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CADTH Reimbursement Review

Fedratinib (Inrebic)

Sponsor: Celgene Inc.

Therapeutic area: Myelofibrosis

Clinical Review
Pharmacoeconomic Review

CADTH

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Abbreviations

AE	adverse event
AML	acute myeloid leukemia
BAT	best available therapy
BFI	Brief Fatigue Inventory
CI	confidence interval
DIPSS	Dynamic International Prognostic Scoring System
DMC	data monitoring committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
ESS	effective sample size
HRQoL	health-related quality of life
IRC	Independent Review Committee
ITC	indirect treatment comparison
ITT	intention to treat
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus kinase
JAKi	Janus kinase inhibitor
LLSC	Leukemia and Lymphoma Society of Canada
LOCF	last observation carried forward
MAIC	matching-adjusted indirect comparison
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MID	minimal important difference
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OS	overall survival
PFS	progression-free survival
PMF	primary myelofibrosis
Post-ET MF	post-essential thrombocythemia myelofibrosis
Post-PV MF	post-polycythemia vera myelofibrosis
RCT	randomized controlled trial
SAE	serious adverse event
STC	simulated treatment comparison
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
TSS	Total Symptom Score
VAS	Visual Analogue Scale
WE	Wernicke encephalopathy

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Myelofibrosis (MF) is a rare bone marrow disorder characterized by excessive production of reticulin and collagen fibres. It belongs to a group of diseases, myeloproliferative neoplasms (MPNs), which originate from acquired mutations that target the hematopoietic stem cell and induce dysregulation of kinase signalling, clonal myeloproliferation, and abnormal cytokine expression. MF includes primary and secondary MF.[1,2] Primary myelofibrosis (PMF) is a chronic, malignant hematological disorder with clinical features of severe anemia, marked hepatosplenomegaly, constitutional symptoms such as fatigue, night sweats, and fever, cachexia, bone pain, splenic infarct, pruritus, thrombosis, bleeding, and shortened survival.[3-6] Secondary MF includes post-polycythemia vera (PV) MF or post-essential thrombocythemia (ET) MF. The splenomegaly in MF is primarily due to hepatic extramedullary hematopoiesis. Symptoms secondary to splenomegaly include pressure and pain in the left upper quadrant of the abdomen, pain in the left shoulder, and early satiety secondary to compression of the stomach. In addition, massive splenomegaly may lead to portal hypertension (and its associated sequelae), splanchnic vein thrombosis, hepatic extramedullary hematopoiesis, and obliterative portal venopathy. Massive splenomegaly can also result in compression of the vena cava or iliac veins, resulting in lower extremity edema. In some cases, the extent of splenomegaly can lead to areas of ischemia resulting in painful splenic infarctions. Splenomegaly has a significant negative impact on patients' overall health-related quality of life (HRQoL).[4] The diagnosis of MPN requires a combination of clinical, laboratory, cytogenetic, and molecular testing.[7,8] MF is suspected when unexplained splenomegaly is detected on physical examination. Approximately 70% of patients with MF are in the intermediate-2 or high-risk categories.[9] The median overall survival (OS) in patients with MF is 11.3 years for low-risk, 7.9 years for intermediate-1 risk, 4.0 years for intermediate-2 risk, and 2.3 years for high-risk MF.[3,10] The prevalence rate of MF in Canada has been estimated as 0.0062% using data in 2016. The Leukemia and Lymphoma Society of Canada (LLSC) reported that in 2016, there were 1,800 cases of MF in Canada.[11]

Table 1: Submitted for Review

Item	Description
Drug product	Fedratinib (Inrebic), 100 mg, capsules, oral
Indication	For the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to ruxolitinib
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 27, 2020
Sponsor	Celgene Inc.

NOC = Notice of Compliance.

Relief of symptoms and improved quality of life are important goals for all patients with PMF.[12] According to the clinical experts consulted by CADTH for this review, patients with intermediate- or high-risk MF in Canada are treated with ruxolitinib. The goals of treatment are to reduce the symptoms of MF, reduce splenomegaly, and improve OS.

Fedratinib (Inrebic) is a Janus kinase (JAK) 2-selective inhibitor with higher potency for JAK2. Abnormal activation of JAK2 is associated with MPNs, including MF and PV.[13] On July 27, 2020, fedratinib was approved by Health Canada for the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk PMF, post-PV MF or post-ET MF, including patients who have been previously exposed to ruxolitinib. Fedratinib is available as 100 mg capsules and the recommended dose of fedratinib is 400 mg taken orally once daily for patients with a baseline platelet count of 50×10^9/L or greater.[13] Fedratinib should be discontinued in patients who are unable to tolerate a dose of 200 mg daily.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Three patient advocacy groups provided input for fedratinib for the treatment of splenomegaly and/or disease-related symptoms in adult patients with MF: LLSC, the Canadian MPN Research Foundation, and the Canadian MPN Network. The LLSC's mission is to cure leukemia, lymphoma, Hodgkin disease, and myeloma, as well as to improve the quality of life of all Canadians affected by blood cancers. The Canadian MPN Network is a patient-led organization whose purpose is to connect and help Canadians across the country who are facing the challenges of living with MPN. The Canadian MPN Research Foundation, founded in 2018, is focused on finding new treatments for Canadians with MPN by stimulating and funding relevant research projects.

The LLSC used an online survey for its submission, which was conducted between October 20, 2020, and November 9, 2020. The Canadian MPN Research Foundation and the Canadian MPN Network provided their insights based on information they had received through discussions with patients and caregivers, as well as a caregiver survey. In addition, further patient and caregiver insights were gathered through a combination of phone and in-person interviews.

The 3 patient groups reported that patients with MF experience fatigue, loss of appetite, bone pain, pain, and discomfort related to their enlarged spleen, fever, and night sweats, shortness of breath, bruising, and bleeding. In addition, the Canadian MPN Research Foundation and the Canadian MPN Network report that patients experience impaired cognition and concentration, as well as psychological effects such as anxiety and difficulty sleeping. These cancer symptoms negatively impact the patient's quality of life.

Patient groups reported that there are limited treatment options for patients diagnosed with MF. Treatments currently available to patients include ruxolitinib and best supportive care, which is focused on alleviating symptoms and improving the patient's HRQoL. When these therapies become ineffective, patients become dependent on blood transfusions. Patients

want treatments that will cure their disease and improve their quality of life. More treatment options are desirable. Cost and accessibility are also factors that need to be considered.

According to the patients who had experience with fedratinib, the drug improved their overall quality of life by decreasing their symptom burden. The patients also reported improved psychosocial functioning. The respondents did not report any adverse effects related to fedratinib.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The experts indicated that current treatment options for MF are limited. The best available first-line therapy is ruxolitinib. However, ruxolitinib is associated with hematological toxicities such as thrombocytopenia and anemia. Patients with cytopenias and/or renal dysfunction are not eligible to receive the optimal dose of ruxolitinib and thus may have suboptimal outcomes. Patients will eventually become refractory to ruxolitinib and there is no standard approach for second-line treatment.

Fedratinib would offer an additional first-line treatment option for treatment of splenomegaly and/or disease symptoms in patients with intermediate or high-risk MF. The decision to use ruxolitinib or fedratinib may be determined based on the individual patient's comorbidities and/or concomitant medications because there is no evidence to inform which drug should be used first at this time as a first-line treatment for patients who are ineligible for ruxolitinib treatment. In addition to first-line therapy, fedratinib may be used as a second-line treatment after ruxolitinib failure.

The experts identified that patients with intermediate- or high-risk MF with disease-related symptoms and/or splenomegaly are suitable for fedratinib treatment.

The experts stated that treatment response is assessed using change in spleen size by bedside physical examination and patient-reported symptom improvement. These measures are subjective and treating physicians are likely to consider improvements reported by the patient to be clinically meaningful. Treatment response should be assessed with each cycle of treatment or every 3 months at minimum.

The experts indicated that fedratinib treatment should be discontinued following disease progression (e.g., return of splenomegaly, worsening of symptoms, or disease progression to accelerated or blast phase) or adverse events (AEs; Wernicke encephalopathy [WE], intolerable gastrointestinal symptoms [nausea, vomiting, diarrhea], and malnutrition).

Clinician Group Input

One joint clinician group input was provided by 4 hematologists and a pharmacist on behalf of the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee.

The clinician group felt that patients with intermediate- or high-risk MF with disease-related symptoms and/or splenomegaly would be suitable for fedratinib treatment. There are clear diagnostic criteria used to diagnose MF. However, underdiagnosis is a challenge due to the lack of a driver mutation in a subset of patients.

The clinician group stated that fedratinib could be used at any time during the patient's treatment for MF, including as a first-line treatment. Following progression on fedratinib,

patients could be treated with hydroxyurea, pegylated interferon, best supportive care, and/or allogenic transplantation in selected patients.

In terms of assessing response to treatment, the clinician group stated that MF assessment score tools and forms are not routinely used in clinical practice. It would be reasonable to use clinical exams, ultrasounds, CT scans, and other objective measures to determine a reduction in spleen size to assess fedratinib response.

The clinician group also advised that treatment with fedratinib should be discontinued if a patient experiences disease progression or serious toxicities related to fedratinib.

Drug Program Input

In response to questions from the drug programs regarding the extended use of fedratinib in a broader population, for example, patients with poorer performance status or those with lower risk MF, the clinical experts consulted by CADTH indicated that the clinicians would like to offer fedratinib treatment to patients with poorer performance status, although there is no evidence currently for fedratinib in this patient population.

The clinical experts also indicated that fedratinib treatment can be used for patients who may have risk factors for encephalopathy; however, it should be used with caution, close monitoring, and careful attention to the patient's thiamine levels.

The experts also stated that there is no evidence to suggest what the optimal treatment sequencing is for MF. They pointed out that both fedratinib and ruxolitinib could be used as first-line therapy. In clinical practice, clinicians may tend to use ruxolitinib first, when more long-term data for ruxolitinib are available, for example, from the COMFORT trials. However, there may be a small group of patients in whom fedratinib would be considered as the optimal first-line treatment.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One double-blind, placebo-controlled, phase III randomized controlled trial (RCT; JAKARTA, N = 289) was included in this systematic review. The objective of the JAKARTA study was to evaluate the efficacy and safety of fedratinib in patients with primary or secondary (post-PV and post-ET) MF. The trial included adult patients (≥ 18 years of age) with intermediate-2 or high-risk PMF, post-PV MF, and post-ET MF. The study participants did not receive prior JAK2 inhibitors. Eligible patients were randomized to receive fedratinib 400 mg, fedratinib 500 mg, or placebo once daily for consecutive 6 cycles of treatment. During the treatment period, patients continued to receive their assigned treatment until disease progression or occurrence of intolerable AEs related to the treatment. Patients originally assigned to placebo were allowed to cross over to fedratinib therapy after week 24 (end of cycle 6), or before if the patient experienced progressive disease. The primary end point was spleen response rate, defined as the proportion of patients with at least a 35% reduction in spleen volume (measured by MRI or CT) from baseline to week 24 and confirmed 4 weeks later. Other efficacy outcomes included OS, progression-free survival (PFS), the proportion of patients with at least 25% to 35% reduction in spleen volume without week 4 confirmation, at least 50% reduction in disease-related symptom scores and HRQoL. Reduction in disease-related symptom scores was evaluated using the modified Myelofibrosis Symptom Assessment

Form (MFSAF). A Total Symptom Score (TSS) was the sum of 6 individual MF symptom scores. A higher score indicates more severe MF symptoms. Harms associated with fedratinib treatment were also examined. Fedratinib 500 mg once daily is not approved by Health Canada. Therefore, fedratinib 400 mg dose is the focus of this current CADTH review.

Note that on November 18, 2013, the sponsor terminated the development of fedratinib due to the risk of encephalopathy associated with fedratinib therapy. All patients enrolled in the study stopped fedratinib treatment. At the time of study termination, all patients had either completed the first 6 cycles or had previously permanently discontinued treatment.

In the JAKARTA study, patient's baseline characteristics were generally similar between groups at baseline. The mean age of the patients was 63 to 65 years. Most patients were White (90%–94%). The majority of study participants had been diagnosed with PMF (> 60%) and had baseline platelet counts of 100 × 10^9/L or greater (> 80%). Patients in the fedratinib group had a longer time since diagnosis (68.5 months in the fedratinib group versus 54.2 months in the placebo group), but more were classified as intermediate risk (60% in the fedratinib group versus 48% in the placebo group). Patients in the fedratinib group reported higher previous use of hydroxyurea (72% in the fedratinib group versus 56% in the placebo group), compared with those in the placebo group.

Efficacy Results

- Survival parameters of OS and PFS were identified as important outcomes in the CADTH review protocol and were planned secondary end points in the JAKARTA study; however, they were not able to be evaluated due to early termination of the study.
- In the JAKARTA study, a greater proportion of patients in the fedratinib 400 mg group (36.5%) achieved spleen response (≥ 35% reduction in spleen volume at week 24 and confirmed 4 weeks later), compared with those in the placebo group (1%), which was a statistically significant difference in favour of fedratinib 400 mg (between-group difference 35.42%; 97.5% confidence interval [CI] 24.2 to 46.7; P < 0.0001). Similar results were observed for other outcomes measuring spleen response, such as a 25% or greater reduction in spleen volume at week 24 and confirmed 4 weeks later and percentage of change in spleen volume from baseline to week 24. According to the clinical experts consulted by CADTH, the benefits gained in spleen response are clinically meaningful.
- Treatment with fedratinib was also associated with statistically significantly greater relief in disease-related symptoms, which was measured by TSS from disease-specific assessment form. At the end of cycle 6, the proportion of patients who had a 50% or greater reduction in the TSS from baseline was 39.6% in the fedratinib 400 mg arm and 8.2% in the placebo arm (mean difference 31.33%; 95% CI, 18.0 to 44.6; P < 0.0001). The clinical experts agree that the between-group differences are clinically meaningful.

HRQoL assessment was evaluated using the EuroQol 5-Dimensions-3 levels questionnaire (EQ-5D-3L). The mean change in EQ-5D utility index scores from baseline to the end of cycle 6 was 0.05 (95% CI, 0 to 0.09) in the fedratinib 400 mg group and −0.05 (95% CI, −0.11 to 0.01) in the placebo group. The mean change in EQ-5D Visual Analogue Scale (VAS) scores in the fedratinib group was 6.2 (95% CI, 1.8 to 10.5) at the end of cycle 6, and −0.9 (95% CI, −7.7 to 5.8) in the placebo group.

Investigated-rated response (using modified International Working Group for Myelofibrosis Research and Treatment [IWG-MRT] criteria) and duration of spleen response were exploratory outcome measures in the JAKARTA study; therefore, no statistical testing was

conducted. The proportion of patients treated with fedratinib who showed investigator-rated clinical improvement was 58.4% and was 3.3% in the placebo group. The median duration of spleen response in the fedratinib 400 mg arm was 18.2 months. The duration in the placebo group was not available at the time of this review.

Two patients in the placebo group had transformation to acute myeloid leukemia (AML); no such patients were identified in the fedratinib 400 mg group.

Harms Results

During the 6-cycle treatment period, almost all patients reported AEs in the JAKARTA study, with 99% of patients in the fedratinib group and 93.7% in the placebo group reporting. The most common AEs reported in both groups were gastrointestinal disorders: 91.7% in the fedratinib group and 49.5% in the placebo group. The incidence of serious adverse events (SAEs) was similar between fedratinib 400 mg (20.8%) and placebo (23.2%), In the fedratinib 400 mg group, cardiac failure in 5 patients, pneumonia in 1 patient, and anemia in 2 patients were considered SAEs. In the placebo group, cardiac failure in 3 patients, anemia in 1 patient, ascites in 3 patients, and 2 cases for each of pneumonia, splenic infarction, and transformation to AML were considered SAEs. More patients in the fedratinib group withdrew from treatment due to AEs (13.5% in the fedratinib group versus 8.4% in the placebo group). More patients in the placebo group died (12.6% versus 7.3% in fedratinib group) and the main reason was disease progression. In the fedratinib group, the primary cause of death was AE in 1 patient (cardiogenic shock) and progressive disease in 4 patients. In the placebo group, the primary cause of death was AE in 4 patients (myocardial ischemia, pneumonia, sepsis, and transfusion-related acute lung injury) and progressive disease in 6 patients.

More patients treated with fedratinib 400 mg (30.2%) reported grade 3 or 4 anemia compared to placebo (7.4%) up to cycle 6. The incidence of grade 3 or 4 thrombocytopenia and neutropenia was similar between the 2 treatment groups. Fedratinib (14.6%) was also found to be related to higher risk of WE compared to placebo (4.2%).

Critical Appraisal

The major limitations of the JAKARTA study include the potential biases on the study results due to the imbalanced patient baseline characteristics and underpowered subgroup analyses. In addition, the dropout rates were high across the treatment groups. The reasons for dropout differed between treatment and placebo. Dropout in the fedratinib arm was mostly due to AEs whereas the primary reason of treatment discontinuation was different in the placebo group and lack of efficacy was likely to be the primary issue. The potential impact of substantial and disproportional missing data may bias some of the efficacy outcome measurements. In addition, due to the early termination of the JAKARTA study, OS and PFS could not be assessed.

Based on the inclusion/exclusion criteria of the JAKARTA study, patients with prior treatment of JAK2 inhibitor would have been excluded. According to the clinical experts consulted by CADTH, in Canada, patients with intermediate- to high-risk MF are more likely to be treated with ruxolitinib first, instead of fedratinib. Therefore, the JAKARTA study does not reflect the anticipated use of fedratinib in the Canadian population. Furthermore, using placebo as a comparator to fedratinib does not reflect the current clinical practice in Canada either, when ruxolitinib is available for these patients. The JAKARTA study did not provide evidence to demonstrate the comparative efficacy and safety versus other Janus kinase inhibitors (JAKis) in this patient population.

Table 2: Summary of Key Results From the JAKARTA Study

Results	Fedratinib 400 mg	Placebo
Spleen response rate (≥ 35% SVR at EOC6, and confirmed 4 weeks thereafter): ITT population		
N	96	96
n (%)	35 (36.5)	1 (1.0)
95% CI	26.8 to 46.1	0 to 3.1
Difference (97.5% CI)	35.42 (24.2 to 46.7)	
P value[a]	< 0.0001	
Spleen response rate (≥ 25% SVR at EOC6, and confirmed 4 weeks thereafter): ITT population		
N	96	96
n (%)	47 (49.0)	2 (2.1)
95% CI	39.0 to 59.0	0 to 4.9
Difference (97.5% CI)	46.88 (35.0 to 58.8)	
P value[a]	< 0.0001	
Percentage of patients with ≥ 50% reduction in TSS from baseline to EOC6: ITT population with non-missing baseline TSS score		
N	91	85
n (%)	36 (39.6)	7 (8.2)
95% CI	29.5 to 49.6	2.4 to 14.1
Difference (95% CI)	31.33 (18.0 to 44.6)	
P value[b]	< 0.0001	
EQ-5D-3L utility index scores: ITT population		
N	73	56
Baseline, mean (SD)	0.70 (0.25)	0.72 (0.26)
EOC6, mean (SD)	0.77 (0.16)	0.70 (0.22)
Change from baseline, mean (SD)	0.05 (0.19)	−0.05 (0.22)
Between-group difference, mean (95% CI)	0.093 (0.02 to 0.16)	
EQ-5D-3L VAS score: ITT population		
N	69	52
Baseline, mean (SD)	61.34 (22.18)	62.51 (21.23)
EOC6, mean (SD)	68.34 (18.02)	61.95 (19.93)
Change from baseline, mean (SD)	6.16 (18.10)	−0.94 (24.36)
Between-group difference, mean (95% CI)	7.10 (−0.54 to 14.74)	
Harms (all-treated population)		
N	96	95

Results	Fedratinib 400 mg	Placebo
AEs, n (%)	95 (99.0)	89 (93.7)
SAEs, n (%)	20 (20.8)	22 (23.2)
WDAE (from study treatment), n (%)	13 (13.5)	8 (8.4)
Deaths, n (%)	7 (7.3)	12 (12.6)
Notable harms, n (%)		
Grade 3 or 4 anemia	29 (30.2)	7 (7.4)
Grade 3 or 4 thrombocytopenia	5 (5.2)	6 (6.3)
Grade 3 or 4 neutropenia	2 (2.1)	0
Potential WE (entire treatment duration)	14 (14.6)	4 (4.2)
Second malignancy (transformation to AML)	0	2 (2.1)
Transfusion dependency (among patients who were transfusion independent at baseline)	22 of 88 (25.0)	11 of 90 (12.2)
Hypersensitivity reaction	NR	NR
Grade 3 or 4 ALT, AST, or TBL elevation	1 (1.0)	2 (2.1)

AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; CI = confidence interval; EOC = end of cycle; EQ-5D-3L = EuroQol 5-Dimensions-3 levels questionnaire; ITT = intention to treat; NR = not reported; SAE = serious adverse event; SD = standard deviation; SVR = spleen volume reduction; TBL = total bilirubin; TSS = Total Symptom Score; VAS = Visual Analogue Scale; WDAE = withdrawal due to adverse event; WE = Wernicke encephalopathy.

[a]P values were calculated based on the chi-square test comparing the fedratinib arm (400 mg) to the placebo arm; CIs were calculated using normal approximation.

[b]P values were calculated based on the chi-square test comparing the fedratinib arm (400 mg) to the placebo arm; CIs were calculated using normal approximation.

Source: Clinical Study Report for JAKARTA.[14]

Indirect Comparisons

Description of Studies

As there was no direct evidence comparing fedratinib to other active therapies for the treatment of splenomegaly and/or disease-related symptoms in patients with MF, 2 indirect treatment comparison (ITC) analyses submitted by the sponsor were summarized and critically appraised. The ITCs included a review of the literature and a matching-adjusted indirect comparison (MAIC) and a simulated treatment comparison (STC; JAKi-experienced comparison only) that compared fedratinib to best available therapy (BAT) for JAKi-experienced adult patients with MF,[15] or compared fedratinib to ruxolitinib for JAKi-naive adult patients with MF.[16] Spleen volume reduction (SVR) and TSS reduction at week 24 were the efficacy outcomes included in the ITCs.

Efficacy Results

In the ITC for JAKi-experienced patients, the results of the MAIC with adjustment for the identified prognostic factors suggested that treatment with fedratinib 400 mg once daily was associated with greater proportion of patients achieving a 35% or greater reduction in spleen volume at week 24, compared to BAT. The difference in the proportion of patients with a 35% or greater SVR between fedratinib 400 mg and BAT was 12.5% (95% CI, 4.5 to 20.9). The results also suggested that treatment with fedratinib was associated with a greater

proportion of patients achieving a 50% or greater reduction in TSS from baseline to week 24, compared to BAT. In this case, the difference in the proportion of patients with a 50% or greater TSS reduction between fedratinib 400 mg and BAT was 17.0% (95% CI, 6.2 to 28.2).

In the ITC for JAKi-naive patients, the results of the MAIC with adjustment for the identified effect modifier suggested that at week 24, treatment with fedratinib 400 mg once daily was associated with slightly greater proportion of patients achieving a 35% or greater reduction in spleen volume as compared to ruxolitinib. The difference in the proportion of patients with a 35% or greater SVR between fedratinib 400 mg and ruxolitinib was 12.3% (95% CI, 0.6 to 24.0). The results also suggested that there were no statistically significant differences between fedratinib and ruxolitinib in achieving a 50% or greater reduction in TSS from baseline to week 24 as the between-group difference was –9.4% (95% CI, –23.9 to 5.2).

Harms Results

Harm outcomes were not included in the ITC. Results were descriptively summarized. No firm conclusions can be made for harm outcomes from the ITC.

Critical Appraisal

Although the methods used to conduct the MAIC follow technical guidance, the analyses have a number of limitations that impact the internal and external validity. There are concerns that not all effect modifiers and prognostic factors have been identified and adjusted for in the analyses, and the availability of data to allow for including all key variables in the weighting process. The small effective sample size (ESS) in the assessment of spleen volume response for JAKi-experienced patients suggests that substantial differences exist between the patient populations in the fedratinib and BAT trials. In addition, in the ruxolitinib-naive ITC, the placebo arm in the JAKARTA and COMFORT-I studies and the BAT arm in the COMFORT-II study were substantially different. It was not appropriate to assume that patients responded similarly to both of them.

Given these issues, there is substantial risk of bias in the MAIC results.

Other Relevant Evidence

Description of Studies

A phase II, single-arm, open-label study (JAKARTA2, N = 97) provided evidence on the treatment with fedratinib in patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF that were previously treated with ruxolitinib. Patients received 400 mg fedratinib orally once daily in repeated 28-day cycles. The trial evaluated patients over 6 cycles (approximately 6 months). If patients did not achieve adequate spleen response (i.e., < 50% reduction in spleen size by palpation) and there was no unacceptable toxicity at the end of cycles 2 and 4, dose escalation was strongly recommended in 100 mg per day increments up to 600 mg per day. The primary outcome of the JAKARTA2 trial was spleen volume response rate, defined as the proportion of patients that had a 35% or greater reduction in spleen volume at the end of cycle 6 relative to baseline, as measured by MRI or CT scan. Secondary end points included spleen volume response rate (≥ 35% reduction) at the end of cycle 3 by MRI or CT, duration of spleen response by MRI or CT, proportion of patients with a 50% or greater reduction in spleen volume by palpation at the end of cycle 6, symptom response rate defined as a 50% or greater reduction in the TSS of the modified MFSAF, and safety.

Efficacy Results

Result suggested that after 6 cycles of treatment with fedratinib, spleen response and symptom response to the treatment were observed. In the primary analysis population (N = 83), 48% of patients exhibited a 35% or greater reduction in spleen volume as measured by MRI or CT scan at the end of cycle 6. At the end of cycle 3, 47% of patients showed a 35% or greater reduction in spleen volume as measured by MRI or CT scan. Furthermore, 31% of patients exhibited a 50% or greater reduction in spleen size, as measured by palpation, at the end of cycle 6. In the MFSAF analysis population (N = 90), 27% of patients reported a 50% or greater reduction in the TSS of the modified MFSAF at end of cycle 6. The potential survival benefit from fedratinib could not be determined because the pre-specified number of events was not reached before the study was terminated.

Harms Results

All patients enrolled in the JAKARTA2 study experienced a treatment-emergent AE (TEAE). Thirty-four percent (N = 33) of patients experienced an SAE. The most common AEs of any grade were diarrhea (62%), nausea (56%), anemia (49%), vomiting (41%), thrombocytopenia (27%), constipation (21%), pruritis (18%), and fatigue (16%). Nineteen (20%) patients experienced an AE that led to permanent fedratinib treatment discontinuation. Eighteen (19%) patients withdrew from the JAKARTA2 study due to AEs. Seven (7%) patients had a TEAE that led to death. Four of these deaths were due to disease progression and the 3 others were due to pneumonia, cardiorespiratory arrest, and shock.

Critical Appraisal

The primary limitations of the JAKARTA2 trial were the open-label administration of fedratinib, absence of a comparator group, small sample size, and early termination. Due to the early termination of the study, multiple protocol-pre-specified end points were not analyzed and the median duration of spleen response was not reached. Importantly, OS could not be analyzed because the pre-specified number of events was not reached before the study was terminated. As a result, no conclusions can be made regarding the effect of fedratinib treatment on survival.

The JAKARTA2 study provides evidence on the use of fedratinib in MF patients previously treated with ruxolitinib. However, the dose of fedratinib used in the JAKARTA2 study is not entirely representative of the Health Canada recommended dose of 400 mg per day. Per the study protocol, if a patient did not experience adequate spleen response at the 400 mg dose, it was strongly recommended that the dose be titrated upwards to a maximum of 600 mg per day. As a result, 34% of patients received a fedratinib dose greater than 400 mg per day. The higher dosage used in the JAKARTA2 study may have resulted in a greater frequency of AEs and SAEs.

Conclusions

One phase III, double-blind, placebo-controlled, RCT (JAKARTA) provided evidence supporting the efficacy and safety of fedratinib in adult patients with intermediate-2 risk or high-risk MF. Compared to placebo, patients who were treated with fedratinib 400 mg once daily showed benefits in SVR and MF-related symptom relief from baseline to the end of cycle 6. Changes in the spleen response and symptom response were considered statistically and clinically relevant. However, whether treatment with fedratinib is associated with any survival benefit is unknown, and the effect on HRQoL remains uncertain. Almost all study participants reported TEAEs. Fedratinib was related to more treatment discontinuation due to AEs, and higher

frequency of cytopenia and potential WE. The JAKARTA study did not provide direct evidence on the relative efficacy and safety of fedratinib versus current standard of care (other JAKis) for patients with MF, or evidence for patients who received previous JAKi treatment.

JAKARTA2 was a phase II, single-arm, open-label study involving ruxolitinib-experienced patients with intermediate- to high-risk MF. The results supported the beneficial effect of fedratinib on reduction in spleen volume and symptom relief. However, limitations of this study, such as small sample size, lack of comparator group, and short study duration contribute uncertainty to the results.

Results from 2 indirect treatment analyses suggested that treatment with fedratinib is associated with higher spleen response rate and higher symptom response rate in a JAKi-experienced patient population, compared to BAT; however, the relative efficacy of fedratinib versus ruxolitinib was not significant in the JAKi-naive patient population. Results of both ITCs are associated with substantial risk of bias.

Introduction

Disease Background

MF is a bone marrow disorder characterized by excessive production of reticulin and collagen fibres. It belongs to a group of disease, MPNs, which originate from acquired mutations that target the hematopoietic stem cell and induce dysregulation of kinase signalling, clonal myeloproliferation, and abnormal cytokine expression. MF includes primary and secondary MF.[1,2] PMF is a chronic, malignant hematological disorder with clinical features of severe anemia, marked hepatosplenomegaly, constitutional symptoms (such as fatigue, night sweats, and fever), cachexia, bone pain, splenic infarct, pruritus, thrombosis, bleeding, and shortened survival.[3-6] MF can also be the outcome of several hematological conditions (e.g., as evolution of a previously known MPN, chronic myeloid leukemia, PV, or ET) and non-hematological conditions (e.g., metastatic cancer, infections such as tuberculosis, fungal infections, and HIV, metabolic disorders, radiation, and toxins). The splenomegaly in MF is primarily due to hepatic extramedullary hematopoiesis. While rarely present in post-ET MF, splenomegaly is commonly seen in about 1-third of patients with post-PV MF and even more frequently in PMF, with 38% of patients having a palpable spleen at least 10 cm below the left costal margin and 23% with a spleen extending more than 16 cm. Symptoms secondary to splenomegaly include pressure and pain in the left upper quadrant of the abdomen, pain in the left shoulder, and early satiety secondary to compression of the stomach. In addition, massive splenomegaly may lead to portal hypertension (and its associated sequelae), splanchnic vein thrombosis, hepatic extramedullary hematopoiesis, and obliterative portal venopathy. Massive splenomegaly can also result in compression of the vena cava/iliac veins, resulting in lower extremity edema. In addition, cellular sequestration leading to exacerbation of existing cytopenias is common and can further limit medicinal options. In some cases, the extent of splenomegaly can lead to areas of ischemia resulting in painful splenic infarctions. Splenomegaly has significant negative impact on patients' overall HRQoL, therefore, reduction in spleen size is 1 of the important treatment goals.[4] The mutation in the JAK2 gene has been found in almost all (95%) patients with post-PV MF and approximately 50% to 60% of those with either post-ET or PMF.[2]

MF is suspected when unexplained splenomegaly is detected on physical examination. The diagnosis of MPN is based on the 2017 WHO criteria and requires a combination of clinical, laboratory, cytogenetic, and molecular testing.[7,8] Several prognostic scoring systems are available to predict survival of patients with PMF. One of them is the International Prognostic Scoring System. Based on the evaluation of various risk factors such as age, constitutional symptoms, level of hemoglobin, white blood cell count, and blood blasts, patients are classified into different risk groups that are associated with differing prognosis. The median OS is 11.3 years for low-risk, 7.9 years for intermediate-1 risk, 4.0 years for intermediate-2 risk, and 2.3 years for high-risk MF.[3,10] Approximately 70% of patients with MF are in the intermediate-2 or high-risk categories.[9]

The prevalence rate of MF in Canada has been estimated as 0.0062% using data from 2016. The LLSC reported that in 2016, there were 1,800 cases of MF in Canada.[11]

Standards of Therapy

Relief of symptoms and improved HRQoL are important goals for all patients with PMF.[12]

Prior to the introduction of JAKis, conventional cytoreductive therapies for patients with symptomatic splenomegaly include hydroxyurea and interferon therapy. Hydroxyurea is an oral ribonucleotide reductase inhibitor and is often employed as first-line cytoreductive therapy in post-PV MF and post-ET MF, while for patients with PMF, hydroxyurea is typically reserved for those who have hyperproliferative features including splenomegaly, leukocytosis, and constitutional symptoms that are not eligible for JAK2 inhibitors.[4] Adverse effects related to the use of hydroxyurea include dose-limiting cytopenias and oral and lower extremity skin ulcers. Unsatisfied effect in reducing spleen size or unacceptable toxicities have been reported for other cytoreductive therapies, such as interferon alfa therapy.[4]

Currently, the mainstay of pharmacologic-induced spleen reduction in MF is the use of JAK1 and JAK2 inhibitors, such as ruxolitinib. Ruxolitinib is a JAK1 and JAK2-selective inhibitor and is indicated for the treatment of splenomegaly and/or its associated symptoms in adult patients with PMF, post-PV MF, or post-ET MF.[17] The effects of ruxolitinib in reducing spleen volume and improving disease-related symptoms have been demonstrated in clinical trials involving patients with intermediate and high-risk MF, as well as patients who were not responsive or intolerant to hydroxyurea.[4] Although the initial response rate to ruxolitinib therapy is high, patients eventually develop intolerance due to dose-dependent drug-related cytopenias or resistance to ruxolitinib after 2 to 3 years of therapy. After ruxolitinib failure, strategies to overcome ruxolitinib resistance or intolerance are limited, and mainly involve different approaches to continued ruxolitinib therapy, including dosing modifications and ruxolitinib rechallenge.[6]

According to the clinical experts consulted by CADTH for this review, patients with intermediate- or high-risk MF in Canada are treated with ruxolitinib. The goals of treatment are to reduce the symptoms of MF, reduce splenomegaly, and improve OS. Prior to ruxolitinib becoming the standard of care, patients were treated with hydroxyurea or interferons. These treatments may still be used in select groups of patients (e.g., interferon for women of childbearing age, hydroxyurea for patients with severe thrombocytopenia).

Despite effective pharmacologic options, there are patients who are ineligible for clinical trials or have progressed with limited treatment options; therefore, more invasive treatment modalities may be given. Splenectomy, splenic irradiation, and partial splenic artery

embolization remain important therapeutic tools to consider in the management of MF-related splenomegaly. Another treatment option for patients with intermediate- or high-risk MF is an allogenic hematopoietic cell transplant but this requires an appropriate donor and the high rates of morbidity and mortality limit eligibility.[3,6] The clinical experts consulted by CADTH noted that while allogenic transplantation can be curative, outcomes are often poor. Allogenic transplantation is associated with high treatment-related mortality, graft failure, graft versus host disease, and infection.

Drug

Fedratinib (Inrebic) is a JAK2-selective inhibitor with higher potency for JAK2 over family members JAK1, JAK3, and tyrosine kinase 2.[17] Abnormal activation of JAK2 is associated with MPNs, including MF and PV. In cell models expressing mutationally active JAK2, fedratinib reduced phosphorylation of signal transducer and activator of transcription 3/5 proteins, inhibited cell proliferation, and induced apoptotic cell death. In mouse models of $JAK2^{V617F}$-driven myeloproliferative disease, fedratinib blocked phosphorylation of signal transducer and activator of transcription 3/5, and improved survival and disease-associated signs.[13]

On July 27, 2020, fedratinib was approved by Health Canada for the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk PMF, post-PV MF or post-ET MF, including patients who have been previously exposed to ruxolitinib.[17] The reimbursement request for fedratinib by the sponsor is as per the Health Canada–approved indication.

Fedratinib is available as 100 mg capsules. The recommended dose of fedratinib is 400 mg taken orally once daily for patients with a baseline platelet count of 50×10^9/L or greater.[17] Fedratinib carries a serious warning regarding potential for development of encephalopathy and the requirement to assess thiamine levels in all patients before starting treatment with fedratinib, and periodically during treatment and as clinically indicated. Dose modifications should be considered in patients who experience hematologic and non-hematologic toxicities, for management of thiamine levels, for patients with WE, and when used concomitantly with strong or moderate CYP3A4 inhibitors. Fedratinib should be discontinued in patients who are unable to tolerate a dose of 200 mg daily.

Table 3 provides details regarding the mechanism of action, indication, route and dose of administration, and adverse effects of fedratinib and ruxolitinib.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

Three patient advocacy groups provided input for fedratinib for the treatment of splenomegaly and/or disease-related symptoms in adult patients with MF: the LLSC, the Canadian MPN Research Foundation, and the Canadian MPN Network.

The LLSC's mission is to cure leukemia, lymphoma, Hodgkin disease, and myeloma, as well as to improve the quality of life of all Canadians affected by blood cancers.

The Canadian MPN Network, founded in 2014, is a patient-led organization whose purpose is to connect and help Canadians across the country who are facing the challenges of living with MPN. The organization provides patient advocacy, patient support groups, and patient communication. They also collaborate with the MPN medical community to provide patient perspectives and effective communications.

The Canadian MPN Research Foundation, founded in 2018, is focused on finding new treatments for Canadians with MPN by stimulating and funding relevant research projects. They work with the medical and research communities to provide current information on research, treatments, and clinical studies for MPN.

The LLSC used an online survey for its submission, which was conducted between October 20, 2020, and November 9, 2020. Respondents included 13 completed surveys from 11 patients and 2 caregivers. All respondents were from Canada: 1 from Ontario, 2 from Alberta, 2 from Nova Scotia, 6 from British Columbia, 1 from Quebec, and 1 from Newfoundland and

Table 3: Key Characteristics of Fedratinib and Ruxolitinib

Characteristic	Fedratinib	Ruxolitinib
Mechanism of action	A selective inhibitor of JAK2	A selective inhibitor of JAK1 and JAK2
Indication[a]	The treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary MF, post-PV MF, or post-ET MF, including patients who have been previously exposed to ruxolitinib	The treatment of splenomegaly and/or its associated symptoms in adult patients with primary MF (also known as chronic idiopathic MF), post-PV MF, or post-ET MF The control of hematocrit in adult patients with PV resistant to or intolerant of a cytoreductive agent
Route of administration	Oral	Oral
Recommended dose	400 mg q.d. for patients with a baseline platelet count of ≥ 50 × 10^9/L	Starting dose for patients with MF: 5 mg to 20 mg orally b.i.d., depending on platelet count Starting dose for patients with PV: 5 mg to 10 mg orally b.i.d., depending on platelet count
Serious adverse effects or safety issues	Serious warnings and precautions: Serious and fatal encephalopathy, including Wernicke encephalopathy; assess thiamine levels in all patients before starting fedratinib, periodically during treatment, and as clinical indicated	Warnings and precautions: • Serious bacterial, mycobacterial, fungal, and viral infections; some cases were life-threatening or lead to death • Decrease in blood cell count: a complete blood count must be performed before initiating therapy with ruxolitinib and during therapy

b.i.d. = twice a day; ET = essential thrombocythemia; JAK = Janus kinase; MF = myelofibrosis; PV = polycythemia vera; q.d. = once daily.

[a]Health Canada–approved indication.

Source: Product monographs for Inrebic[13] and Jakavi.[17]

Labrador. Patient ages ranged from 35 to 74 years old. Most patients had been diagnosed with MF within the past 6 years. None of the respondents had experience with fedratinib.

The Canadian MPN Research Foundation and the Canadian MPN Network provided their insights based on information they had received through discussions with patients and caregivers, as well as a caregiver survey. In addition, further patient and caregiver insights were gathered through a combination of phone and in-person interviews. The interviewers facilitated a discussion focused on the patients' disease experience, and patients were asked about their quality of life and how it has changed while receiving their current treatment. Of the 25 patient respondents, 10 were from Canada, 12 were from Europe, and 3 from the US. Of the 25 caregivers surveyed, 10 were from Canada, 12 were from Europe, and 3 from the US. Data from the Canadian respondents were gathered from May 2020 to August 2020; data from the European and American respondents were gathered in October 2019. Four patients and 4 caregivers had experience with fedratinib in the second-line setting after ruxolitinib through participation in a clinical trial.

Disease Experience

The 3 patient groups reported that patients with MF experience fatigue, loss of appetite, bone pain, pain, and discomfort related to their enlarged spleen, fever, and night sweats, shortness of breath, bruising, and bleeding. In addition, the Canadian MPN Research Foundation and the Canadian MPN Network reported that patients experience impaired cognition and concentration as well as psychological effects such as anxiety and difficulty sleeping. These cancer symptoms negatively impact the patient's quality of life.

According to the patient respondents to the LLSC survey, the MF symptoms that have the greatest impact on their quality of life are fatigue, bone pain, loss of appetite, weight loss, and shortness of breath. Patients also expressed concern about survival as they have the potential to die from MF, which is an incurable cancer. Additional symptoms that impact the patients' quality of life included fever, night sweats, bruising, bleeding, and feelings of pain or discomfort on their left side under their ribs. Some patients reported few symptoms with minimal impact on their quality of life whereas others reported a significant negative impact on quality of life. Multiple patients reported that their cancer symptoms had negative effects on their social life and interpersonal relationships. Some patients reported that they are unable to work due to their disease and associated symptoms. Below are comments from patients regarding their experiences with MF:

- "Daily life - low tolerance for stress, low energy, constant bone pain. Social life — has very little energy/interest in socializing — it takes too much effort."
- "Occasionally, the dull ache associated with my enlarged spleen makes it more difficult to fall asleep and I'm careful not to work too hard at some activities (e.g., cross country skiing, leaf raking). Overall, I am at an early stage of myelofibrosis, very active, and symptoms are manageable for now."
- "Too tired to socialize, cook, go out, work, have a life! I am grumpy and short tempered. No patience. Hard on relationship."

