibrosis who are JAK inhibitor-naïve with splenomegaly or MPN symptoms and clinically relevant anemia, as well as those experiencing anemia or intolerance on other JAK inhibitor 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 three 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 six months, a loss of a prior response, or grade 3 adverse events that do not resolve with dose modification.

Finally, experts advised that momelotinib should be prescribed and monitored by hematologists or oncologists with expertise in myelofibrosis, 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 the Leukemia & Lymphoma Society of Canada (LLSC) and the Canadian MPN Clinician Group, as well as the Ontario Health (Cancer Care Ontario) Hematology Cancer disease site Drug Advisory Committee (OH-CCO's Drug Advisory Committee). Both clinician groups emphasized the significant unmet need for effective treatments to manage anemia in myelofibrosis, aligning with the clinical experts consulted for this submission, who also identified anemia management as a critical challenge. While both the clinician groups and CDA-AMC's clinical experts recognized the potential of momelotinib to benefit patients with myelofibrosis-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 CDA-AMC's 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 100-120 g/L). Momelotinib could be particularly beneficial in cases where treatment with ruxolitinib has led to anemia. pERC agreed with the experts.
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 subsequent lines of therapy. 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 evidence is limited, and treatment decisions should be individualized based on patient response and specific clinical scenarios. pERC agreed, highlighting that treatment decisions are based individualized based on the symptomatic treatment needs.

JAK = Janus Kinase.

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 myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis who are Janus Kinase (JAK) inhibitor naïve or have been treated with a JAK inhibitor.

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. SIMPLIFY-1 (N = 432) was a phase III, double-blind, multicenter study that compared momelotinib with ruxolitinib in JAK inhibitor-naïve patients with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF. The primary endpoint was the spleen response rate (SRR) at Week 24, defined as a ≥35% reduction in spleen volume from baseline. Secondary outcomes included the Total Symptom Score (TSS) response rate defined as the proportion of patients achieving 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 at or more than 8 g/dL. SIMPLIFY-2 (N = 156) was a phase III, open-label, multicenter study that evaluated the efficacy of momelotinib versus the best available therapy (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 endpoint was the SRR at Week 24, with secondary outcomes including TSS response rate and overall survival (OS). MOMENTUM (N = 195) was a phase III, double-blind, multicenter study that focused on patients with symptomatic and anemic MF who had received prior JAK inhibitor therapy. The trial compared momelotinib with danazol, with the primary endpoint 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 comprised of patients with intermediate-2 or high-risk MF. Across the three trials, over half of the patients were male, the majority were white, and the mean age was mid-to-late 60s. Specifically, in SIMPLIFY-1, 56.5% of patients were male and 43.5% were female, with 82.6% identifying as White, 9.2% as Asian, 0.9% as Black, and 7.9%% as other or not reported. In SIMPLIFY-2, 59.6% were male and 40.4% female, with 81.4% identifying as White, 3.8% as Black, and 14.7% as other or not reported. In MOMENTUM, 63.1% of patients were male and 36.9% were female, with 80.5% identifying as White, 9.2% as Asians, 2.1% as Black, and 6.2% as other. With the exception of anemia-related characteristics in MOMENTUM where 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 three 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 achieved 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 SIMPLIFY-2, 43.3% of patients in the momelotinib group achieved 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 achieved 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 red blood cell (RBC) transfusions at Week 24 in SIMPLIFY-1 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 SIMPLIFY-2, 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 MOMENTUM, 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 SIMPLIFY-1, 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 SIMPLIFY-2, the splenic response rate 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 MOMENTUM the splenic response 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 SIMPLIFY-1, 28.4% of patients in the momelotinib group achieved 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 value 0.98). In SIMPLIFY-2, 26.2% of patients in the momelotinib group experience 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 one adverse event (AE). In SIMPLIFY-1, 92.5% of patients in the momelotinib group experienced at least one AE compared to 95.4% in the ruxolitinib group. In SIMPLIFY-2, 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 one AE compared to 95.4% in the danazol group. Thrombocytopenia and anemia were commonly reported AEs across these trials. In SIMPLIFY-1, thrombocytopenia occurred in 18.7% of momelotinib patients and 29.2% of ruxolitinib patients, while anemia was reported in 14.5% of momelotinib patients and 37.5% of ruxolitinib patients. In SIMPLIFY-2, thrombocytopenia was observed in 10.6% of momelotinib patients and 5.8% of BAT patients, and anemia was reported in 13.5% of momelotinib patients compared to 17.3% in the BAT group. In the MOMENTUM study, thrombocytopenia was seen in 22.3% of momelotinib patients versus 10.8% of danazol patients, while anemia was observed in 7.7% of momelotinib patients and 6.2% of danazol patients.