MF affects not just those who are diagnosed, but also their caregivers. The Canadian MPN Research Foundation and the Canadian MPN Network reported that caregivers are required to take on increased responsibilities in the home and perform additional activities to assist their loved 1 with their physical and mental needs. They reported that caregivers experience

anxiety related to watching their loved 1 experience the symptoms of MF (e.g., fatigue, impaired cognition, decreased concentration, decreased mobility, and muscle loss).

The Canadian MPN Research Foundation and the Canadian MPN Network reported that is important to patients and caregivers that treatments for MF control the patient's symptoms of fatigue, bone pain, splenomegaly, and loss of appetite/weight loss to improve their quality of life.

Experiences With Currently Available Treatments

The Canadian MPN Research Foundation and the Canadian MPN Network reported that there are limited treatment options for patients diagnosed with MF. Treatments currently available to patients include ruxolitinib and best supportive care, which is focused on alleviating symptoms and improving the patient's HRQoL. When these therapies become ineffective, patients become dependent on blood transfusions.

Patient respondents from the LLSC survey reported receiving a variety of treatments for MF: drug therapy (n = 6), chemotherapy (n = 3), splenectomy (n = 3), and stem cell/bone marrow transplant (n = 2). These treatments included ruxolitinib, interferon, epoetin alfa, hydroxyurea, and blood transfusions. Side effects associated with these treatments included hair loss, low blood cell counts, anemia, fatigue, cough, rashes, weakness, shortness of breath, headaches, poor concentration, and emotional challenges. Below are comments from patients regarding their experiences with current therapies:

- "Chemo although nasty, tolerable symptoms with chemo sessions and other treatments while in the hospital…Splenectomy was far worse than the entire transplant treatment. Long painful, recovery, disfiguring foot long scar down abdomen."
- "Put on Jakavi 15. Much improved, and blood count went from as low as 57 up steadily to current 109 so went from almost no energy to functional."
- "Interferon: mega side effects. Unable to work full-time and lost my job. Hair loss. Thin delicate skin. Lost eyebrows. Splenectomy- after many years of discomfort and inability to eat much, OR was great! Positive: no shaving needed!"
- "I was on a series of different drugs for Myelofibrosis. Hydroxyurea - For about 3 years with little impact Jakavi - for about 3 years BMT Transplant in 2017."

Patients that responded to the LLSC survey reported a mixture of both positive and negative experiences accessing treatments. Negative experiences were related to challenges with receiving their MF diagnosis, telemedicine, and the cost of treatments. According to the Canadian MPN Research Foundation and the Canadian MPN Network, some patients are ineligible for treatment with ruxolitinib due to their blood counts, experience ruxolitinib treatment failure, and/or become intolerant to treatment. Below are comments provided by patients regarding their experiences with accessing health care and treatments:

- "It was all positive. I call the pharmacy and ruxolitinib is delivered to my home in days."
- "I had been telling my family doctor for a year or so that I was abnormally tired and that was "not me." Had blood tests been done early, my myelofibrosis would have been detected earlier."
- "Interferon is very expensive and my health insurance doesn't cover it all. My province will not cover it either."

- "Started interferon in January. In April I was unable to see family dr (COVID) so he prescribed me migraines meds for persistent headaches over the phone. Turned out to be eye problems from interferon when migraine meds weren't working and saw optometrist. June had severe case of hives and angioedema. Again couldn't see family dr so he prescribed steroids (again over the phone) which landed me in the hospital with several gastritis in July from steroids."

Improved Outcomes

The majority of respondents to the LLSC survey indicated that they want treatments that will cure their MF and improve their quality of life (e.g., reduce bone pain). The LLSC survey patient respondents also reported that they want more treatment options, including for when they progress on ruxolitinib. Patients indicated they want a MF treatment that could make an impact on the disease, could be provided as an outpatient treatment, and accessed close to home. Cost and side effects were also identified as important factors.

The Canadian MPN Research Foundation and the Canadian MPN Network emphasized the need for a cure for MF and that patients want to have a normal life span (i.e., increased survival). The organizations also reported that patients and caregivers want treatments that improve their HRQoL by better controlling the patient's symptoms of fatigue, bone pain, enlarged spleen, and loss of appetite/weight loss. The Canadian MPN Research Foundation and the Canadian MPN Network emphasize that currently there are few treatment options available for patients with MF that improve their HRQoL.

Experience With Drug Under Review

The Canadian MPN Research Foundation and the Canadian MPN Network received feedback from 4 Canadian patients and 4 caregivers that had experience with fedratinib as a second-line treatment after ruxolitinib through a clinical trial. The patients reported that fedratinib treatment improved their overall quality of life by decreasing their symptom burden. The Canadian MPN Research Foundation and the Canadian MPN Network report that fedratinib improved the patients' symptoms of fatigue, loss of appetite, bone pain, night sweats, and cognitive impairment. The patients also reported decreased anxiety related to their disease. In addition, the Canadian MPN Research Foundation and the Canadian MPN Network found that caregivers report that the patients' psychosocial functioning was improved by participating in the clinical trial of fedratinib. The patients and caregivers did not report any adverse effects related to fedratinib to the Canadian MPN Research Foundation and the Canadian MPN Network.

Additional Information

The Canadian MPN Research Foundation and the Canadian MPN Network believe that fedratinib will provide an additional treatment option to patients with MF that has the potential to improve their HRQoL. In addition, fedratinib will provide hope to patients that have been diagnosed with an incurable disease. The organizations also proposed that fedratinib could decrease costs to the health care system by delaying disease progression and patients becoming dependent on blood transfusions. The Canadian MPN Research Foundation and the Canadian MPN Network believe that fedratinib will have a positive impact on patients, their caregivers, and the health care system.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of MF.

Unmet Needs

Current treatment options for MF are limited. The best available first-line therapy is ruxolitinib. However, ruxolitinib is associated with hematological toxicities such as thrombocytopenia and anemia. Patients with cytopenias and/or renal dysfunction are not eligible to receive the optimal dose of ruxolitinib and thus may have suboptimal outcomes. Patients will eventually become refractory to ruxolitinib and there is no standard approach for second-line treatment. The median duration of response to ruxolitinib in the COMFORT-I[18] and COMFORT-II[19] trials was approximately 3 years. In addition, none of the available treatments for MF are disease modifying and they are not proven to increase OS compared to BAT or placebo. Furthermore, not all patients respond to the limited number of available treatments.

An ideal treatment would prolong OS, be disease modifying (i.e., reduce the clonal burden and reverse fibrosis), delay leukemic progression, and improve HRQoL. An ideal treatment would also reduce symptoms and improve splenomegaly without having a negative effect on blood counts. Symptoms of MF that need to be controlled by treatments include anorexia, fatigue, and night sweats. Improving splenomegaly reduces the symptoms of early satiety, abdominal pain, and cytopenias. Improved symptom control through an effective treatment would allow patients to continue to work.

Place in Therapy

Fedratinib would offer an additional first-line treatment option for treatment of splenomegaly and/or disease symptoms in patients with intermediate or high-risk MF. In some scenarios, such as reducing splenic volume before allogeneic transplantation, fedratinib treatment may prevent the need for splenectomy or splenic radiation. Fedratinib could be used as a first-line treatment for patients that are ineligible for ruxolitinib treatment. This would include patients with a platelet count less than 50×10^9/L with creatinine clearance less than 60 mL per minute, platelets less than 100×10^9/L with end-stage renal disease, and platelets less than 50×10^9/L with mild to severe hepatic impairment. Physicians may prefer to treat patients that are eligible for ruxolitinib with ruxolitinib first due to their greater experience and comfort with the drug. In addition to first-line therapy, fedratinib may be used as a second-line treatment after ruxolitinib failure.

Patient Population

- Patients with intermediate- or high-risk MF with disease-related symptoms and/or splenomegaly are suitable for fedratinib treatment. There are clear diagnostic criteria used to diagnose MF. However, underdiagnosis is a challenge due to the lack of a driver mutation in a subset of patients.
- Current guidelines recommend ruxolitinib or fedratinib monotherapy as first-line treatment for patients with intermediate- or high-risk MF with disease-related symptoms and/or

splenomegaly. The decision to use ruxolitinib or fedratinib may be determined based on the individual patient's comorbidities and/or concomitant medications because there is no evidence to inform which drug should be used first at this time. Patients who are ineligible for ruxolitinib treatment would be suitable for first-line treatment with fedratinib. In addition, patients that have experienced ruxolitinib failure may benefit from fedratinib as second-line treatment.

Patients with a thiamine deficiency (before repletion) would not be suitable for fedratinib treatment due to an increased risk for encephalopathy. Furthermore, patients with accelerated or blast phase disease would be unlikely to benefit from fedratinib.

Assessing Response to Treatment

In clinical practice, MF treatment response is assessed using change in spleen size by bedside physical examination and patient-reported symptom improvement. These measures of response are subjective and treating physicians are likely to consider improvements reported by the patient to be clinically meaningful. Treatment response should be assessed with each cycle of treatment or every 3 months at minimum.

Discontinuing Treatment

Fedratinib treatment should be discontinued following disease progression or AEs. Disease progression could be defined as return of splenomegaly, worsening of symptoms, or disease progression to accelerated or blast phase. AEs requiring treatment discontinuation could include WE, intolerable gastrointestinal symptoms (nausea, vomiting, and diarrhea), and malnutrition.

Prescribing Conditions

Fedratinib should be administered in outpatient cancer or hematology clinics. Treatment should be managed by a hematologist or oncologist experienced in caring for patients with MF.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

One joint clinician input was provided by 4 hematologists and a pharmacist on behalf of the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee. The clinicians providing input practice in the province of Ontario.

Unmet Needs

No input was provided.

Place in Therapy

The clinician group providing input had experience using fedratinib. They stated that fedratinib could be used at any time during the patient's treatment for MF, including as a first-line treatment. However, they indicated that they may prefer to use ruxolitinib for first-line treatment and use fedratinib as second-line therapy. Following progression on fedratinib, the clinical group thought that patients could be treated with hydroxyurea, pegylated interferon, best supportive care, and/or allogenic transplantation in select patients.

Patient Population

The clinicians providing input felt that use of fedratinib in clinical practice should align with the study populations in the JAKARTA and JAKARTA2 trials, but that there should be flexibility regarding the patient's blood counts and their eligibility for treatment with fedratinib. The clinician group advised that patients who have a neurologic impairment or nutritional issues may not be suitable candidates for fedratinib treatment.

Assessing Response to Treatment

The clinician group stated that MF assessment score tools and forms are not routinely used in clinical practice. The clinician group advised that calculating splenic volume from scans may not be routinely available for patients with MF. The clinician group stated that they thought it would be reasonable to use clinical exams, ultrasounds, CT scans, and other objective measures to determine a reduction in spleen size to assess fedratinib response.

Discontinuing Treatment

The clinician group believed that treatment with fedratinib should be discontinued if a patient experiences disease progression or serious toxicities related to fedratinib.

Prescribing Conditions

No input was provided.

Additional Considerations

The clinician group providing input felt that it would be reasonable to extend fedratinib treatment to patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3 to align with the criteria from the previous ruxolitinib review.

The clinician group highlighted that fedratinib has a serious warning in the product monograph that serious and fatal encephalopathy (including WE) has occurred in patients treated with fedratinib.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Key clinical factors that Provincial Advisory Group identified as factors that could impact the implementation included:

- place in therapy of fedratinib relative to ruxolitinib
- eligible patient population.

Clinical Evidence

The clinical evidence included in the review of fedratinib is presented in 3 sections. The first section, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
1. In clinical practice, is there evidence to extend the use of fedratinib to (provided all other eligibility criteria are met):	
a. patients with an ECOG PS of 3 (to align with criteria from the ruxolitinib review);	a. The clinical experts consulted by CADTH were not aware of any evidence outside of the JAKARTA and JAKARTA2 trials; however, they recognized that physicians would like to offer fedratinib treatment to patients with an ECOG PS of 3, but acknowledged that there is no evidence for fedratinib in this patient population.
b. patients with low-risk or intermediate-risk level 2 symptomatic MF;	b. Patients with lower risk MF generally would not require treatment, but if symptomatic, clinicians would want to treat them. The COMFORT trial, which had a similar study design and examined the effect of ruxolitinib, showed that response in patients with lower risk disease was identical to those with higher risk disease. Based on this, even though there is no direct evidence for fedratinib, the clinical experts felt that it would be reasonable to assume that symptomatic patients with lower risk disease would still benefit from the treatment.
c. patients with prior treatment with a JAK2 inhibitor.	c. The JAKARTA2 trial provides evidence for patients with prior treatment with JAK2 inhibitor. JAKARTA2 is summarized in the Other Relevant Evidence section of this report.
2. In the JAKARTA trial, encephalopathy was reported with treatment with fedratinib at 500 mg daily. Is there evidence to support in clinical practice, whether there is a patient population that is at higher risk of developing encephalopathy, for whom fedratinib should not be used?	In practice, the clinicians check patients' thiamine levels first, before providing fedratinib. Other risk factors for encephalopathy include malnutrition at baseline and alcoholism. However, these do not necessarily mean that fedratinib should not be used in these patients. Fedratinib should be used with caution, close monitoring, and careful attention to thiamine levels.
3. Please consider if there is evidence to support the optimal treatment sequencing with fedratinib with available treatments for MF (i.e., hydroxyurea and ruxolitinib).	
a. Is there a preference to use fedratinib as an additional option (in the first-line setting as a replacement to ruxolitinib) or an additional line of therapy (following ruxolitinib treatment)?	
i. In what clinical scenarios would ruxolitinib or fedratinib be the preferred first-line treatment for intermediate myelofibrosis? Please comment on the preference considering patient preference, efficacy, safety, and administration.	i. Currently, there is no evidence to suggest what the optimal treatment sequencing is for MF. The clinical experts consulted by CADTH indicated that both fedratinib and ruxolitinib could be used as first-line therapy. In clinical practice, clinicians are more likely to use ruxolitinib first, as more long-term data for ruxolitinib are available (e.g., in the COMFORT trials). There may be a small group of patients in whom fedratinib would be considered as the optimal first-line treatment.
ii. What are the available treatment options following progression on fedratinib (e.g., ruxolitinib)?	ii. Patients who had disease progression when on fedratinib are unlikely to be treated with ruxolitinib again if they have already had prior ruxolitinib therapy. The treatment options available in this situation are limited. The possible options would be traditional treatments such as hydroxyurea or interferon.

Drug program implementation questions	Clinical expert response
4. The JAKARTA trial allowed treatment with fedratinib until disease progression or unacceptable toxicity. Patients were assessed at 6 months to determine response to therapy. In clinical practice, is there evidence to support the following.	
a. What treatment discontinuation criteria would be used?	a. Treatment discontinuation is related to the balance of symptom burden vs. side effects. If the patients are not measurably better on treatment, then they would discontinue the treatment. There is no checklist (e.g., specified reduction in total symptoms score) to determine when the treatment should be stopped.
b. What assessment score tool is currently used to determine response to treatment (i.e., does this align with what was used in the JAKARTA trial)? What assessment score tool is recommended to determine response to treatment?	b. In practice, the clinicians primarily ask the patients about their symptoms, rather than using an assessment score tool to determine response to treatment.
c. What is the recommended frequency of scans to determine response to treatment?	c. The experts indicated that scans are generally used in clinical trials because accurate results can be obtained. In practice, the clinician may simply use palpations or a measuring tape to evaluate the change in spleen size.

ECOG PS = Eastern Cooperative Oncology Group Performance Status; JAK = Janus kinase; MF = myelofibrosis.

priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of fedratinib (100 mg capsules for oral administration) for the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF, including patients who have been previously exposed to ruxolitinib.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS* Peer Review of Electronic Search Strategies checklist.[20]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. The search strategy comprised

both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Inrebic (fedratinib). Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Population	Adult patients with intermediate-2 or high-risk primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF Subgroups: • disease subtype: primary MF, post-polycythemia vera MF, post-essential thrombocythemia MF • risk status: intermediate-2 risk, high risk • JAK mutation status: wild type, mutant • previous treatment with JAK2 inhibitor (e.g., ruxolitinib): naive or experienced
Intervention	Fedratinib 400 mg q.d., orally
Comparator	Ruxolitinib Hydroxyurea Interferons Best supportive care Placebo
Outcomes	**Efficacy outcomes:** • survival (overall, progression-free) • spleen response (e.g., change from baseline in spleen size or volume) • change from baseline in disease-related symptoms (e.g., fatigue, night sweats, pruritus, abdominal discomfort, early satiety, bone, or muscle pain) • HRQoL • response rate (e.g., CR + PR) • duration of response • transformation to AML **Harms outcomes:** • AEs • SAEs • WDAEs • mortality • notable harms/harms of special interest (e.g., grade 3 or 4 anemia, neutropenia, or thrombocytopenia; second malignancy; transfusion dependency; hypersensitivity reaction; elevated liver enzymes; encephalopathy)
Study designs	Published and unpublished phase III and IV RCTs

AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; HRQoL = health-related quality of life; JAK = Janus kinase; MF = myelofibrosis; PR = partial remission; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on November 25, 2020. Regular alerts updated the search until the meeting of the CADTH pan-Canadian Oncology Drug Review Expert Committee on April 15, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist.[21] Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of 1 study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 6.

Description of Studies

One double-blind, placebo-controlled, multi-centre, phase III RCT (JAKARTA) was included in this systematic review.[14] The JAKARTA study evaluated the efficacy and safety of fedratinib in patients with intermediate-2 or high-risk MF, post-PV MF, or post-ET MF with splenomegaly who had not received previous treatment with JAKi.

Following a 1- to 28-day screening period, eligible patients (N = 289) were randomized via an interactive voice response system to receive fedratinib either 400 mg or 500 mg or matching placebo at a 1:1:1 ratio. There were no stratification factors used in the randomization. The study drug was self-administered orally once a day on an outpatient basis for at least 6 consecutive 28-day cycles. Patients continued to receive their assigned treatment until they experienced disease progression or relapse, excess toxic effect, or other criteria outlined in the study protocol. Patients who were originally assigned to the placebo arm were allowed to cross over to received fedratinib 400 mg or 500 mg, if they had completed 6 cycles of treatment and met the protocol-specified entry eligibility criteria, or if they had experienced progressive disease before completing the 6 cycles of treatment. Fedratinib 500 mg once daily is not approved by Health Canada; therefore, fedratinib 400 mg once daily is the focus of the current CADTH review.

Note that on November 18, 2013, the sponsor terminated the development of fedratinib due to the risk of encephalopathy associated with fedratinib therapy. All patient enrolled in the study stopped fedratinib treatment. All patents, including those previously who had

discontinued from treatment, were given the option to receive thiamine supplementation for at least 90 days and were followed for safety for 3 months after initiation of thiamine supplementation. At the time of study termination, the majority of patients in all treatment groups had completed 6 cycles of treatment: 64.2% of patients in the placebo group and 82.3% of patients in the fedratinib 400 mg group.

An independent Data Monitoring Committee (DMC) reviewed the progress and conduct of the study, reviewed the unblinded safety data, and advised the sponsor and the Steering Committee regarding potential amendments to the protocol that the DMC members deemed necessary to ensure the safety of subjects and data integrity. An Executive Steering Committee (also referred to as the "Steering Committee") supervised the progress of the trial toward its overall objectives, reviewed relevant information that could have affected the study conduct and discussed implementation of the DMC's recommendations. The Steering Committee did not have access to unblinded data.

Details of the study design of JAKARTA are presented in Figure 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

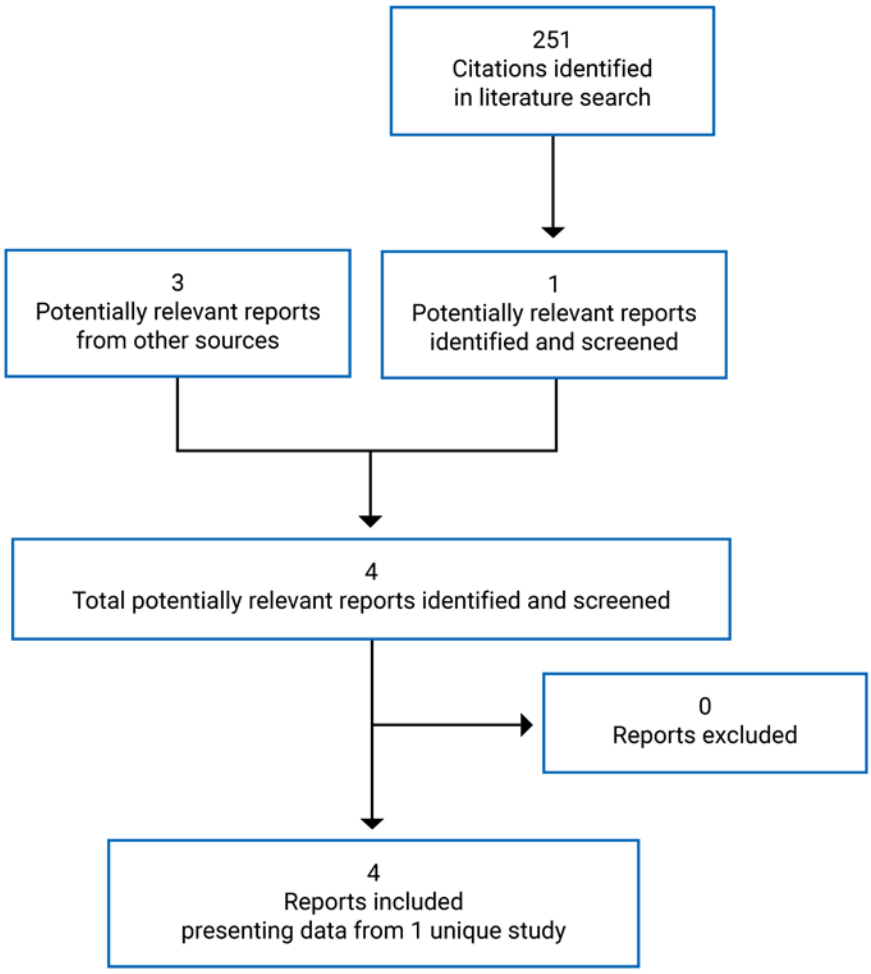


Table 6: Details of Included Studies

Detail	JAKARTA
Designs and populations	
Study design	Phase III, multi-centre, DB, placebo-controlled RCT
Locations	94 sites in Canada, US, Europe, Australia, Asia, South America, and Africa
Randomized (N)	289
Inclusion criteria	Diagnosis of PMF or post-PV MF or post-ET MF MF classified as high-risk or intermediate-risk level 2 Enlarged spleen, palpable ≥ 5 cm below costal margin ≥ 18 years of age ECOG PS score of 0, 1, or 2 at study entry Laboratory values within 14 days before the initiation of fedratinib or placebo: • ANC ≥ 1.0 × 10^9/L • platelet count ≥ 50 × 10^9/L • serum creatinine ≤ 1.5 times ULN • serum amylase and lipase ≤ 1.5 times ULN Life expectancy ≥ 6 months Willingness to comply with scheduled visits, treatment plans, laboratory assessments, and other study-related procedures
Exclusion criteria	Known active hepatitis A, B, or C, and hepatitis B and C carriers AST or ALT ≥ 2.5 times ULN TBL: exclude if ≥ 3 times ULN; patients with TBL between 1.5 to 3.0 times ULN were excluded if the direct bilirubin fraction was ≥ 25% of the total History of chronic liver disease Splenectomy Any chemotherapy, IMM drug therapy, anagrelide, immunosuppressive therapy, corticosteroids < 10 mg/day prednisone or equivalent, growth factor treatment or hormones < 14 days before initiation of study drugs; darbepoetin use < 28 days before initiation of study drugs; hydroxyurea < 14 days before initiation of study drug Major surgery < 28 days or radiation < 6 months before initiation of study drug Prior treatment with a JAK2 inhibitor Concomitant treatment with or use of agents known to be moderate or severe inhibitors or inducers of cytochrome P450 3A4

Detail	JAKARTA
	Treatment with ASA in doses > 150 mg Active acute infection requiring antibiotics Uncontrolled congestive heart failure, angina, MI, cerebrovascular accident, coronary /peripheral artery bypass graft surgery, TIA, or pulmonary embolism < 3 months before initiation of study drug Participation in any study of an investigational agent < 30 days before initiation of study drug Known HIV or AIDS-related illness Any severe acute or chronic medical, neurologic, or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study drug administration, may have interfered with the informed consent process or with compliance with the requirements of the study or may have interfered with interpretation of study results and would render the patient inappropriate for entry into the study Presence of any significant gastric or other disorder that would inhibit absorption of oral medication
Drugs	
Intervention	Fedratinib 400 mg q.d., orally, for ≥ 6 consecutive 4-week cycles Fedratinib 500 mg q.d., orally, for ≥ 6 consecutive 4-week cycles[a]
Comparator(s)	Matching placebo
Duration	
Phase	
Screening	Day 1 to day 28
DB	At least 6 consecutive 28-day cycles (planned); the study was terminated early on November 18, 2013
Follow-up	30 days
Thiamine supplementation period	90 days
Outcomes	
Primary end point	Spleen response rate: the proportion of patients with ≥ 35% reduction in spleen volume (measured by MRI or CT scan) from baseline to week 24 (end of cycle 6)

Detail	JAKARTA
Secondary and exploratory end points	**Secondary** • % of patients with ≥ 50% reduction in TSS (measured by modified MFSAF) from baseline to week 24 • OS • PFS • % of patients with ≥ 25% reduction in spleen volume (measured by MRI or CT scan) from baseline to week 24 and confirmed 4 weeks later • duration of spleen response (measured by MRI or CT) **Exploratory** • response by investigator: rates of CR, PR, CI, SD, and PD based on modified IWG-MRT response criteria (measured by MRI, CT, and bone marrow puncture when scheduled) • HRQoL (measured by EQ-5D) • change in MPN-associated symptoms from baseline to cycle 7 (measured by MPN-SAF) • JAK2 V617F allele burden change from baseline to cycle 6 and at cycles 9, 12, 15, 18, 21, and 24 from baseline • bone marrow assessments: cytogenetics, cellularity, blast count, and presence or absence of reticulin fibrosis **Safety** • AEs • deaths • laboratory data • vital signs • other (e.g., body weight, physical examinations, pregnancy tests, and ECOG PS)
Notes	
Publications	Pardanani et al. (2015)[22]

AE = adverse event; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = clinical improvement; CR = complete remission; DB = double blind; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EQ-5D = EuroQol 5-Dimensions questionnaire; ET = essential thrombocythemia; HRQoL = health-related quality of life; IMM = immunomodulatory; IWG-MRT = International Working Group for Myelofibrosis Research and Treatment; JAK = Janus kinase; MF = myelofibrosis; MFSAF = Myelofibrosis Symptom Assessment Form; MI = myocardial infarction; MPN = myeloproliferative neoplasm; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PMF = primary myelofibrosis; PV = polycythemia vera; PR = partial remission; q.d. = once daily; RCT = randomized controlled trial; SD = stable disease; TBL = total bilirubin; TIA = transient ischemic attack; TSS = Total Symptom Score; ULN = upper limit of normal.

Note: Three additional reports were included: sponsor-submitted Drug Reimbursement Review,[11] Health Canada reviewer's report,[23] and FDA reports.[24]

[a]Fedratinib 500 mg per day is not a Health Canada–approved dosage.

Source: Clinical Study Report for JAKARTA.[14]

Populations

Inclusion and Exclusion Criteria

Adult patients (≥ 18 years of age) with a diagnosis of PMF, post-PV MF, or post-ET MF were enrolled in the JAKARTA study. MF was classified as intermediate-2 or high-risk, and patients were required to have an enlarged spleen, palpable 5 cm or greater below costal margin. The participants were required to be JAKi-naive and had a baseline platelet count of 50 × 10^9/L or greater.

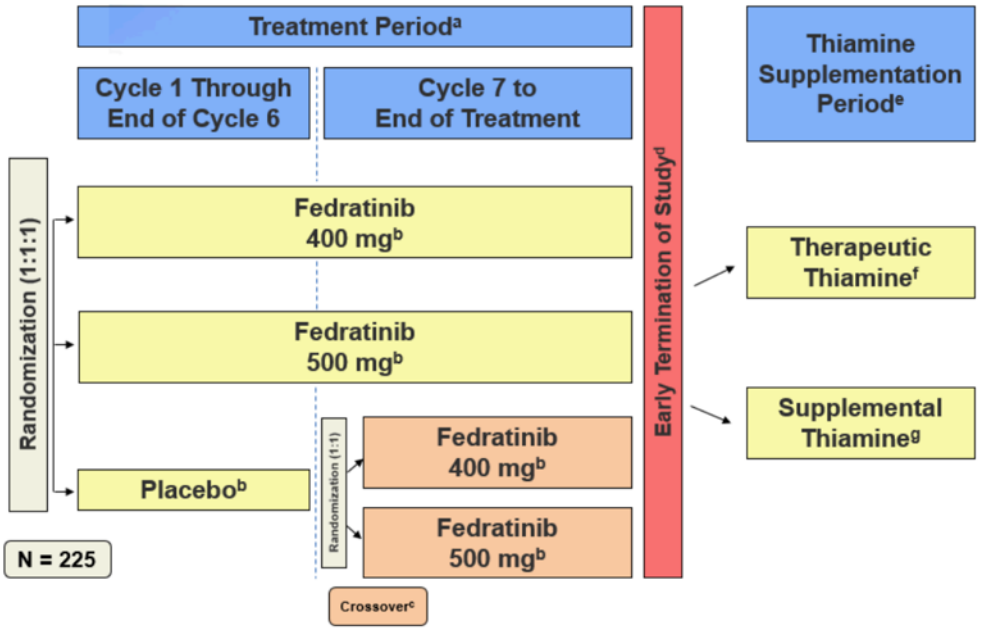
Patients were excluded if they had ECOG PS of 3 or higher, had known active hepatitis A, B or C, prior treatment with JAKis, active infection requiring antibiotics, or previous experience with specific drug therapies, as indicated in Table 6.

Details of inclusion and exclusion criteria in the JAKARTA study are provided in Table 6.

Baseline Characteristics

In the JAKARTA study, baseline characteristics were generally similar between groups at baseline (Table 7). The mean age of the patients was 63 to 65 years. Most patients were and White (90% to 94%). The majority of study participants had a diagnosis of PMF (> 60%) and had baseline platelet count of 100 × 10^9/L or greater (> 80%). Patients in the fedratinib group

Figure 2: Study Design of JAKARTA



IWG-MRT = International Working Group for Myelofibrosis Research and Treatment.

[a] The Treatment Period refers to the date of the first dose of any study drug up to 30 days after the last dose of any study drug. Treatment continued as long as patients were benefiting (defined as having complete or partial remission, clinical improvement, or stable disease) and had not experienced progressive disease or relapse (as defined by the modified IWG-MRT criteria) or unacceptable toxicity requiring discontinuation of study drug.

[b] Fedratinib and placebo were administered on a daily basis, in consecutive 28-day cycles.

[c] Eligible patients initially randomized to placebo were allowed to cross over to receive fedratinib 400 mg or 500 mg after a second 1:1 randomization in either of the 2 following scenarios: when a patient had completed 6 cycles of treatment, had completed the end-of-cycle 6 imaging assessments, and had met the protocol-specified entry eligibility criteria and when a patient had experienced progressive disease before completing the first 6 cycles of treatment based on protocol-defined criteria and had met the protocol-specified entry eligibility criteria.

[d] Sanofi terminated the development of fedratinib on November 18, 2013.

[e] Per-Protocol Amendment 4, which was implemented after the clinical hold, all patients permanently discontinued fedratinib treatment. All patients, including those previously discontinued from treatment, were given the option to receive thiamine supplementation for at least 90 days and were followed for safety for 90 ± 3 days after initiation of thiamine supplementation.

[f] All patients with neuropsychiatric or cardiac symptoms consistent with thiamine deficiency were to begin immediate treatment with thiamine at therapeutic dosages in accordance with institutional practice.

[g] Patients without symptoms or signs of thiamine deficiency started thiamine daily supplementation.

Source: Clinical Study Report for JAKARTA.[14]

had longer time since diagnosis (68.5 months in the fedratinib group versus 54.2 months in the placebo group), but more were classified as intermediate-risk (60% in the fedratinib group versus 48% in the placebo group). Patients in the fedratinib group reported higher previous use of hydroxyurea (72% in the fedratinib group versus 56% in the placebo group), compared with those in the placebo group.

Interventions

After screening, eligible patients were randomized (1:1:1) to receive oral fedratinib 400 mg, 500 mg, or matching placebo once daily for at least 6 consecutive 28-day cycles, on an outpatient basis. After the end of cycle 6, patients in the 2 fedratinib groups continued to receive their assigned treatment until they experienced disease progression or relapse, intolerable adverse effects, or other criteria outlined in the protocol. Dosing was interrupted following the occurrence of certain AEs, with the recommendation that dosing be restarted at a level 100 mg per day below that at which the event was observed. For patients who were originally assigned to the placebo group, crossover to fedratinib was permitted after 24 weeks or before if the patient experienced progressive disease. Crossover patients were randomized (1:1) to 1 of the 2 fedratinib doses.

Fedratinib and placebo capsules and packaging were indistinguishable. Patients, investigators, the sponsor, and other personnel responsible for the study conduct and data analyses were blinded to treatment allocation. Following rerandomization, treatment with fedratinib was open label; however, the blind for dose level was maintained for all patients, the investigators, and sponsor's personnel involved with the conduct of the study.

Patients could withdraw (i.e., permanently discontinue) from treatment with fedratinib at any time and irrespective of reason, or the investigator could decide to permanently discontinue treatment.

Patients were withdrawn from treatment for any of the following reasons:

- unacceptable toxicity
- disease progression following the crossover guidelines
- undergoing splenectomy
- relapse according to modified IWG-MRT criteria
- need for intervention or therapy (determined by the investigator to be medically necessary) that was precluded by protocol
- noncompliance with treatment or voluntary withdrawal of consent.

In addition, the sponsor could have decided at any time to stop the trial prematurely for any reason.

In the JAKARTA study, patients were not allowed to receive any other drug treatment for MF during the study. Treatment with cytotoxic or immunosuppressive therapy, including hydroxyurea or systemic corticosteroids (e.g., > 10 mg/day prednisone or equivalent for > 5 days), was prohibited. In addition, transfusions were allowed, as clinically indicated. Erythropoietin and darbepoetin were not allowed during the study. Use of granulocyte growth factors (e.g., granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor) was permitted.

Table 7: Summary of Baseline Characteristics — ITT Population

Characteristic	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 96
Age (years), mean (SD)	62.9 (9.6)	64.9 (9.5)
Sex, n (%)		
Male	54 (56.3)	55 (57.3)
Female	42 (43.8)	41 (42.7)
Race, n (%)		
White	86 (89.6)	90 (93.8)
Asian	8 (8.3)	5 (5.2)
Black	1 (1.0)	1 (1.0)
Other	1 (1.0)	0
Type of MF, n (%)		
Primary MF	62 (64.6)	58 (60.4)
Post-PV MF	24 (25.0)	27 (28.1)
Post-ET MF	10 (10.4)	11 (11.5)
Time since diagnosis of MF (months), mean (SD)	68.5 (73.6)	54.2 (69.1)
Risk status, n (%)		
Intermediate-2	57 (59.4)	46 (47.9)
High risk	39 (40.6)	50 (52.1)
JAK2 mutational profile, n (%)		
Wild type	30 (31.3)	32 (33.3)
Mutant	62 (64.6)	59 (61.5)
Missing	4 (4.2)	5 (5.2)
Fibrosis grade, n (%)		
0	1 (1.0)	3 (3.1)
1	7 (7.3)	2 (2.1)
2	36 (37.5)	40 (41.7)
3	49 (51.0)	47 (49.0)
Missing	3 (3.1)	4 (4.2)
Constitutional symptoms, n (%)	73 (76.0)	70 (72.9)
ECOG PS status, n (%)		
0	41 (42.7)	31 (32.3)
1	47 (49.0)	56 (58.3)

Characteristic	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 96
2	8 (8.3)	8 (8.3)
Missing	0	1 (1.0)
RBC transfusion dependence status, n (%)		
Yes	8 (8.3)	6 (6.3)
No	88 (91.7)	90 (93.8)
Platelet count × 10^9/L, mean (SD) in all-treated population	286.2 (227.1)	260.7 (204.9)
Platelet count, n (%) in all-treated population		
< 50 × 10^9/L	1 (1.0)	0
50 × 10^9/L to < 100 × 10^9/L	13 (13.5)	18 (18.9)
≥ 100 × 10^9/L	82 (85.4)	77 (81.1)
Total symptom score, mean (SD)	17.6 (13.5)	14.7 (12.0)
Total symptom score, (measured by modified MFSAF in Symptom Analysis population), mean (SD)	18.0 (13.4)	15.4 (11.8)
Prior hydroxyurea, n (%)	69 (71.9)	54 (56.3)
Spleen volume (mL), mean (SD)	2,754.7 (1,353.3)	2,927.7 (1,483.8)
Spleen size (cm), mean (SD)	16.1 (7.5)	16.4 (7.0)
Spleen size > 10 cm (by palpation), n (%)	68 (70.8)	71 (74.0)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = essential thrombocythemia; ITT = intention to treat; JAK = Janus kinase; MF = myelofibrosis; MFSAF = Myelofibrosis Symptom Assessment Form; PV = polycythemia vera, RBC = red blood cell; SD = standard deviation.

Source: Clinical Study Report for JAKARTA.[14]

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the JAKARTA study is provided in Table 8. These end points are further summarized below. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 3.

Survival (OS and PFS)

OS was defined as the time interval from the date of randomization to the date of death due to any cause.

PFS was defined as the time interval from the date of randomization to the date of the first investigator-assessed disease progression or the date of death due to any cause, whichever comes first.

Disease progression was defined as any 1 of the following:

- progressive splenomegaly defined as enlargement of spleen volume by MRI (or CT scan in patients with contraindications for MRI) of 25% or greater compared to baseline value

- leukemic transformation confirmed by a bone marrow blast count of at least 20% or the occurrence of a granulocytic sarcoma (chloroma)
- an increase in peripheral blood blast percentage of at least 20% that lasts for at least 1 week.

Spleen Response

Spleen response rate was defined as the proportion of patients with a 35% or greater reduction in volume of spleen size at the end of cycle 6 (week 24), measured by MRI (or CT scan in patients with contraindications for MRI) and compared to the baseline value by a central imaging laboratory, where the reviewers were blinded to the study drug or placebo. A confirmatory imaging was required 4 weeks after end of cycle 6. This was the primary efficacy end point in the JAKARTA study.

Change in Disease-Related Symptoms

Change in MF-related symptoms was evaluated using modified MFSAF and Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).

With the modified MFSAF, the following MF-associated symptoms were assessed at their worst moment during the previous 24 hours: night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. These were measured on a scale from 0 (absent) to 10 (worst imaginable). The TSS is the sum of the scores for each symptom. Lower scores suggest a lower symptom burden to the patient than higher scores. The modified MFSAF and related TSS have been validated in patients with MF.

The MPN-SAF questionnaire is a validated disease-specific instrument. It assesses fatigue (using the Brief Fatigue Inventory [BFI – Cancer 1999][25]) and additional MPN-associated symptoms for presence and severity during the week before the assessment on a scale from 0 (absent) to 10 (worst imaginable). It is completed by the patient in paper format before any

Table 8: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	JAKARTA
OS	Secondary
PFS	Secondary
Spleen response rate (the proportion of patients with ≥ 35% reduction in spleen volume at EOC6, and confirmed 4 weeks thereafter)	Primary
Symptom response rate (the proportion of patients with ≥ 50% reduction from baseline to EOC6 in TTS of modified MFSAF diary)	Secondary
Spleen response rate (the proportion of patients with ≥ 25% reduction in spleen volume at EOC6, and confirmed 4 weeks thereafter)	Secondary
Change in HRQoL (using EQ-5D-3L)	Exploratory
Duration of spleen response	Secondary
Response by investigator (rates for CR, PR, CI, SD, and PD based on modified IWG-MRT response criteria)	Exploratory

CI = clinical improvement; CR = complete remission; EOC6 = end of cycle 6; EQ-5D-3L = EuroQol 5-Dimensions 3-levels questionnaire; HRQoL = health-related quality of life; IWG-MRT = International Working Group for Myelofibrosis Research and Treatment; MFSAF = Myelofibrosis Symptom Assessment Form; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial remission; SD = stable disease; TSS = Total Symptom Score.

Source: Clinical Study Report for JAKARTA.[14]

other assessments are performed by the investigator or study staff at the screening and at day 1 of cycle 7.

Health-Relate Quality of Life

In the JAKARTA study, HRQoL was measured with the EQ-5D at baseline compared with the end of cycle 6 and to the end of treatment.

Response Rate (Complete Remission and Partial Remission)

Rates of patients with complete remission, partial remission, stable disease, clinical improvement, and relapse were measured by the modified IWG-MRT response criteria at the end of cycle 6 by the investigator in the JAKARTA study.

Duration of Spleen Response

Duration of spleen response was defined as the time from the date of the first response by Independent Review Committee (IRC) to the date of subsequent progressive disease by IRC or death, whichever is earlier:

Duration of spleen response (months) = [Earlier of (date of subsequent progressive disease by IRC, date of death) – date of first response by IRC + 1] × (12/365.25)

Duration of spleen response is determined only for patients who have a response by IRC; this value was missing for other patients.

In the absence of the subsequent progressive disease by IRC or death before the analysis cut-off date, the duration of spleen response will be censored at the date of the last valid assessment performed before the analysis cut-off date.

Transformation to AML

This outcome was determined by bone marrow blast count of 20% or greater or the occurrence of a granulocytic sarcoma in the JAKARTA study.

Statistical Analysis

In general, for continuous parameters, descriptive statistics, such as the mean, the standard deviation (SD), the median, minimum, and maximum were presented. For categorical parameters, counts, and percentages of the events were presented.

There was no imputation for missing data, unless otherwise specified. When computing percentages, missing values were not included in the denominator count.

There were multiple comparisons in this phase III study. Bonferroni adjustment was used to test the primary hypothesis to compare the spleen response rates of each treatment arm to the placebo at a 2-sided, 2.5% alpha level. A fixed sequence procedure (with the following sequence order: (1) spleen response rate, (2) symptom response rate, (3) RR25, (4) OS, and (5) PFS was planned for the multiplicity considerations for each of the fedratinib arms (400 mg and 500 mg) at a 2-sided, 2.5% alpha level. With this procedure, the formal inferential testing was performed for a step only when statistical significance was declared for the end points tested in the previous steps. If the testing sequence stopped at a particular step, the remaining end points in the testing sequence were not formally tested for statistical significance. Therefore, the overall alpha level for the primary end point and the key secondary end points was maintained at a 5% level.

No formal interim analysis was planned for the JAKARTA study.

Primary Outcome of the JAKARTA Study

For sample size calculation, to maintain a 5% alpha level of the primary analyses, a 2.5% alpha was allocated to the comparison of each of fedratinib 400 mg and fedratinib 500 mg dose groups with the placebo control. Assuming the spleen response rate was 30% in either the fedratinib group or 5% in the placebo group, 63 patients per group were needed to provide 90% power at a 2-sided, 2.5% alpha level. Assuming there was about 15% drop out rate, the spleen response rate would be 26% in either the fedratinib group or 4.3% in the placebo group in the intention-to-treat (ITT) population. Thus 75 patients per study arm (total 225 patients) are planned to be randomized.

A chi-square test was performed to compare each dose to the placebo at a 2-sided, 2.5% alpha level. The spleen response rates and 95% CIs were provided for each group as well as for the difference in spleen response rates and 97.5% CIs of the difference for each dose to placebo. Patients without a valid spleen volume assessment at the end of cycle 6 measured by MRI (or CT scan in patients with contraindications for MRI) were considered nonresponders; patients without a valid confirmation spleen volume assessment at 4 weeks after the end of cycle 6 measured by MRI (or CT scan in patients with contraindications for MRI) that was a 35% or greater reduction from baseline (confirmation of response at end of cycle 6) were considered nonresponders; and patients who had disease progression before end of cycle 6 were considered nonresponders.

A logistic regression model was performed using the demographic and baseline characteristics as covariates. It provided estimate of treatment effect on spleen response rate adjusted for covariates. Multivariate analyses with model selection procedure for interaction of a covariate with treatment were explored for evaluating robustness of the primary analysis. If an interaction term was found statistically significant or if there was an imbalance in the covariate then a univariate model would be used to adjust for confounding effect of this covariate.

Sensitivity analysis of spleen response rate was performed using a chi-square test that was similar to the primary analysis of spleen response where the patients without a valid spleen volume assessment at the end of cycle 6 measured by MRI (or CT scan in patients with contraindications for MRI) would have the end of cycle 6 spleen volume assessment imputed by the last post-baseline valid spleen volume assessment before end of cycle 6; the imputed data did not require confirmation 4 weeks after the end of cycle 6.

Subgroup analysis by demographic or patients' baseline characteristics, such as age, type of MF, baseline MF risk, platelet counts, ECOG PS, or constitutional symptoms at baseline, were performed to examine the consistency of the treatment effect on spleen response rate, as appropriate. It is unclear whether the subgroup analyses were preplanned.

Secondary Outcomes of the JAKARTA Study

A chi-square test was performed to compare each dose to the placebo at a 2-sided, 2.5% alpha level. The proportions and 95% CIs were provided for each group as well as for the difference in proportions and 97.5% CI of the difference for each dose to placebo.

The sponsor terminated the development of fedratinib on November 18, 2013. Protocol Amendment 4 (dated November 27, 2013) was issued after the date of the final statistical analysis plan (April 26, 2013) and after the date of database lock for the primary analysis

(May 1, 2013). Other than an update to the duration of response for patients initially randomized to fedratinib and the response rate analysis for the patients who crossed over to fedratinib, no further analyses were performed on any efficacy data. Safety tables were prepared for data reported from the end of the TEAE period to the end of the additional 90-day thiamine supplementation period.

Subgroup analyses were planned for the secondary efficacy outcomes such as OS and PFS. Sensitivity analyses were also planned for OS and PFS.

Analysis Populations

The ITT population included all randomized patients who signed informed consent.

Evaluable patient population consisted of the subset of the ITT population with a paired baseline and at least 1 post-baseline MRI (CT in case of contraindications for MRI), and who had received a minimum of 50% of the targeted dose for 3 cycles, or who had progressed or died within the first 3 treatment cycles.

The all-treated population consisted of the subset of the ITT population that took at least 1 dose of study drug (even if partial).

The crossover safety population included all patients from the placebo arm who crossed over to receive fedratinib, either 400 mg (n = 35) or 500 mg (n = 36).

The symptom analysis population included ITT patients evaluable at baseline (for symptom assessment).

All efficacy analyses were performed in the ITT and evaluable patient populations. The ITT population is the primary population for all efficacy parameters.

Results

Patient Disposition

In the JAKARTA study, a total of 351 patients were screened, of which 289 were randomized to receive fedratinib 400 mg (n = 96), fedratinib 500 mg (n = 97), or placebo (n = 96). One patient randomized to placebo died before receiving treatment. A total of 288 patients were treated: 96 received fedratinib 400 mg, 97 received fedratinib 500 mg, and 95 received placebo. There were 75 patients in the fedratinib 400 mg arm, 66 patients in the fedratinib 500 mg arm, and 61 patients in the placebo arm who completed 6 cycles of treatment. At the time of study termination, all patients had either completed the first 6 cycles or had previously permanently discontinued treatment. The proportion of patients who completed the 6 cycles of treatment was higher in the 2 fedratinib groups.

The main reason for premature study discontinuation was AEs, and the rates of AEs leading to treatment discontinuation were higher in the 2 fedratinib groups, with 13.5% in the fedratinib 400 mg arm, 24.7% in the fedratinib 500 mg arm, and 8.4% in the placebo arm discontinuing.

Seventy-one patients in the placebo arm were rerandomized to fedratinib 400 mg (35 patients) or 500 mg (36 patients). Ten were rerandomized with early crossover before the end of cycle 6 and 61 were rerandomized after the completion of cycle 6.

Details of patient disposition for the JAKARTA study are provided in Table 9.

Exposure to Study Treatments

The median duration of exposure up to 6 cycles for the all-treated population was 24.0 weeks for each treatment arm. Exposure of up to 6 cycles in the total number of person-months, which represents the total number of months of treatment for all patients in each treatment arm, was lower (426.0) in the placebo arm than in the 400 mg arm (485.6), which reflects the early crossover for the 10 patients in the placebo arm who crossed over to receive fedratinib before the end of cycle 6.

At the time of study termination, the majority of patients in both treatment arms had completed 6 cycles of study treatment: 82.3% in the fedratinib 400 mg arm and 64.2% in the placebo arm.

More dose reductions or interruptions occurred in the fedratinib 400 mg group compared to placebo (Table 10).

Table 9: Patient Disposition

Disposition	JAKARTA		
	Fedratinib 400 mg	Fedratinib 500 mg	Placebo
Screened, N	351		
Randomized, N	96	97	96
Not treated	0	0	1 (1.0)
Treated	96 (100.0)	97 (100.0)	95 (99.0)
Completed 6 cycles, n (%)	75 (78.1)	66 (68.0)	61 (63.5)
Discontinued from study up to end of cycle 6, n (%)	21 (21.9)	31 (32.0)	24 (25.3)
Reason for discontinuation, n (%)			
Adverse events	13 (13.5)	24 (24.7)	8 (8.4)
Poor compliance to protocol	1 (1.0)	0	0
Disease progression	1 (1.0)	1 (1.0)	4 (4.2)
Other reasons			
Consent withdrawn	0	3 (3.1)	5 (5.3)
Patient request	2 (2.1)	1 (1.0)	4 (4.2)
Other	4 (4.2)	2 (2.1)	3 (3.2)
ITT, n (%)	96 (100.0)	97 (100.0)	96 (100.0)
All-treated population, n (%)	96 (100.0)	97 (100.0)	95 (99.0)
Evaluable patient population, n (%)	88 (91.7)	76 (78.4)	82 (85.4)
Symptom analysis population, n (%)	89 (92.7)	89 (91.8)	81 (84.4)
Crossover safety population, n (%)	NA	NA	71 (74.0)

ITT = intention to treat; NA = not applicable.
Source: Clinical Study Report for JAKARTA.[14]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 2 for other detailed efficacy data.

Survival

Analysis of OS and PFS was not performed due to early termination of the study.

Spleen Response

The primary outcome was spleen response defined as a 35% or greater reduction in spleen volume at end of cycle 6, and confirmed 4 weeks thereafter in the JAKARTA study. At the end of cycle 6 (week 24), a greater proportion of patients in the fedratinib 400 mg group (35 patients [36.5%]) achieved spleen response, compared with those in the placebo group (1 patient, [1%]), which was a statistically significant difference in favour of fedratinib 400 mg (between-group difference, 35.42%; 97.5% CI, 24.2 to 46.7; P < 0.0001). Similar results were reported for the outcomes of a 25% or greater reduction in spleen volume at the end of cycle 6. A greater proportion of patients in the fedratinib group (47 patients, 49%) achieved a 25% or greater reduction in spleen volume compared with those in the placebo group (2 patients, 2.1%). The between-group difference was statistically significant in favour of fedratinib (mean difference = 46.9%; 97.5% CI, 35.0 to 58.8; P < 0.0001). In addition, treatment with fedratinib was related to a greater reduction in spleen volume at the end of cycle 6, compared to

Table 10: Extent of Exposure up to Cycle 6 — All-Treated Population

Extent of exposure	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 95
Duration of exposure, weeks		
Mean (SD)	22.0 (6.06)	19.5 (7.42)
Median (range)	24 (1 to 30)	24 (1.7 to 26.4)
% of patients completed 6 cycles, n (%)	79 (82.3)	61 (64.2)
Total number of person-months	485.6	426.0
Actual dose intensity, mg/week		
Mean (SD)	2,640 (285.4)	3,433 (195.3)
Median (range)	2,800 (1,463 to 2,800)	3,500 (2,357 to 3,500)
Relative dose intensity, %		
Mean (SD)	94.3 (10.19)	98.1 (5.58)
Median (range)	100 (52.2 to 100)	100 (67.3 to 100)
Dose modification, n (%)		
≥ 1 level dose reduction	20 (20.8)	6 (6.3)
> 2 level dose reduction	1 (1.0)	0
Dose interruption for ≥ 7 consecutive days, n (%)	15 (15.6)	5 (5.3)

SD = standard deviation.

Source: Clinical Study Report for JAKARTA.[14]

placebo (percentage change in spleen volume from baseline: −35.6% in the fedratinib group versus 10.3% in the placebo group; between-group difference = −45.88%).

Details of spleen response are reported in Table 11.

Results of subgroup analyses on primary efficacy outcome (based on type of MF, risk status, and JAK mutational profile) suggested a consistent treatment effect in spleen response rate

Table 11: Spleen Response — ITT population

Spleen response	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 96
Spleen response rate (≥ 35% reduction in spleen volume at EOC6, and confirmed 4 weeks thereafter)		
n (%)	35 (36.5)	1 (1.0)
95% CI	26.8 to 46.1	0 to 3.1
Difference (97.5% CI)	35.42 (24.2 to 46.7)	
P value[a]	< 0.0001	
Spleen response rate (≥ 25% reduction in spleen volume) at EOC6		
n (%)	47 (49.0)	2 (2.1)
95% CI	39.0 to 59.0	0 to 4.9
Difference (97.5% CI)	46.88 (35.0 to 58.8)	
P value[a]	< 0.0001	
Spleen response rate (≥ 35% reduction in spleen volume at EOC6)		
n (%)	45 (46.9)	1 (1.0)
95% CI	36.9 to 56.9	0 to 3.1
Difference (97.5% CI)	45.83 (34.2 to 57.5)	
P value[a]	< 0.0001	
% change in spleen volume at EOC6, mL (ITT population with available baseline and EOC6 assessments)		
Number of patients contributing to the analysis	75	58
Baseline, mean (SD)	2,755 (1,353.3)	2,928 (1,483.8)
Spleen volume at EOC6, mean (SD)	1,728 (1,015.5)	3,068 (1,626.3)
% Change from baseline, mean (SD)	−35.6 (18.59)	10.3 (19.74)
Treatment group difference vs. placebo (97.5% CI)	−45.880 (−53.452 to −38.307)	
P value[b]	< 0.001	

CI = confidence interval; EOC6 = end of cycle 6; ITT = intention to treat; SD = standard deviation.

[a]P values were calculated based on the chi-square test comparing the fedratinib arm (400 mg) to the placebo arm; CIs were calculated using normal approximation.

[b]P values and 97.5% CIs were calculated based on the t-test.

Source: Clinical Study Report for JAKARTA.[14]

in favour of fedratinib 400 mg over placebo for each of the evaluated subgroups of the ITT population (Table 43 in Appendix 2).

Change in Disease-Related Symptoms

Symptom response was defined as the proportion of patients with a 50% or greater reduction in the TSS from baseline to the end of cycle 6.

Of the 289 patients in the ITT population, 267 had an available TSS at baseline (85 of 96 in the placebo arm and 91 of 96 in the fedratinib 400 mg treatment arm). The proportion of patients in the ITT population with non-missing baseline TSS (including patients with baseline TSS = 0) who had a 50% or greater reduction in the TSS from baseline to the end of cycle 6 was 39.6% (95% CI, 29.5 to 49.6) in the fedratinib 400 mg arm and 8.2% (95% CI, 2.4 to 14.1) in the placebo arm. The between-group difference was 31.33 (95% CI, 18.0 to 44.6). The fedratinib 400 mg arm showed statistically significant differences compared with placebo based on a step-down procedure for controlling multiplicity of the statistical comparison (P < 0.0001 for the comparison versus placebo) (Table 12).

At the end of cycle 6, the symptom response rate (≥ 50% reduction in TSS) for the symptom analysis population was 40.4% in the fedratinib 400 mg arm and 8.6% in the placebo arm. These results are aligned to those of the ITT population (Table 12).

In addition, symptom relief was measured using median percentage change from baseline to day 1 of cycle 7 in 17 individual symptom scores in the MPN-SAF, change in a fatigue score, as well as improvement in patient's overall HRQoL. This was an exploratory outcome in the

Table 12: Symptom Response Rate by EOC6: ITT Population With Non-Missing Baseline TSS and Symptom Analysis Population

Symptom response	JAKARTA	
	Fedratinib 400 mg	Placebo
% of patients with ≥ 50% reduction in TSS from baseline to EOC6: ITT population		
N	91	85
n (%)	36 (39.6)	7 (8.2)
95% CI	29.5 to 49.6	2.4 to 14.1
Difference, 95% CI	31.33 (18.0 to 44.6)	
P value[a]	< 0.0001	
% of patients with ≥ 50% reduction in TSS from baseline to EOC6: Symptom analysis population		
N	89	81
n (%)	36 (40.4)	7 (8.6)
95% CI	30.3 to 50.6	2.5 to 14.8
Difference, 95% CI	31.81 (18.2 to 45.4)	
P value [a]	< 0.0001	

CI = confidence interval; EOC6 = end of cycle 6; ITT = intention to treat; TSS = Total Symptom Score.

[a]P values were calculated based on the chi-square test comparing the fedratinib arm to the placebo arm; CIs were calculated using normal approximation.

Source: Clinical Study Report for JAKARTA.[14]

JAKARTA study. No formal statistical comparison was conducted between fedratinib 400 mg and placebo. The results suggested improvements in some of the individual symptoms of MPN-SAF, as follows.

- early satiety: −62.5% versus −20.0%
- abdominal pain: −33.3% versus −25.0%
- abdominal discomfort: −64.6% versus 0%
- inactivity: −66.7% versus 0%
- headaches: −66.7% versus −50.0%
- concentration: −50.0% versus −40.0%
- dizziness/vertigo/light-headedness: −40% versus −50%
- numbness/tingling in hands and feet: v58.3% versus −50.0%
- difficulty sleeping: −66.7% versus −41.7%
- depression or sad mood: −33.3% versus −25.0%
- sexual desire or function: −31.0% versus −14.3%
- cough: −50% versus −50%
- night sweats: −85.7% versus −47.2%
- pruritis: −60.0% versus −55.0%
- bone pain: −25.0% versus −6.3%
- fever: −100% versus −100%
- unintentional weight loss: −100.0% versus −66.7%
- fatigue average score: −12.50% versus −16.3%
- overall HRQoL: 0 versus 0

Health-Related Quality of Life

In the JAKARTA study, the mean change in EQ-5D utility index scores from baseline to the end of cycle 6 was 0.05 (95% CI, 0 to 0.09) in the fedratinib 400 mg arm and −0.05 (95% CI, −0.11 to 0.01) in the placebo arm.

The mean change in EQ-5D VAS scores in the fedratinib group was 6.2 (95% CI, 1.8 to 10.5) at the end of cycle 6 and −0.9 (95% CI, −7.7 to 5.8) in the placebo group.

Details of change in HRQoL scores are presented in Table 13.

Response Rate

Based on the investigator's assessment using the modified IWG-MRT criteria in the ITT population, at the end of cycle 6, the proportion of patients who exhibited clinical improvement was 58.4% in the fedratinib 400 mg arm and 3.3% in the placebo arm. No patients in the fedratinib group compared to 7 patients (11.7%) in the placebo group had progressive disease. Thirty-two patients (41.6%) in the fedratinib group and 51 patients (85.50%) in the placebo group were categorized as having stable disease (Table 14).

Duration of Response

Based on Kaplan-Meier estimates, the median duration of spleen response in the fedratinib 400 mg arm was 18.2 months. The duration in the placebo arm was still not available. It is

recognized that 11.1% (6 of 54) of responders in the 400 mg arm progressed or died during the study (Table 15, Figure 3).

Transformation to AML

Transformation to AML was assessed as a safety outcome in the JAKARTA study. Two patients in the placebo arm reported transformation to AML. Transformation to AML was not reported in the fedratinib 400 mg arm.

Harms

Only those harms identified in the review protocol are reported below. See Table 16 for detailed harms data.

Table 13: Change in EQ-5D Scores

EQ-5D score	JAKARTA	
	Fedratinib 400 mg	Placebo
EQ-5D utility index scores		
N	73	56
Baseline, mean (SD)	0.70 (0.25)	0.72 (0.26)
EOC6, mean (SD)	0.77 (0.16)	0.70 (0.22)
Change from baseline, mean (SD)	0.05 (0.19)	−0.05 (0.22)
Between-group difference, mean (95% CI)	0.093 (0.02 to 0.16)	
EQ-5D VAS score		
N	69	52
Baseline, mean (SD)	61.34 (22.18)	62.51 (21.23)
EOC6, mean (SD)	68.34 (18.02)	61.95 (19.93)
Change from baseline, mean (SD)	6.16 (18.10)	−0.94 (24.36)
Between-group difference, mean (95% CI)	7.10 (−0.54 to 14.74)	

CI = confidence interval; EOC6 = end of cycle 6; EQ-5D: EuroQol 5-Dimensions questionnaire; SD = standard deviation; VAS = Visual Analogue Scale.
Source: Clinical Study Report for JAKARTA.[14]

Table 14: Response Rate by Investigator at EOC6 — ITT Population

Response rate	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 96
Number of patients contributing to the analysis	77	60
Clinical improvement, n (%)	45 (58.4)	2 (3.3)
Progressive disease, n (%)	0	7 (11.7)
Stable disease, n (%)	32 (41.6)	51 (85.0)

EOC6 = end of cycle 6; ITT = intention to treat.
Source: Clinical Study Report for JAKARTA.[14]

Adverse Events

Most (≥ 93.7%) patients in the 2 treatment arms of the all-treated population had at least 1 TEAE up to 6 cycles. The risks of AEs were similar between fedratinib 400 mg and placebo. Most TEAEs reported up to 6 cycles were grade 1 or 2.

In both treatment arms, TEAEs (all grades) were most frequently reported up to 6 cycles in the gastrointestinal disorders system organ class, with a frequency that was nearly double in the fedratinib arms (approximately 91% in each arm) compared with the placebo arm (49.5%). Diarrhea was reported in 65.6% of patients in the fedratinib group and 15.8% in the placebo group; nausea was reported in 61.5% of patients in the fedratinib group and 14.7% in the placebo group; vomiting was reported in 38.5% of patients in the fedratinib group and 5.3% in the placebo group. Anemia was another common AE associated with fedratinib treatment and was reported in 39.6% of those in the fedratinib group and 13.7% in the placebo group.

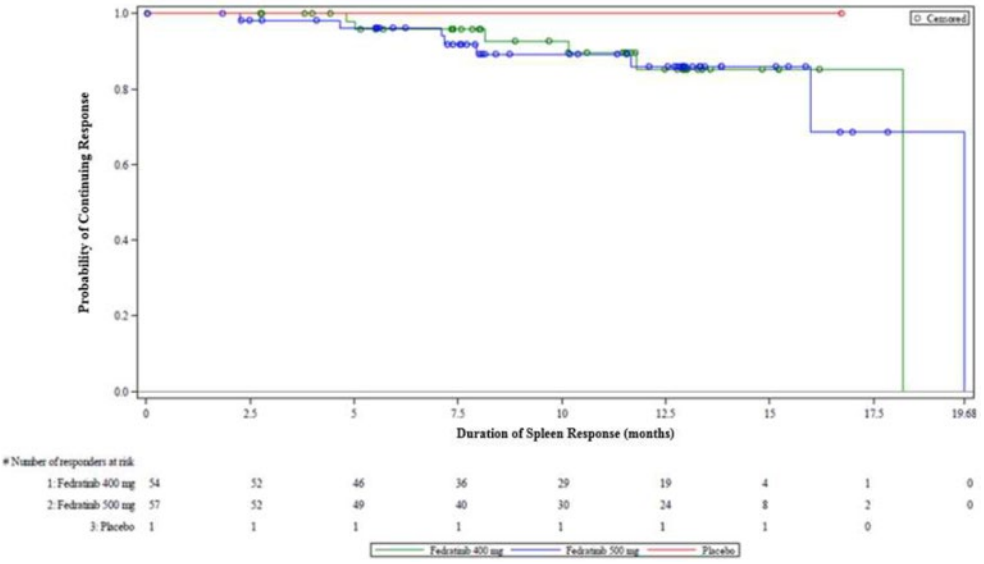
Table 15: Kaplan-Meier Analysis of Duration of Spleen Response — ITT Population

Kaplan-Meier analysis	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 96
Number of patients contributing to the analysis	54	1
Events, n (%)	6 (11.1)	0
Median, months (95% CI)	18.2 (NA)	NA

CI = confidence interval; ITT = intention to treat; NA = not applicable.

Source: Clinical Study Report for JAKARTA.[14]

Figure 3: Kaplan-Meier Plots of Duration of Spleen Response — ITT Population



ITT = intention to treat.

Source: Clinical Study Report for JAKARTA.[14]

Serious Adverse Events

The frequency of patients with treatment-emergent SAEs up to 6 cycles was 20.8% in the fedratinib 400 mg arm and 23.2% in the placebo arm. In the fedratinib 400 mg arm, cardiac failure in 5 patients, pneumonia in 1 patient, and anemia in 2 patients were considered SAEs. In the placebo arm, cardiac failure in 3 patients, anemia in 1 patient, ascites in 3 patients, and 2 cases of each of pneumonia, splenic infarction, and transformation to AML were considered SAEs.

Withdrawals Due to Adverse Events

The frequency of patients with TEAEs (all grades) leading to permanent treatment discontinuation up to 6 cycles was higher in the fedratinib arms (13 patients, 13.5%) than in the placebo arm (8 patients, 8.4%). The events leading to treatment discontinuation included cardiac failure, increased blood creatinine, myocardial ischemia, thrombocytopenia, and diarrhea in the fedratinib group. In the placebo group, 2 cardiac failures led to treatment discontinuation.

Mortality

More deaths were reported in the placebo arm, with 12 deaths (12.6%) in the placebo arm versus 7 deaths (7.3%) in the fedratinib 400 mg arm. Progressive disease was the main reason for death, and 4 patients (4.2%) in the fedratinib group and 6 patients (6.3%) in the placebo group died due to progressive disease. There was 1 patient (1.0%) in the fedratinib group and 4 patients (4.2%) in the placebo group who died due to AEs. Two patients (2.1%) in the fedratinib group and 2 patients (2.1%) in the placebo group died due to other reasons. Other primary causes of death, 1 patient each, were global heart insufficiency and pneumonia in the placebo arm; heart failure and unknown cause in the 400 mg arm; and colon neoplasm (adenocarcinoma), sepsis/pneumonia/MF, and unknown cause in the 500 mg arm.

Notable Harms

More patients treated with fedratinib 400 mg (30.2%) reported grade 3 or 4 anemia compared to placebo (7.4%) up to cycle 6. The incidence of grade 3 or 4 thrombocytopenia and neutropenia was similar between the 2 treatment groups.

During the entire treatment duration, the frequencies of patients with TEAEs associated with signs or symptoms of WE were higher for patients in the 400 mg arms (14.6%) compared with the placebo arm (4.2%). In the fedratinib 400 mg group, the TEAEs associated with any sign or symptoms of WE were hypoesthesia, dysgeusia, and vision blurred, aphonia, delirium, disturbance in attention, herpes zoster, hyperesthesia, hypogeusia, neuralgia, paresthesia, and polyneuropathy. In the placebo group, the TEAEs associated with any sign or symptoms of WE included herpes zoster, hyperesthesia, paresthesia, and dysphonia.

Critical Appraisal

Internal Validity

JAKARTA was a phase III, double-blind, placebo-controlled RCT. Appropriate methods were used to randomize patients to treatments and conceal treatment allocation. Even though an appropriate method of blinding has been used, it may have been difficult to maintain blinding of treatments due to the associated symptom relief and potential AEs from treatment. Reporting of patient-rated outcomes, such as symptom reduction and HRQoL, and some of the harm outcomes may have been biased.

Table 16: Summary of Harms up to Cycle 6 — All-Treated Population

Harms	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 95
Patients with ≥ 1 adverse event		
n (%)	95 (99.0)	89 (93.7)
Gastrointestinal disorders	88 (91.7)	47 (49.5)
Diarrhea	63 (65.6)	15 (15.8)
Nausea	59 (61.5)	14 (14.7)
Vomiting	37 (38.5)	5 (5.3)
Abdominal pain	12 (12.5)	14 (14.7)
Constipation	9 (9.4)	7 (7.4)
Blood and lymphatic system disorders	44 (45.8)	23 (24.2)
Anemia	38 (39.6)	13 (13.7)
Thrombocytopenia	10 (10.4)	8 (8.4)
Investigations	39 (40.6)	15 (15.8)
Blood creatinine increased	10 (10.4)	1 (1.1)
Musculoskeletal and connective tissue disorders	32 (33.3)	20 (21.1)
Muscle spasms	11 (11.5)	1 (1.1)
Pain in extremity	10 (10.4)	4 (4.2)
General disorders and administration site conditions	28 (29.2)	32 (33.7)
Fatigue	12 (12.5)	9 (9.5)
Asthenia	8 (8.3)	6 (6.3)
Patients with ≥ 1 SAE		
n (%)	20 (20.8)	22 (23.2)
Cardiac failure	5 (5.2)	3 (3.2)
Anemia	2 (2.1)	1 (1.1)
Ascites	0	3 (3.2)
Pneumonia	1 (1.0)	2 (2.1)
Splenic infarction	0	2 (2.1)
Transformation to AML	0	2 (2.1)
Patients who stopped treatment due to adverse events		
n (%)	13 (13.5)	8 (8.4)
Cardiac failure	3 (3.1)	2 (2.1)
Blood creatinine increased	2 (2.1)	0

Harms	JAKARTA	
	Fedratinib 400 mg N = 96	Placebo N = 95
Myocardial ischemia	2 (2.1)	0
Thrombocytopenia	2 (2.1)	0
Diarrhea	2 (2.1)	0
Lipase increased	1 (1.0)	0
Death		
n (%)	7 (7.3)	12 (12.6)
Progressive disease	4 (4.2)	6 (6.3)
Adverse event	1 (1.0)	4 (4.2)
Other[a]	2 (2.1)	2 (2.1)
Notable harms, n (%)		
Grade 3 or 4 anemia	29 (30.2)	7 (7.4)
Grade 3 or 4 thrombocytopenia	5 (5.2)	6 (6.3)
Grade 3 or 4 neutropenia	2 (2.1)	0
Potential WE (entire treatment duration)	14 (14.6)	4 (4.2)
Second malignancy (transformation to AML)	0	2 (2.1)
Transfusion dependency (among patients who were transfusion independent at baseline)	22/88 (25.0)	11/90 (12.2)
Hypersensitivity reaction	NR	NR
Grade 3 or 4 ALT, AST, or TBL elevation	1 (1.0)	2 (2.1)

ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; NR = not reported; SAE = serious adverse event; TBL = total bilirubin; WE = Wernicke encephalopathy.

[a]Other primary causes of death (1 patient each) included global heart insufficiency and pneumonia in the placebo arm, heart failure and unknown cause in the fedratinib 400 mg arm, and colon neoplasm (adenocarcinoma), sepsis/pneumonia/myelofibrosis, and unknown cause in the fedratinib 500 mg arm.

Source: Clinical Study Report for JAKARTA.[14]

In general, patients' characteristics appear to be balanced at baseline between groups, although imbalanced patient characteristics were also observed. Compared to the placebo group, patients in the fedratinib group had longer time since disease diagnosis, were inclined to be intermediate risk (rather than high risk), and more likely to receive previous hydroxyurea therapy. Longer duration of the disease and more previous treatments may be related to more severe condition and poorer response to the treatment under review. Therefore, the treatment effect of fedratinib could be underestimated. However, the impact on study findings is unlikely to be significant.

In this study, 75% to 78% of the study participants completed their treatment at the end of cycle 6; therefore, 22% to 25% of participants discontinued their treatment early, which could have some impact on the study results. These dropout rates were high, and the reasons for dropout differed between treatment and placebo. Dropout in the fedratinib arm was mostly due to AEs, whereas the primary reason of discontinuation was different in the placebo group. Lack of efficacy was likely to be the main issue for discontinuation in the placebo

group, which was consistent with the slightly higher rate of disease progression. Moreover, the data imputation methods are lacking. For the primary end point, even though the patients who dropped out earlier would be treated as nonresponders, those who dropped out of the fedratinib arm due to AEs were more likely to be responders. This would likely bias toward underestimating the treatment effect of the study drug.

Multiplicity was controlled for in the JAKARTA study based on a step-down procedure, with the primary and key secondary outcome measures being included. However, there was insufficient follow-up data on the patients for the estimation of OS. Survival data could not be assessed due to early study termination and therefore precludes the testing of other secondary end points beyond OS in the hierarchical testing, for example, PFS.

Predefined subgroup analyses based on various patients' baseline characteristics were conducted to examine the consistency of the primary analysis results across subgroup levels. The results of subgroup analyses were generally aligned with the primary analysis. Due to the small number of patients in the subgroups, the subgroups may not have been adequately powered to detect whether the treatment effect of fedratinib may differ.

OS and PFS are important clinical outcomes. However, data are not available to be analyzed due to the termination of the JAKARTA study. It is unclear whether the benefit from spleen response and symptom relief can be translated to prolonged survival in patients with intermediate- or high-risk MF. Symptom improvement was measured with a modified MFSAF, it is unclear how this instrument differs from the original version. There was no information regarding its validity and responsibility in the study population. A minimal important difference (MID) has not been established in patients with MF either. Furthermore, symptom response was only evaluated in patients with non-missing TSS at baseline. The potential impact of excluding patients without baseline TSS on study results is uncertain.

External Validity

According to the clinical experts involved in the review, the inclusion and exclusion criteria for the study are reasonable and generally consistent with clinical practice. In addition, the study population in JAKARTA is reflective of a typical Canadian population with intermediate- to high-risk MF, according to patients' baseline characteristics.

However, patients previously treated with JAK2 inhibitors would not have been enrolled in this study. The JAKARTA study compared fedratinib with placebo in patients who were JAK2 inhibitor naive. In Canada, patients with intermediate- to high-risk MF are more likely to be treated with ruxolitinib first, instead of fedratinib. Therefore, the JAKARTA study does not reflect the anticipated use of fedratinib in Canadian population. Furthermore, using placebo as a comparator to fedratinib does not reflect the current clinical practice in Canada either, when ruxolitinib is available for these patients. There is also no evidence from the JAKARTA study to demonstrate comparative efficacy and safety of fedratinib versus other JAKis.

In addition, due to the relatively short duration related to early termination of the JAKARTA study, some important clinical outcomes cannot be sufficiently examined, such as survival and safety in the long-term. Six cycles of treatment would not be long enough for these outcome assessments.

In summary, generalizability of the study results to the Canadian patient population could be limited.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

As there was no direct evidence comparing fedratinib to other active therapies for the treatment of splenomegaly and/or disease-related symptoms in patients with MF, a review of indirect evidence was undertaken. In addition to reviewing the sponsor's submission, CADTH conducted a literature search to identify potentially relevant ITCs in patients with MF. A focused literature search for network meta-analyses (NMAs) dealing with MF was run in MEDLINE All (1946–) and Embase (1974–) on November 25, 2020. No limits were applied. Titles, abstracts, and full text articles were screened for inclusion by 1 reviewer based on the population, intervention, comparator, and outcome criteria outlined in Table 5.

No potentially relevant ITCs were identified in the literature search. Two sponsor-submitted ITCs were included in this review.[15,16] These ITCs were used to inform the pharmacoeconomic models.

Description of Indirect Comparisons

The sponsor-submitted ITCs included a review of the literature, an MAIC, and an STC (JAKi-experienced comparisons only) that compared fedratinib to BAT for JAKi-experienced patients with MF,[15] or compared fedratinib to ruxolitinib for JAKi-naive patients with MF.[16]

Methods of Sponsor-Submitted ITCs of JAKi-Experienced and JAKi-Naive Patients With MF

Objectives

The objective of the sponsor-submitted report for JAKi-experienced patients with MF was to conduct a feasibility assessment and if possible, an ITC, to evaluate the relative efficacy and safety of fedratinib versus BAT for this population.

The objective of the sponsor-submitted report for JAKi-naive patients with MF was to conduct a feasibility assessment and if possible, an ITC, to evaluate the relative efficacy and safety of fedratinib versus ruxolitinib for this population.

Study Selection Methods

JAKi-Experienced Patients:

The RCTs and single-arm trials that were used to inform the ITC were identified through a systematic literature search conducted by the ITC authors. Studies were only considered for analyses if they investigated SVR by MRI or CT and/or TSS reduction. Multiple databases were searched to identify clinical trials that evaluated the efficacy and safety of drug therapies for MF. Two reviewers independently screened and selected studies. Data extraction was performed by 1 reviewer, with extraction verified by a second reviewer. Quality of the included studies was assessed using the standard National Institute for Health and Care Excellence (NICE) checklist (for RCTs) or the Downs and Black checklist (for non-RCTs).

JAKi-Naive Patients:

The RCTs that were used to inform the ITC were identified through a systematic literature search conducted by the ITC authors. Studies were only considered for analyses if they investigated SVR by MRI or CT and/or TSS reduction. Multiple databases were searched to identify clinical trials that evaluated the efficacy and safety of drug therapies for MF. Two reviewers independently screened and selected studies. Data extraction was performed by

1 reviewer, with extraction verified by a second reviewer. Quality of the included RCTs was assessed using the standard NICE checklist.

Inclusion and exclusion criteria for the clinical studies for each of the ITCs are presented in Table 17.

ITC Analysis Methods

JAKi-Experienced Patients

A feasibility assessment was conducted to determine if it was possible to perform an ITC using summary level data or an MAIC for the outcomes of SVR and TSS reduction. The study design, patient population, intervention, comparator, and outcome criteria were examined to determine the comparability of the included studies for analyses. As JAKARTA2 is a single-arm trial, a common comparator is not available among included clinical trials. Therefore, standard ITC techniques such as Bucher method or NMAs which require a common comparator to estimate relative treatment effects were deemed inappropriate. Two alternative methods were planned: MAIC and the STC. These are alternative ITC approaches that may be used for some comparisons when an NMA is unfeasible due to excessive heterogeneity in patient-level characteristics or lack of a common comparator. They can be used to adjust for heterogeneity related to differences in baseline patient characteristics. For the MAIC to produce unbiased treatment effects estimates, an unanchored MAIC (as applies to the JAKi-experienced patients) must adjust for all effect modifiers and all prognostic factors. With MAIC, individual patients treated with fedratinib from the JAKARTA2 study were assigned statistical weights that adjust for their over or underrepresentation relative to that observed in the population treated with BAT.

The first step in the weighting process is to identify a list of variables that should be considered as treatment effect modifiers and prognostic factors and therefore must be included in this process to adjust for bias related to these variables. Variable selections were conducted by examining baseline patient characteristics reported in the studies, fitting univariate and multivariable logistic regression models to identify potentially important variables and consulting an external clinical expert. Then a logistic regression model (including all variables identified from step 1 that are available in the individual patient-level data from the JAKARTA2 study and the aggregate data from the BAT studies) was used to estimate propensity scores for each patient in JAKARTA2. Subsequently, weights are generated for each patient in the JAKARTA2 study based on the estimated propensity scores for that patient.

After weighting, average baseline characteristics that were included in the weighting process would be considered balanced for the patients treated with fedratinib and those treated with BAT. Following estimation of the weights, the robustness of the analyses was evaluated by approximating the ESS, which is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. A small ESS relative to the original sample size of the JAKARTA2 study indicates that the weights are highly variable due to a lack of population overlap, and that the estimate may be unstable. After the weighting procedure was conducted and weights derived, efficacy outcomes were compared between balanced treatment groups. In this analysis, risk difference of SVR and TSS reduction was calculated. The corresponding CIs of the risk difference was calculated using a Bootstrap estimator, to account for the fact that weights were estimated rather than fixed and known.

Table 17: Study Selection Criteria and Methods for ITCs

Criteria	ITC compared FEDR with BAT in JAKi-experienced patients with MF	ITC compared FEDR with RUX in JAKi-naive patients with MF
Population	Adult patients with intermediate-1 or intermediate-2 and high-risk MF, or MF of indeterminate/undescribed risk, with prior exposure to JAKi treatment	Adult patients with intermediate-1 or intermediate-2 and high-risk MF, or MF of indeterminate/undescribed risk, with no prior exposure to JAKi treatment
Intervention/comparators	Anagrelide Azacytidine Cytarabine Danazol Darbepoetin alpha Decitabine Epoetin alpha Epoetin beta Fedratinib Flucytosine Guadecitabine Hydroxyurea Interferon Lenalidomide Melphalan Mercaptopurine Momelotinib Pacritinib Prednisolone Prednisone Pomalidomide Ruxolitinib Thalidomide Thioguanine Zebularine Non-pharmacological interventions (Allo-Sct) Placebo Best supportive care Any other pharmacological agents Splenectomy	

Criteria	ITC compared FEDR with BAT in JAKi-experienced patients with MF	ITC compared FEDR with RUX in JAKi-naive patients with MF
Outcomes	Spleen volume Total symptom score (from any instrument) Overall survival Progression-free survival Leukemia-free survival Patient-reported outcomes Safety Tolerability **Subgroups** • age • region • baseline platelet counts • patients with/without prior Jaki exposure • primary/secondary MF • prognostic score (intermediate-1, intermediate-2, high-risk/intermediate-2, high-risk)	
Study design	RCTs Single-arm trials	RCTs
Exclusion criteria	Patients with low-risk MF, healthy volunteers, children only (< 18 years) Studies assessing interventions that were not included Pharmacokinetic outcomes only, economic outcomes only Letters, comments, and editorials, non-systematic reviews, case reports and case series, pre-clinical trials and animal experiments, publications with redundant information Non-English	
Databases searched	MEDLINE In-Process, Embase, MEDLINE, The Cochrane Library, key international HTA websites, conference proceedings from ASH, BSH, EHA, and ASCO, and references cited in systematic reviews; searches completed on August 20, 2018	
Selection process	2 independent reviewers selected studies	
Data extraction process	1 reviewer extracted the data, and the second reviewer checked the data	
Quality assessment	All included RCTs were assessed using the standard NICE checklist accepted by the majority of HTA agencies; non-RCTs were evaluated using the Downs and Black checklist	

ASCO = American Society of Clinical Oncology; ASH = American Society for Hematology; BAT = best available therapy; BSH = British Society for Haematology; EHA = The European Hematology Association; FEDR = fedratinib; HTA = health technology assessment; ITC = indirect treatment comparison; JAKi = JAK inhibitor; MF = myelofibrosis; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; RUX = ruxolitinib; SCT = stem cell transplantation.

Source: Sponsor-submitted ITCs for JAKi-experienced population[15] and JAKi-naive population.[16]

In the ruxolitinib-experienced ITC, STC was used to adjust for between-trial differences in baseline characteristics by fitting an outcome regression model to the JAKARTA2 trial data. Outcomes of interest were included, as well as all covariates that were effect modifiers or prognostic variables. This model was then used to predict the percentage of patients treated with fedratinib who experienced SVR or TSS reduction using the covariate values observed in the comparator evidence. The resulting estimator is unbiased if there are no unmeasured effect modifiers or prognostic variables in imbalance between the populations.

Safety data across the included studies were descriptively summarized. The percentage of the following AEs was presented: patients with at least 1 TEAE, at least 1 grade 3 or 4 TEAE, at least 1 SAE, those who permanently discontinued treatment due to TEAEs, those with dose interruption or dose reduction, and deaths.

JAKi-Naive Patients

A feasibility assessment was conducted to determine if it was possible to perform an ITC using summary level data or an MAIC for the outcomes of SVR and TSS reduction. The study design and patient population, intervention, comparator, and outcome criteria were examined to determine the comparability of the included studies for analyses. As there was a common comparator (placebo or BAT) among the included studies, an anchored ITC may be feasible. When treatment effects within each included study are not homogeneous across those variables that differ between studies, methods that adjust for these treatment effect modifiers need to be considered, such as the MAIC. In the anchored setting, MAIC requires all effect modifiers to be adjusted for, while no purely prognostic variables should be included to avoid loss of precision. With MAIC, individual patients treated with fedratinib from the JAKARTA study were assigned statistical weights that adjust for their over or underrepresentation relative to that observed in the population treated with ruxolitinib.