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

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

Discontinuations due to AEs were relatively common. In SIMPLIFY-1, 12.6% of momelotinib patients discontinued treatment due to AEs compared to 5.6% in the RUX group. In SIMPLIFY-2, discontinuation rates were 21.2% in the momelotinib group versus 1.9% in the BAT group. In MOMENTUM, 17.7% of MMB patients discontinued treatment compared to 23.1% in the DAN group. Thrombocytopenia was a key reason for discontinuation, especially in SIMPLIFY-2, where it led to treatment cessation in 4.8% of

momelotinib -treated patients and was not reported in the BAT group. In MOMENTUM, thrombocytopenia caused discontinuation in 0.8% of momelotinib patients versus 3.1% of DAN patients.

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

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

Critical Appraisal

The studies included in this review are generally well-designed, with randomized controlled trials and active comparator arms, which strengthen their internal validity. SIMPLIFY-1 and MOMENTUM were double-blind studies, while SIMPLIFY-2 was open-label, increasing the potential for bias, particularly in subjective outcomes like the TSS. The studies used robust randomization and allocation concealment methods, with non-inferiority to be met if the lower 95%CI does not go below the null, this margin was established based on prior evidence, which were 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 SIMPLIFY-2 introduces a risk of bias in favor of momelotinib, especially for patient-reported outcomes. A significant limitation across all studies is the high rate of treatment discontinuation, which was particularly imbalanced in MOMENTUM, where 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 complicates the interpretation of these results, particularly in SIMPLIFY-2 where 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 myelofibrosis (MF) patients, including those who are JAK inhibitor (JAKi)-naïve, 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 MOMENTUM, 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 (MID) 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
- Splenic Response Rate - Follow-up: Week 24
- Total Symptom Score Response Rate - Follow-up: Week 24
- Serious Adverse Events - Follow-up: Week 24

Table 3: Summary of Findings for Momelotinib Versus Ruxolitinib for Treatment-Naïve Patients With Myelofibrosis

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,z]	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/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,z]	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 (achieve 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[c,z]	Momelotinib likely result in little-to-no difference in splenic response rate when compared to Ruxolitinib.
Symptoms Response (achieve a ≥ 50% reduction in TSS at Week 24 versus baseline as measured by the modified MPN-SAF)							
Total Symptom Score 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,z]	Momelotinib results in a decrease in number of patients who are responders based on total symptoms score compared to Ruxolitinib The clinical relevance of the decrease is uncertain.
Harms							
Serious Adverse Events 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[d,z]	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.

CI = confidence interval; NR = not reported; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; RCT = randomized controlled trial; SD = standard deviation..

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 confidence interval that excludes the null suggest benefit as judged by the CDA-AMC review team.

[b] Results for absolute between-group difference with 95% CI for the full study population was 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 confidence interval that excludes the null suggest benefit as judged by the CDA-AMC review team.

[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 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.

[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. Rated down 2 level for very serious imprecision as the lower bound of the CI suggests benefit and the upper bound of the 95% CI suggests harm.
[z] end point not adjusted for multiple testing, thus should be used as supportive evidence.