The weighting process in the analysis for patients who were JAKi-naive was similar to that for patients who were JAK2-experienced. First, a list of variables that should be considered as treatment effect modifiers (to adjust for bias related to these variables) was identified. Then a logistic regression was performed for each end point (SVR and TSS reduction in this case), using JAKARTA data. An interaction term for randomized treatment and each baseline characteristic being investigated for treatment effect modification was included as well. For each model, a likelihood ratio test was performed and the P values for the interaction terms were compared. P values of less than 0.1 suggested that a variable could be an effect modifier. It was unknown whether a clinical expert was consulted. Then a logistic regression model (including all variables identified from step 1 that are available in the individual patient-level data from the JAKARTA study and the aggregate data from the ruxolitinib studies) was used to estimate propensity scores for each patient in JAKARTA. Subsequently, weights are generated for each patient in the JAKARTA study based on the estimated propensity scores for that patient.

After weighting, average baseline characteristics would be considered balanced for the patients treated with fedratinib and those treated with ruxolitinib. Following estimation of the weights, the robustness of the analyses was evaluated by approximating the ESS. After the weighting procedure was conducted and weights derived, efficacy outcomes were compared between balanced treatment groups. In this analysis, risk difference of SVR and TSS reduction was calculated. The corresponding CIs of the risk difference was calculated using a Bootstrap estimator, to account for the fact that weights were estimated rather than fixed and known.

Bucher pairwise ITC and NMAs for SVR and TSS reduction were also conducted for comparison.

Safety data across the included studies were descriptively summarized. The percentage of the following AEs was presented: patients with at least 1 TEAE, at least 1 grade 3 or 4 TEAE, at least 1 SAE, those who permanently discontinued treatment due to TEAEs, those with dose interruption or dose reduction, and deaths.

Results of ITC for JAKi-Experienced Patients With MF

Summary of Included Studies

A total of 15 RCTs and 169 non-RCTs were identified from the literature review, and 3 of them (JAKARTA2, PERSIST-2 and SIMPLIFY-2) were determined as relevant for this ITC. These trials investigated either fedratinib or BAT in a patient population that had received prior JAKi treatment and investigated SVR and/or TSS reduction (Table 18).

One study was a phase II, single-arm study, while the other 2 were phase III RCTs. The patients enrolled had intermediate to high risk of MF. The inclusion criteria for prior JAKi treatment differed across the 3 studies. All patients in the JAKARTA2 study received prior ruxolitinib for at least 14 days, or fewer than 14 days if patients had discontinued ruxolitinib due to intolerability or allergy. Patients in the PERSIST-2 study were JAKi-naive or could have received up to a maximum of 2 prior JAKis. Patients in the SIMPLIFY-2 study had been previously treated with ruxolitinib or were receiving ruxolitinib at the time of enrolment into the study. In terms of platelet count inclusion criteria, the JAKARTA2 study included patients with a platelet count of 50×10^9/L or greater, whereas the PERSIST-2 study included patients with a platelet count of 100×10^9/L or less. There was no limit on platelet count in the SIMPLIFY-2 study. There were also differences in the inclusion criteria among the 3 studies with respect to risk status measured with Dynamic International Prognostic Scoring System (DIPSS) score, as well as ECOG PS. The proportion of patients with a 35% or greater SVR and the proportion of patients with a 50% or greater reduction in TSS (measured with modified MFSAF in the JAKARTA2 study, and MPN-SAF in the PERSIST-2 and SIMPLIFY-2 studies) from baseline to week 24 were both measured in the 3 studies.

Patients' baseline data that may be used to identify prognostic factors are summarized in Table 19. Imbalances in patients' baseline characteristics between the JAKARTA2, SIMPLIFY-2, and PERSIST-2 studies were observed for the JAK2 mutational profile, prior ruxolitinib treatment, prior ruxolitinib treatment duration, white blood cell count, ECOG PS, DIPSS risk status, and transfusion dependence.

The PERSIST-2 study had a mixed population of ruxolitinib-naive and ruxolitinib-experienced patients. According to the clinical expert consulted by the sponsor, the baseline characteristics of patients in PERSIST-2 ITT population were not expected to represent the subgroup of patients who had received prior ruxolitinib. Therefore, adjusted analyses using the PERSIST-2 study as the BAT evidence was not possible. Accordingly, identification of prognostic factors was only limited to JAKARTA2 and SIMPLIFY-2 studies. The ITC authors also indicated that treatment effect modifiers could not be identified due to a paucity in the literature on this topic for JAKi-experienced patients, and exploratory analyses to identify treatment effect modifiers using the JAKARTA2 patient-level data were not possible given that JAKARTA2 was a single-arm trial.

After the variable selection process and consultation with an external hematologist, prognostic factors that were used to adjust the ITC for SVR included ECOG PS and transfusion dependence status, whereas ECOG PS and DIPSS were used to adjust the ITC for TSS reduction (Table 20 and Table 21).

Results

Spleen Volume Reduction

Following the weighting procedure which weighted on ECOG PS and transfusion dependence, the weighted baseline characteristics for patients in the JAKARTA2 study were compared

Table 18: Summary of Trials Included in the MAIC — JAKi-Experienced Population

Study	Study design	N	Population	Interventions	Control
JAKARTA2	Phase II, single-arm, OL	97	PMF, PPV MF, and PET MF; intermediate-1 with symptoms, Intermediate-2, and high-risk	Fedratinib 400 mg, once daily (starting dose) (n = 97 for the ITT population)	NA
PERSIST-2	Phase III RCT, OL	72 (BAT arm)	PMF, PPV MF, and PET MF; Intermediate-1, intermediate-2, and high-risk	Pacritinib 400 mg, once daily (n = 75 for the ITT efficacy population) Pacritinib 200 mg, twice daily (n = 74 for the ITT efficacy population)	BAT (n = 72 for the ITT efficacy population): • Ruxolitinib (45%) • Watch and wait (19%) • Hydroxyurea (19%) • Prednisone (13%) • Danazol (5%) • Thalidomide (3%) • Decitabine (2%) • Interferon-alpha (2%)
SIMPLIFY-2	Phase III RCT, OL	52 (BAT arm)	PMF, PPV MF, PET MF; intermediate-1 with symptomatic splenomegaly/ hepatomegaly, intermediate-2, and high-risk	Momelotinib 200 mg once daily (n = 104 for the ITT population)	BAT (n = 52 for the ITT population): • Ruxolitinib (89%) • Hydroxyurea (23%) • Corticosteroids (12%)

BAT = best available therapy; ITT = intention to treat; JAKi = Janus kinase inhibitor; MAIC = matching-adjusted indirect comparison; MF = myelofibrosis; NA = not applicable; OL = open label; PET = post-essential thrombocythemia; PMF = primary myelofibrosis; PPV = post-polycythemia vera; RCT = randomized controlled trial.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

Table 19: Comparison of Study Characteristics Between Included Trials — JAKi-Experienced Population

Characteristics	JAKARTA2 Fedratinib 400 mg N = 97	PERSIST-2 BAT N = 72	SIMPLIFY-2 BAT N = 52
Platelet count × 10^9/L			
Mean (SD)	198.46 (167.669)	NR	126.5 (95.9)
Median (min, max)	147.0 (48.0, 929)	NR	NR
MF subtype, n (%)			
PMF	53 (54.6)	43 (59.7)	30 (57.7)
Post-PV MF	25 (25.8)	16 (22.2)	12 (23.1)
Post-ET MF	19 (19.6)	13 (18.1)	10 (19.2)
Risk status, n (%)			
Intermediate-1	16 (16.5)[a]	13 (18.1)	16 (30.8)[b]
Intermediate-2	47 (48.5)	37 (51.4)	28 (53.8)
High-risk	34 (35.1)	22 (30.6)	8 (15.4)
JAK2 mutational profile, n (%)			
Wild type	29 (29.9)	NR	12 (23.1)
Mutant	61 (62.9)	51 (70.8)	37 (71.2)
Missing/unknown	7 (7.2)	NR	3 (5.8)
ECOG PS, n (%)			
0	26 (26.8)	NR	19 (36.5)
1	45 (46.4)	NR	26 (50.0)
2	23 (23.7)	NR	7 (13.5)
3	NA	NR	NA
Missing	3 (3.1)	3 (4)	NA
0 to 1	71 (73.2)	54 (75.0)[c]	45 (86.5)
2 to 3	23 (23.7)	15 (21)[c]	7 (13.5)
Prior RUX treatment, n (%)			
Prior RUX	97 (100)	33 (45.8)	52 (100)
RUX-naive	0	39 (54.2)	0
[redacted]	[redacted]	[redacted]	[redacted]
Transfusion dependent, n (%)	14 (14.4)	14 (19.4)	27 (51.9)

Characteristics	JAKARTA2 Fedratinib 400 mg N = 97	PERSIST-2 BAT N = 72	SIMPLIFY-2 BAT N = 52
Hemoglobin (g/dL)			
Mean (SD)	10.09 (1.795)	NR	9.5 (1.6)
n (%) < 10	51 (52.6)	41 (56.9)	NR
Palpable spleen length (cm), median (range)	18 (5 to 36)	13 (2 to 34)	NR
WBC count > 25 × 10^9/L, n (%)	26 (26.8)	14 (19.4)	NR
[redacted]	[redacted]	[redacted]	[redacted]
Age (years)			
Mean (SD)	66.5 (8.14)	NR	69.4 (7.4)
Median (min to max)	67.0 (38 to 83)	69 (32 to 83)	NR
Gender, n (%)			
Male	53 (54.6)	39 (54.2)	24 (46.2)
Race, n (%)			
White	92 (94.8)	NR	44 (84.6)
Asian	4 (4.1)	NR	NR
Black/African American	1 (1.0)	NR	0
Other	NA	NR	4 (7.7)
Unknown	NA	NR	8 (15.4)
Mean TSS[c] (SD) [N]	20.65 (12.14) [90]	NR	20.5 (16) [NR]

BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = essential thrombocythemia; ITT = intention to treat; JAK = Janus kinase; max = maximum; MF = myelofibrosis; min = minimum; NA = not available; NR = not reported; PMF = primary myelofibrosis; PV = polycythemia vera; RUX = ruxolitinib; SD = standard deviation; TSS = Total Symptom Score; WBC = white blood cell.

[a]Intermediate-1 with symptoms.

[b]Intermediate-1 with symptomatic splenomegaly or hepatomegaly.

[c]ECOG PS reported in categories 0 to 1 and 2 to 3.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

with the comparator (SIMPLIFY-2 BAT arm). A small ESS for the JAKARTA2 study population was observed, ESS 34.4 (35.5% of the original sample size) compared to the original sample size of 97. Removal of transfusion dependence status resulted in an increased ESS of 91.7 (Table 22).

Results of the unadjusted and adjusted ITCs for the proportion of patients achieving a 35% or greater SVR from baseline to week 24 are provided in Table 23. After weighting for baseline ECOG PS, the difference in the proportion of patients with a 35% or greater SVR between fedratinib 400 mg and BAT was 27.0% (95% CI, 15.7 to 38.7) with MAIC and 26.5% (95% CI, 15.0 to 38.0) with STC. After adjustment for baseline ECOG PS and transfusion dependence status using MAIC, the difference in the proportion of patients with a 35% or greater SVR between fedratinib 400 mg and BAT was 12.5% (95% CI, 4.5 to 20.9).

Table 20: Investigation of Prognostic Factors for SVR

Available baseline characteristics from SIMPLIFY-2	JAKARTA-2 univariate analyses: likelihood-ratio test results in P value < 0.1	JAKARTA-2 multivariable analyses: chosen in forward selection by AIC	Potential imbalance between JAKARTA-2 and SIMPLIFY-2 (standardized difference >10%)	Identified as having clinically meaningful difference by an external hematologist
Age	No	Yes	Yes	No
Sex	No	Yes	Yes	No
BMI	No	No	Yes	No
Race	No	No	Yes	No
MF subtype	No	Yes	No	No
TSS	No	Yes	No	No
ECOG PS	Yes	Yes	Yes	Yes
Ruxolitinib treatment duration	No	No	Yes	No
Mutational profile	No	No	Yes	No
DIPSS	No	No	Yes	Yes
Transfusion dependence	Yes	NA	Yes	Yes
Platelet count	No	No	Yes	No
Absolute neutrophil count	No	No	No	No
Hemoglobin	No	No	Yes	No

AIC = Akaike information criterion; BMI = body mass index; DIPSS = Dynamic International Prognostic Scoring System; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MF = myelofibrosis; NA = not applicable; TSS = Total Symptom Score.

Note: grey highlight indicates variables that were identified by an external hematologist as having a clinically meaningful imbalance and also identified as being an important prognostic factor in the JAKARTA-2 study (from either the univariate or multivariable analyses).

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

Table 21: Investigation of Prognostic Factors for TSS Reduction

Available baseline characteristics from SIMPLIFY-2	JAKARTA-2 univariate analyses: likelihood-ratio test results in P value < 0.1	JAKARTA-2 multivariable analyses: chosen in forward selection by AIC	Potential imbalance between JAKARTA-2 and SIMPLIFY-2 (standardized difference > 10%)	Identified as having clinically meaningful difference by an external hematologist
Age	Yes	Yes	Yes	No
Sex	No	No	Yes	No
BMI	No	Yes	Yes	No
Race	No	No	Yes	No
MF subtype	No	No	No	No
TSS	No	No	No	No
ECOG PS	No	Yes	Yes	Yes
Ruxolitinib treatment duration	No	Yes	Yes	No
Mutational profile	No	No	Yes	No
DIPSS	No	Yes	Yes	Yes
Transfusion dependence	No	No	Yes	Yes
Platelet count	No	No	Yes	No
Absolute neutrophil count	No	No	No	No
Hemoglobin	No	No	Yes	No

AIC = Akaike information criterion; BMI = body mass index; DIPSS = Dynamic International Prognostic Scoring System; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MF = myelofibrosis; TSS = Total Symptom Score.

Note: grey highlight indicates variables that were identified by an external hematologist as having a clinically meaningful imbalance and also identified as being an important prognostic factor in the JAKARTA-2 study (from either the univariate or multivariable analyses).

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

TSS Reduction

Following the weighting procedure which weighted on ECOG PS and DIPSS, the weighted baseline characteristics for patients in the JAKARTA2 study were compared with the comparator (SIMPLIFY-2 BAT arm). A relatively small ESS for the JAKARTA2 study population was observed (ESS, 81.6; 84.2% of the original JAKARTA2 sample size) compared to the original sample size of 97 (Table 24).

Table 22: Sample Size/ESS and Baseline Characteristics Before and After Weighting — SVR Comparison in JAKi-Experienced Population

Population	N/ESS	ECOG PS 0 or 1 (%)	Transfusion dependence (%)
SIMPLIFY-2 BAT arm	N = 52	86.5	51.9
JAKARTA2 before matching	N = 97	76.3	14.4
JAKARTA2 after matching on ECOG PS and transfusion dependence	ESS = 34.4 (35.5% of original JAKARTA2 sample size)	86.5	51.9
JAKARTA2 after matching on ECOG PS	ESS = 91.7 (94.5% of original JAKARTA2 sample size)	86.5	NA

BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; JAKi = Janus kinase inhibitor; NA = not applicable; SVR = spleen volume reduction.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

Table 23: Unweighted and Weighted ITC Results for SVR at Week 24 — Fedratinib 400 mg Versus BAT

Method	Variables included in adjustment	JAKARTA2 Fedratinib 400 mg	SIMPLIFY-2 BAT
Unadjusted ITC	NA	30.9% (n = 30; N = 97)	5.8% (n = 3; N = 52)
		Risk difference = 25.2% (95% CI, 14 to 36.3)	
MAIC	ECOG PS	32.7% (95% CI, 23.5 to 42.5)	5.8% (n = 3; N = 52)
		Risk difference = 27.0% (95% CI, 15.7 to 38.7)	
STC	ECOG PS	32.3% (95% CI, 22.7 to 41.9)	5.8% (n = 3; N = 52)
		Risk difference = 26.5% (95% CI, 15.0 to 38.0)	
MAIC	ECOG PS transfusion dependence	18.3% (95% CI, 13.1 to 23.6)	5.8% (n = 3; N = 52)
		Risk difference = 12.5% (95% CI, 4.5 to 20.9)	

BAT = best available therapy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITC = indirect treatment comparison; NA = not applicable; MAIC = matching-adjusted indirect comparison; STC = simulated treatment comparison; SVR = spleen volume response.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

Results of the unadjusted and adjusted ITCs for the proportion of patients achieving a 50% or greater TSS reduction from baseline to week 24 are provided in Table 25. After weighting for baseline ECOG PS and DIPSS, the difference in the proportion of patients with a 50% or greater TSS reduction between fedratinib 400 mg and BAT was 17.0% (95% CI, 6.2 to 28.2) with MAIC and 17.1% (95% CI, 5.8 to 28.3) with STC.

Safety

Harm outcomes were descriptively summarized. In general, the percentage of patients who experienced AEs, grade 3 or 4 AEs, SAEs, and treatment discontinuation due to AEs was higher in the JAKARTA2 study compared with those in the PERSIST-2 and SIMPLIFY-2 studies.

Results of ITC for JAKi-Naive Patients With MF

Summary of Included Studies

A total of 15 RCTs and 169 non-RCTs were identified from the literature review, and 3 of them (JAKARTA, COMFORT-I, and COMFORT-II) were determined as relevant for this ITC. These trials investigated either fedratinib or ruxolitinib in a patient population that had no prior JAKi treatment and investigated SVR and/or TSS reduction (Figure 4 and Table 27).

Table 24: Sample Size/ESS and Baseline Characteristics Before and After Weighting — TSS Reduction Comparison in JAKi-Experienced Population

Baseline characteristic	N of ESS	ECOG PS of 0 or 1 (%)	DIPSS: intermediate-1 or 2 (%)
SIMPLIFY-2 BAT arm	N = 52	86.5	84.6
JAKARTA2 before matching	N = 97	76.3	64.9
JAKARTA2 after matching on ECOG PS and DIPSS	ESS = 81.6 (84.2% of original JAKARTA2 sample size)	86.5	84.6

BAT = best available therapy; DIPSS = Dynamic International Prognostic Scoring System; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; JAKi = Janus kinase inhibitor; TSS = Total Symptom Score.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

Table 25: Unadjusted and Adjusted ITC Results for TSS Reduction at Week 24 — Fedratinib 400 mg Versus BAT

Method	Variables included in adjustment	JAKARTA2 Fedratinib 400 mg	SIMPLIFY-2 BAT
Unadjusted ITC	NA	24.7% (n = 24; N = 97)	5.9% (n = 3; N = 51)
		Risk difference = 18.9% (95% CI, 8.1 to 29.6)	
MAIC	ECOG PS DIPSS	22.9% (95% CI, 14.3 to 32.4)	5.9% (n = 3; N = 51)
		Risk difference = 17.0% (95% CI, 6.2 to 28.2)	
STC	ECOG PS DIPSS	22.9% (95% CI, 13.7 to 32.2)	5.9% (n = 3; N = 51)
		Risk difference = 17.1% (95% CI, 5.8 to 28.3)	

BAT = best available therapy; CI = confidence interval; DIPSS = Dynamic International Prognostic Scoring System; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITC = indirect treatment comparison; NA = not applicable; MAIC = matching-adjusted indirect comparison; STC = simulated treatment comparison; TSS = Total Symptom Score.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

The JAKARTA and COMFORT-I studies were double-blind, placebo-controlled RCTs while COMFORT-II was an open-label, BAT-controlled RCT. In the COMFORT-II study, 67% of the patients treated with BAT received an active treatment and the most commonly received treatments were antineoplastic agents. The patients enrolled in the COMFORT-II trial had an International Prognostic Scoring System score of 2 or greater, indicating intermediate-2 to high risk of disease. Two different doses of fedratinib or ruxolitinib were given to the patients in all trials. Crossover to the fedratinib or ruxolitinib arms were allowed, although the criteria for crossover differed among the trials. In the JAKARTA study, patients could crossover to the fedratinib therapy if disease progression occurred, which was defined based on increase

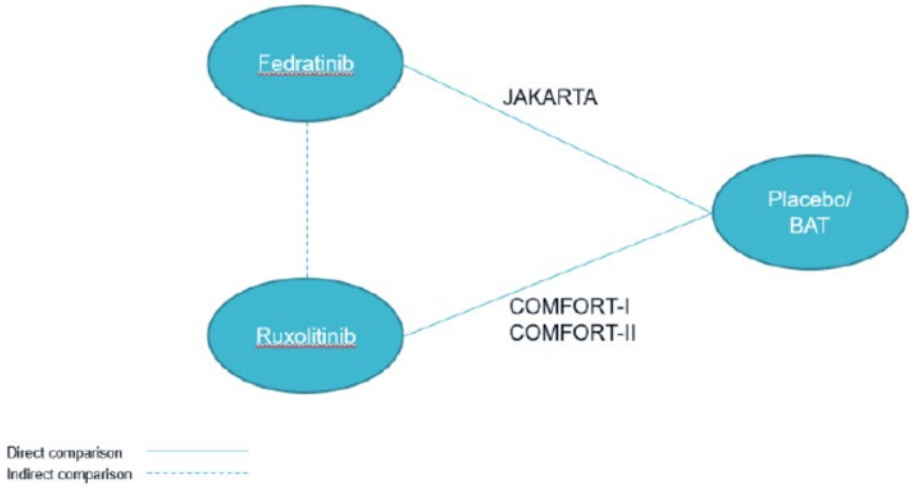
Table 26: Harm Outcomes Reported in the JAKARTA2, PERSIST-2, and SIMPLIFY-2 Studies

Harm outcomes	JAKARTA2 Fedratinib 400 mg N = 97	PERSIST-2 BAT N = 98	SIMPLIFY-2 BAT N = 52
Patients with ≥ 1 AE, n (%)	97 (100)	87 (89)	46 (89)
Patients with ≥ 1 SAE, n (%)	33 (34.0)	30 (31)	12 (23)
Patients with ≥ 1 grade 3 or 4 AE, n (%)	61 (62.9)	48 (49)	NR
Patients who discontinued treatment due to AEs, n (%)	19 (19.6)	4 (4)	1 (2)
Patients with AEs leading to death, n (%)	7 (7.2)	9 (9)	4 (8)
Patients with dose interruption for ≥ 7 consecutive days, n (%)	25 (25.8)	10 (10)	NR
Patients with dose reduction, n (%)	38 (39.2)	7 (7)	NR

AE = adverse event; BAT = best available therapy; NR = not reported; SAE = serious adverse event.

Source: Sponsor-submitted ITC for JAKi-experienced patients with MF.[15]

Figure 4: Overall Network for JAKi-Naive Patients



BAT = best available therapy.

Source: Sponsor-submitted ITC for Janus kinase inhibitor–naive patients with MF.[16]

in spleen volume, leukemic transformation, or increase in peripheral blood blast percentage. In the COMFORT-I and COMFORT-II studies, patients could crossover to the ruxolitinib therapy when there was an increase in spleen volume or experienced worsening symptoms. Patients in the JAKARTA study were required to have an ECOG PS of 2 or less, whereas in the COMFORT-I and COMFORT-II studies, patients with an ECOG PS of 3 were also enrolled. Patients in the JAKARTA study were required to have a baseline platelet count of at least 50 × 10^9/L, but in the COMFORT-I and COMFORT-II studies, patients were only eligible if their baseline platelet count was at least 100 × 10^9/L. Therefore, subgrouping of the JAKARTA trial data to only include patients with a platelet count of at least 100 × 10^9/L has been investigated for the SVR and TSS reduction outcomes.

The primary efficacy end point in the JAKARTA and COMFORT-I studies was proportion of patients with a 35% or greater SVR at week 24, and patients in the JAKARTA study were required to confirm the spleen response 4 weeks after the end of cycle 6. The primary end point in COMFORT-II was proportion of patients with a 35% or greater SVR at week 48. The proportion of patients who had a 50% or greater reduction in TSS from baseline to week 24 was a secondary end point in the JAKARTA and COMFORT-I studies, and this was not examined in the COMFORT-II study. Inconsistency was also observed in TSS calculation at week 24 between the JAKARTA and COMFORT-I trials.

Table 27: Summary of Trials Included in the MAIC — JAKi-Naive Population

Study	Study design	Population	Interventions	Control
JAKARTA	Phase III, DB RCT	PMF, PPV MF, and PET MF IPSS score ≥ 2	• Fedratinib 400 mg q.d. (n = 96) • Fedratinib 500 mg q.d. (n = 97) (Patients with platelet count ≥ 50,000/μL were enrolled for both doses)	Placebo (n = 96)[a]
COMFORT-I	Phase III, DB RCT	PMF, PPV MF, and PET MF IPSS score ≥ 2	Ruxolitinib b.i.d. (n = 155) • 20 mg dose: baseline platelet count > 200,000/μL • 15 mg dose: baseline platelet count between 100,000/μL and 200,000/μL	Placebo (n = 154)[b]
COMFORT-II	Phase III, RCT, OL	PMF, PPV MF, and PET MF IPSS score ≥ 2	Ruxolitinib b.i.d. (n = 146) • 20 mg dose: baseline platelet count > 200,000/μL • 15 mg dose: baseline platelet count between 100,000/μL and 200,000/μL	BAT (n = 73)[c]

BAT = best available therapy; b.i.d. = twice a day; DB = double blind; IPSS = International Prognostic Scoring System; JAKi = Janus kinase inhibitor; MAIC = matching-adjusted indirect comparison; MF = myelofibrosis; OL = open label; PET = post-essential thrombocythemia; PMF = primary myelofibrosis; PPV = post-polycythemia vera; q.d. = once daily; RCT = randomized controlled trial.

[a]In JAKARTA, 71 patients from the placebo arm were re-randomized to 1 of the fedratinib arms at crossover (10 before the end of cycle 6), as per protocol.

[b]In COMFORT-I, 111 patients crossed over to ruxolitinib (median time to crossover of 41 weeks), as per protocol.

[c]In the COMFORT-II BAT arm, 67% of subjects received at least 1 active treatment which included: antineoplastic agents (37 subjects [51%]), hydroxycarbamide (34 patients [47%]), glucocorticoids (12 patients [16%]), epoetin alpha (5 patients [7%]), immunomodulators (5 patients [7%]), purine analogues (4 patients [6%]), androgens (3 patients [4%]), interferons (3 patients [4%]), nitrogen mustard analogues (2 patients [3%]), and pyrimidine analogues (2 patients [3%]). In COMFORT-II, 45 patients crossed over to ruxolitinib (median time to crossover of 66 weeks).

Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

Patients' baseline data that may be used to identify treatment effect modifiers are summarized in Table 28. Imbalances in patients' baseline characteristics between the JAKARTA, COMFORT-I, and COMFORT-II studies were observed for previous hydroxyurea use, MF subtype, time since MF diagnosis, risk status, JAK2 mutational profile, and palpable spleen length.

All aforementioned potentially unbalanced baseline characteristics were included in subgroup analyses presented in the JAKARTA study, for the primary efficacy end point (proportion of patients who had a ≥ 35% reduction in spleen volume from baseline to week 24 and who had confirmation of response 4 weeks later) (Table 4). In addition, logistic regression models with an interaction term for randomized treatment and each baseline characteristic of interest have been fitted to the JAKARTA trial data for the end points of SVR (without confirmation) and TSS reduction. A likelihood ratio test was performed to assess the significance of the interaction term and potential treatment effect modifier was identified when P values were less than 0.1. After the variable selection process, JAK2 status and constitutional symptoms were determined to be potential effect modifiers for SVR; however, constitutional symptoms were not reported for the COMFORT-I and COMFORT-II studies, and therefore could not be included in the MAIC. No effect modifiers were identified for TSS reduction assessment.

Results

Following the weighting procedure which weighted on JAK2 status, the robustness of the analyses was considered by approximating the ESS. Weighted baseline characteristics for patients in the JAKARTA study were compared with those in the COMFORT-I study. A slightly small ESS of 177.9 (92.7% of the original JAKARTA sample size) for the JAKARTA study population was observed compared to the original sample size of 192 (Table 29).

Following the weighting procedure which weighted on JAK2 status, the robustness of the analyses was examined by approximating the ESS. Weighted baseline characteristics for patients in the JAKARTA study were compared with those in the COMFORT-II study. A slightly small ESS of 184.1 (95.9% of the original sample size) for the JAKARTA study population was observed compared to the original sample size of 192 (Table 30).

Spleen Volume Reduction

Results of ITCs for the proportion of patients achieving a 35% or greater SVR from baseline to week 24 are provided in Table 31. After adjustment for JAK2 status, the difference in the proportion of patients with a 35% or greater SVR between fedratinib 400 mg and ruxolitinib was 12.3% (95% CI, 0.6 to 24.0). The results for the proportion of patients achieving a 35% or greater SVR from baseline to week 24 derived from the frequentist NMA was 9.4% (95% CI, −2.2 to 20.9). Results in the subgroup of the JAKARTA ITT population with platelet counts of 100×10^9/L or greater and no confirmation of response were consistent with the ITT population.

TSS Reduction

Results of the ITCs showed that the between-group difference was −9.4% (95% CI, −23.9 to 5.2), suggesting that there was no statistically significant difference in a 50% or greater reduction in TSS between treatment with fedratinib 400 mg and ruxolitinib from baseline to week 24 (Table 32).

Table 28: Comparison of Study Characteristics Between Included Trials — JAKi-Naive Population

Baseline characteristics	JAKARTA		COMFORT-I		COMFORT-II	
	Fedratinib 400 mg N = 96	Placebo N = 96	Ruxolitinib (15 or 20 mg) N = 155	Placebo N = 154	Ruxolitinib (15 or 20 mg) N = 146	BAT N = 73
Previous hydroxyurea use, n (%)	69 (71.9)	54 (56.3)	104 (67.1)	87 (56.5)	110 (75.3)	50 (68.5)
ECOG PS						
n (%) 0	41 (42.7)	31 (32.3)	47 (31.1)	38 (25.5)	58 (39.7)	26 (35.6)
n (%) 1	47 (49.0)	56 (58.3)	87 (57.6)	82 (55.0)	77 (52.7)	37 (50.7)
n (%) 2	8 (8.3)	8 (8.3)	14 (9.3)	25 (16.8)	10 (6.8)	9 (12.3)
n (%) 3	NA	NA	3 (2.0)	4 (2.7)	1 (0.7)	1 (1.4)
n (%) Missing	0	1 (1.0)	4 (2.6)	5 (3.2)	0	0
Platelet count × 10^9/L, median (min, max)	220.5 (31.0, 1155.0)	187.0 (51.6, 1075.0)	262 (81, 984)	238 (100, 887)	244 (NR, NR)	228 (NR, NR)
MF subtype						
n (%) PMF	62 (64.6)	58 (60.4)	70 (45.2)	84 (54.5)	77 (52.7)	39 (53.4)
n (%) Post-PV MF	24 (25.0)	27 (28.1)	50 (32.3)	47 (30.5)	48 (32.9	20 (27.4)
n (%) Post-ET MF	10 (10.4)	11 (11.5)	35 (22.6)	22 (14.3)	21 (14.4)	14 (19.2)
Mean TSD, months (SD)	68.53 (73.585)	54.24 (69.091)	58.8 (73.2)	55.2 (74.4)	31.1 (NR)	33.2 (NR)
Risk status,						
% Intermediate-2	57 (59.4)	46 (47.9)	64 (41.3)	54 (35.1)	74 (50.7)	37 (50.7)
% High risk	39 (40.6)	50 (52.1)	90 (58.1)	99 (64.3)	72 (49.3)	36 (49.3)
JAK2 mutational profile						
n (%) Wild type	30 (31.3)	32 (33.3)	40 (25.8)	27 (17.5)	35 (24.0)	20 (27.4)
n (%) Mutant	62 (64.6)	59 (61.5)	113 (72.9)	123 (79.9)	110 (75.3)	49 (67.1)
n (%) Missing/unknown	4 (4.2)	5 (5.2)	2 (1.3)	4 (2.6)	1 (0.7)	4 (5.5)
Fibrosis grade						
% 0	1 (1.0)	3 (3.1)	2 (1.3)	1 (0.6)	3 (2.1)	2 (2.7)
% 1	7 (7.3)	2 (2.1)	14 (9.0)	18 (11.7)	21 (14.4)	3 (4.1)
% 2	36 (37.5)	40 (41.7)	63 (40.6)	51 (33.1)	55 (37.7)	27 (37.0)
% 3	49 (51.0)	47 (49.0)	65 (41.9)	71 (46.1)	59 (40.4)	34 (46.6)
% Missing	3 (3.1)	4 (4.2)	11 (7.1)	13 (8.4)	7 (4.8)	6 (8.2)
Median spleen volume, mL[a] (min, max)	2,652.0 (316, 6430)	2,660.0 (662, 7911)	2,597.7 (478.1, 7461.8)	2,566.3 (521.0, 8880.7)	2,407.6 (451.3, 7765.6)	2,317.9 (728.5, 7701.1)

Baseline characteristics	JAKARTA		COMFORT-I		COMFORT-II	
	Fedratinib 400 mg N = 96	Placebo N = 96	Ruxolitinib (15 or 20 mg) N = 155	Placebo N = 154	Ruxolitinib (15 or 20 mg) N = 146	BAT N = 73
Palpable spleen length > 10 cm,[b] n (%)	68 (70.8)	71 (74.0)	123 (79.4)	126 (81.8)	99 (67.8)	55 (75.3)
Age (years), median (min, max)	63.0 (39, 86)	66.0 (27, 85)	66.0 (43, 91)	70.0 (40, 86)	67.0 (35, 83)	66.0 (35, 85)
Gender, % male	54 (56.3)	55 (57.3)	79 (51.0)	88 (57.1)	83 (56.8)	42 (57.5)
Race						
% White	89.6	93.8	138 (89.0)	139 (90.3)	118 (80.8)	67 (91.8)
% Asian	8.3	5.2	5 (3.2)	4 (2.6)	NR	NR
% Black/African American	1.0	1.0	6 (3.9)	7 (4.5)	NR	6
% Other	1.0	0	6 (3.9)	4 (2.6)	0	1 (1.4)
% Unknown	NA	NA	NA	NA	28 (19.2)	5 (6.8)
Mean TSS[c] (SD) [N]	17.56 (13.530) [N = 91]	14.72 (11.954) [N = 85]	18.2 (NR)	16.9 (NR)	NA	NA

BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group performance status; JAK2 = Janus kinase 2; max = maximum; min = minimum; MF = myelofibrosis; NA = not applicable; NR = not reported; PMF = primary myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis; SD = standard deviation; TSD = time since diagnosis; TSS = total symptom score.

[a]Reported as cm^3 in the COMFORT-I and COMFORT-II studies.

[b]For the COMFORT-I and COMFORT-II studies, percentages are for palpable spleen length ≥ 10 cm.

[c]In the JAKARTA study, the TSS was defined as the average value of the daily total score of the 6-item measures of the week: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain.

Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

Safety

Harm outcomes were descriptively summarized. In general, the percentage of patients who experienced AEs, grade 3 or 4 AEs, SAEs, and treatment discontinuation due to AEs was similar in patients treated with fedratinib compared with those treated with ruxolitinib (Table 33).

Table 29: Sample Size/ESS and Baseline Characteristics Before and After Weighting the JAKARTA ITT Population to the COMFORT-I Population — JAKi-Naive Population

Population	N/ESS	% JAK2: mutant	% JAK2: wild type	% JAK2: missing
COMFORT-I	N = 309	76.4	21.7	1.9
JAKARTA before matching	N = 192	63.0	32.3	4.7
JAKARTA after matching on JAK2 status	ESS = 177.9 (92.7% of original JAKARTA sample size)	76.4	21.7	1.9

ESS = effective sample size; ITT = intention to treat; JAK = Janus kinase.

Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

Critical Appraisal of Sponsor-Submitted ITCs

JAKi-Experienced Population

In this ITC, studies were identified and selected using a systematic review approach, for example, multiple databases were searched, and 2 independent reviewers performed study selection. Data extraction was conducted by 1 reviewer and checked by a second reviewer. Quality assessment of the included studies were performed using validated instruments.

The authors conducted a thorough review of the study design, inclusion and exclusion criteria, patient population characteristics, and outcomes measured in the clinical trials and identified a number of differences in study design and patient's baseline characteristics among studies that could potentially threaten the validity of an ITC. The rationale for conducting an adjusted indirect comparison, such as an MAIC, instead of a standard NMA was provided. The ITC authors indicated that standard NMA techniques were not appropriate due to lack of a common comparator between the studies. MAIC analyses were deemed feasible because individual patient data were available for the JAKARTA2 study.

Imbalances in baseline characteristics were observed across included studies, such as JAK2 mutational profile, risk status, prior ruxolitinib treatment, ECOG PS, or transfusion dependence. In addition, 1 of the included studies, PERSIST-2, was a mixed population of ruxolitinib-naive and ruxolitinib-experienced patients. This population was not expected to represent the subgroup of patients who had received prior ruxolitinib, which suggested more progressive disease, longer history of disease, potentially older age, higher ECOG PS, and more likely to be high risk based on DIPSS, and so on. Therefore, identification of prognostic factors was only limited to JAKARTA2 and SIMPLIFY-2 studies. According to the sponsor, "Treatment effect modifiers could not be identified due to a paucity in the literature on this topic for JAKi-exposed patients and exploratory analyses to identify treatment effect modifiers using the JAKARTA2 patient-level data are not possible given that JAKARTA2 is a single-arm trial." When unmeasured/unadjusted effect modifiers cannot be identified, they cannot be controlled for in the MAIC analysis, which would be a potential source of bias in study results.

During the process of identifying prognostic factors, the following baseline characteristics were considered important prognostic factors for the outcome of SVR: ECOG PS, MF subtype, sex, age, and baseline TSS (transfusion dependence was not included in the multivariable model for SVR due to "the problems with complete separation"). Other baseline characteristics, such as JAK2 mutational profile, baseline spleen volume, intermediate/high risk, platelet group, and prior ruxolitinib duration, were not considered important prognostic

Table 30: Sample Size/ESS and Baseline Characteristics Before and After Weighting the JAKARTA ITT Population to COMFORT-II Population — JAKi-Naive Population

Population	N/ESS	% JAK2: mutant	% JAK2: wild type	% JAK2: missing
COMFORT-II	N = 219	72.6	25.1	2.3
JAKARTA before matching	N = 192	63.0	32.3	4.7
JAKARTA after matching on JAK2 status	ESS = 184.1 (95.9% of JAKARTA sample size)	72.6	25.1	2.3

ESS = effective sample size; ITT = intention to treat; JAK = Janus kinase; JAKi = Janus kinase inhibitor.

Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

Table 31: ITC Results for SVR at Week 24 — Fedratinib 400 mg Versus Ruxolitinib

Outcome	Methods	JAKARTA		COMFORT-I		COMFORT-II	
		Fedratinib 400 mg	Placebo	Ruxolitinib	Placebo	Ruxolitinib	BAT
≥ 35% SVR from baseline to week 24 (no confirmation of response 4 weeks later)	No analysis performed	46.9% (n = 45; N = 96)	1.0% (n = 1; N = 96)	41.9% (n = 65; N = 155)	0.7% (n = 1; N = 153)	31.9% (n = 46; N = 144)	0 (n = 0; N = 72)
	Bucher ITC	NA		Risk difference = 4.6% (95% CI, −8.3 to 17.4)		Risk difference = 13.9% (95% CI, 1.2 to 26.6)	
	MAIC using Bucher methodology	NA		Risk difference = 7.9% (95% CI, −5.2 to 20.9)		Risk difference = 16.3% (95% CI, 3.5 to 29.0)	
	Frequentist NMA	NA		Risk difference = 9.4% (95% CI, −2.2 to 20.9)			
	MAIC using frequentist NMA methodology	NA		Risk difference = 12.3% (95% CI, 0.6 to 24.0)			
≥ 35% SVR from baseline to week 24 (subgroup of JAKARTA ITT population with platelet counts ≥ 100 × 10^9/L and no confirmation of response)	No analysis performed	48.8% (n = 40; N = 82)	1.3% (n = 1; N = 77)	41.9% (n = 65; N = 155)	0.7% (n = 1; N = 153)	31.9% (n = 46; N = 144)	0 (n = 0; N = 72)
	Bucher ITC	NA		Risk difference = 6.2% (95% CI, −7.4 to 19.8)		Risk difference = 15.5% (95% CI, 2.1 to 29.0)	
	MAIC using Bucher methodology	NA		Risk difference = 10.4% (95% CI, −3.2 to 24.1)		Risk difference = 18.5% (95% CI, 5.1 to 31.9)	
	Frequentist NMA	NA		Risk difference = 11.0% (95% CI, −1.4 to 23.4)			
	MAIC using frequentist NMA methodology	NA		Risk difference = 14.7% (95% CI, 2.4 to 27.1)			

BAT = best available therapy; CI = confidence interval; ITC = indirect treatment comparison; ITT = intention to treat; MAIC = matching-adjusted indirect comparison; NA = not applicable; NMA = network meta-analysis; SVR = spleen volume response.

Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

factors for this outcome. According to an external clinical expert consulted by sponsor, differences observed between the studies for ECOG PS, DIPSS, and transfusion dependence status were also clinically meaningful in the assessment of SVR. Finally, prognostic factors that were used to adjust the ITCs were:

- ECOG PS and transfusion dependence for "SVR"
- ECOG PS and DIPSS for "TSS reduction"

Table 32: ITC Results for TSS Reduction at Week 24 — Fedratinib 400 mg Versus Ruxolitinib

Outcome	Methods	JAKARTA		COMFORT-I		COMFORT-II	
		Fedratinib 400 mg	Placebo	Ruxolitinib	Placebo	Ruxolitinib	BAT
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]		[redacted]		[redacted]	

BAT = best available therapy; [redacted]; ITC = indirect treatment comparison; [redacted]; TSS = Total Symptom score.
Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

Table 33: Harm Outcomes Reported in the JAKARTA, COMFORT-I, and COMFORT-II Studies

AEs, n (%)	JAKARTA (24 weeks)		COMFORT-I (24 weeks)		COMFORT-II (48 weeks)	
	Fedratinib 400 mg N = 96	Placebo N = 95	Ruxolitinib N = 155	Placebo N = 151	Ruxolitinib N = 146	BAT N = 73
Patients with ≥ 1 AE	95 (99.0)	89 (93.7)	151 (97.4)	148 (98.0)	145 (99.3)	66 (90.4)
Patients with ≥ 1 SAE	20 (20.8)	22 (23.2)	43 (27.7)	53 (35.1)	44 (30.1)	21 (28.8)
Patients with ≥ 1 grade 3 or 4 AE	50 (52.1)	29 (30.5)	73 (47.1)	67 (44.4)	61 (41.8)	18 (24.7)
Patients who discontinued treatment due to AEs	13 (13.5)	8 (8.4)	17 (11.0)	16 (10.6)	12 (8.2)	4 (5.5)
Patients with AEs leading to death	1 (1.0)	6 (6.3)	9 (5.8)	11 (7.3)	6 (4.1)	4 (5.5)
Grade 3 or 4 anemia	40 (41.7)	23 (24.2)	70 (45.2)	29 (19.2)	61 (42)	23 (31)
Grade 3 or 4 thrombocytopenia	11 (11.5)	9 (9.5)	20 (12.9)	2 (1.3)	12 (8)	5 (7)

AE = adverse event; BAT = best available therapy; SAE = serious adverse event.
Source: Sponsor-submitted ITC for JAKi-naive patients with MF.[16]

Identifying all effect modifiers and prognostic factors are essential in unanchored MAIC. However, it is possible that not all important prognostic factors have been identified in this ITC. One expert was consulted by the sponsor for expert opinion during the prognostic factor/effect modifier selection process. Other professionals in this disease area may have different thoughts. According to the clinical experts consulted by CADTH, cytogenetics, fibrosis grade, and blood blast count are also potential prognostic factors that should be considered. In addition, when adjustment was made for ECOG PS or ECOG PS and transfusion dependence for the assessment of SVR, the ESS was notably different in these 2 scenarios and substantially reduced for the latter (91.7 for ECOG PS only and 34.4 for ECOG PS and transfusion dependence). As a result, some patients may be assigned extreme weights which could make the estimates unstable. The approach that the sponsor used does not comply with the recommended approach for identifying prognostic factors as described by the NICE Decision Support Unit Technical Support Document 18 report.[26] Specifically, the sponsor used their data to inform the selection of prognostic factors. The NICE report recommends that variables be identified a priori based on either literature review, expert opinion, or external data sources. In addition, variables should be included regardless of whether a covariate was imbalanced between the study, so their consideration about whether the observed differences were clinically meaningful is not relevant.

The authors provided the results from naive comparison, unadjusted, and adjusted ITCs for the assessments of SVR and TSS reduction. These analyses showed variation in treatment effect estimates (although all between-group differences were statistically significant), depending on the analysis methods or adjustment factors. However, given the limitations of these data (including no effect modifiers identified and not all prognostic factors identified, small sample size, and small evidence base), there is substantial risk of bias in the MAIC results.

Safety data were not included in the ITC analyses. Results of AEs in the 3 studies were descriptively summarized. Therefore, conclusions on the relative safety of fedratinib to BAT in JAKi-experienced population cannot be drawn.

In terms of external validity, fedratinib was compared to BAT in this ITC. However, BAT was not consistent between the PERSIST-2 and SIMPLIFY-2 studies. Other treatments may also be considered a BAT, according to the clinical expert consulted by CADTH, such as antibiologics or transfusion. Therefore, generalizability of the study result to a Canadian population may be limited.

JAKi-Naive Population

In this ITC, studies were identified and selected using a systematic review approach. For example, multiple databases were searched, and 2 independent reviewers performed study selection. Data extraction was conducted by 1 reviewer and checked by a second reviewer. Quality assessment of the included studies were performed using validated instruments.

The ITC authors reviewed the study design, patient population, intervention, comparators, and outcomes measured in the included RCTs to determine the comparability of the studies identified for analyses. An anchored ITC was deemed feasible when there was common comparator included in each study for the respective intervention of interest. Randomization of the RCTs was preserved using this method. Assuming treatment effects within each trial were homogeneous across the variables that differ between trials, ITCs using Bucher method were performed for the outcomes of SVR and TSS reduction at the end of cycle 6, as well as an NMA using a fixed effect model. ITCs were also conducted using MAIC when assuming

treatment effects within each trial were not homogeneous across those variables that differ between trials. Based on the study data presented, the authors provided a rationale to justify the MAIC approach, which is acceptable.

After reviewing the baseline characteristics in the JAKARTA, COMFORT-I, and COMFORT-II studies, imbalances were observed across the included studies for the following baseline characteristics: previous hydroxyurea use, MF subtype, time since MF diagnosis, risk status, JAK2 mutational profile, and spleen length. Results of subgroup analyses by these characteristics in the JAKARTA study suggested that there was consistent benefit in SVR in favour of fedratinib over placebo in these subgroups. In addition, a logistic regression analysis was performed using JAKARTA trial data which included an interaction term of randomized treatment and each baseline characteristic being investigated for treatment effect modification, and a P value of less than 0.1 suggested a potential treatment effect modifier. Based on the results of the above analyses, the ITC authors concluded that JAK2 status and constitutional symptoms were potential treatment effect modifiers for SVR. However, "constitutional symptoms" was not reported in COMFORT-I and COMFORT-II and therefore could not be included in an adjusted analysis. For TSS reduction, no treatment effect modifiers were identified during investigation into treatment effect modifiers. Therefore, JAK2 status was the only treatment effect modifier that was identified in the ITC. It is possible that not all effect modifiers have been identified. According to the clinical experts consulted by CADTH, in addition to JAK2 status, patients with different MF subtypes and risk status may respond differently and therefore may be also considered treatment effect modifiers. Thrombocytopenia is also a potential effect modifier in the anchored ITC for JAKi-naive patient population and should be adjusted for in the analysis.

In COMFORT-I and COMFORT-II, placebo and BAT were comparators for ruxolitinib, and it was assumed that patients responded similarly to both of them. However, there were differences between the placebo arm in the JAKARTA and COMFORT-I studies and the BAT arm in the COMFORT-II study. BAT in the COMFORT-II study included any commercially available agents (as monotherapy or in combination) or no therapy at all and which could be changed during the treatment phase. Significant difference exists between these comparators, therefore patients' response to these treatments tended to be different.

The robustness of the analyses was examined by estimating the ESS. The ESS was similar to the original sample size in the JAKARTA study in different scenarios, suggesting the majority of original sample contributed to adjusted outcomes.

The authors provided the results from naive comparison, ITC using the Bucher method, ITC using frequentist NMA, and adjusted ITC using MAIC (JAK2 status as a treatment effect modifier) for the assessments of SVR and TSS reduction. These analyses showed variation in treatment effect estimates and CIs were wide, although similar trends were observed. Given the limitations of these data (only 1 effect modifier was identified, small sample size, and small evidence base), there is substantial risk of bias in the ITC results.

Safety data were not included in the ITC analyses. Results of AEs in the 3 studies were descriptively summarized. Therefore, conclusions on the relative safety of fedratinib to ruxolitinib in JAKi-naive population cannot be drawn.

Summary

The sponsor submitted 2 indirect treatment analyses to compare fedratinib 400 mg once daily to BAT in patients who had received prior JAKis, and to compare fedratinib 400 mg once daily to ruxolitinib in patients who had not been treated with prior JAKis.

In the ITC for JAKi-experienced patients, individual patient data from the JAKARTA2 trial was used to weight and adjust patients to those included in the comparator trials. MAIC was deemed necessary due to the lack of common comparator among the included trials and the differences across trials in the patient populations enrolled. The comparator trials (PERSIST-2 and SIMPLIFY-2) included patients who were assigned to BAT, pacritinib, or momelotinib. There were differences between trials in the JAK2 mutational profile, prior ruxolitinib treatment, white blood cell count, ECOG PS, DIPSS risk status, and transfusion dependence. ECOG PS and transfusion dependence were identified as prognostic factors for the assessment of spleen volume response at week 24, and ECOG PS and DIPSS risk status were identified as prognostic factors for the assessment of TSS reduction at week 24. Pairwise comparisons between fedratinib and BAT were conducted using MAIC methods. The results of MAIC with adjustment for the identified prognostic factors suggested that treatment with fedratinib 400 mg once daily was associated with a greater proportion of patients achieving a 35% or greater reduction in spleen volume at week 24, compared to BAT. The results also suggested that treatment with fedratinib was associated with greater proportion of patients achieving a 50% or greater reduction in TSS from baseline to week 24, compared to BAT.

In the ITC for JAKi-naive patients, individual patient data from the JAKARTA trial was used to match and adjust patients to those included in the comparator trials. Anchored MAIC was considered feasible, and standard indirect comparisons were also performed for comparison. The comparator trials (COMFORT-I and COMFORT-II) included patients who were assigned to ruxolitinib, BAT, or placebo. There were differences between trials in the previous hydroxyurea use, MF subtype, time since MF diagnosis, risk status, JAK2 mutational profile, and spleen length. JAK2 status was identified as a treatment effect modifier for the assessment of spleen volume response at week 24. No effect modifier was identified for the assessment of TSS. Pairwise comparisons between fedratinib and ruxolitinib were conducted using MAIC methods. The results of MAIC with adjustment for the identified effect modifier suggested that at week 24, treatment with fedratinib 400 mg once daily was associated with slightly greater proportion of patients achieving a 35% or greater reduction in spleen volume as compared to ruxolitinib. The results also suggested that there was no statistically significant difference between fedratinib and ruxolitinib in achieving a 50% or greater reduction in TSS from baseline to week 24.

Although the methods used to conduct the MAIC follow technical guidance, the analyses have a number of limitations that impact the internal and external validity. There are concerns that not all effect modifiers and prognostic factors have been identified and adjusted for in the analyses, and the availability of data to allow for including key variables in the weighting process. The small ESS for JAKi-experienced patients in the assessment of spleen volume response suggests that substantial differences exist between the patient populations in the fedratinib and BAT trials.

Given these issues, there is substantial concern for the risk of bias in the MAIC results.

Other Relevant Evidence

This section includes an additional study (JAKARTA2) included in the sponsor's submission to CADTH that was considered to address important gaps in the evidence included in the systematic review.

Methods

The JAKARTA2 trial (N = 97) was an international, multi-centre, open-label, single-arm, phase II study investigating the efficacy and safety of fedratinib in patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF that were previously treated with ruxolitinib. Patients were resistant or intolerant to ruxolitinib per investigator assessment. The first patient study visit occurred on April 30, 2012, and the last patient study visit occurred on May 7, 2014.

Patients received 400 mg fedratinib orally once daily in repeated 28-day cycles. The trial evaluated patients over 6 cycles (approximately 6 months). If patients did not achieve adequate spleen response (i.e., < 50% reduction in spleen size by palpation) and there was no unacceptable toxicity at the end of cycles 2 and 4, dose escalation was strongly recommended in 100 mg per day increments up to 600 mg per day. Efficacy assessments by MRI or CT scan were performed at the end of cycles 3 and 6. The primary outcome of the JAKARTA2 trial was spleen volume response rate, defined as the proportion of patients that had a 35% or greater reduction in spleen volume at the end of cycle 6 relative to baseline, as measured by MRI or CT scan.

During the JAKARTA2 trial, 4 protocol amendments were implemented. The key changes implemented with each amendment are summarized in Table 34. The JAKARTA2 study was placed on full clinical hold by the FDA on November 15, 2013, due to patients developing WE. As per the final protocol amendment, all patients were required to discontinue fedratinib treatment and the trial was terminated on November 18, 2013. All patients were given the option to receive thiamine supplementation for 90 days or more and followed for safety for 90 days. The final JAKARTA2 study design is depicted in Figure 5.

Populations

The JAKARTA2 study included patients that were resistant or intolerant to prior ruxolitinib treatment. Patients met the following key eligibility criteria: aged 18 years or older; diagnosed with primary, post-PV, or post-ET MF; intermediate-1 (with symptoms), intermediate-2, or high-risk disease; palpable splenomegaly (≥ 5 cm below the left costal margin); ECOG PS score of 2 or less; previously treated with ruxolitinib for at least 14 days; and considered to be resistant or intolerant to ruxolitinib by their treating investigator. Patients were excluded if they had a platelet count of less than 50×10^9/L or absolute neutrophil count of less than 1.0×10^9/L within 14 days before initiating study treatment, splenectomy, or life expectancy of less than 6 months.

Baseline characteristics are summarized in Table 35. The median patient age was 67 years. The majority of patients were male (55%), White (95%), diagnosed with PMF (55%), not dependent on red blood cell transfusions (86%), and reported experiencing constitutional symptoms at the time of enrolment (96%). All patients enrolled in the study had received prior treatment with ruxolitinib. Median duration of ruxolitinib exposure was 10.7 months, with a range of 0.1 to 62.4 months. Overall, 79% of patients had received at least 2 prior anticancer therapies and the most common anticancer therapy besides ruxolitinib was hydroxycarbamide (68%).

Interventions

Patients self-administered 400 mg fedratinib orally per day starting on day 1 of cycle 1. If the patient did not experience a 50% or greater spleen size reduction by palpation compared to baseline, it was strongly recommended in the trial protocol that the dose of fedratinib be titrated upwards in 100 mg per day increments to maximum of 600 mg per day at the end of cycles 2 and 4. Each treatment cycle consisted of 28 days. Patients continued to receive continuous cycles of fedratinib for as long as they experienced clinical benefit. Fedratinib was discontinued if patients experienced progressive disease or unacceptable toxicity.

Chemotherapy (e.g., hydroxyurea), immunomodulatory drug therapy (e.g., interferon-alpha), anagrelide, immunosuppressive therapy, corticosteroids of 10 mg per day or more prednisone

Table 34: Summary of Protocol Amendments Implemented in the JAKARTA2 Study

Protocol amendment	Summary of key changes
Protocol amendment 1 (February 23, 2012)	Added exclusion criteria to exclude patients at risk of liver function test abnormalities Added instructions for dose modifications in the event of liver function test abnormalities Clarified that oral contraceptives and hormonal replacement therapies including estrogen and progesterone should not be used as concomitant medications during study treatment
Protocol amendment 2 (February 29, 2012)	Added instructions for dose modifications in the event of grade 4 ECG abnormalities and ECG evaluations if a grade ≥ 3 ECG abnormality is detected; added instructions on ECG recoding
Protocol amendment 3 (November 28, 2012)	Changed from using IPSS to DIPSS for myelofibrosis high-risk/intermediate classification for inclusion criteria Expanded inclusion criteria to include patients with intermediate-1 risk disease with symptoms Expanded inclusion criteria to include patients that were intolerant or allergic to ruxolitinib after receiving treatment with ruxolitinib for < 14 days Increased study sample size from 41 to 70 patients to increase statistical power for testing response rate beyond a clinically important threshold (10%) and to evaluate subgroups Added an interim analysis and interim report to be completed after approximately 33% of patients were enrolled and completed cycle 3 of fedratinib treatment. Modified the following secondary and exploratory end points: • Spleen response rate (≥ 35% reduction in volume from baseline) by MRI or CT at any time up to cycle 6 was replaced with spleen response rate at end of cycle 3 • Added percent change of spleen volume at end of cycle 3 and 6 by MRI or CT • Added spleen response rate (≥ 25% reduction in volume from baseline) by MRI or CT at end of cycle 3 • Number of cycles that patients had a spleen response by palpation was replaced with the number of cycles that patients had a spleen response by palpation, defined as ≥ 50% reduction in spleen size from baseline
Protocol amendment 4 (November 27, 2013)	All patients were permanently discontinued from further fedratinib treatment because the sponsor terminated the fedratinib development program. Patients were given the option to receive thiamine supplementation for 90 days and to be followed for safety during this period. A DSMB were to meet at least quarterly.

DIPSS = Dynamic International Prognostic Scoring System; DSMB = Data Safety and Monitoring Board; ECG = electrocardiogram; IPSS = International Prognostic Scoring System.

Source: Clinical Study Report for JAKARTA2.[27]

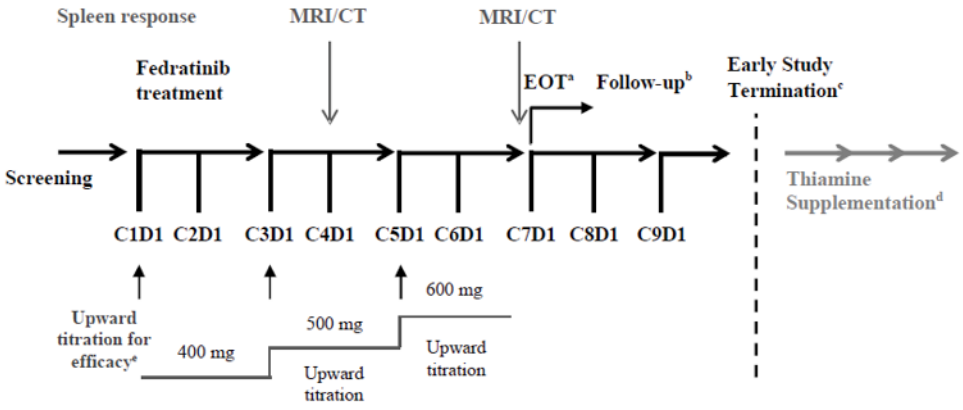
or equivalent, growth factor treatment (e.g., erythropoietin), or hormones were prohibited within 14 days of starting fedratinib treatment. Patients also could not receive concomitant treatment with known moderate or severe inhibitors or inducers of CYP3A4.

Outcomes

The primary outcome of the JAKARTA2 trial was spleen volume response rate, defined as the proportion of patients that had a 35% or greater reduction in spleen volume at the end of cycle 6 relative to baseline, as measured by MRI or CT scan. Secondary end points identified as relevant to this review included spleen volume response rate (≥ 35% reduction) at the end of cycle 3 by MRI or CT, duration of spleen response by MRI or CT, proportion of patients with a 50% or greater reduction in spleen volume by palpation at the end of cycle 6, symptom response rate defined as a 50% or greater reduction in the TSS of the modified MFSAF, and safety and tolerability. HRQoL measured by the European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30, version 3.0) was analyzed as an exploratory end point. Refer to Appendix 4 for a detailed description of the modified MFSAF, TSS, and EORTC QLQ-C30.

Additional exploratory end points were pre-specified in the study protocol but not analyzed due to the early termination of the study and treatment. These end points included OS, complete remission rate, partial remission rate, stable disease rate, progressive disease rate, relapse rate, change in symptoms by the MPN-SAF and BFI.

Figure 5: JAKARTA2 Study Schema



C = cycle; D = day; EOT = end of treatment.

[a] Patients who completed 6 cycles of treatment and did not continue treatment or discontinued the treatment early for any reason underwent an end-of-treatment assessment within a week after their last dose of study drug.

[b] The follow-up visit was conducted 30 days after the last dose of study drug.

[c] The JAKARTA2 trial was terminated on November 18, 2013.

[d] Per the fourth protocol amendment implemented after the clinical hold, all patients permanently discontinued fedratinib treatment and were given the option to receive thiamine supplementation for 90 days or more and were followed for safety for 90 plus or minus 3 days after initiating thiamine supplementation.

[e] Within the first 6 cycles of treatment, upward titration of fedratinib was strongly recommended if the patient's spleen response did not achieve a 50% or greater reduction in spleen size by palpation and there was no unacceptable toxicity.

Source: Clinical Study Report for JAKARTA2.[27]

Table 35: Baseline Characteristics of Patients Enrolled in the JAKARTA2 Study

Characteristic	JAKARTA2 study, N = 97
Age, years	
Mean (SD)	66.5 (8.1)
Median (range)	67.0 (38 to 83)
Sex, n (%)	
Female	44 (45.4)
Male	53 (54.6)
Race	
White	92 (94.8)
Black	1 (1.0)
Asian	4 (4.1)
Disease type, n (%)	
Primary MF	53 (54.6)
Post-PV MF	25 (25.8)
Post-ET MF	19 (19.6)
Risk status, n (%)	
Intermediate-1 with symptoms	16 (16.5)
Intermediate-2	47 (48.5)
High	34 (35.1)
Time since diagnosis of MF, years	
Mean (SD)	6.2 (5.6)
Median (range)	4.1 (0.3 to 24.5)
Resistant or intolerant to ruxolitinib per investigator assessment	
Resistant	64 (66.0)
Intolerant	32 (33.0)
Other: lack of efficacy	1 (1.0)
RBC transfusion dependence status, n (%)	
Yes	14 (14.4)
No	83 (85.6)
JAK2 mutational profile, n (%)	
Wild type	29 (29.9)
Mutant	61 (62.9)
Missing	7 (7.2)

Characteristic	JAKARTA2 study, N = 97
ECOG performance status, n (%)	
0	26 (26.8)
1	45 (46.4)
2	23 (23.7)
Missing	3 (3.1)
Constitutional symptoms,[a] n (%)	
Yes	93 (95.9)
No	4 (4.1)
Spleen volume, mL	
Mean (SD)	3,094.8 (1,458.7)
Median (range)	2,893.5 (737.0 to 7,815.0)
Spleen size below lower costal region, cm	
Mean (SD)	18.1 (7.4)
Median (range)	18.0 (5.0 to 36.0)
Platelet count, n (%)	
50 to < 100 × 10^9/L	33 (34.0)
≥ 100 × 10^9/L	64 (66.0)
Hemoglobin level, n (%)	
< 10 g/dL	51 (52.6)
≥ 10 g/dL	46 (47.4)

ECOG = Eastern Cooperative Oncology Group; ET = essential thrombocytopenia; JAK = Janus kinase; max = maximum; MF = myelofibrosis; min = minimum; PV = polycythemia vera; RBC = red blood cell; SD = standard deviation.

[a]Baseline myeloproliferative neoplasm symptom assessment form score of greater than 0; symptoms include night sweats, itching, abdominal discomfort, abdominal pain, early satiety, or bone pain.

Source: Clinical Study Report for JAKARTA2.[27]

Statistical Analysis

Multiple analysis populations were used in the analysis of the JAKARTA2 study. The ITT population includes all patients that were enrolled in the JAKARTA2 study. The per-protocol population includes all treated patients with a baseline and post-baseline MRI or CT scan of spleen volume. The MFSAF analysis population includes all treated patients with an evaluable baseline and at least 1 post-baseline assessment of the modified MFSAF TSS. The EORTC QLQ-C30 analysis population includes all treated patients with a baseline and least 1 post-baseline assessment of the EORTC QLQ-C30 questionnaire.

In the original statistical analysis plan, the primary efficacy analysis was to be carried out in the per-protocol population, using the last observation carried forward (LOCF) method if data were missing for the primary end point (spleen volume response rate at end of cycle 6) only. No imputation was planned for missing data for other end points. However, the JAKARTA2 study was terminated early after fedratinib development was placed on clinical hold due to patients experiencing WE. As a result, the statistical analysis plan was modified to limit

the analysis of some protocol-pre-specified end points. Additional efficacy analyses were conducted without the LOCF and using the ITT principle.

Subgroup analyses were performed in patients that were resistant versus intolerant to ruxolitinib per investigator assessment as well as the following demographic and prognostic variables: age, race, sex, ECOG PS, type of MF, baseline spleen volume, baseline spleen size, risk category, mutation profile, and baseline hemoglobin count. The subgroup analyses were not pre-specified.

Safety was evaluated in the all-treated population, which included all enrolled patients that took at least 1 dose of study drug.

Results

Patient Disposition

The disposition of patients enrolled in the JAKARTA2 study is summarized in Table 36. A total of 97 patients were enrolled in the JAKARTA2 trial and 100% received fedratinib treatment. All patients (100%) discontinued the study early, with the majority (n = 63 [65%]) due to early study termination. Reasons for discontinuation before study termination included AEs (19%), disease progression (6%), patient decision (3%), poor quality of life (1%), wish to pursue alternative therapies and treatment (2%), lack of clinical benefit (1%), and allogenic stem cell transplant (1%). After the study was terminated, 81 (84%) patients participated in the 90-day thiamine supplementation period.

Table 36: Patient Disposition

Disposition	JAKARTA2 study N (%)
Screened	NR
Enrolled	97
Treated	97 (100)
Completed study	0 (0)
Discontinued study	97 (100)
Adverse event	18 (19)
Disease progression	6 (6)
Study terminated by sponsor	63 (65)
Other	10 (10)
Per-protocol population	83 (86)
MFSAF analysis population	90 (93)
EORTC QLQ-C30 analysis population	90 (93)
Thiamine supplementation follow-up population	81 (84)

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; MFSAF = Myelofibrosis Symptom Assessment Form; NR = not reported.

Source: Clinical Study Report for JAKARTA2.[27]

Exposure to Study Treatments

All patients (N = 97) enrolled in the JAKARTA2 trial received at least 1 dose of the study treatment and 95% patients received 80% or more of the intended dose. The median number of fedratinib cycles received at the time of study termination was 6 (range, 1 to 20). Overall, 18% of patients received 0 to 3 cycles, 33% received 3 to 6 cycles, 26% received 6 to 9 cycles, 9% received 9 to 12 cycles, and 14% received more than 12 cycles. The median duration of exposure was 24.4 weeks (range, 0.7 to 79.4 weeks). The maximum daily dose received was 400 mg in 64 (66%) patients, 500 mg in 17 (18%) of patients, and 600 mg in 15 (16%) patients. One patient received an accidental overdose of 800 mg instead of 400 mg on day 8 of cycle 4. The mean cumulative dose was 77,915.5 mg (SD, 56,648.3 mg)

Overall, 38 (39%) patients had a dose reduction due to toxicity. Twenty-one (22%) patients had a 1-level dose reduction; 13 (13%) had a 2-level dose reduction. Twenty-five (26%) patients had a dose interruption for 7 or more consecutive days.

Efficacy

Spleen Response

Spleen response in the primary analysis population (per protocol with LOCF) and supportive ITT population are summarized in Table 37. Results from the ITT population are presented in addition to the primary analysis results because the sponsor identified this analysis as a potentially more objective and conservative evaluation of fedratinib. The primary outcome of the study was spleen volume response rate (≥ 35% reduction) at the end of cycle 6. In the JAKARTA2 study, 48% (95% CI, 37% to 59%) of patients in the primary analysis population with LOCF exhibited a 35% or greater reduction in spleen volume at end of cycle 6. In the ITT population without LOCF, 31% (95% CI, 22% to 41%) of patients exhibited a 35% or greater reduction in spleen volume at end of cycle 6. The waterfall plot of percent change in spleen volume from baseline to the end of cycle 6 of fedratinib treatment in the per-protocol population is depicted in Figure 6.

When measuring spleen response by palpation, 31% of patients in the per-protocol population exhibited a 50% or greater reduction in size at the end of cycle 6. At the end of cycle 3, 47% of patients in the per-protocol population showed a 35% or greater reduction in spleen volume by MRI or CT and 34% exhibited a 50% or greater reduction in size by palpation. The median duration of spleen response, defined as the time from first date of spleen response (i.e., ≥ 35% SVR from baseline) until disease progression (i.e., ≥ 25% spleen volume increase from baseline) or death, was not reached. The Kaplan-Meier curve of duration of spleen response is depicted in Figure 7.

Subgroup analyses were performed for the primary end point by type of MF, risk status, and JAK mutation status. The proportion of patients exhibiting a 35% or greater SVR at the end of cycle 6 in the subgroups of the primary analysis population (per protocol with LOCF) are summarized in Table 38.

Symptoms

Symptom response rate (i.e., proportion of patients with ≥ 50% reduction in the TSS of the modified MFSAF) at end of cycle 3 was 31% (95% CI, 22% to 42%) in the MFSAF analysis population. Symptom response rate at the end of cycle 6 was 27% (95% CI, 18% to 37%) in the MFSAF analysis population. Of the 51 patients with an evaluable modified MFSAF TSS assessment at the end of cycle 6, the median percent change was −44.3%. Furthermore, 82%

(N = 42 of 51) of the patients had a decrease in modified MFSAF TSS at the end of cycle 6, as depicted in Figure 8.

Health-Related Quality of Life

Completion rates of the questionnaire ranged from 76% to 96% over the 6 treatment cycles. The mean change from baseline to end of cycle 6 in EORTC QLQ-C30 functional scores and EORTC QLQ-C30 symptom scores are summarized in Table 40. Over the 6 treatment cycles, there was a mean increase in all EORTC QLQ-C30 functional scales. Mean symptom scores decreased for fatigue, pain, dyspnea, insomnia, appetite loss, and financial difficulties. Mean symptom scores increased for nausea and vomiting, diarrhea, and constipation.

Table 37: Spleen Response Outcomes in the JAKARTA2 Study: Per-Protocol (Primary Analysis) Population and ITT Population

Outcome	Per-protocol population (N = 83) with LOCF	ITT population (N = 97) without LOCF
Spleen volume measured by MRI or CT scan		
Spleen volume response rate (≥ 35% reduction) at end of cycle 6		
n (%)	40 (48.2)	30 (30.9)
95% CI	37.1 to 59.4	21.9 to 41.1
% change in spleen volume at end of cycle 6		
n	82	51
Median (95% CI)	−34.0 (−36.0 to −24.8)	−38.0 (−41.9 to −26.9)
Spleen volume response rate (≥ 35% reduction) at end of cycle 3		
n (%)	39 (47.0)	39 (40.2)
95% CI	35.9 to 58.3	30.4 to 50.7
Duration of spleen response (≥ 35% reduction any time on treatment)		
Patients assessed, n	NR	47
Events, n (%)	NR	2 (4.3)
Months, median (95% CI)	NR	Not reached (7.2 to not reached)
Spleen size measured by palpation		
Spleen response rate (≥ 50% reduction) at end of cycle 6		
n (%)	NR	30 (30.9)
95% CI	NR	21.9 to 41.1
Spleen response rate (≥ 50% reduction) at end of cycle 3		
n (%)	NR	33 (34.0)
95% CI	NR	24.7 to 44.3

CI = confidence interval; ITT = intention to treat; LOCF = last observation carried forward; NR = not reported.
Source: Clinical Study Report for JAKARTA2.[27]

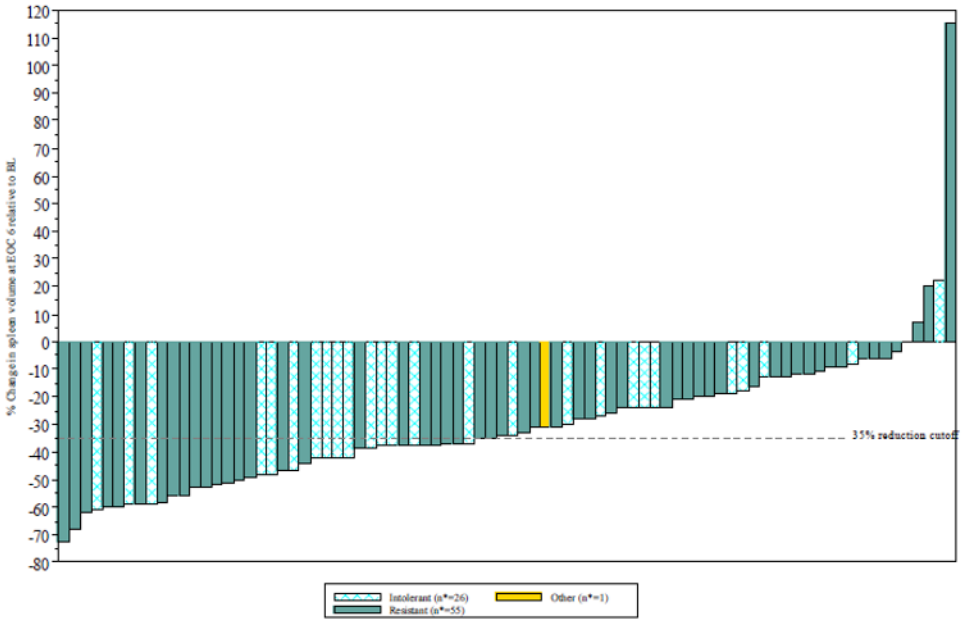
Harms

Harms outcomes in the JAKARTA2 study are summarized in Table 41. All patients enrolled in the JAKARTA2 study experienced a TEAE and 63% (n = 61) of patients had a grade 3 or 4 TEAE. Eighteen (19%) patients withdrew from the study due to AEs. The most common AEs of any grade were diarrhea (62%), nausea (56%), anemia (49%), vomiting (41%), thrombocytopenia (27%), constipation (21%), pruritis (18%), and fatigue (16%). Nineteen (20%) patients experienced an AE that led to permanent fedratinib treatment discontinuation. AEs that led to treatment discontinuation included encephalopathy (n = 1), increased blood creatinine (n = 1), increased gamma-glutamyl transferase (n = 1), decreased platelet count (n = 1), decreased weight (n = 1), gastrointestinal disorders (n = 3), anemia (n = 1), and thrombocytopenia (n = 1).

Regarding notable harms identified in the CADTH review protocol, 38% of patients experienced grade 3 or 4 anemia, and 22% of patients experienced grade 3 or 4 thrombocytopenia in the all-treated population. No cases of grade 3 or 4 neutropenia were reported. One (1%) patient experienced transformation to AML and 2 (2%) patients became transfusion dependent. Three (3.1%) patients experienced a grade 3 or 4 elevated liver enzyme (alanine aminotransferase). One (1%) patient experienced encephalopathy.

During the JAKARTA2 study, 34% (n = 33) of patients experienced a SAE. The most frequent SAEs were infections (8%); respiratory, thoracic, and mediastinal disorders (7%); and injury,

Figure 6: Waterfall Plot of the Percent Change in Spleen Volume at the End of Cycle 6 Relative to Baseline in the JAKARTA2 Study — Per-Protocol Population With LOCF



BL = baseline; EOC = end of cycle; LOCF = last observation carried forward.

Note: Spleen volume was measured by MRI or CT scan. Blinded review occurred via a central imaging laboratory. The LOCF method imputed the missing spleen volume measurement at end of cycle 6 with the spleen volume measurement at end of cycle 3, except for subjects who discontinued before end of cycle 6 due to disease progression.

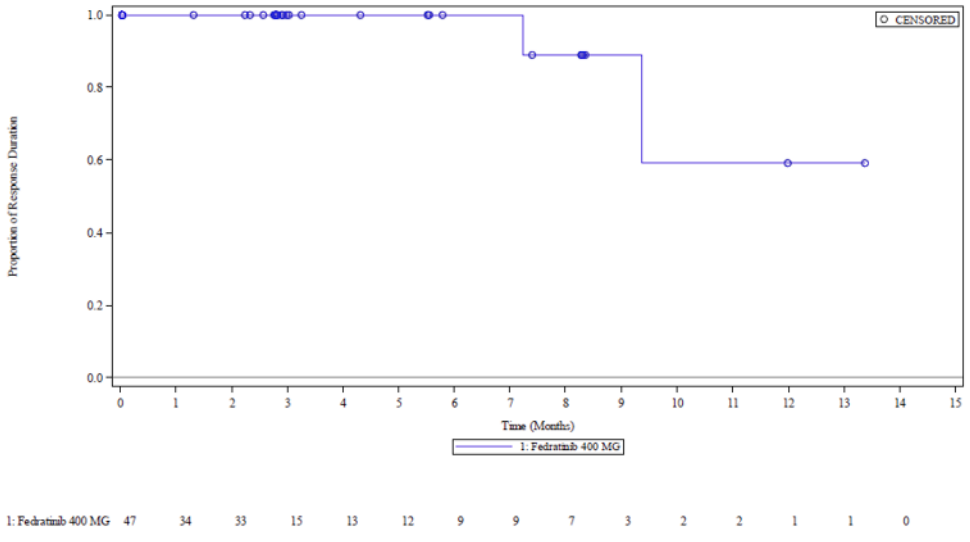
Source: Clinical Study Report for JAKARTA2.[27]

Table 38: Subgroup Analyses of Spleen Volume Response Rate (≥ 35% Reduction) at the End of Cycle 6 in the JAKARTA2 Study — Per-Protocol Population With LOCF

Subgroup	Per-Protocol Population with LOCF, N = 83		
	N	Responders, n (%)	95% CI
Disease subtype			
Primary MF	43	20 (46.5)	31.2 to 62.3
Post-PV MF	24	13 (54.2)	32.8 to 74.4
Post-ET MF	16	7 (43.8)	19.8 to 70.1
Baseline risk status			
Intermediate-1 with symptoms	13	8 (61.5)	31.6 to 86.1
Intermediate-2	44	21 (47.7)	32.5 to 63.3
High	26	11 (42.3)	23.4 to 63.1
JAK mutation status			
Mutant	53	29 (54.7)	40.4 to 68.4
Wild type	25	8 (32.0)	14.9 to 53.5
Missing	5	3 (60.0)	14.7 to 94.7

CI = confidence interval; ET = essential thrombocythemia; JAK = Janus kinase; LOCF = last observation carried forward; MF = myelofibrosis; PV = polycythemia.
Source: Clinical Study Report for JAKARTA2.[27]

Figure 7: Kaplan-Meier Plot of Duration of Spleen Response (≥ 35% Volume Reduction at Any Time on Treatment) in the JAKARTA2 Study — ITT Population



ITT = intention to treat.
Note: Horizontal axis shows patients at risk.
Source: Clinical Study Report for JAKARTA2.[27]

poisoning, and procedural complications (4%). Seven (7%) patients had a TEAE that led to death. Four of these deaths were due to disease progression and the 3 others were due to pneumonia, cardiorespiratory arrest, and shock.

Overall, 7 (7%) patients died during the on-treatment phase of the study, 11 (11%) patients died in the post-treatment phase, and 5 (5%) patients died during the thiamine supplementation follow-up phase.

Critical Appraisal

Internal Validity

The primary limitations of the JAKARTA2 trial were the open-label administration of fedratinib, absence of a comparator group, small sample size, and early termination.

Due to the open-label design, the study investigators and patients were aware of the treatment status. Open-label administration of fedratinib may have biased the reporting of

Table 39: Modified MFSAF Symptom Scores and Percent Change From Baseline to End of Cycle 6 in the JAKARTA2 Study — MFSAF Analysis Population

MFSAF symptom	MFSAF analysis population, N = 90		
	Baseline	End of cycle 6	
	Observed	Observed	% change from baseline
Night sweats			
n	90	51	42
Mean (SD)	3.44 (2.57)	1.45 (1.92)	−54.10 (67.52)
Pruritis			
n	90	51	35
Mean (SD)	2.27 (2.52)	1.44 (2.00)	−36.09 (101.06)
Abdominal discomfort			
n	90	51	48
Mean (SD)	4.07 (2.75)	2.38 (2.25)	−14.53 (136.82)
Early satiety			
n	90	51	46
Mean (SD)	4.43 (2.55)	2.42 (2.18)	−7.94 (276.16)
Pain under ribs on left side			
n	90	51	41
Mean (SD)	2.86 (2.69)	1.24 (1.61)	−44.95 (116.24)
Bone or muscle pain			
n	90	51	45
Mean (SD)	3.59 (2.79)	2.88 (2.40)	34.22 (256.82)

MFSAF = Myelofibrosis Symptom Assessment Form; SD = standard deviation.

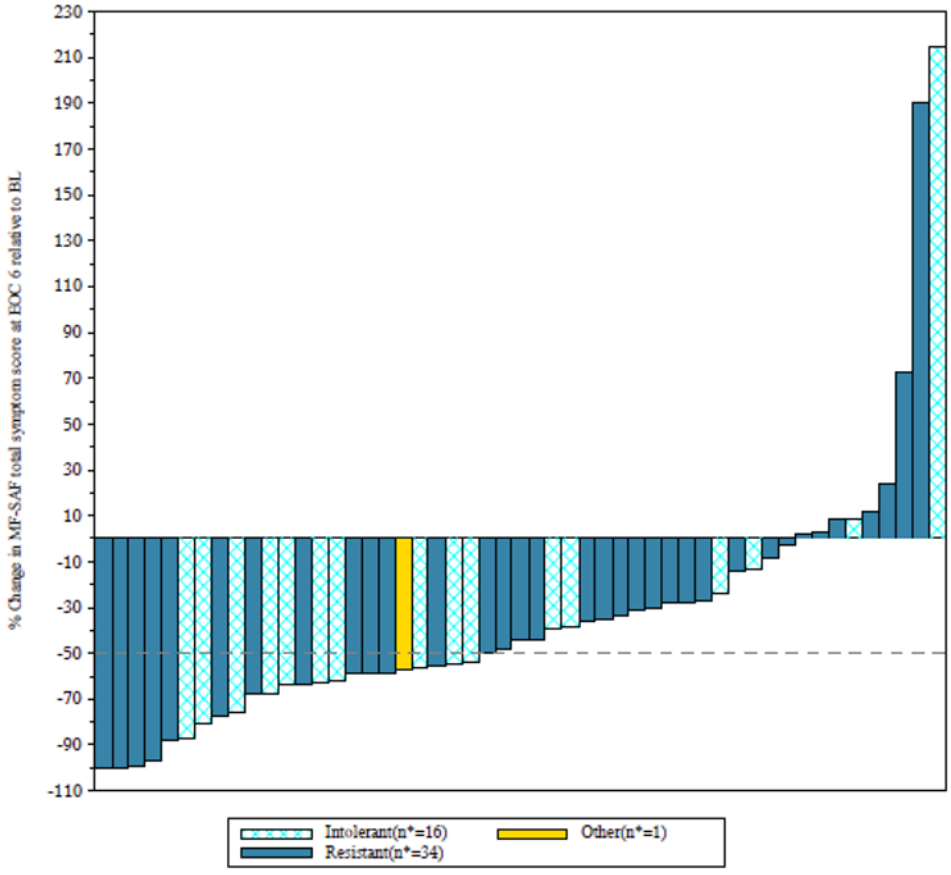
Source: Clinical Study Report for JAKARTA2.[27]

end points, especially for patient-reported outcomes such as MF symptoms measured by the modified MFSAF TSS and HRQoL measured by the EORTC QLQ-C30.

Since the JAKARTA2 study had no active treatment or placebo control groups, it is difficult to make a conclusion on the efficacy of fedratinib based on the data obtained from this study. Although results suggest that fedratinib treatment may be associated with SVRs, no conclusions can be made regarding the efficacy of fedratinib relative to currently used treatment options for patients with MF who are resistant or intolerant to ruxolitinib.

The JAKARTA2 study was a phase II trial that enrolled a total of 97 patients. Furthermore, the number of available patients providing data collected at the end of cycle 6 was low. Due to the small sample size, the results of the JAKARTA2 study must be interpreted with caution. Lastly, due to the early termination of the study, multiple protocol-pre-specified end points were not analyzed, and the median duration of response was not reached.

Figure 8: Waterfall Plot of the Percent Change in Modified MFSAF TSS From Baseline to End of Cycle 6 in the JAKARTA2 Study — MFSAF Analysis Population



BL = baseline; EOC = end of cycle; MFSAF = Myelofibrosis Symptom Assessment Form; TSS = Total Symptom Score.
Source: Clinical Study Report for JAKARTA2.[27]

Importantly, OS could not be analyzed because the pre-specified number of events was not reached before the study was terminated. As a result, no conclusions can be made regarding the effect of fedratinib treatment on survival.

External Validity

The majority of patients in the JAKARTA2 study were men, White, diagnosed with PMF, and had a median age of 67 years. The trial enrolled patients with intermediate-1 with symptoms, intermediate-2, and high-risk disease. The clinical experts consulted by CADTH indicated that the study population is representative of Canadian patients with MF.

The diagnostic and disease risk criteria used in the trial reflect Canadian practice and were considered appropriate by the clinical experts consulted by CADTH.

The JAKARTA2 trial enrolled patients that were resistant or intolerant to ruxolitinib treatment, which currently is the standard first-line treatment for MF patients in Canada. The JAKARTA2 study addresses an evidence gap since the JAKARTA study restricted enrolment to patients that had not been previously treated with ruxolitinib and the clinical experts consulted by CADTH indicated that fedratinib may be used as a second-line treatment after ruxolitinib in Canadian clinical practice.

Table 40: Mean Change from Baseline in EORTC QLQ-C30 Functional and Symptom Scores in the JAKARTA2 Study — EORTC QLQ-C30 Analysis Population

EORTC QLQ-C30 items	EORTC QLQ-C30 analysis population, N = 74
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire; [redacted]
Source: Clinical Study Report for JAKARTA2.[27]

Table 41: Treatment-Emergent Adverse Events Occurring in 10% or More of Patients in the JAKARTA2 Study — All-Treated Population

Adverse event	All-treated population, N = 97
Patients with ≥ 1 AE	
n (%)	97 (100.0)
Gastrointestinal disorders	81 (83.5)
Blood and lymphatic system disorders	58 (59.8)
Infections	51 (52.6)
General disorders	46 (47.4)
Nervous system disorders	35 (36.1)
Respiratory, thoracic, and mediastinal disorders	34 (35.1)
Skin and subcutaneous tissue disorders	33 (34.0)
Patients with ≥ 1 SAE	
n (%)	33 (34.0)
Infections	8 (8.2)
Respiratory, thoracic, and mediastinal disorders	7 (7.2)
Cardiac disorders	6 (6.2)
Blood and lymphatic system disorders	4 (4.1)
Injury, poisoning, and procedural complications	4 (4.1)
Gastrointestinal disorders	3 (3.1)
General disorders	3 (3.1)
Neoplasms	3 (3.1)
Metabolism and nutrition disorders	3 (3.1)
Nervous system disorders	2 (2.1)
Vascular disorders	2 (2.1)
WDAEs	
n (%)	18 (18.6)
Patients who permanently stopped treatment due to AEs	
n (%)	19 (19.6)
Gastrointestinal disorders	4 (4.1)
Investigations	4 (4.1)
Blood and lymphatic system disorders	3 (3.1)
Cardiac disorders	2 (2.1)
Deaths	
n (%)	7 (7.2)

Adverse event	All-treated population, N = 97
Progressive disease	4 (4.1)
Adverse event	3 (3.1)
Notable harms, n (%)	
Grade 3 or 4 anemia	37 (38.1)
Grade 3 or 4 thrombocytopenia	21 (21.6)
Grade 3 or 4 neutropenia	NR
Neoplasms	3 (3.1)
Transfusion dependency	2 (2.1)
Hypersensitivity reaction	NR
Grade 3 or 4 elevated ALT	3 (3.1)
Potential WE	1 (1.0)

AE = adverse event; ALT = alanine aminotransferase; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event; WE = Wernicke encephalopathy.

Source: Clinical Study Report for JAKARTA2.[27]

The dose of fedratinib used in the JAKARTA2 study is not entirely representative of the Health Canada recommended dose of 400 mg per day. Per the study protocol, if a patient did not experience adequate spleen response at the 400 mg dose, it was strongly recommended that the dose be titrated upwards to a maximum of 600 mg per day. The clinical experts consulted by CADTH indicated that clinicians likely would not prescribe fedratinib at a dose of greater than 400 mg per day in Canadian practice. As a result, 34% of patients received a fedratinib dose greater than 400 mg per day. The higher dosage used in the JAKARTA2 study may have resulted in a greater frequency of AEs and SAEs.

Discussion

Summary of Available Evidence

One double-blind, placebo-controlled, phase III RCT (JAKARTA, N = 289) was included in this systematic review. The objective of the JAKARTA study was to evaluate the efficacy and safety of fedratinib in patients with primary or secondary (post-PV and post-ET) MF. The trial included adult patients (≥ 18 years of age) with intermediate-2 or high-risk PMF, post-PV MF, and post-ET MF. The study participants did not receive prior JAK2 inhibitors. Eligible patients were randomized to receive fedratinib 400 mg, fedratinib 500 mg, or placebo once daily for consecutive 6 cycles of treatment. During the treatment period, patients continued to receive their assigned treatment until disease progression or occurrence of intolerable AEs related to the treatment. Patients originally assigned to placebo were allowed to cross over to fedratinib therapy after week 24, or before if the patient experienced progressive disease. The primary end point was the proportion of patients with at least a 35% reduction in spleen volume (measured by MRI or CT) from baseline to week 24 and confirmed 4 weeks later. Other efficacy outcomes include proportion of patients with at least 35% reduction in spleen volume

without week 4 confirmation, at least 50% reduction in disease-related symptom scores and HRQoL. Harm outcomes associated with the use of fedratinib were also examined.

The major limitations of the JAKARTA trial include the potential biases on the study results due to the imbalanced patients' baseline characteristics and high discontinuation rates. The reasons for discontinuation differed between the treatment groups: the primary reason of treatment discontinuation in the fedratinib arm was due to AEs, whereas lack of efficacy was the primary reason in the placebo group. The potential impact of substantial and disproportional missing data may bias some of the efficacy outcome measurements. The study was terminated early due to higher rates of WE in the fedratinib groups.

Interpretation of Results

Efficacy

Survival (OS and PFS) was identified as an important outcome in the CADTH review protocol, and OS and PFS were planned secondary end points in the JAKARTA study; however, they were not able to be evaluated due to early termination of the study.

In the JAKARTA study, a greater proportion of patients in the fedratinib 400 mg group (36.5%) achieved spleen response (≥ 35% reduction in spleen volume at week 24 and confirmed 4 weeks later), compared with those in the placebo group (1%), which was a statistically significant difference in favour of fedratinib 400 mg (between-group difference, 35.42%; 97.5% CI, 24.2 to 46.7; P < 0.0001). Similar results were observed for other outcomes measuring spleen response, such as ≥ 25% reduction in spleen volume at week 24 and confirmed 4 weeks later and percentage of change in spleen volume from baseline to week 24. According to the clinical experts consulted by CADTH, the benefit gained in spleen response are clinically meaningful.

Treatment with fedratinib was also associated with statistically significantly greater relief in disease-related symptoms, which was measured by TSS from disease-specific assessment form. At the end of cycle 6, the proportion of patients who had a 50% or greater reduction in the TSS from baseline to the EOC6 was 39.6% in the fedratinib 400 mg arm and 8.2% in the placebo arm (mean difference, 31.33%; P < 0.0001). The clinical experts agreed that the between-group differences are clinically meaningful. Another instrument, MPN-SAF score, was an exploratory outcome in the JAKARTA study. No formal statistical comparison was conducted between treatment groups.

HRQoL assessment was an exploratory outcome in the JAKARTA study. It was evaluated using EQ-5D. A formal statistical comparison was not performed for this outcome, either the utility index or the VAS scores, therefore the potential impact of fedratinib on HRQoL remains unknown. EQ-5D is a generic quality of life assessment tool. Even though it has been widely used in many disease areas, it has not been validated in patients diagnosed with MF. Overall, the potential benefit of fedratinib on HRQoL remains unknown.

Investigator-rated response (using modified IWG-MRT criteria) and duration of spleen response were exploratory outcome measures in the JAKARTA study; therefore, no statistical testing was conducted. Although the evidence may suggest that patients treated with fedratinib showed a higher rate of investigator-rated clinical improvement compared to patients in the placebo group, no inferences can be made in the absence of statistical testing. The median duration of spleen response in the fedratinib 400 mg arm was 18.2 months. The duration in the placebo group was not available at the time of this review.

Two patients in placebo group had transformation to AML; no such patients were identified in the fedratinib 400 mg group.

A key gap in the evidence provided by the JAKARTA study is that no patients included in the study had previous experience with ruxolitinib. The clinical experts consulted by CADTH anticipated that in addition to first-line therapy, fedratinib may be used as a second-line treatment after ruxolitinib failure. A phase II, single-arm study (JAKARTA2, N = 97) provided evidence on the treatment with fedratinib in patients who were resistant or intolerant to ruxolitinib treatment. Spleen response and symptom response were assessed. Result suggested that after 6 cycles of treatment with fedratinib, spleen response, and symptom response to the treatment were observed. The primary limitations of the JAKARTA2 trial were the open-label administration of fedratinib, absence of a comparator group, small sample size, and early termination. Due to the early termination of the study, multiple protocol-pre-specified end points were not analyzed, and the median duration of response was not reached. Importantly, OS could not be analyzed because the pre-specified number of events was not reached before the study was terminated. As a result, no conclusions can be made regarding the effect of fedratinib treatment on survival.

There was no direct evidence available to explore the relative efficacy and safety of fedratinib to current standard of care for patients with MF. The sponsor submitted 2 ITCs to compare fedratinib 400 mg once daily to BAT in patients who had received prior JAKis, and to compare fedratinib 400 mg once daily to ruxolitinib in patients who had not been treated with prior JAKis. The ITC results suggested that in JAKi-experienced population, treatment with fedratinib 400 mg once daily was associated with greater proportion of patients achieving a 35% or greater reduction in spleen volume and a 50% or greater reduction in TSS from baseline to week 24, compared to BAT. In the JAKi-naive population, no differences were detected between fedratinib and BAT for the outcomes of SVR and symptom response. However, due to the limitations of these 2 ITCs (e.g., not all effect modifiers and prognostic factors can be identified) there is substantial uncertainty in the ITC results.

Harms

During the 6 cycles treatment period, almost all patients reported AEs in the JAKARTA study, including 99% in the fedratinib group and 93.7% in the placebo group. The common AEs reported in the fedratinib group were gastrointestinal disorders such as diarrhea and nausea. The incidence of SAE was similar between fedratinib 400 mg (20.8%) and placebo (23.2%). In the fedratinib 400 mg group, cardiac failure in 5 patients and anemia in 2 patients were considered SAEs. More patients in the fedratinib group withdrew from the treatment due to AEs (13.5% in the fedratinib group versus 8.4% in the placebo group). More patients in the placebo group (12.6%) died than in the fedratinib group (7.3%) and the main reason was disease progression. In the fedratinib group, the primary cause of death was AE in 1 patient (cardiogenic shock) and progressive disease in 4 patients. Fedratinib was also found to be related to higher risk of WE and grade 3 or 4 anemia compared to placebo.

Conclusions

One phase III, double-blind, placebo-controlled, RCT (JAKARTA) provided evidence supporting the efficacy and safety of fedratinib in adult patients with intermediate-2 risk or high-risk MF. Compared to placebo, patients who were treated with fedratinib 400 mg once daily showed

benefits in SVR and MF-related symptom relief from baseline to the end of cycle 6. Changes in the spleen response and symptom response were considered statistically and clinically relevant. However, whether treatment with fedratinib is associated with any survival benefit is unknown, and the effect on HRQoL remains uncertain. Almost all study participants reported TEAEs. Fedratinib was related to more treatment discontinuation due to AEs, and higher frequency of cytopenia and potential WE. The JAKARTA study did not provide direct evidence on the relative efficacy and safety of fedratinib versus current standard of care (other JAKis) for patients with MF, or evidence for patients who received previous JAKi treatment.

JAKARTA2 was a phase II, single-arm, open-label study involving ruxolitinib-experienced patients with intermediate- to high-risk MF. The results supported the beneficial effect of fedratinib on reduction in spleen volume and symptom relief. However, limitations of this study, such as small sample size, lack of comparator group, and short study duration contribute uncertainty to the results.

Results from 2 indirect treatment analyses suggested that treatment with fedratinib is associated with higher spleen response rate and higher symptom response rate in a JAKi-experienced patient population, compared to BAT; however, the relative efficacy of fedratinib versus ruxolitinib was not significant in the JAKi-naive patient population. Results of both ITCs are associated with substantial risk of bias.

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Appendix 1: Literature Search Strategy

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: November 25, 2020

Alerts: Weekly search updates until project completion

Study types: No filters were applied to limit retrieval by study type

Limits

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 42: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for 1 character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.ot	Original title
.nm	Name of substance word
.rn	Registry number

Syntax	Description
.dq	Candidate term word (Embase)
.pt	Publication type
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

Search strategy:

1. (Inrebic* or fedratinib* or TG-101348 or TG101348 or SAR-302503 or SAR302503 or SAR-302503A or SAR302503A or 6L1XP550I6 or UH9J2HBQWJ).ti,ab,kf,ot,hw,nm,rn.
2. use medall
3. *Fedratinib/ or (Inrebic* or fedratinib* or TG-101348 or TG101348 or SAR-302503 or SAR302503 or SAR-302503A or SAR302503A).ti,ab,kw,dq.
4. 3 use oemezd
5. 4 not (conference review or conference abstract).pt.
6. 2 or 5
7. remove duplicates from 6

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

Search terms: Inrebic/fedratinib, myelofibrosis

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

Search terms: Inrebic/fedratinib, myelofibrosis

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

Search terms: Inrebic/fedratinib, myelofibrosis

EU Clinical Trials

Register European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms: Inrebic/fedratinib, myelofibrosis

Canadian Cancer Trials

Produced by the Canadian Partnership Against Cancer Corporation. Targeted search used to capture registered clinical trials.

Search terms: Inrebic/fedratinib, myelofibrosis

Grey Literature

Search dates: November 20 to 30, 2020

Keywords: Inrebic/fedratinib, myelofibrosis

Limits: Publication years: none

Updated: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 2: Detailed Outcome Data

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Subgroup analyses on the primary outcome (≥ 35% reduction in spleen response rate at end of cycle 6 with confirmation 4 weeks later), based on type of MF, MF risk status, and mutational profile, suggested a consistent benefit in spleen response rate in favour of fedratinib 400 mg over placebo for each of the evaluated subgroups of the ITT Population, for spleen response rate confirmed 4 weeks later, especially for "risk status" and "MF types."

Table 43: Spleen Response — Subgroup Analyses (ITT population)

Subgroups	JAKARTA	
	Fedratinib 400 mg (N = 96)	Placebo (N = 96)
Type of MF		
PMF		
N	62	58
n (%), 95% CI	21 (33.9) 22.1 to 45.7	1 (1.7) 0 to 5.1
Difference (95% CI)	32.15 (19.9 to 44.4)	
P value	< 0.0001	
Post-PV MF		
N	24	27
n (%), 95% CI	9 (37.5) 18.1 to 56.9	0
Difference (95% CI)	37.5 (18.1 to 56.9)	
P value	0.0005	
Post-ET MF		
N	10	11
n (%), 95% CI	5 (50) 19.0 to 81.0	0
Difference (95% CI)	50.00 (19.0 to 81.0)	
P value	0.0072	
Risk status		
Intermediate-2 risk		
N	57	46
n (%), 95% CI	23 (40.4) 27.6 to 53.1	1 (2.2) 0 to 6.4
Difference (95% CI)	38.18 (24.8 to 51.6)	

Subgroups	JAKARTA	
	Fedratinib 400 mg (N = 96)	Placebo (N = 96)
P value	< 0.0001	
High risk		
N	39	50
n (%), 95% CI	12 (30.8) 16.3 to 45.3	0
Difference (95% CI)	30.77 (16.3 to 45.3)	
P value	< 0.0001	
Mutational profile		
Mutant		
N	62	59
n (%), 95% CI	25 (40.3) 28.1 to 52.5	0
Difference (95% CI)	40.32 (28.1 to 52.5)	
P value	< 0.0001	
Wild type		
N	30	32
n (%), 95% CI	9 (30.0) 13.6 to 46.4	1 (3.1) 0 to 9.2
Difference (95% CI)	26.88 (9.4 to 44.3)	
P value	0.0040	

CI = clinical improvement; MF = myelofibrosis; PMF = primary myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis.

Source: Clinical Study Report for JAKARTA.[14]

Appendix 3: Description and Appraisal of Outcome Measures

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Modified MFSAF diary and its TSS
- Myeloproliferative neoplasm symptom assessment form (MPN-SAF)
- EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L)
- European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30)

Findings

Table 44: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Modified MFSAF and its TSS	The modified MFSAF is a myelofibrosis-specific, patient-reported measure of HRQoL. Six myelofibrosis symptoms (night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain) are rated at their worst moment during the previous 24 hours. Each symptom is measured on a scale from 0 (absent) to 10 (worst imaginable). The TSS is the sum of the scores for each symptom.	**Validity** Validity of the modified MFSAF and its TSS was examined in patients with myelofibrosis and received treatment of ruxolitinib or placebo. It was found to correlate well with PGIC and the EORTC QLQ-C30. **Reliability** ICCs were 0.98 for patients treated with ruxolitinib and 0.97 for those treated with placebo.	MID ranged from 3.8 to 5.7 using different methods.

Outcome measure	Type	Conclusions about measurement properties	MID
MPN-SAF	The MPN-SAF is a myelofibrosis-specific, patient-reported measure of HRQoL. The MPN-SAF assesses the presence and severity of 17 myelofibrosis symptoms: early satiety, abdominal pain, abdominal discomfort, inactivity, headaches, concentration, dizziness/ vertigo/ light-headedness, numbness/ tingling in hands and feet, difficulty sleeping, depression or sad mood, sexual desire or function, cough, night sweats, pruritis, bone pain, fever, and unintentional weight loss) during the prior week on a scale from 0 (absent) to 10 (worst imaginable). The MPN-SAF also includes fatigue assessment via the BFI and overall QoL.	**Validity** Validity was assessed in a single study, which showed strong correlation (Pearson correlation > 0.50, P < 0.001) of multiple MPN-SAF items (overall QoL, fatigue, early satiety, abdominal pain, abdominal discomfort, inactivity, headache, concentration, dizziness, numbness, insomnia, sad mood, sexuality, night sweats, pruritus, bone pain) with relevant EORTC QLQ-C30 function and symptom scales (pain, fatigue, appetite/early satiety, insomnia, global health status/QoL). **Reliability** Reliability was evaluated in a single study via test-retest assessment. ICCs indicated that the items fatigue, inactivity, insomnia, and night sweats were highly reproducible on serial survey administration. The items with the lowest reproducibility were fever, cough, and weight loss. **Responsiveness** No information found.	Not identified.
EQ-5D-3L	The EQ-5D-3L is a generic, preference-based, HRQoL measure consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels representing no problems (1), some problems (2), and extreme problems (3).	The EQ-5D-3L questionnaire was not validated in the patient population/ indication.	Not identified in the patient population of interest.

Outcome measure	Type	Conclusions about measurement properties	MID
EORTC QLQ-C30	The EORTC QLQ-C30 is a generic cancer measure of HRQoL. The instrument consists of 30 questions across 6 functioning scales (physical, role, cognitive, emotional, social, and global QoL) and 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact).	**Validity** Comparison of the EORTC QLQ-C30 to 2 myelofibrosis-specific HRQoL instruments indicate that the QLQ-C30 captures functioning and generic cancer symptoms (pain and fatigue). The instrument does not capture MF-specific symptoms (e.g., pruritis and night sweats). Dimensions such as constipation and diarrhea may be less relevant in myelofibrosis patients. **Reliability** No information found. **Responsiveness** No information found.	Not identified in the patient population of interest.

BFI = Brief Fatigue Inventory; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; HRQoL = health-related quality of life; ICC = intraclass coefficient; MID = minimal important difference; MFSAF = Myelofibrosis Symptom Assessment Form; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; PGIC = Patient Global Impression of Change Scale; QoL = quality of life; TSS = total symptom score.

Modified Myelofibrosis Symptom Assessment Form and Total Symptom Score

The MFSAF is a MF-specific, patient-reported measure of HRQoL.[28,29] The MFSAF is a 20-item instrument that assesses fatigue, early satiety, abdominal pain or discomfort, inactivity, cough, night sweats, pruritis, bone pain, fever, unintentional weight loss, and overall quality of life (QoL). Each item is measured on a scale from 0 to 10, representing absent to worst imaginable respectively. The MFSAF has been validated in 2 studies.[28,29] However, the JAKARTA and JAKARTA2 studies used a modified version of the MFSAF. In the modified instrument, 6 symptoms of MF are rated at their worst moment during the previous 24 hours: night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. Each symptom is measured on a scale from 0 to 10, representing absent to worst imaginable respectively. The TSS is the sum of the scores for each of the 6 symptoms. The modified MFSAF does not include a measure of global QoL.

In the COMFORT-I study, relationship between TSS improvement and other patient-reported outcomes, such as the Patient Global Impression of Change (PGIC) Scale and EORTC QLQ-C30, were evaluated. The results showed that 91% of the patients who were treated with ruxolitinib and had a ≥ 50% reduction in TSS of the modified MFSAF described their condition as "much improved" or "very much improved," while 74% of the patients who were treated with placebo and had < 50% reduction in TSS described their condition as "unchanged" or "worsening." In addition, ruxolitinib-treated patients who had a ≥ 50% reduction in TSS achieved significantly greater improvements in the EORTC QLQ-C30 subscales, however patients who were treated with placebo showed deterioration in their HRQoL measured by the EORTC QLQ-C30. Moreover, In the ruxolitinib arm, improvements in TSS and the PGIC score correlated with reductions in spleen size; patients who had a ≥ 35% reduction in spleen volume had the greatest improvement in symptoms and perceived change in condition. The test-retest reliability intraclass correlation coefficients were 0.98 for patients treated with ruxolitinib and 0.97 for those treated with placebo.[30]

The MID of TSS in the modified MFSAF was estimated in patients with MF. The MID ranged between 3.8 and 5.7 using different methods.[30]

Myeloproliferative Neoplasm Symptom Assessment Form

The MPN-SAF is a patient-reported measure of HRQoL that is specific for patients with MPNs, including MF, PV, and essential thrombocythemia.[31] The MPN-SAF assesses the presence and severity of 17 MPN symptoms during the prior week on a scale from 0 (absent) to 10 (worst imaginable): early satiety, abdominal pain, abdominal discomfort, inactivity, headaches, concentration, dizziness/vertigo/light-headedness, numbness/tingling in hands and feet, difficulty sleeping, depression or sad mood, sexual desire or function, cough, night sweats, pruritis, bone pain, fever, and unintentional weight loss. The MPN-SAF also includes fatigue assessment via the BFI and overall QoL. The validity and reliability of the MPN-SAF was evaluated in a single study.

Validity

The MPN-SAF was validated in a prospective study that included 96 patients with MF, 145 patients with PV, and 161 patients with essential thrombocythemia. The MPN-SAF was derived from the previously validated MF-SAF, which was specific to patients with MF.[29,31] Convergent validity was assessed by testing the strength of correction with the EORTC QLQ-C30. Strong correlations existed between individual items represented on the MPN-SAF and the EORTC QLQ-C30, including pain, fatigue (BFI), appetite, and insomnia ($P < 0.001$). The MPN-SAF items displayed strong association (Pearson correlation > 0.50) with relevant EORTC QLQ-C30 function scales, including QoL ($r = 0.52$ with overall QoL), physical function ($r = 0.51$ with inactivity, $r = 0.66$ with mean BFI, $r = 0.56$ with BFI worst fatigue), role function ($r = 0.55$ with 0.55 with overall QoL, $r = 0.61$ with mean BFI, $r = 0.50$ with BFI worst fatigue, $r = 0.65$ with concentration), cognitive function ($r = 0.65$ with concentration), social function ($r = 0.54$ with mean BFI), and emotional function ($r = 0.51$ with mean BFI, $r = 0.72$ with sad mood). In addition, the MPN-SAF scales displayed strong association (Pearson correlation > 0.50) with EORTC QLQ-C30 with the symptom scales of fatigue ($r = 0.57$ with overall QoL, $r = 0.75$ with mean BFI, $r = 0.56$ with inactivity), pain ($r = 0.55$ with abdominal pain, $r = 0.57$ with bone pain), insomnia ($r = 0.77$), and appetite loss ($r = 0.52$ with early satiety).

Reliability

Reliability of MPN-SAF was evaluated through serial administration of the instrument for test-retest assessment.[31] A subsample of 53 patients participated in the repeated survey, with a mean (SD) time between surveys of 190 (63 days), ranging from 43 to 257 days. The following MPN-SAF items demonstrated high correlation ($r > 0.50$, $P < 0.001$): fatigue/mean BFI ($r = 0.74$), early satiety ($r = 0.55$), abdominal pain ($r = 0.54$), abdominal discomfort ($r = 0.54$), inactivity ($r = 0.72$), headache ($r = 0.62$), concentration problems ($r = 0.70$), dizziness ($r = 0.57$), numbness ($r = 0.69$), insomnia ($r = 0.72$), sad mood ($r = 0.57$), sexuality problems ($r = 0.68$), night sweats ($r = 0.73$), pruritus ($r = 0.69$), and bone pain ($r = 0.59$). Intraclass correlation coefficients (ICCs) for test-retest reliability indicated that mean BFI (ICC = 0.735), inactivity (ICC = 0.708), insomnia (ICC = 0.720), and night sweats (ICC = 0.724) were highly reproducible on serial survey administration. The items with the lowest reproducibility were fever ($r = –0.08$, ICC = –0.068), cough ($r = 0.38$, ICC = 0.348), and weight loss ($r = 0.46$, ICC = 0.409).

Responsiveness to Change

No information on the MPN-SAF's responsiveness to change was found.

Minimal Important Difference

No information on the MID of the MPN-SAF was found.

EuroQol 5-Dimensions 3-Levels

The EQ-5D-3L is a generic, preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments. The instrument consists of 2 parts. The first part is a descriptive system that classifies respondents (aged ≥ 12 years) into 1 of 243 distinct health states. The descriptive system consists of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose 1 level that reflects their own health state for each of the 5 dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights. The second part is a 20 cm EQ VAS that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ VAS that best represents their own health on that day. The EQ-5D-3L produces 3 types of data for each respondent:

- a profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor (e.g., 11121, 33211);
- a population preference-weighted health index score based on the descriptive system; and,
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding severe problems on all 5 attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. There is a 5-level version of the EQ-5D (the EQ-5D-5L) that is now available and also commonly used.

The EQ-5D-3L has been extensively validated across countries around the world and in various conditions. However, the EQ-5D-3L has not been validated in patient with MF specifically, therefore its validity, reliability, and responsiveness to change have not been evaluated in the patient population of interest. No information on the MID of the EQ-5D-3L in MF patients was found. The MID for the EQ-5D-3L ranges from 0.033 to 0.074 in the general population.[32]

European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire

The EORTC QLQ-C30 is a generic cancer measure of HRQoL. The instrument consists of 30 questions across 6 functioning scales and 9 symptom scales. The functioning scales include physical, role, cognitive, emotional, social, and global QoL. The symptom scales include fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact. Multiple validated EORTC QLQ-C30 add-on cancer-specific modules exist, but there is no module for MF.

Validity

Validity of the EORTC QLQ-C30 in MF patients was evaluated in a single study and the results were reported in a conference abstract.[33] The study compared the EORTC QLQ-C30 to 2 MF-specific measures, the MFSAF and FACT-Lym, using data from patients enrolled in the COMFORT-I (N = 309) and COMFORT-II (N = 219) trials. The QLQ-C30 dimensions of physical function, role function, emotional function, social function, pain, and fatigue were strongly correlated ($\rho > 0.5$) with equivalent items/dimensions in the MFSAF and FACT-Lym. However, all QLQ-C30 dimensions were weakly correlated ($\rho < 0.3$) to MF-specific symptoms (e.g., night sweats and pruritis). Greater than 50% of patients reported no problems in QLQ-C30 dimensions such as nausea and vomiting, constipation, and diarrhea, indicating a potential ceiling effect.

Reliability

No information on the QLQ-C30s reliability in MF patients was found.

Responsiveness to Change

No information on the QLQ-C30s responsiveness to change in MF patients was found.

Minimal Important Difference

A generic cancer MID of 10 has been estimated by the developers of the EORTC QLQ-C30.[34] No MID in MF patients specifically has been identified.

CADTH

Pharmacoeconomic Review

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Abbreviations

AML	acute myeloid leukemia
BAT	best available therapy
BIA	budget impact analysis
CUA	cost-utility analysis
EQ-5D	EuroQol 5-Dimensions 3-Levels questionnaire
ICER	incremental cost-effectiveness ratio
JAKi	Janus kinase inhibitor
MF	myelofibrosis
OS	overall survival
QALY	quality-adjusted life-year
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Conclusions

Fedratinib reduces spleen volume and disease-related symptoms compared to best available therapy (BAT) in patients with myelofibrosis (MF). However, the effects of fedratinib on health-related quality of life are uncertain. However, its long-term effects and comparative effects relative to other Janus kinase inhibitors (JAKis; i.e., ruxolitinib) are highly uncertain.

CADTH undertook reanalyses to address limitations in the sponsor's submission, including basing treatment response on spleen volume reduction and patient-reported symptoms, revising the composition of the BAT basket of treatments, adopting an alternative parametric distribution for the extrapolation of fedratinib overall survival (OS), and removing costs related to thiamine testing. CADTH could not address the lack of direct comparative clinical data or uncertainty with the results of the sponsor's indirect treatment comparisons. As such, CADTH reanalyses focused on the cost-effectiveness of fedratinib relative to BAT in JAKi-naive patients, on the basis of the direct evidence from the JAKARTA trial. Exploratory analyses were conducted to explore the cost-effectiveness of fedratinib compared with ruxolitinib (in JAKi-naive patients) and with BAT (in ruxolitinib-experienced patients).

In JAKi-naive patients, fedratinib was more costly and more effective than BAT, with an incremental cost-effectiveness ratio (ICER) of $416,446 per quality-adjusted life-year (QALY). Price reduction analyses suggest that, even if fedratinib was offered at no cost (100% price reduction), fedratinib would not be cost-effective at a $50,000 per QALY threshold due to the cost of subsequent therapies (i.e., a proportion of those who did not respond or lose response to fedratinib were assumed to be subsequently managed by ruxolitinib).

Table 1: Submitted for Review

Item	Description
Drug product	Fedratinib (Inrebic), 100 mg oral capsules
Submitted price	Fedratinib, 100 mg: $84.39 per capsule
Indication	For the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to ruxolitinib
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 27, 2020
Reimbursement request	As per indication
Sponsor	Celgene Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Discrete event simulation model
Target population	Patients with intermediate-2 and high-risk myelofibrosis, presenting as primary, post-polycythemia vera, or post-essential thrombocythemia myelofibrosis Stratified analyses based on past treatment exposure, defined as follows: • Patients without previous JAKi exposure (JAKi-naive) • Patients with previous ruxolitinib exposure (ruxolitinib-experienced)
Treatment	Fedratinib
Comparators	JAKi-naive patients: ruxolitinib and BAT (consisting of hydroxyurea, prednisone, danazol, busulfan, cytarabine, peginterferon alfa-2a, and watchful waiting) Ruxolitinib-experienced patients: BAT (consisting of ruxolitinib, hydroxyurea, prednisone, danazol, and watchful waiting)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (35 years)
Key data source	• JAKi-naive patients: fedratinib and BAT informed by randomized, placebo-controlled trial, JAKARTA; ruxolitinib informed by indirect comparisons based on the JAKARTA trial compared to the COMFORT-I and/or COMFORT-II trials • Ruxolitinib-experienced patients: fedratinib informed by single-arm trial, JAKARTA2; BAT informed by indirect comparisons based on the JAKARTA2 trial compared to the SIMPLIFY-2 and PERSIST-2 trials
Submitted results	• JAKi-naive patients: sequential ICER of fedratinib vs. ruxolitinib = $2,119,620 per QALY (incremental costs = $94,080; incremental QALYs = 0.04) • Ruxolitinib-experienced patients: ICER of fedratinib vs. BAT = $63,636 per QALY (incremental costs = $44,027; incremental QALYs = 0.69)

Component	Description
Key limitations	• The comparative clinical efficacy of fedratinib is highly uncertain. There is no direct head-to-head evidence comparing fedratinib and ruxolitinib in the JAKi-naive subgroup or comparing fedratinib and BAT in the ruxolitinib-experienced subgroup, and there is substantial uncertainty in the results of the sponsor's indirect treatment comparisons. • The sponsor's submitted pharmacoeconomic analysis does not adequately reflect the clinical management of myelofibrosis patients. Treatment effectiveness is modelled in terms of a reduction in spleen volume, whereas, in practice, treatment decisions may be made based on patient-reported symptoms and/or spleen volume. The sponsor further assumed that a 35% reduction in baseline spleen volume would be the threshold for treatment discontinuation which does not align with the feedback obtained by clinical experts consulted by CADTH. • The majority of treatments included by the sponsor as BAT are not used in the treatment of myelofibrosis in Canada. • The long-term extrapolation of the effects of fedratinib, including overall survival, duration of treatment response, and time to discontinuation, is highly uncertain. The predicted overall survival curve for fedratinib in the sponsor's model lacked face validity and was overestimated according to the clinical experts consulted on this review. • Thiamine testing is not uniformly reimbursed publicly across Canadian jurisdictions and may be paid out-of-pocket by patients.
CADTH reanalysis results	• In light of the high level of uncertainty associated with the comparative clinical evidence, CADTH reanalyses focused on the JAKi-naive subgroup and a pairwise comparison of fedratinib and BAT. In the CADTH reanalysis, treatment response was redefined in terms of symptom and spleen response, the composition of BAT was revised, an alternative parametric distribution of fedratinib overall survival was adopted, and the cost of thiamine testing was removed. • JAKi-naive patients: ICER = $416,446 per QALY for fedratinib compared to BAT (incremental cost of $231,996; incremental QALYs of 0.56). There is no price for fedratinib at which an ICER of $50,000 could be achieved. • CADTH was unable to derive a base-case reanalysis for the ruxolitinib-experienced subgroup or evaluate the cost-effectiveness of fedratinib compared to ruxolitinib in the JAKi-naive subgroup owing to limitations of the sponsor's indirect treatment comparisons and the paucity of direct evidence. Exploratory analyses were undertaken; however, cautious interpretation is required.

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LY = life-year; QALY = quality-adjusted life-year; vs = versus.

The CADTH base-case results are highly sensitive to the long-term OS of patients taking fedratinib. The OS of such patients is highly uncertain owing to a lack of long-term follow-up data and immature OS data from the JAKARTA trial. The majority of the incremental benefits with fedratinib treatment were gained in the post-trial period on the basis of extrapolated trial findings rather than observed benefits. Further, although in the CADTH base-case treatment response was redefined as patient-reported symptoms and/or spleen volume reduction, the definition of treatment response remains suboptimal, in that the threshold for treatment discontinuation was not aligned with clinical practice.

Clinical experts consulted by CADTH for this review indicated that fedratinib would most likely be used in patients who had previously had a ruxolitinib treatment failure, although there is no evidence to suggest the optimal sequencing. CADTH conducted exploratory analyses in this population; however, the results should be interpreted cautiously owing to a lack of direct evidence and limitations with the sponsor's indirect treatment comparisons.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input from caregivers and patients with MF was received from 3 patient groups: The Leukemia & Lymphoma Society of Canada, the Canadian Myeloproliferative Neoplasms Research Foundation, and the Canadian Myeloproliferative Neoplasms Network. Respondents noted that the symptoms associated with MF negatively affect their quality of life and that it is important to patients that treatments for MF reduce their fatigue, bone pain, splenomegaly, and loss of appetite and/or weight loss. Patients had experience with many treatments for MF, including ruxolitinib, interferon, and hydroxyurea, with reported side effects including hair loss, low blood cell counts, anemia, fatigue, cough, rashes, weakness, shortness of breath, headaches, and impaired concentration. Some patients had experience with fedratinib and reported that their quality of life was improved because of decreased symptom burden. Patients expressed a desire for treatments that would cure their MF, improve their health-related quality of life (i.e., by reducing symptoms), and increase their survival. Cost of treatment and side effects were also reported to be important to patients.

One joint clinician input was received from the province of Ontario from 4 hematologists and 1 pharmacist with expertise in the diagnosis and management of MF. Treatment options available for intermediate- and high-risk MF include ruxolitinib, although some patients may receive hydroxyurea, interferons (although not publicly funded in all jurisdictions), or best supportive care. The clinicians indicated experience using fedratinib and stated that, although fedratinib could be used at any time during the patient's treatment for MF, preference would be to use ruxolitinib for first-line treatment and to use fedratinib as second-line therapy given the lack of direct head-to-head trials comparing ruxolitinib to fedratinib in the first-line setting and the serious warning in the fedratinib's product monograph regarding serious and fatal encephalopathy. Although MF assessment score tools are not routinely used in clinical practice, clinicians felt it would be reasonable to use clinical exams, ultrasounds, CT scans, and other objective measures to determine a reduction in spleen size.

Provincial Advisory Group input indicated that ruxolitinib and hydroxyurea are funded in almost all jurisdictions. Drug plans noted that, while the oral route of administration is favourable to patient access, this may limit access for patients who live in provinces that have different funding mechanisms for IV and oral oncology medications. The plans noted that drug wastage would be minimized because fedratinib is available as 100 mg tablets; however, patients receiving fedratinib may require additional health care resources (e.g., pharmacy, nursing, and clinic visits), as well as more frequent scans to assess spleen size and monitor for side effects (e.g., encephalopathy).

Several of these concerns were addressed in the sponsor's model:

- Although the financial burden imposed by MF on patients was not considered in the base case given the public health care payer perspective, lost working hours owing to hospital visits and assessments associated with MF were incorporated in a scenario analysis.
- Drug wastage was assumed for ruxolitinib but not fedratinib.
- Mortality was modelled by the extrapolation of OS curves.

In addition, CADTH addressed some of these concerns as follows.

- The sponsor's model defined clinical efficacy (i.e., treatment response) in terms of percentage reduction in spleen volume from baseline, assessed by MRI or CT. Clinical experts indicated, however, that such objective measures are not routinely practised and that treatment effectiveness is determined by patient-reported symptoms and/or spleen volume. In the CADTH base case, treatment efficacy redefined as improvement in patient-reported symptoms and/or spleen volume.
- Although the sponsor's analysis incorporated utility values based on spleen volume reduction, CADTH selected an alternative set of health state utility values. Quality of life improvements associated with a treatment response were instead based on symptom response or spleen volume size.
- The sponsor assumed that BAT would be a basket of treatments including hydroxyurea, prednisone, danazol, busulfan, cytarabine, peginterferon alfa-2a, and watchful waiting, and, in ruxolitinib-experienced patients, ruxolitinib. Based on clinical experts' input, CADTH reanalyses redefined BAT to be comprised of hydroxyurea, peginterferon alpha-2a, and supportive care.

CADTH was unable to address the following concerns raised from stakeholder input.

- Additional costs associated with monitoring spleen size, based on objective measurements (e.g., ultrasounds, CT scans) were not captured owing to a lack of data regarding the probability and frequency in which these would be performed in clinical practice.
- Although non-hematologic adverse events (grade ≥3) were included in the model, the costs and consequences of encephalopathy were not captured.

Economic Review

The current review is for fedratinib (Inrebic) for splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF, including patients who have been previously exposed to ruxolitinib.[1]

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

Fedratinib is indicated for the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF, including patients previously exposed to ruxolitinib.[2] The sponsor submitted a stratified cost-utility analysis (CUA) to assess the cost-effectiveness of fedratinib among 2 subgroups: among patients without prior exposure to JAKis (JAKi-naive patients) and among patients previously exposed to ruxolitinib (ruxolitinib-experienced patients). Ruxolitinib is a JAKi approved for the treatment of splenomegaly and/or associated symptoms within the Health Canada-indicated population. The modelled population is consistent with the reimbursement request. Among the JAKi-naive patient subgroup, fedratinib was compared to ruxolitinib and BAT. Among the ruxolitinib-experienced patient subgroup, fedratinib was compared to BAT. The composition of BAT reflected a basket of

treatments and varied between subgroups and previous treatment history. Generally, the sponsor assumed that BAT included hydroxyurea, peginterferon alfa-2a, medication for symptomatic management (e.g., prednisone, danazol, busulfan, cytarabine), or watchful waiting; ruxolitinib was further part of the basket in the ruxolitinib-experienced subgroup in patients who had 1 prior exposure to a JAKi (Table 12).