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 JAKi-experienced Patients With Myelofibrosis

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,z]	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/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,z]	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.
Splenic Response (achieve a spleen volume reduction of ≥ 35% from baseline at the Week 24 assessment as measured by MRI or CT scans)							
Splenic Response Rate 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[c]	The evidence is very uncertain about the effect of momelotinib on splenic response rate when compared to Best Available Treatment
Symptoms Response (achieve a ≥ 50% reduction in TSS at Week 24 versus baseline as measured by the modified MPN-SAF)							
Total Symptom Score 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[d,z]	Momelotinib may result in an increase in number of patients who are responders based on total symptoms score compared to Best Available Treatment. The clinical relevance of the increase is uncertain.
Harms							
Serious Adverse Events 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[e,z]	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.

CI = confidence interval; NR = not reported; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; RCT = randomized controlled trial; SD = standard deviation.

[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 confidence interval 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] Results for absolute between-group difference with 95% CI for the full study population was 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.
[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 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.
[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 risk of bias due to open-label design in a subjective outcome, 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.. Rated down 2 level for very serious imprecision as the lower bound of the CI suggests benefit and the upper bound of the 95% CI suggests harm.
[z] end point not adjusted for multiple testing, thus should be used as supportive evidence.

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 JAKi-experienced Patients With Myelofibrosis And Are Anemic

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,z]	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,z]	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 (achieve a spleen volume reduction of ≥ 35% from baseline at the Week 24 assessment as measured by MRI or CT scans)							
Splenic Response Rate 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[c]	Momelotinib likely results in an increase in splenic response rate when compared to Danazol. The clinical relevance of the increase is uncertain.
Symptoms Response (achieve a ≥ 50% reduction in TSS at Week 24 versus 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[c]	Momelotinib likely results in an increase in number of patients who are responders based on total symptoms score compared to Danazol.The clinical relevance of the decrease is uncertain.
Harms							
Serious Adverse Events 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[d,z]	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.

CI = confidence interval; NR = not reported; MFSAF = Myelofibrosis Symptom Assessment Form; RCT = randomized controlled trial; SD = standard deviation.

[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] 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.

[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. 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 discontinuation.
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. Rated down 2 level for very serious imprecision as the lower bound of the CI suggests benefit and the upper bound of the 95% CI suggests harm.
[z] end point not adjusted for multiple testing, thus should be used as supportive evidence.

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 three open-label extension studies – SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM.

Description of Studies

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

The open-label extension of MOMENTUM 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 MOMENTUM. Patients who completed the 24-week randomized treatment phase in MOMENTUM, 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 SIMPLIFY-1 and 28.2 months (range, 0.3 to 50.4) in SIMPLIFY-2. In the open-label extension phase of SIMPLIFY-1, the majority of patients in the continuing momelotinib (40.4%) and switching to momelotinib treatment groups (48.7%) had high-risk MF per the IPSS 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 less than 10 g/dL hemoglobin level were higher in the switch to momelotinib (56.3%) treatment group than in the continuing momelotinib (37.4%) group.

In SIMPLIFY-2, 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 DIPSS criteria, and over 60% of patients in both treatment groups had a positive JAK2V617F mutation status (60.9% vs 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 ECOG performance status 1 was higher in the continuing momelotinib (64.1%) treatment group than in the switch to the momelotinib (47.5%) group. Further, a numerically smaller proportion of patients in the continuing momelotinib group (4.7%) had ECOG performance status 2 than those in the switch to momelotinib group (15.0%). While there were no patients ECOG performance status 3 in the continuing momelotinib group, 5% of patients in the switch to momelotinib group had ECOG performance status 3. The proportion of patients with less than 8 g/dL hemoglobin level were higher in the continuing momelotinib group (28.1%) than those in the switch to momelotinib group (7.5%).