Fedratinib is available as 100 mg capsules. The recommended dosage is 400 mg once daily for patients with a baseline platelet count of 50 × 10^9/L or greater.[2] A complete blood count should be obtained before initiating fedratinib and during treatment as clinically indicated.[2] At a submitted price of $84.39 per capsule,[1] the annual cost of fedratinib within the submitted economic model was $121,819 per patient. For ruxolitinib, the sponsor calculated the annual drug acquisition cost to be $65,648. The relative dose intensities of fedratinib and ruxolitinib were both assumed to be 98.8%, and 5% drug wastage was further assumed for ruxolitinib.[1] In the JAKi-naive group, the annual cost of BAT was assumed to be $1,225. In the ruxolitinib-experienced group, the annual cost of BAT was assumed to be $30,125 for patients with previous exposure to 1 JAKi and $659 for patients after exposure to 2 JAKis (Table 12).

The clinical outcomes of interest were QALYs and life-years. The economic analysis was undertaken from the perspective of the publicly funded health care payer over a lifetime horizon (35 years). Discounting (1.5% per annum) was applied to both costs and outcomes.

Model Structure

The sponsor submitted a discrete event simulation to assess the cost-effectiveness of fedratinib relative to ruxolitinib and BAT in the JAKi-naive subgroup, and to BAT in the ruxolitinib-experienced subgroup. Each patient entered the model on treatment and had their disease trajectories separately tracked over their lifetime, with movement through the model-based on-treatment response, time to treatment discontinuation (Figure 2), duration of treatment response (Figure 3), progression to acute myeloid leukemia (AML), and OS (Figure 4 and Figure 5). The model generated patients with unique health profiles. At baseline, patients were assigned a time to treatment discontinuation and time to death. For those who remained alive and on treatment at 24 weeks, treatment response (≥35% reduction in spleen volume from baseline, herein referred to as "spleen response") was assessed. Patients receiving a JAKi who had a treatment response remained on their current treatment, while those whose spleen volume was not reduced by at least 35% from baseline (i.e., nonresponders) discontinued JAKi treatment. Patients receiving BAT remained on BAT regardless of spleen response at 24 weeks. Nonresponders to their initial JAKi treatment were assumed to receive BAT (as part of which, 44.9% of patients were assumed to receive ruxolitinib). Third-line treatment following failure of second-line treatment was modelled to be BAT (without ruxolitinib). In both subgroups, patients remained on BAT until death.

Possible events captured thereafter included loss of treatment response, treatment discontinuation, progression to AML, and end of life (i.e., palliative care or death). An individual's life course of events was based on random sampling of the respective time-to-event distributions to determine which event would occur next. Events could occur at any time within the model as per the parametric survival curve rather than at fixed cycle lengths. For all patients who entered the palliative care state from the AML state or while on BAT, the sponsor assumed that palliative care would be received for 8 weeks before death. Patients taking fedratinib or ruxolitinib received up to 8 weeks of palliative care, depending on the patient's remaining life expectancy at the time of treatment discontinuation. The consequences of the

event sequence on utilities and costs were tracked for each modelled patient and aggregated over time to reflect the expected outcomes for the full patient cohort.

Model Inputs

The characteristics of the JAKi-naive subgroup were based on participants in the JAKARTA trial, a multinational, double-blind, randomized controlled trial involving adult patients (N = 289) with no prior JAKi experience who were randomized to receive fedratinib (400 mg or 500 mg once daily) or placebo. The characteristics of the ruxolitinib-experienced subgroup were based on the JAKARTA2 study, a multinational, single-arm trial involving adult patients (N = 97) who received fedratinib (400 mg once daily) after at least 2 weeks of previous exposure to ruxolitinib. The sponsor assumed that the JAKARTA and JAKARTA2 trial populations are reflective of the population of JAKi-naive and ruxolitinib-experienced patients, respectively, who would be eligible to receive fedratinib in Canada.[1] The baseline characteristics of the JAKARTA trial population were mean age of 64.2 years, 58.82% male, mean weight of 68.66 kg, mean body surface area of 1.79, and 84.38% with a baseline platelet count of 100,000/µl or greater. The baseline characteristics of the JAKARTA2 trial population were: mean age of 67.02 years, 54.32% male, mean weight of 72.87 kg, mean body surface area of 1.85, and 65.43% with a baseline platelet count of 100,000/µl or greater.

Clinical parameters were obtained from multiple studies for fedratinib (JAKARTA for treatment-naive; JAKARTA2 for treatment-experienced) and ruxolitinib (COMFORT-I,[3,4] and COMFORT-II[5,6]). The sponsor assumed that clinical parameters for BAT would be equal to either the placebo arm of the JAKARTA or COMFORT-I studies, or the BAT arm of the COMFORT-II study. Within the first 24 weeks, events captured included early death and early discontinuation. Patients who died before 24 weeks were determined by sampling from treatment- and subgroup-specific parametric curves for OS (details reported in the following paragraph). Among the patients who remained alive, the probability of discontinuing fedratinib before 24 weeks ("early discontinuation") was based on data from the JAKARTA or JAKARTA2 trials while the COMFORT-II trial informed discontinuation of ruxolitinib in the JAKi-naive group.[7] Treatment effectiveness (i.e., spleen response) was assessed at 24 weeks. The proportion of patients who experienced a spleen response was based on the sponsor's commissioned indirect treatment comparisons, stratified by subgroup (JAKi-naive and ruxolitinib-experienced).[8,9]

Time to treatment discontinuation, duration of treatment response, and OS were extrapolated from clinical trial data using treatment-independent parametric curves for each subgroup. The parametric functions were chosen by the sponsor on the basis of goodness-of-fit statistics (Akaike Information Criterion, Bayesian Information Criterion), visual fit, and/or plausibility as determined by clinical experts consulted by the sponsor.[1] The source of the clinical data and parametric functions adopted by the sponsor are summarized in Table 13. OS (time to death) in the model was estimated based on the initial treatment received by the patient in the model, with mortality capped by the general population life expectancy. Progression to AML was assumed to be constant across treatments and was sampled from an exponential distribution of AML progression for ruxolitinib in the COMFORT-II trial. OS following progression to AML was assumed to be consistent across treatment and patient subgroups and was based on a US retrospective, single-centre, cohort study.[10]

The sponsor's model incorporated non-hematologic adverse events (grade ≥3) although hematologic adverse events (i.e., thrombocytopenia, anemia, neutropenia) were excluded as these were assumed to be implicitly captured as part of the existing costs and health

state utility values.[1] For fedratinib, adverse events data were obtained from the JAKARTA (JAKi-naive) and JAKARTA2 (ruxolitinib-experienced) trials. In the JAKi-naive subgroup, adverse events associated with ruxolitinib and BAT were obtained from the COMFORT-II trial,[5] while adverse events associated with BAT were obtained from the SIMPLIFY 2 trial[11] for the ruxolitinib-experienced subgroup.

Utilities for each health state were assumed to be equivalent between JAKis and BAT. For the JAKi-naive subgroup, baseline utility was based on the baseline EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) data for patients who received fedratinib in the JAKARTA trial. The change in utility value as a result of having a spleen response was fit to trial EQ-5D-3L data in a linear regression that incorporated patients' baseline EQ-5D-3L value and spleen response as covariates. JAKi-naive patients who did not have a spleen response at 24 weeks were assumed to incur no utility benefit. For the ruxolitinib-experienced subgroup, baseline utility was derived from non-preference-based data collected via the Myelofibrosis Symptom Assessment Form and the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire core model collected at baseline in the JAKARTA2 trial. Specifically, the Myelofibrosis Symptom Assessment Form and European Organisation for Research and Treatment of Cancer Quality of Life questionnaire core model were combined to derive a "preference-based index" (Myelofibrosis 8 Dimensions). A similar approach was taken by the sponsor to derive the utility values that depend on treatment response with the exception that the regression analysis included a gender coefficient. In the ruxolitinib-experienced subgroup, women had a lower utility value at baseline ([redacted]) compared to men ([redacted]). In this subgroup, the sponsor assumed that patients who had no spleen response at 24 weeks or who lose treatment response would have an improvement in utility from baseline (women: [redacted]; men: [redacted]). In both subgroup analyses, response was assumed to occur after 4 weeks in treatment. Utilities for the AML and palliative care states were obtained from the literature,[12,13] and the sponsor assumed that the utility value for palliative care could not exceed that of AML.[1] Disutilities were included for non-hematologic adverse events and were assumed to last for 4 weeks.

The model included costs related to drugs (acquisition, administration), adverse events, health care resource utilization, treatment of AML, and palliative care. Drug acquisition costs for fedratinib were based on the sponsor's submitted price,[1] while the price of ruxolitinib and BAT were obtained from Ontario's Exceptional Access Program,[14] the Ontario Drug Benefit Formulary,[15] and past CADTH Pan-Canadian Oncology Drug Reviews.[16] Administration costs were incorporated for cytarabine (administered as part of BAT). Adverse event costs were incorporated per event. Time-varying health care resource utilization (e.g., emergency department visits, primary care visits, hospital admissions, outpatient visits, monitoring, and red blood cell transfusion), based on clinical expert input, was assumed to be equal across JAKis but different for BAT with costs based on the Ontario Schedule of Benefits for Physician Services.[17] The sponsor assumed that patients receiving fedratinib would undergo thiamine testing monthly for the first 3 months, then once every 3 months thereafter,[2] with the cost obtained from the Notre-Dame Hospital's list of tests.[18] Costs associated with the treatment of AML were obtained from a 2007 UK analysis[19] with costs converted to Canadian dollars and inflated to 2020.[20] Palliative care was assumed to cost $1,716 per patient per week.[1]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (1,000 iterations, each with 1,000 simulated patients). The probabilistic findings are presented below, stratified by patient subgroup. Additional results from the sponsor's submitted economic evaluation base case are presented in

Appendix 3. The submitted analyses were based on the publicly available prices of the comparator treatments.

Base-Case Results

Among JAKi-naive patients, fedratinib was associated with an incremental cost of $94,080 and 0.04 additional QALYs compared with ruxolitinib over a 35-year horizon, resulting in an ICER of $2,119,620 per QALY (Table 3). In the sponsor's base case, fedratinib had a 0% probability of being the most cost-effective strategy at a willingness-to-pay (WTP) threshold of $50,000 per QALY.

Results were driven by the small differences in QALYs between fedratinib and ruxolitinib (incremental QALYs, 0.04 [i.e., 16 additional days of perfect health over a lifetime]) and the increased drug acquisition costs associated with fedratinib (incremental costs, $94,133). The sponsor's probabilistic base case was not reproducible over multiple model runs at 1,000 iterations owing to the small differences in the incremental QALYs between ruxolitinib and fedratinib.

Among ruxolitinib-experienced patients, fedratinib was associated with an incremental cost of $44,027 and 0.69 additional QALYs compared with BAT over a 35-year horizon (Table 4). This resulted in an ICER of $63,636 per QALY gained for fedratinib compared with BAT. In the sponsor's base case, fedratinib had an 29% probability of being cost-effective at a WTP threshold of $50,000 per QALY. Results were driven by drug acquisition costs (incremental costs, $34,208).

Sensitivity and Scenario Analysis Results

The sponsor assessed the impact of several model parameters in probabilistic scenario analyses. Several of these had notable effects on the ICER and are summarized in Appendix 3.

Table 3: Summary of the Sponsor's Economic Evaluation Results — JAKi-Naive Patients

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
BAT	46,186	1.96	Ref.
Ruxolitinib	268,149	3.77	122,980
Fedratinib	362,229	3.81	2,119,620

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; QALY = quality-adjusted life-year; Ref. = reference.
Source: Sponsor's pharmacoeconomic submission.[1]

Table 4: Summary of the Sponsor's Economic Evaluation Results — Ruxolitinib-Experienced Patients

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. BAT ($/QALY)
BAT	106,058	Ref.	1.83	Ref.	Ref.
Fedratinib	150,085	44,027	2.53	0.69	63,636

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; Ref. = reference; vs. = versus .
Source: Sponsor's pharmacoeconomic submission.[1]

Among JAKi-naive patients, several scenarios resulted in fedratinib being dominated by ruxolitinib (i.e., fewer QALYs at a higher cost for fedratinib compared to ruxolitinib; Table 14); these included disabling the stopping rule (i.e., patients without a spleen response at 24 weeks continued to receive a JAKi) and assuming equal OS among JAKis. Other notable impacts that resulted in the ICER increasing included when treatment effectiveness was defined as either a reduction in spleen volume or an improvement in patient-reported symptoms, and when fedratinib was assumed to be equal to ruxolitinib in terms of time to treatment discontinuation, duration of response, and OS.

Among ruxolitinib-experienced patients, several similar scenarios resulted in notable increases to the ICER, including disabling the stopping rule, and basing treatment effectiveness on spleen volume or improved patient-reported symptoms (versus spleen response in the base case). Notably, when BAT was assumed to not include ruxolitinib (i.e., ruxolitinib-experienced patients would not continue to receive ruxolitinib after a treatment failure), the ICER increased by 160% relative to the base case (ICER: $165,162 per QALY).

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis.

- **Comparative clinical efficacy is highly uncertain**. There have been no head-to-head trials of fedratinib and ruxolitinib in JAKi-naive patients or of fedratinib and BAT in ruxolitinib-experienced patients. The sponsor conducted 2 indirect treatment comparisons to provide comparative clinical effectiveness data (i.e., spleen volume reduction, Total Symptom Score) to inform the economic model. Although the methods used to conduct the indirect treatment comparisons followed technical guidance, the CADTH Clinical Report raised several concerns regarding the interpretation of the findings of the indirect treatment comparisons, including the small number of included studies and limited data for matching and adjustment of clinically important baseline characteristics. As such, there is substantial uncertainty with the interpretation of the clinical findings of the indirect treatment comparisons. Data informing the ruxolitinib-experienced subgroup analyses were obtained from the JAKARTA2 trial. Given its single-arm trial design and the aforementioned limitations noted regarding the indirect treatment comparison, it is unclear whether patients would have had better or worse outcomes with fedratinib when compared with BAT after a previous ruxolitinib failure.

  Other key model parameters (i.e., time to discontinuation, duration of treatment response, OS) were incorporated directly from clinical trials involving fedratinib, ruxolitinib, or BAT, without adjustment or accounting for differences in patient characteristics. CADTH notes that, owing to the direct use of clinical trial data, it is not possible to determine if any observed differences in time to discontinuation, duration of treatment response, and OS between the therapies are solely due to the treatment or, rather, due to bias or confounding factors (e.g., differences in study populations, definitions of outcomes, or study designs). As further noted in the Clinical Review, the JAKARTA2 trial was limited by a number of issues including short treatment duration, small number of participants, premature study discontinuation, immature data, and multiple protocol amendments. Together, this brings greater uncertainty to the naive estimates taken to inform the clinical inputs. The incremental gains in QALYs and life-years predicted by the sponsor's model for fedratinib versus ruxolitinib in the JAKi-naive subgroup, and for fedratinib versus BAT in the ruxolitinib-experienced subgroup, should be interpreted with a higher degree of uncertainty than is reflected in the sponsor's probabilistic analysis.

- CADTH determined that, for the JAKi-naive subgroup, a full sequential analysis including ruxolitinib would be inappropriate owing to the limitations of the sponsor's indirect treatment comparisons and the paucity of direct evidence. CADTH reanalyses for the JAKi-naive subgroup are thus presented as pairwise comparisons (fedratinib versus BAT). The cost-effectiveness of fedratinib relative to ruxolitinib in this population was considered as part of an exploratory scenario analysis in which clinical equivalence was assumed in light of feedback from clinical experts consulted on this review who stated this may be a reasonable assumption. The cost-effectiveness of fedratinib among ruxolitinib-experienced patients was similarly explored in an exploratory scenario analysis.

- **The use of spleen volume alone as a measure of treatment effectiveness does not reflect the clinical management of MF.** Clinical effectiveness in the sponsor's model was based on spleen volume, with treatment response defined as a 35% or greater reduction in spleen volume after 24 weeks of treatment. Spleen volume was measured in the JAKARTA trials by MRI or CT scan. In the sponsor's model, patients who did not meet this threshold after 24 weeks of treatment were considered nonresponders and assumed to discontinue treatment.[1] The clinical experts consulted by CADTH indicated that a threshold of a 35% reduction from baseline is not typically used in clinical practice to define a treatment response, and that treatment decisions are generally made on the basis of patient-reported symptoms and/or bedside palpations to assess spleen volume. This is consistent with the National Comprehensive Cancer Network's 2020 guidelines,[21] which recommend that response assessment should be based on the improvement of disease-related symptoms. Indeed, a reduction in symptoms was noted as being important to patients in the patient group input received by CADTH for this review. According to the clinical experts, treatment response should be assessed with each cycle of treatment, or every 3 months at minimum, and fedratinib treatment should be discontinued due to disease progression or adverse events. In the absence of adverse events, clinical experts consulted for this review indicated that patients showing any level of symptom reduction or spleen volume reduction would continue to receive JAKi treatment for at least 6 months, owing to limited treatment options. Registered clinician input further noted that MF assessment score tools are not routinely used in clinical practice and that symptom evaluation are based on subjective patient reports.
    - In CADTH's reanalysis, an alternative definition of treatment response was adopted, based on either a reduction in spleen volume (≥35% from baseline) or an improvement in patient-reported symptoms (≥50% reduction in Total Symptom Score from baseline). Patients who met either threshold were considered treatment responders at the 24-week response assessment. Given that the available options to define treatment response within the model do not fully reflect current clinical practice, scenario analyses were further conducted adopting other definitions for treatment response (i.e., based on spleen volume only or based on symptom response only). Owing to data limitations, CADTH was unable to change the definition for duration of treatment response (i.e., this remained based on spleen response in CADTH reanalyses). CADTH further conducted a scenario analysis that assumed patients would not discontinue treatment at 24 weeks (i.e., time to discontinuation informed by the time-to-discontinuation curve).
- **Treatments included in BAT are not reflective of the management of MF in Canada.** In the sponsor's analysis, the composition of BAT was based on the PERSIST-1 study,[22] the PERSIST-2 study,[23] and the opinion of clinical experts consulted by the sponsor. Generally, BAT was assumed to include hydroxyurea, prednisone, danazol, busulfan, cytarabine,

peginterferon alfa-2a, and watchful waiting. The clinical experts consulted by CADTH indicated that many of the treatments included by the sponsor as part of BAT do not reflect best practice for the treatment of MF. Additional treatments (e.g., prednisone, danazol, busulfan, cytarabine) may be used to treat patient symptoms but would not be expected to vary across treatment arms.

In addition, ruxolitinib was included as part of the composition of BAT in the ruxolitinib-experienced subgroup. For patients who are intolerant to or who have failed ruxolitinib, hydroxyurea, peginterferon alpha-2a, or supportive care would be given according to the clinical experts consulted by CADTH. Notably, the clinical experts indicated that patients who had previously experienced a ruxolitinib treatment failure would not continue to receive ruxolitinib as part of BAT.

  - In the CADTH base case for the JAKi-naive subgroup, BAT (as a comparator) was assumed to be comprised of hydroxyurea (50% of patients), peginterferon alpha-2a (5% of patients), and supportive care (i.e., no active treatment; 45% of patients) based on the feedback received by clinical experts consulted by CADTH. No changes were made to the composition of BAT as subsequent treatment upon nonresponse or loss of response of fedratinib (i.e., 44.9% of patients would receive ruxolitinib). However, a scenario analysis was conducted assuming patients could only receive 1 JAKi over their lifetime (i.e., patients would not be eligible to receive ruxolitinib upon fedratinib failure). In exploratory analyses involving the ruxolitinib-experienced subgroup, ruxolitinib was removed from BAT (i.e., the same composition of BAT was assumed for the JAKi-naive and ruxolitinib-experienced subgroups).

- **The long-term extrapolation of the effects of fedratinib is highly uncertain.** The model's efficacy data (i.e., spleen volume reduction, Total Symptom Score), as well as time to treatment discontinuation, duration of treatment response, and OS were based on observations from the JAKARTA and JAKARTA2 trials. There is no long-term data available for patients taking fedratinib, owing to a clinical hold imposed by the FDA in 2013.[1] The sponsor noted that this "may introduce bias to the…long-term extrapolations for various outcomes in the model due to the shortened follow-up period."[1] The extrapolated estimates for fedratinib were highly variable across input parameters and dependent on the assumed statistical distribution (Appendix 3). Further, the OS data from the JAKARTA and JAKARTA2 trials are immature, which introduces additional uncertainty into the long-term extrapolation.

  CADTH reviewers noted that the sponsor's model predicts a survival advantage with fedratinib compared to ruxolitinib among JAKi-naive patients and with fedratinib compared to BAT among ruxolitinib-experienced patients. The JAKARTA trial was not powered to detect differences in survival between fedratinib and BAT. According to clinical experts consulted on this review, the predicted OS obtained from the sponsor's chosen parametric distribution (Weibull) for the JAKi-naive patients lacked face validity. The Weibull distribution predicted a median OS of approximately 5 years for patients taking fedratinib which clinical experts felt to be too optimistic. Further, there is no direct evidence comparing the survival of ruxolitinib-experienced patients who received fedratinib or ruxolitinib. The JAKARTA2 trial, which is the sole source of fedratinib data for the ruxolitinib-experienced subgroup, was a single-arm trial with no comparison group; thus, the survival benefit predicted for fedratinib relative to BAT is highly uncertain.

  - Given the lack of OS data beyond the trial period and uncertainty associated with the extrapolated data, the external validity of the sponsor's predicted survival benefit with fedratinib is highly uncertain. As such, the predicted gain of life-years and QALYs associated with fedratinib relative other treatments should be interpreted with caution.

In the CADTH base case, an alternative parametric distribution for OS was adopted (Gompertz) for the JAKi-naive subgroup, which was considered by clinical experts to be aligned with survival expected for this patient population (median OS was approximately 3.7 years). Given the uncertainty with the long-term evidence, CADTH further conducted a scenario analysis to demonstrate how sensitive the model is to the assumed OS benefit associated with fedratinib.

- **The economic model lacked transparency.** The Excel model was hard coded, with results generated by a series of Visual Basic macros, including multiple sub macros. Verification of this code and following how patients moved through health states was not possible. CADTH noted that the model generated impossible values for some patients, such as negative time spent in certain health states (e.g., AML). Programming of the model appears to have permitted probabilistic draws to be taken independently for the same event by the same patients across different treatment strategies. As such, in a proportion of simulations in both the sponsor's base case (Figure 6) and the CADTH reanalysis (Figure 7), the model predicts lower QALYs with fedratinib compared with BAT, which is inconsistent with clinical evidence. Guidelines on the modelling of discrete event simulation instead recommend that separate streams of common random numbers are applied to different events to reduce the possibility that different random numbers are selected for the same event by the same patient under different strategies.[24] CADTH was further unable to verify how the random number seed functioned in the model, and the model's user guide did not address this model function.
    - CADTH was unable to correct this limitation.

Additional limitations were identified, but were not considered to be key limitations:

- **Costs related to thiamine testing were included in the sponsor's base case.** Thiamine testing is indicated before initiating fedratinib treatment and periodically during treatment or as clinically indicated.[2] The sponsor included the cost of thiamine testing in their economic analysis; however, clinical experts consulted by CADTH indicated that thiamine testing is not uniformly reimbursed publicly across Canadian jurisdictions and may be paid out-of-pocket by patients.
    - The cost of thiamine testing was removed from the CADTH base case to reflect jurisdictions who do not cover thiamine testing. Cost of thiamine testing was reintroduced in a scenario analysis to assess its impacts in jurisdiction with public reimbursement.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 5).

CADTH Reanalyses of the Economic Evaluation

Several limitations with the sponsor's submission could not be adequately addressed. CADTH could not address the lack of comparative clinical data for fedratinib versus ruxolitinib for the JAKi-naive subgroup or for fedratinib versus BAT for the ruxolitinib-experienced subgroup. As such, the CADTH base case was limited to the JAKi-naive subgroup and only included pairwise comparisons of fedratinib versus BAT.

Exploratory analyses were undertaken to assess the cost-effectiveness of fedratinib versus ruxolitinib in JAKi-naive patients, as well as the cost-effectiveness of fedratinib versus BAT in ruxolitinib-experienced subgroups. The approach and results of these analyses are presented in Appendix 4.

Table 5: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
Patients enrolled in JAKARTA and JAKARTA2 trials were assumed to be representative of patients in Canada who would be eligible for fedratinib.	Reasonable. Clinical experts consulted by CADTH indicated that study populations are generally representative of patients with MF, although patients may have a slightly lower ECOG performance status in clinical practice.
The rate of progression to the AML health state in the model was assumed to be equivalent for fedratinib, ruxolitinib, and BAT.	Uncertain, but likely conservative. The sponsor's assumption that the rate of transformation to AML for fedratinib would be equivalent to that observed in the COMFORT-II trial for ruxolitinib and BAT was not justified. Although the JAKARTA trial noted that the proportion of participants who progressed to AML was similar between fedratinib and placebo, these data were limited by a short follow-up period.
Participants who experienced a treatment response after 24 weeks of treatment were assumed to start accruing a utility benefit after the first 4 weeks of treatment.	Uncertain, but unlikely to affect the ICER given the small duration relative to the overall analysis time horizon.
The utility value for the palliative care state was capped at the utility value for the AML state (i.e., the palliative care utility could not exceed that of AML).	Inappropriate. The sponsor's utility value for patients receiving palliative care (0.59) was derived from EQ-5D-3L data from patients with end-stage breast, prostate, or colorectal cancer, a different condition than that under review. However, the impact of capping utility to the AML state (0.53) is likely minimal given the limited amount of time spent in the palliative care state (up to 8 weeks).
In the ruxolitinib-experienced subgroup, the sponsor incorporated sex-specific utility values, with women assigned lower utility values at baseline than men and expected to receive less utility gains if responding to treatment. Ruxolitinib-experienced patients who had no response to treatment or who lost treatment response were assumed to retain a utility benefit compared to their baseline values.	Inappropriate. Clinical experts consulted by CADTH indicated that patients with MF would be expected to have lower quality of life over time in the absence of a treatment response. Further, clinical experts indicated that the sponsor's assumption of different quality of life between sexes is not consistent with their clinical experience. In the exploratory analyses involving ruxolitinib-experienced patients, CADTH aligned the utility assumptions with those made for the JAKi-naive subgroup. Specifically, utilities were assumed to be equal between men and women, and nonresponders were assumed to incur no utility benefit.
Only non-hematologic adverse events of at least grade 3 severity were included in the sponsor's model. The costs and health effects of hematologic adverse events (e.g., thrombocytopenia, anemia) were assumed to be captured by resource utilization and health state utility values.	Inappropriate. Hematologic adverse events are commonly experienced by patients taking a JAKi.[21] As noted in the CADTH Clinical Review, anemia (grade 3 or 4) was more commonly reported among patients who received fedratinib compared with placebo (fedratinib: 30.2%; placebo: 7.4%), while the incidence of thrombocytopenia was similar (fedratinib: 5.2%; placebo: 6.3%). Because the sponsor assumed that health state utility values and health care resource use would be equal between fedratinib and ruxolitinib, differences in costs and health effects related to hematologic adverse events between JAKis would not be accounted for. Not including costs and health effects related to anemia may bias the findings in favour of fedratinib.

Sponsor's key assumption	CADTH comment
Health care resource utilization was assumed to be equivalent between fedratinib and ruxolitinib and was assumed to vary based on time spent in the model (0 to 12 weeks, 12 to 24 weeks, 24 to 36 weeks, 36 to 48 weeks, 48 to 108 weeks, 108 to 144 weeks, and > 144 weeks).	Uncertain. The assumption that resource utilization would be equivalent between fedratinib and ruxolitinib was not justified by the sponsor. Drug plan input obtained by CADTH for this review indicated that patients receiving fedratinib may require additional health care resources (e.g., pharmacy, nursing, and clinic visits), as well as more frequent scans to assess spleen size and monitor for side effects (e.g., encephalopathy). Increased health care resource utilization by patients taking fedratinib would increase the ICER relative to BAT and ruxolitinib; however, the extent of the impact is unclear. The rationale for defining the time range is further unclear.
Relative dose intensity of fedratinib was assumed to be 98.8% on the basis of the JAKARTA trial. The relative dose intensity of ruxolitinib was assumed to be equal to that of fedratinib.	Uncertain. The assumption that relative dose intensity would be equal for fedratinib and ruxolitinib was not justified by the sponsor. Ruxolitinib dose reductions were common in the COMFORT-II trial[3] and these dose reductions may reduce the drug acquisition costs associated with ruxolitinib.
The sponsor assumed that there would be 5% drug wastage of ruxolitinib based on frequent dose adjustments; 0% wastage was assumed for fedratinib.	Reasonable. Clinical experts consulted by CADTH indicated that the sponsor's assumption of zero wastage for fedratinib was appropriate given that dose adjustments would likely occur in 100 mg increments which is consistent with the 100 mg strength of fedratinib. The sponsor's assumption of 5% wastage is consistent with the CADTH Pan-Canadian Oncology Drug Review's Expert Committee Recommendations for ruxolitinib which noted that wastage related to ruxolitinib dose adjustments should be considered.[25]

AML = acute myeloid leukemia; BAT = best available therapy; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQol 5-Dimensions questionnaire; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; MF = myelofibrosis; vs. = versus .

Base-Case Results: JAKi-Naive Subgroup

CADTH undertook reanalyses that addressed limitations within the model, as summarized in Table 6. Notably, in the CADTH base case, treatment response was based on a composite outcome of a reduction in spleen volume or patient-reported symptoms; however, owing to a lack of data, duration of treatment response remains based on spleen volume reduction.

The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts.

CADTH undertook a stepped analysis, incorporating each change proposed in Table 6 into the sponsor's base case to highlight the impact of each change (Table 7; disaggregated results are presented in Table 15 in Appendix 4).

In CADTH's base case, fedratinib was associated with higher costs (incremental, $231,996) and higher QALYs (incremental, 0.557) than BAT over a 35-year horizon. The ICER for fedratinib versus BAT was $416,446 per QALY. There is a 0% probability that fedratinib is optimal compared to BAT at a WTP threshold of $50,000 per QALY. The incremental QALYs with fedratinib treatment in the first year was 0.046, indicating that the majority of the incremental benefits were accrued in the post-trial period and were derived on the basis of extrapolated trial findings rather than observed benefit. (While the median treatment duration in the BEACON trial was 24 weeks, the minimum analysis horizon in the sponsor's model was

1 year.) Drug acquisition costs for fedratinib are key drivers of the ICER, representing 82.6% of total costs (Table 15).

Scenario Analysis Results

A price reduction analysis was performed based on the sponsor's base case and CADTH's reanalysis (Table 8). For the sponsor's base case, only the pairwise comparison against BAT is reported for comparability to the CADTH reanalysis. For all price reductions explored (including if fedratinib is offered at no cost), fedratinib would not be considered cost-effective compared to BAT at a WTP threshold of $50,000 per QALY. This observation was driven by the fact that CADTH kept with the sponsor's assumption that a proportion of fedratinib nonresponders would subsequently receive ruxolitinib as second-line treatment before proceeding to third-line BAT (without ruxolitinib).

Several scenario and sensitivity analyses were conducted on the CADTH base case. These scenario analyses explored the impact of the following model parameters and assumptions: the definition of treatment effectiveness, assuming that patients with no treatment response at 24 weeks discontinue treatment, and the inclusion of costs related to thiamine testing, adopting a societal perspective that captures productivity costs and revising the composition of second-line BAT to remove ruxolitinib (Table 16).

Of these, CADTH's ICER most notably reduced when it was assumed patients would not receive ruxolitinib following nonresponse or loss of response to fedratinib ($88,698 per QALY). This highlights that the costs of subsequent therapies can be a key driver within the analysis in terms of what treatments are permitted as second-line therapy. Furthermore, the model was sensitive to the alternative parametric curve (i.e., Weibull) that was chosen for

Table 6: CADTH Revisions to the Submitted Economic Evaluation — JAKi-Naive Subgroup

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Comparators	Ruxolitinib and BAT	BAT
2. Definition of treatment effectiveness	Spleen response (≥35% reduction from baseline)	Spleen response (≥35% reduction from baseline) or symptom response (≥50% reduction in Total Symptom Score from baseline)[a]
3. Composition of BAT as a comparator	Include hydroxyurea, prednisone, danazol, busulfan, cytarabine, peginterferon alfa-2a, or watchful waiting (proportions reported in Table 12)	50% of patients on hydroxyurea, 5% on peginterferon alpha-2a, and the remainder on watchful waiting
4. Parametric extrapolation of overall survival for fedratinib	Weibull parametric curve	Gompertz parametric curve
5. Cost of thiamine testing	Included	Not included
CADTH base case	—	1 + 2 + 3 + 4 + 5

BAT = best available therapy; JAKi = Janus kinase inhibitor.

[a]Duration of treatment response remained based on spleen volume reduction owing to a lack of provided data for spleen and treatment response.

the extrapolation of OS for fedratinib ($187,688 per QALY), indicating that assumed survival benefit modelled for fedratinib was a key driver within the CADTH base case. However, as noted by the clinical experts consulted by CADTH, the Weibull distribution was considered to provide an estimation for fedratinib that was too optimistic with respect to OS.

Exploratory Analysis Results

CADTH undertook 2 exploratory analyses: an assessment of the cost-effectiveness of fedratinib compared to ruxolitinib in JAKi-naive patients, and an assessment of the cost-effectiveness of fedratinib compared to BAT in ruxolitinib-experienced patients. These analyses should be considered exploratory owing to the absence of direct clinical comparative data, as well as the substantial uncertainty associated with the findings of the sponsor's indirect treatment comparisons, as noted in the CADTH Clinical Review. Given the aforementioned limitations with the suboptimal definition of treatment response, scenario

Table 7: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)
Sponsor's base case	BAT	46,186	1.96	Reference
	Ruxolitinib	268,149	3.77	122,980[a]
	Fedratinib	362,229	3.81	2,119,620
CADTH reanalysis 1	BAT	46,186	1.96	Reference
	Fedratinib	362,229	3.81	170,903
CADTH reanalysis 2	BAT	46,133	1.93	Reference
	Ruxolitinib	297,510	3.79	134,978
	Fedratinib	383,093	3.71	Dominated (by ruxolitinib)
CADTH reanalysis 3	BAT	47,241	1.95	Reference
	Ruxolitinib	267,469	3.74	122,942
	Fedratinib	360,505	3.79	2,068,722
CADTH reanalysis 4	BAT	46,320	1.96	Reference
	Fedratinib	260,515	2.51	Extendedly dominated
	Ruxolitinib	268,327	3.75	123,933
CADTH reanalysis 5	BAT	46,261	1.97	Reference
	Ruxolitinib	268,717	3.78	123,164
	Fedratinib	362,717	3.83	1,798,144
CADTH base case (1 + 2 + 3 + 4 + 5)	BAT	47,393	1.92	Reference
	Fedratinib	279,388	2.48	416,446

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

[a]The results for the sequential analyses involving ruxolitinib may not be stable between model runs owing to small incremental QALYs between ruxolitinib and fedratinib. The CADTH base case, in which ruxolitinib has been removed, is stable between model runs.

analyses were further conducted which varied its definition and whether treatment response would lead to patient discontinuation within these exploratory analyses.

JAKi-Naive Subgroup

CADTH's exploratory analyses adopted assumptions similar to those in the CADTH base-case reanalysis, with the exception of OS. On the basis of clinical expert's feedback, treatment efficacy (treatment response, duration of treatment response, OS) was assumed to be equivalent for fedratinib and ruxolitinib. Clinical experts indicated that the median OS predicted by Weibull distribution for ruxolitinib (approximately 5 years) was too optimistic; however, the structure of the sponsor's model did not permit a shorter median OS to be adopted for the OS of ruxolitinib. As such, the Weibull distribution was adopted for both to fedratinib and ruxolitinib to ensure the predicted OS would be similar across JAKis.

Among JAKi-naive patients, CADTH's exploratory analyses found that fedratinib was dominated by ruxolitinib (i.e., associated with higher costs [incremental, $97,186] and lower QALYs [incremental, −0.06] compared to ruxolitinib; Table 18). Owing to the limitations noted above for OS, the ICER for ruxolitinib compared with BAT is likely underestimated.

Ruxolitinib-Experienced Subgroup

CADTH's exploratory analyses adopted assumptions similar to those in the CADTH base-case reanalysis, where applicable, for the ruxolitinib-experienced subgroup. Clinical experts indicated that the OS predicted by the sponsor's chosen parametric distribution (Gompertz) for fedratinib was too optimistic (median survival: approximately 3 years) compared with BAT (median survival: approximately 1 year) for patients after a ruxolitinib failure. However, there were no parametric curves provided that had better face validity. Thus, the Gompertz distribution was maintained in these exploratory analyses for fedratinib. As such, the OS predicted for fedratinib is likely overestimated. Additionally, ruxolitinib was removed as part

Table 8: CADTH Price Reduction Analyses

Analysis	ICERs for fedratinib vs. BAT ($/QALY)	
Price reduction	Sponsor base case	CADTH reanalysis
No price reduction	170,903	416,446
10%	161,304	379,565
20%	153,678	352,492
30%	140,459	313,352
40%	130,817	283,846
50%	123,006	245,610
60%	107,992	227,108
70%	100,144	185,606
80%	90,982	154,301
90%	80,468	125,685
99.9%	70,537	93,654

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus .
Note: Based on the publicly available prices of the comparator treatments.

of the basket of BAT comparators, as clinical experts consulted by CADTH indicated that patients would not continue to receive ruxolitinib after a previous treatment failure.

Among ruxolitinib-experienced patients, CADTH's exploratory analyses found that fedratinib was associated with higher costs (incremental, $125,679) and higher QALYs (incremental, 0.67) compared with BAT (ICER $187,605 per QALY; Table 18). However, cautious interpretation is required owing to a lack of direct evidence, highly uncertain comparative effectiveness, and overestimated OS benefits.

Issues for Consideration

- Thiamine testing is indicated before initiating fedratinib treatment and during treatment.[2] Thiamine testing is not uniformly reimbursed publicly across Canadian jurisdictions, and was removed from the CADTH base case to reflect jurisdictions who do not cover thiamine testing. Cost of thiamine testing was reintroduced in a scenario analysis to assess its impacts in jurisdiction with public reimbursement.
- The Provincial Advisory Group indicated the potential for indication creep to patients with polycythemia vera or graft-versus-host disease. These patients were considered outside the scope for the current review and, as such, the cost-effectiveness in these populations is unknown.
- Clinical experts consulted for this review indicated that there may be a preference to use fedratinib as second-line treatment (i.e., after ruxolitinib) owing to greater familiarity with ruxolitinib. As indicated by the budget impact assessment (BIA; Appendix 5), this approach is expected to add to the total budget of treating MF, rather than displacing costs. However, owing to the limitations identified (lack of direct evidence and highly uncertain comparative effectiveness), CADTH explored cost-effectiveness of fedratinib in this population in scenario analyses only (Appendix 4), and these findings should be interpreted with caution.

Overall Conclusions

Fedratinib may reduce spleen volume and disease-related symptoms compared to BAT, although the effects of fedratinib on health-related quality of life are uncertain. The comparative effects of fedratinib relative to other JAKis (i.e., ruxolitinib) are highly uncertain owing to a lack of direct comparative evidence and limitations within the sponsor's indirect treatment comparisons. Similarly, the long-term effects of fedratinib in patients with MF are uncertain.

CADTH undertook analyses to address limitations in the sponsor's submission, including basing treatment response on spleen volume reduction and patient-reported symptoms, revising the composition of the basket of treatments that define the BAT comparator, adopting an alternative parametric distribution for the extrapolation of fedratinib OS, and removing costs related to thiamine testing. CADTH could not address the lack of direct comparative clinical data or uncertainty with the results of the sponsor's indirect treatment comparisons. As such, CADTH reanalyses assessed the cost-effectiveness of fedratinib relative to BAT among JAKi-naive patients. Based on these revisions, fedratinib is not cost-effective at a WTP threshold of $50,000 per QALY among JAKi-naive patients. Specifically, fedratinib was associated with an ICER of $416,446 per QALY gained compared to BAT. These findings were most sensitive to the long-term OS of patients taking fedratinib and were driven by the price of fedratinib. For the CADTH base case, none of the simulations resulted in fedratinib being optimal at a WTP threshold of $50,000 per QALY among JAKi-naive patients owing to the cost of subsequent therapies. CADTH kept with the sponsor's assumption that a

proportion (44.9%) of those who did not respond or lose response to fedratinib (44.9%) would be managed by ruxolitinib as second-line therapy.

The CADTH reanalyses are highly uncertain owing to a lack of long-term follow-up data and immature OS data from the JAKARTA trial. Of concern is the fact that the majority of the incremental benefits with fedratinib treatment were gained in the post-trial period on the basis of extrapolated trial findings rather than observed benefits. Further, although the CADTH base case redefined treatment response based on patient-reported symptoms and/or spleen volume reduction, this definition of treatment response remains suboptimal and the threshold for treatment discontinuation was not aligned with clinical practice.

CADTH conducted exploratory analyses to explore the cost-effectiveness of fedratinib compared with ruxolitinib in JAKi-naive patients. CADTH exploratory analyses adopted changes implemented in the CADTH base-case reanalysis (i.e., definition of treatment effectiveness, composition of BAT, removal of thiamine testing costs). Additionally, the efficacy of fedratinib and ruxolitinib was assumed to be equivalent, on the basis of clinical experts' input and a lack of direct head-to-head evidence. In this exploratory analysis, fedratinib is dominated by ruxolitinib (i.e., fedratinib is associated with higher costs and fewer QALYs compared to ruxolitinib) among JAKi-naive patients.

Clinical experts consulted by CADTH for this review indicated that fedratinib would most likely be used in patients who had previously had a ruxolitinib treatment failure. CADTH conducted exploratory analyses in this population to assess the cost-effectiveness of fedratinib compared with BAT. In addition to the changes implemented in the CADTH base case, in this exploratory analysis, ruxolitinib was removed from the basket of BAT treatments, utilities were assumed to be equal between men and women, and nonresponders were assumed to incur no utility benefit. Among ruxolitinib-experienced patients, CADTH's exploratory analyses suggest that fedratinib is more costly and more effective than BAT, with an ICER of $187,605 per QALY. Cautious interpretation is required owing to the absence of direct evidence and the identified limitations with the sponsor's indirect treatment comparisons.

Overall, it is highly unlikely that fedratinib would be considered a cost-effective use of Canadian health care resources, at a $50,000 per QALY threshold, even if a substantial price reduction is obtained.