Efficacy Results

In SIMPLIFY-1, 87 (40.5%) of the 215 patients in the momelotinib group had a splenic response at any time during the double-blind or open-label extension phase. An additional 84 (42.6%) responses were observed in the ruxolitinib-randomized group following crossover to momelotinib in the open-label extension phase. In the total momelotinib exposure period, 171 (41.5%) of 412 patients had a splenic response at any time. In SIMPLIFY-2, 14 (13.5%) of the 104 patients in the momelotinib group and 9 (17.3%) of 52 patients in the BAT group (including patients who switched from BAT to momelotinib) had a splenic response at any time in the randomized or open-label extension phase.Seven (17.5%) of 40 patients randomized to BAT who switched from BAT to momelotinib during the open-label extension phase were responders at any timepoint. In MOMENTUM, most (n = 19/29; 79.2%) patients in the continuing momelotinib group and 50.0% (n = 1/2) of patients in the switch from danazol to momelotinib group who were responders at week 24 were also classified as responders at week 48. Of non-responders at week 24 in the continuing to momelotinib (n = 43) and switch from danazol to momelotinib (n = 28) groups, 23.3% and 10.7% were classified as responders at week 48, respectively.

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

Harms Results

In SIMPLIFY-1, the overall frequencies of TEAEs (89.8% vs 78.4%), were numerically higher in patients who switched from ruxolitinib to momelotinib than those who continued momelotinib, respectively 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% vs 27.5%), the SAEs (23.4% vs 15.8%), and TEAEs leading to treatment discontinuation (14.7% vs 8.8%), with numerically higher proportions for patients who switched from ruxolitinib to momelotinib than those who continued momelotinib. The most reported AEs occurring in ≥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 (AESI) were reported: peripheral neuropathy (5.3% vs. 7.6%), non-hematological (77.2% vs. 87.3%), cataract (4.7% vs. 3.6%) and first dose effect (NR vs. 2.0%). Regarding deaths due to TEAE not related to disease progression, 10.5% deaths occurred in the continuing momelotinib group and 8.6% in the switch from ruxolitinib to momelotinib group.

In SIMPLIFY-2, the overall frequencies of TEAEs (100% vs 93.8%), grade 3 or 4 AEs (55.0% vs 28.1%), SAEs (27.5% vs 20.3%), TEAEs leading to treatment discontinuation (37.5% vs 7.8%), and AEs leading to treatment interruption and/or dose reduction (19.2% vs 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 ≥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 reported SAEs occurring in ≥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 AESI were reported: peripheral neuropathy (10.9% vs. 20.0%), non-hematological (98.4% vs. 100%), cataract (1.6% vs. 0%), and first dose effect (NR vs. 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 group.

In MOMENTUM, following 24 weeks of treatment with momelotinib in the open-label treatment phase, the overall frequencies of TEAEs (89.2% vs 85.4%), grade ≥3 TEAEs (51.6% vs 48.8%), and serious TEAEs (32.3% vs 29.3%) were numerically slightly higher in patients who continued momelotinib than those who switched from danazol to momelotinib. The most reported AEs occurring in ≥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 ≥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, acute myeloid leukemia (AML), and transformation to AML (no events in the continuing momelotinib group for AML and transformation to AML and in the switch from danazol to momelotinib group for anemia). No deaths due to TEAE not related to disease progression were reported in any of the treatment groups.

Critical Appraisal

Internal Validity

The open-label extension phase design of SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM 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 SIMPLIFY-2, the proportion of patients with at least one 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 CSRs provided by the sponsors. In SIMPLIFY-1 and SIMPLIFY-2, the number of patients who discontinued treatment prior to 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 three 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 two retrospective analyses and one interim results 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

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF) who are Janus Kinase inhibitor (JAKi)-naïve 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-naïve: ruxolitinib JAKi-experienced: best available therapy (BAT)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (33 years)
Key data sources	SIMPLIFY-1 and SIMPLIFY-2 were used to inform efficacy and safety data for the JAKi-naïve and JAKi-experienced populations, respectively. MOMENTUM was also used to inform safety data for both populations.

Component	Description
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-naïve 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-naïve and the remaining 85% are JAKi-experienced, a price reduction of 27% would be required for momelotinib to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained when considering a blended population.

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. CDA-AMC reanalysis suggests that reimbursing momelotinib for the treatment of disease-related splenomegaly or symptoms, and anemia in adult patients with primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis who are JAKi-naïve 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 Villneuve, and Danica Wasney.

Meeting date: November 13, 2024

Regrets:

None

Conflicts of interest:

None