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Appendix 1: Cost Comparison Table

Note that this appendix has been formatted for accessibility but has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 9: CADTH Cost Comparison Table for Prescription Drugs Indicated for Myelofibrosis

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Cost per 28-day cycle ($)
Fedratinib (Inrebic)	100 mg	Cap	84.3930[a]	400 mg daily	337.57	9,452
Ruxolitinib (Jakavi)	5 mg 10 mg 15 mg 20 mg	Tab	86.6275[b]	5 mg to 20 mg twice daily	173.26	4,851

[a]Sponsor-submitted price.

[b]Ontario Exceptional Access Program (accessed January 2020).[14]

Table 10: CADTH Cost Comparison Table for Treatments Used Off-Label for Myelofibrosis

Treatment	Strength	Form	Price	Recommended dosage	Daily cost ($)	Cost per 28-day cycle ($)
Hydroxyurea	500 mg	Cap	1.0203[a]	500 mg to 2 g daily	1.02 to 4.08	29 to 114
Peginterferon alpha-2a (Pegasys)	360 mcg/mL	Single-use pre-filled syringe or autoinjector 1 × 0.5 mL	419.7000[b]	90 mcg to 180 mcg weekly	29.98 to 59.96	839 to 1,679

Note: Prices were accessed January 2021 and do not include dispensing fees. All doses for off-label therapies were provided by clinical experts consulted by CADTH for this review.

[a]Ontario Drug Benefit Formulary.[15]

[b]Ontario Exceptional Access Program.[14]

Appendix 2: Submission Quality

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 11: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	The interventions included as part of the "best available therapy" comparator arm do not reflect clinical management of myelofibrosis in Canada (see main report).
Model has been adequately programmed and has sufficient face validity	No	No trace was provided to understand how patients progress between health states. The sponsor's model permits improbable values, such as negative amounts of time spent in the AML health state (see main report).
Model structure is adequate for decision problem	No	The sponsor's model was unnecessarily complex (see main report).
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	A number of discrepancies were noted between the Pharmacoeconomic Report[1] and the sponsor's Excel model. For example, peginterferon alfa-2a was not listed as a part of BAT in the Pharmacoeconomic Report; however, in the Excel model, 1.89% of patients were assumed to receive peginterferon alfa-2a as part of BAT in the JAKi-naive group. Other discrepancies were noted within the Pharmacoeconomic Report. For example, on page 127, the sponsor states "In the base case, disutilities for adverse events were included;" while on page 128, the sponsor states "Adverse event disutilities not applied in the base case." Based on the submitted Excel file, disutilities appear to have been applied in the sponsor's base case.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 12: Composition and Drug Acquisition Costs for Best Available Therapy in the Sponsor's Pharmacoeconomic Model

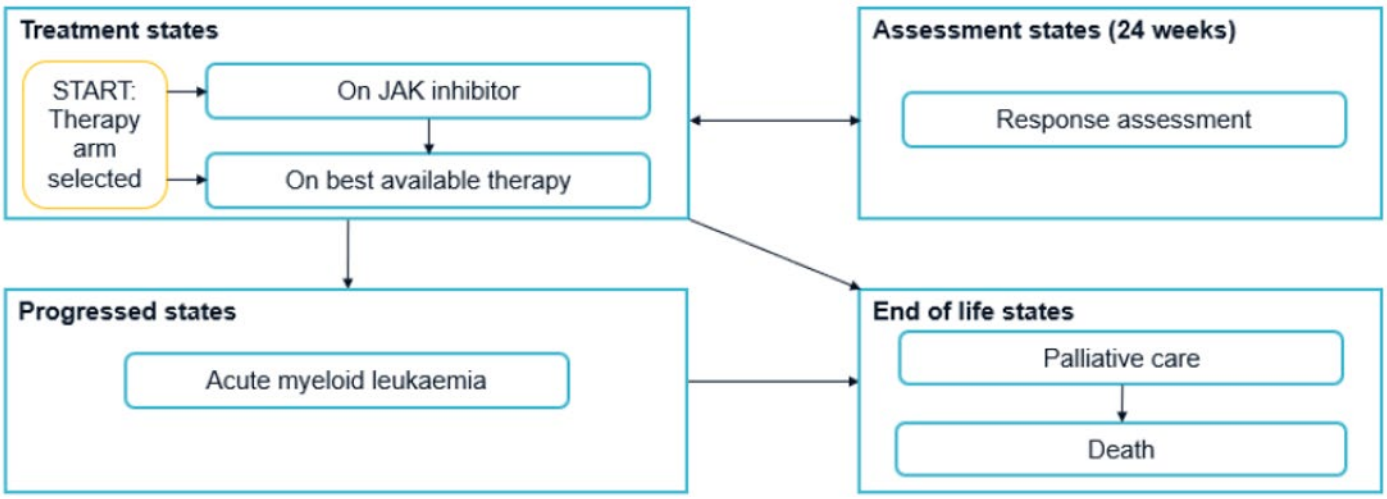
Treatment	JAKi-naive patients[a]	Ruxolitinib-experienced patients[b]	After 2 JAK inhibitors[b]
Percentage of patients assumed to receive each treatment			
Busulfan	1.8%	NA	NA
Cytarabine	1.8%	NA	NA
Danazol	3.7%	4.8%	10.9%
Hydroxyurea	55.2%	18.3%	41.4%
Prednisone/prednisolone	10.1%	12.5%	28.3%
Peginterferon alfa-2a	1.8%	NA	NA
Ruxolitinib	NA	44.90%	NA
Watchful waiting	25.47%	19.4%	19.4%
Drug acquisition costs ($)			
Annual cost	1,225	30,125	659

NA = not applicable.

[a]Based on the BAT arm of the PERSIST-1 study[22] and clinical experts' opinion.[1]

[b]Based on the BAT arm of the PERSIST-2 study[23] and clinical experts' opinion.[1]

Figure 1: Model Structure



JAK = Janus kinase.

Source: Sponsor's pharmacoeconomic submission.[1]

Parametric Curves

Table 13: Summary of the Clinical Data and Statistical Distribution for the Extrapolation of Observed Effects in the Sponsor's Base Case

Outcome	Treatment group	Source of clinical data	Statistical distribution (sponsor's base case)
JAKi-naive subgroup			
Time to treatment discontinuation[a]	Fedratinib	JAKARTA	Weibull
	Ruxolitinib	COMFORT-II	Exponential
	BAT	NA	NA
Duration of treatment response	Fedratinib	JAKARTA	Exponential
	Ruxolitinib	COMFORT-I[b]	Generalized gamma
	BAT	NA	NA
Overall survival	Fedratinib	JAKARTA	Weibull
	Ruxolitinib	COMFORT-I, COMFORT-II[c]	Weibull
	BAT	JAKARTA	Gompertz
Ruxolitinib-experienced subgroup			
Time to treatment discontinuation[a]	Fedratinib	JAKARTA2	Exponential
	BAT	NA	NA
Duration of treatment response	Fedratinib	JAKARTA2[d]	Log-normal
	BAT	NA	NA
Overall survival	Fedratinib	JAKARTA2[d]	Gompertz
	BAT	Schain 2019[26,e]	Weibull

BAT = Best available therapy; NA = not applicable.

[a]After 24-week assessment of treatment response.

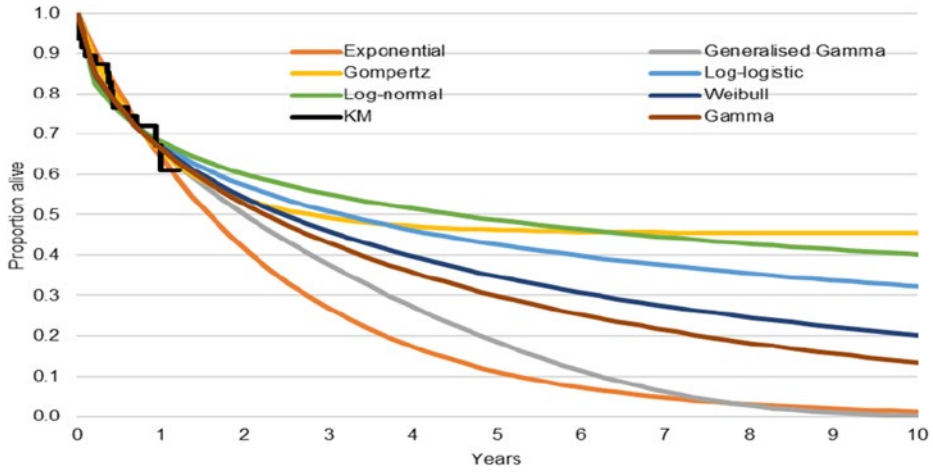
[b]Five-year data.

[c]Pooled analysis of COMFORT-I and II data.[27]

[d]Intermediate-2/high-risk subgroup.

[e]Patients with myelofibrosis who received a "conventional agent" (glucocorticoid, hydroxyurea, busulfan, danazol, peginterferon alfa-2a, thalidomide) after ruxolitinib treatment failure (n = 190).[26]

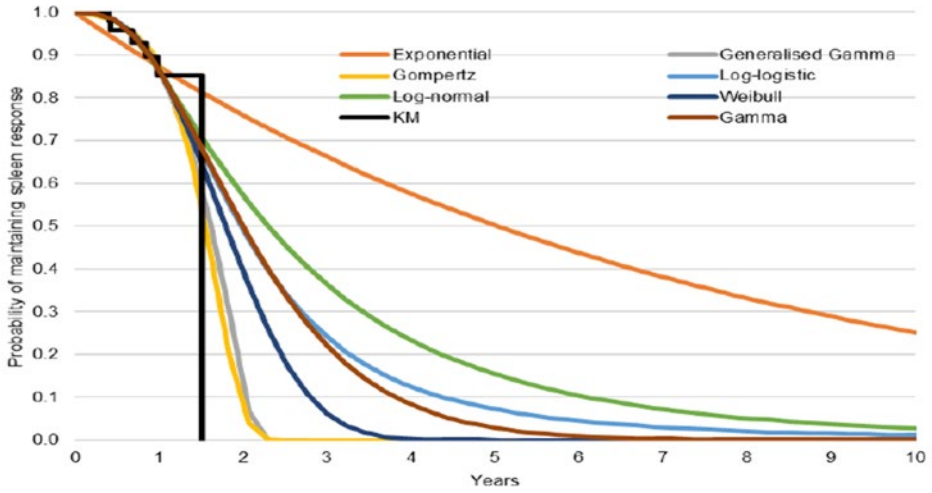
Figure 2: Kaplan-Meier Plot From the JAKARTA Trial and Extrapolations for Time to Treatment Discontinuation — Fedratinib (JAKi-Naive)



KM = Kaplan-Meier.

Source: Sponsor's pharmacoeconomic submission.[1]

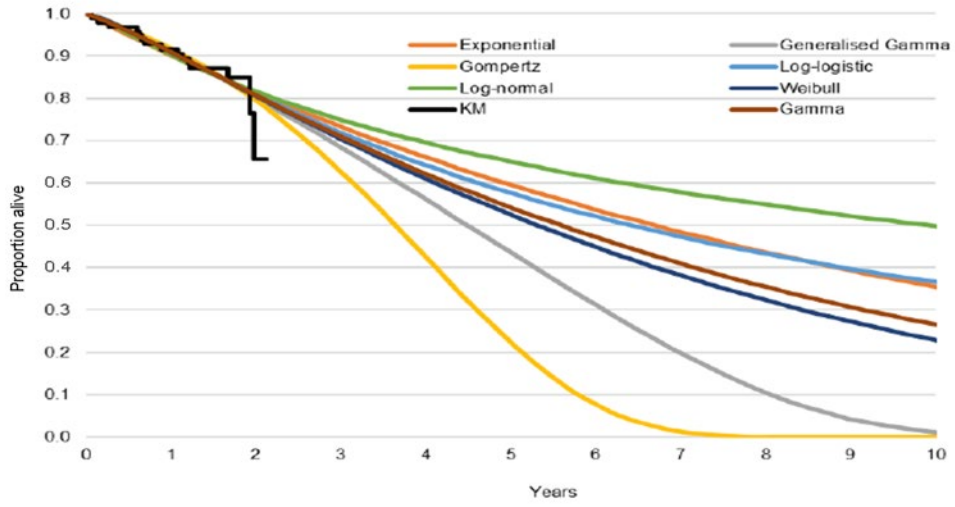
Figure 3: Kaplan-Meier Plot From the JAKARTA Trial and Extrapolations for Duration of Spleen Response — Fedratinib (JAKi-Naive)



KM = Kaplan-Meier.

Source: Sponsor's pharmacoeconomic submission.[1]

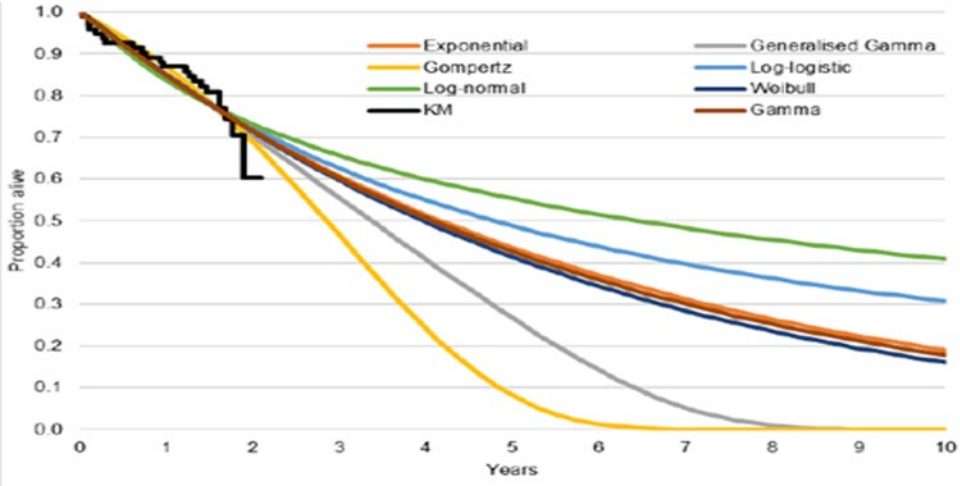
Figure 4: Kaplan-Meier Plot From the JAKARTA Trial and Extrapolations for Overall Survival — Fedratinib (JAKi-Naive)



KM = Kaplan-Meier.

Source: Sponsor's pharmacoeconomic submission.[1]

Figure 5: Kaplan-Meier Plot From the JAKARTA Trial and Extrapolations for Overall Survival — Best Available Therapy (JAKi-Naive)



KM = Kaplan-Meier.

Source: Sponsor's pharmacoeconomic submission.[1]

Figure 6: Scatterplot of the Sponsor's Probabilistic Base Case — JAKi-Naive Patients

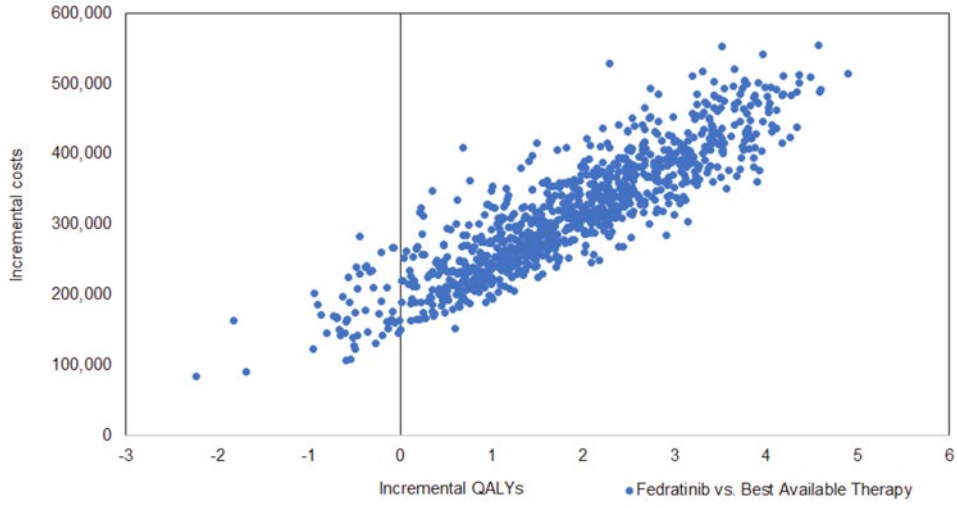


Table 14: Probabilistic Results of the Sponsor's Key Scenario Analyses — JAKi-Naive Patients

Scenario*	Treatment	Sequential ICER ($/QALY)
Sponsor's base case	BAT	Reference
	Ruxolitinib	122,980
	Fedratinib	2,119,620
1. Nonresponders at 24 weeks continued to receive JAKi treatment (stopping rule disabled)	BAT	Reference
	Ruxolitinib	131,343
	Fedratinib	Dominated
2. Treatment effectiveness defined as a spleen response (≥ 35% reduction in spleen volume from baseline) OR symptom response (≥ 50% reduction in Total Symptom Score from baseline)	BAT	Reference
	Ruxolitinib	134,787
	Fedratinib	8,874,758
3. Overall survival for fedratinib assumed to be equal to ruxolitinib	BAT	Reference
	Ruxolitinib	123,381
	Fedratinib	Dominated
4. Time to discontinuation, duration of response, and overall survival for fedratinib assumed to be equal to ruxolitinib	BAT	Reference
	Ruxolitinib	123,648
	Fedratinib	6,623,529

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; QALY = quality-adjusted life-year.

*Scenario analyses conducted by the sponsor in which there was a large effect on the ICER.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Detailed Results of CADTH Base Case

Table 15: Disaggregated Summary of CADTH's Economic Evaluation Results — JAKi-Naive Patients

Parameter	Fedratinib	BAT	Incremental	Percentage (of total incremental)
Discounted LYs				
Health state				
On JAKi	1.472	0.000	1.472	212.1%
On BAT	1.963	2.695	−0.733	−105.6%
AML/progressed	0.011	0.012	−0.001	−0.1%
Palliative care	0.095	0.140	−0.045	−6.5%
Total	3.541	2.847	0.694	100%
Discounted QALYs				
Health state				
On JAKi	1.09	0.000	1.09	196.1%
On BAT	1.33	1.84	−0.51	−91.7%
AML/progressed	0.01	0.01	−0.001	−0.2%
Palliative care	0.05	0.07	−0.02	−4.1%
Total	2.49	1.92	0.56	100%
Discounted costs ($)				
Health state				
On JAKi	191,697	0	191,697	82.6%
On BAT	78,347	33,961	44,386	19.1%
AML/progressed	790	859	−69	0%
Palliative care	8,554	12,572	−4,018	−1.7%
Total	279,388	47,393	231,996	100%
Category[a]				
Drug acquisition	236,334	4,675	231,659	NA
JAKi	235,770	0	235,770	NA
Administration	0	0	0	NA
Adverse events	78	54	24	NA

Parameter	Fedratinib	BAT	Incremental	Percentage (of total incremental)
Resource use	33,633	29,232	4,401	NA
ICER ($/QALY)	416,446			

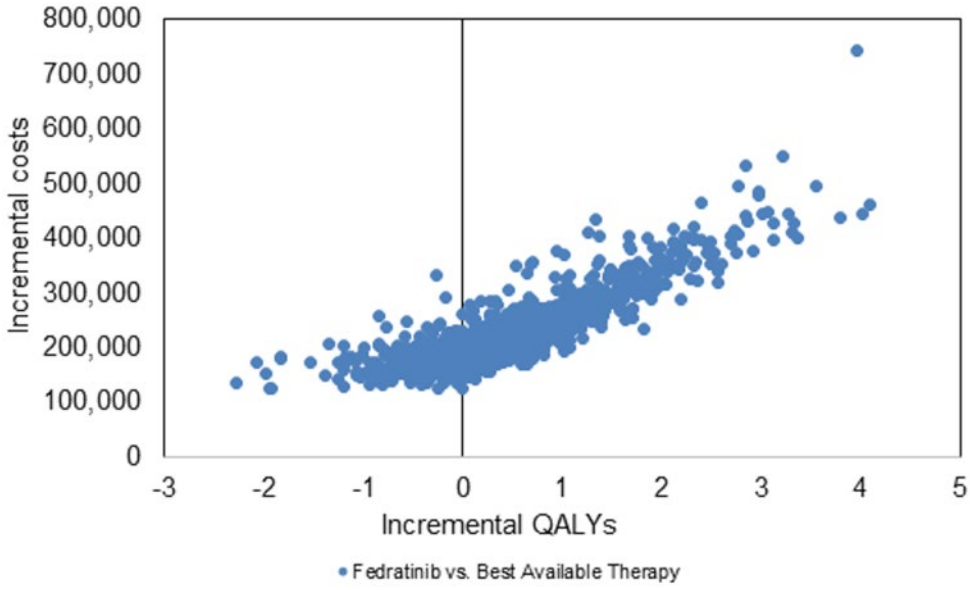
AML = acute myeloid leukemia; BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus Kinase inhibitor; LY = life-year; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

[a]Costs by category do not sum to Total Costs.

Scenario Analyses

Figure 7: Scatterplot of the CADTH Probabilistic Base Case



ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 16: CADTH Scenario Analyses — JAKi-Naive Subgroup

Parameter	CADTH base case	CADTH scenario
Scenario Analyses		
1. Definition of treatment effectiveness	Defined as spleen response (≥35% reduction from baseline) OR symptom response (≥50% reduction in Total Symptom Score from baseline).	Defined as spleen response (≥35% reduction from baseline).
2. Definition of treatment effectiveness	As above	Defined as symptom response (≥50% reduction from baseline).
3. Stopping rule	Enabled (patients with less than 35% reduction in spleen volume from baseline discontinued JAKi treatment).	Disabled (discontinuation of treatment determined only by 'time-to-discontinuation' parametric curve).
4. Overall survival	Based on Gompertz parametric curve.	Based on Weibull parametric curve.
5. Thiamine testing	The cost of thiamine testing was removed from the base-case analysis, as it is inconsistently reimbursed by public payers across Canada.	Cost of thiamine testing included.
6. Perspective	Public health care payer	Societal (productivity costs included).
7. Composition of second-line BAT	Includes ruxolitinib (44.9%)	Removes ruxolitinib (i.e., assumes patients can only receive 1 JAKi within their lifetime)

BAT = best available therapy.

Figure 8: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis

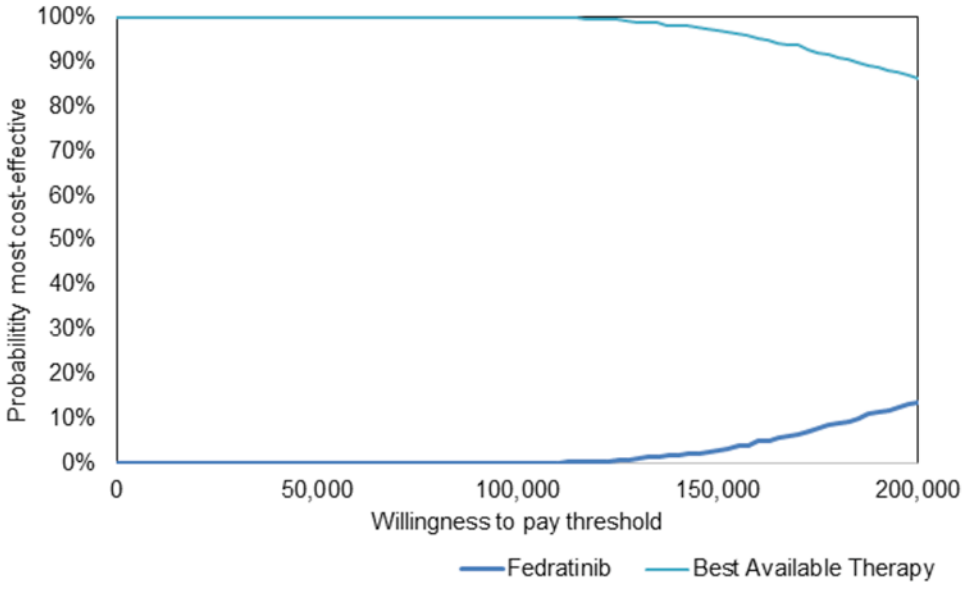


Table 17: Probabilistic Results of CADTH's Scenario Analyses

Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Scenario 1: Treatment effectiveness defined as spleen response (≥35% reduction from baseline)			
BAT	47,396	1.95	Reference
Fedratinib	260,315	2.51	386,126
Scenario 2: Treatment effectiveness defined as symptom response (≥50% reduction from baseline)			
BAT	47,281	1.98	Reference
Fedratinib	251,614	2.56	353,487
Scenario 3: Treatment discontinuation is determined by time-to-discontinuation curves for all patients (i.e., nonresponders are not assumed to discontinue treatment immediately at 24 weeks)			
BAT	47,618	1.93	Reference
Fedratinib	296,111	2.48	452,835
Scenario 4: Overall survival of patients taking fedratinib based on Weibull parametric curve			
BAT	47,009	1.90	Reference
Fedratinib	380,486	3.68	187,688
Scenario 5: Thiamine testing costs included			
BAT	47,718	1.94	Reference
Fedratinib	278,805	2.47	439,807
Scenario 6: Societal perspective			
BAT	61,399	1.95	Reference
Fedratinib	293,918	2.47	429,229
Scenario 7: Composition of BAT in second-line therapy (i.e., removal of ruxolitinib)			
BAT	47,545	0.108	Reference
Fedratinib	226,889	0.155	88,698

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

Exploratory Scenario Analyses

JAKi-Naive Subgroup

Exploratory analyses were undertaken to assess the cost-effectiveness of fedratinib relative to ruxolitinib and BAT. The following changes that were implemented in the CADTH base-case reanalysis remained in the exploratory analyses: definition of treatment effectiveness, composition of BAT, removal of thiamine testing costs. Additionally, the efficacy of fedratinib and ruxolitinib (treatment response, duration of treatment response, OS) were assumed to be equivalent, on the basis of clinical experts' input and a lack of direct head-to-head evidence. OS was assumed to be equivalent for fedratinib and ruxolitinib (i.e., a Weibull extrapolation of COMFORT-I and COMFORT-II ruxolitinib data[27] was adopted for both JAKis); however, clinical experts considered the OS predicted to be too optimistic.

The summary results of the CADTH exploratory reanalyses for JAKi-naive patients are presented in Table 18.

Table 18: CADTH Exploratory Analyses — JAKi-Naive Patients

Analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)
Exploratory analysis				
Treatment effectiveness defined as spleen response (≥35% reduction from baseline) or symptom response (≥50% reduction from baseline)	BAT	47,404	1.92	Reference
	Ruxolitinib	294,428	3.77	133,632
	Fedratinib	391,614	3.72	Dominated
Scenario analyses				
Scenario 1: Treatment effectiveness defined as spleen response (≥35% reduction from baseline)	BAT	48,110	1.99	Reference
	Ruxolitinib	270,321	3.76	126,159
	Fedratinib	337,242	3.73	Dominated
Scenario 2: Treatment effectiveness defined as symptom response (≥50% reduction from baseline)	BAT	47,998	2.01	Reference
	Ruxolitinib	278,574	3.82	127,715
	Fedratinib	355,515	3.79	Dominated
Scenario 3: Treatment discontinuation is determined by time-to-discontinuation curves for all patients[a]	BAT	47,470	1.92	Reference
	Ruxolitinib	302,049	3.77	138,258
	Fedratinib	409,689	3.73	Dominated

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a]Patients who did not have a treatment response at the 24-week assessment were assumed to remain on JAKi treatment, with discontinuation based on time-to-discontinuation curves.

Note: The analyses are based on the publicly available Ontario Drug Benefit Exceptional Access Program list price for ruxolitinib.[14] Actual prices paid by public plans for ruxolitinib are unknown.

Ruxolitinib-Experienced Subgroup

Exploratory analyses were undertaken to assess the cost-effectiveness of fedratinib relative to BAT. Changes implemented in the CADTH base-case reanalysis for JAKi-naive patients were retained here: definition of treatment effectiveness, composition of BAT, removal of thiamine testing costs. Ruxolitinib was removed from the basket of BAT treatments, as indicated by clinical experts consulted by CADTH. Additionally, utilities were assumed to be equal between men and women, and nonresponders were assumed to incur no utility benefit.

Clinical experts consulted by CADTH indicated that the parametric curves provided by the sponsor for OS for fedratinib among ruxolitinib-experienced patients were too optimistic (median OS about 3 years). Owing to limitations with the data available, CADTH was not able to address this limitation.

The summary results of the CADTH exploratory and scenario reanalyses for ruxolitinib-experienced patients are presented in Table 19.

Table 19: CADTH Exploratory Analyses — Ruxolitinib-Experienced Patients

Analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)
Exploratory analysis				
Treatment effectiveness defined as spleen response (≥35% reduction from baseline) or symptom response (≥50% reduction from baseline)	BAT	37,911	1.66	Reference
	Fedratinib	163,590	2.33	187,605
Scenario analyses				
Scenario 1: Treatment effectiveness defined as spleen response (≥35% reduction from baseline)	BAT	38,705	1.69	Reference
	Fedratinib	151,138	2.33	174,671
Scenario 2: Treatment effectiveness defined as symptom response (≥50% reduction from baseline)	BAT	38,318	1.68	Reference
	Fedratinib	127,351	2.29	147,100
Scenario 3: Treatment discontinuation is determined by time-to-discontinuation curves for all patients[a]	BAT	38,422	1.68	Reference
	Fedratinib	184,782	2.36	216,195

BAT = best available therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

[a]Patients who did not have a treatment response at the 24-week assessment were assumed to remain on JAKi treatment, with discontinuation based on time-to-discontinuation curves.

Appendix 5: Submitted BIA and CADTH Appraisal

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 20: Summary of Key Take-Aways

Key Take-Aways of the BIA
• CADTH identified the following key limitations with the sponsor's analysis: ◦ The composition of BAT does not reflect the clinical management of myelofibrosis (MF) in Canada. ◦ Patients were assumed to remain on JAKis for the 3-year analysis horizon, which is inconsistent with the sponsor's economic analysis. ◦ Inclusion of "clinical trials" as part of the current intervention mix is not appropriate. ◦ Costs related to thiamine testing were included despite variable public coverage. • CADTH reanalysis included: changing the composition of the BAT treatment group, aligning BIA inputs to those applied in the pharmacoeconomic analysis (e.g., the annual cost of BAT and ruxolitinib), incorporating JAKi treatment discontinuation, removing clinical trials as a comparator, and removing the cost of thiamine testing. • Based on the CADTH reanalyses, the budget impact from the introduction of fedratinib for the full Health Canada–approved indication is expected to be $13,266,154 in Year 1, $16,491,031 in Year 2, and $13,442,406 in Year 3 with a 3-year total budget impact of $43,199,591 when considering drug costs only. The 3-year budget impact of reimbursing fedratinib among the JAKi-naive subgroup was estimated to be $4,622,039 and $38,577,552 among the ruxolitinib-experienced subgroup. The estimated budge impact is sensitive to the prevalence of MF and the expected treatment duration for JAKis.

Summary of Sponsor's BIA

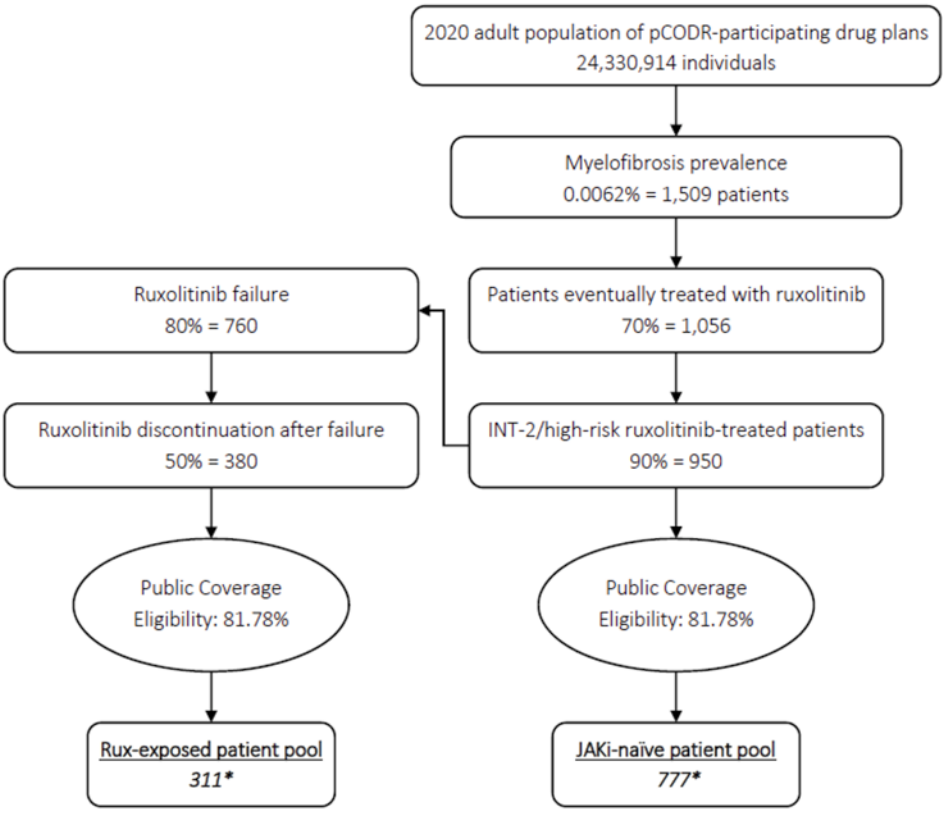
The sponsor submitted a budget impact analysis[28] estimating the incremental budget impact of reimbursing fedratinib for the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF. The BIA was undertaken from the perspective of the Canadian public drug plans over a 3-year time horizon, and the sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Non-Insured Health Benefits Program. Key inputs to the BIA are documented in Figure 9 and Table 20. The sponsor performed subgroup analyses for patients with no prior JAKi experience (JAKi-naive) and for those with previous ruxolitinib use (ruxolitinib-experienced). The reference scenario in the JAKi-naive subgroup reflected ruxolitinib or BAT, while the treatments in the ruxolitinib-experienced subgroup consisted of BAT or clinical trials.

The sponsor used an epidemiologic approach to estimate the number of eligible patients with MF (Figure 9). The estimated prevalence of MF was based on the reported number of patients with MF in Canada in 2016.[29] The remaining parameters to derive the size of the target population were based on sponsor assumptions. The sponsor assumed that 50% of patients would be at least 65 years of age and would be eligible for public payer coverage based on the median ages in the JAKARTA (64 years) and JAKARTA2 (67 years) trials; the remaining 50% of patients were assumed to have access reflective of coverage rates for adult patients aged less than 65 years in each jurisdiction. In the sponsor's base case, costs related to drug acquisition, dispensing fees, markup, and thiamine testing were captured. A scenario analysis was conducted from a health care payer perspective, which additionally included costs related to grade ≥3 adverse events.

Key assumptions to the BIA included:

- Half of the patients in the BAT group were assumed to continue on a "suboptimal" dose of ruxolitinib after a prior treatment failure.[28]
- Patients would remain on JAKis for the entire duration of the BIA.

Figure 9: Sponsor's Estimation of the Size of the Eligible Population



*Annual growth rate of 1.55% then applied in each of the subsequent years in the analysis

Source: Sponsor's pharmacoeconomic submission.[28]

Table 21: Summary of Key Model Parameters

Parameter	Sponsor's estimate
Target population	
Annual population growth	1.55%
Number of patients eligible for drug under review[a]	(Year 1 / year 2 / year 3)
JAKi-naive	802 / 814 / 827
Ruxolitinib-experienced	321 / 326 / 331
Market uptake (3 years)	
Uptake (reference scenario)	
JAKi-naive population	[redacted]
Fedratinib	[redacted]
Ruxolitinib	[redacted]
BAT	[redacted]
Ruxolitinib-experienced population[b]	
Fedratinib	[redacted]
Ruxolitinib	[redacted]
BAT	[redacted]
Clinical trials	[redacted]
Uptake (new drug scenario)[b]	
JAKi-naive population	
Fedratinib	[redacted]
Ruxolitinib	[redacted]
BAT	[redacted]
Ruxolitinib-experienced population	
Fedratinib	[redacted]
BAT	[redacted]
Clinical trials	[redacted]
Cost of treatment (per patient)	
Annual cost of treatment[c,d]	
JAKi-naive population	
Fedratinib[e]	$122,065
Ruxolitinib	$62,522
BAT[f]	$744
Ruxolitinib-experienced population	
Fedratinib[e]	$122,065

Parameter	Sponsor's estimate
BAT[g]	$28,502

BAT = best available therapy; JAKi = Janus kinase inhibitor; Y = year.

[a]Number of eligible patients based on the reference scenario. The number of patients in the New Drug Scenario differs in the sponsor's submission (JAKi-naive patients [year 1 / year 2 / year 3]: 764 / 773 / 777; ruxolitinib-experienced patients: 318 / 285 / 298).

[b]May not sum to 100% owing to rounding.

[c]Dose intensities for fedratinib and ruxolitinib were assumed to be 98.8%, based on median dose intensity in JAKARTA.[28]

[d]The price of fedratinib was based on the sponsor's submitted price. Other drug prices were obtained from the Ontario Drug Benefit Formulary,[15] with the exception of cytarabine.[16]

[e]Includes the cost of thiamine testing ($41.13; first year: 6 tests; subsequent years: 5 tests).[18]

[f]BAT in the JAKi-naive subgroup was assumed to include hydroxyurea (56.6% of patients); danazol (3.77%) prednisolone (3.77%); prednisone (6.60%), cytarabine (1.89%); peginterferon alpha-2a (1.89%); watchful waiting (25.47%).

[g]BAT in the ruxolitinib-experienced subgroup was assumed to include ruxolitinib (44.9% of patients); hydroxyurea (19.39%); danazol (5.10%) prednisolone (6.63%); prednisone (6.63%); watchful waiting (19.39%).

Summary of the Sponsor's BIA Results

The sponsor estimated the net 3-year budget impact of introducing fedratinib for the JAKi-naive patient subgroup to be $4,288,809 (year 1: $29,866; year 2: $2,384,272; year 3: $1,874,671). Specific to ruxolitinib-experienced patient subgroup, the 3-year budget impact was estimated to be $35,312,537 (year 1: $10,930,330; year 2: $10,769,399; year 3: $13,612,808). The budget impact for the full Health Canada indication was projected by the sponsor to be $39,601,346 over 3 years.

Under a health care payer perspective, the estimated 3-year budget impact of reimbursing fedratinib was $4,285,364 for the JAKi-naive subgroup (year 1: $28,456; year 2: $2,383,507; year 3: $1,873,401) and $35,333,042 for the ruxolitinib-experienced subgroup (year 1: $ 10,938,442; year 2: $10,774,190; year 3: $13,620,410). For the full Health Canada indication, the impact was estimated to be $39,618,406.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **The composition of BAT does not reflect the clinical management of MF in Canada.** As noted in the CADTH appraisal of the sponsor's economic evaluation, the composition of BAT used in the sponsor's analysis does not reflect the clinical management of MF in Canada. The sponsor assumed that patients with a previous ruxolitinib failure would continue to receive ruxolitinib as part of BAT. The inclusion of ruxolitinib as part of BAT was responsible for a large proportion of drug acquisition costs, which biased the sponsor's budget impact results in favour of fedratinib.
    - In CADTH reanalyses, ruxolitinib was removed from BAT in the ruxolitinib-experienced subgroup. The composition of BAT was aligned with that adopted in the CADTH reanalyses of the pharmacoeconomic model (Table 6).
- **Discontinuation of JAKis was not considered in the sponsor's BIA.** In the BIA, patients who initiate fedratinib or ruxolitinib were assumed to remain on treatment for the analysis' entire 3-year time horizon, which is inconsistent with the assumption in the sponsor's economic model that patients would discontinue treatment at 24 weeks if they had not experienced a favourable treatment response. As noted in the CADTH clinical report, 21.9% of patients had discontinued fedratinib by the end of 6 treatment cycles (24 weeks) in the JAKARTA trial. Based on parametric modelling used to inform the sponsor's economic model for

time to treatment discontinuation, 46% and 27% of JAKi-naive and ruxolitinib-experienced patients, respectively, would be expected to remain on fedratinib after 3 years. Not including discontinuation in the BIA is a conservative assumption.

  - In CADTH reanalyses, the duration of fedratinib treatment was aligned with the sponsor's submitted pharmacoeconomic model and was assumed to be equivalent for fedratinib and ruxolitinib. Patients taking BAT were assumed to remain on BAT for the duration of the BIA. The impact of no treatment discontinuation on the estimated budget impact was assessed in scenario analyses. CADTH was unable to assess the impact of adopting a stopping rule given the structure of the BIA model.

- **Inclusion of "clinical trials" as part of the current intervention mix.** The sponsor assumed that [redacted]% to [redacted]% of ruxolitinib-experienced patients eligible for fedratinib would instead participate in a clinical trial; it is unclear how this proportion was estimated. The inclusion of clinical trials as a relevant comparator in the sponsor's BIA was considered inappropriate, as these patients are not receiving approved therapies for the treatment of MF. Patients entering clinical trials receive investigational therapy from the trial sponsor and costs would not be borne by the public health care payers. Further, the inclusion of clinical trials as a comparator does not align with the sponsor's submitted economic evaluation of fedratinib, which did not consider investigative therapies as an appropriate comparator.
  - In CADTH reanalyses, the proportion of patients assigned to clinical trials by the sponsor were instead proportionally reassigned fedratinib or BAT.
- **Misalignment of model inputs between the sponsor-submitted economic analysis and BIA.** CADTH noted that several model inputs and assumptions in the BIA were not aligned with the cost-effectiveness analysis submitted by the sponsor. The annual cost of BAT differed in both the JAKi-naive group and the ruxolitinib-experienced group between the economic analysis and the BIA. Drug wastage due to ruxolitinib dose changes was further excluded from the sponsor's BIA, which is inconsistent with the submitted economic evaluation.
  - To align the economic evaluation and the BIA, the CADTH base case incorporated wastage (5%) for ruxolitinib. No changes were needed to the costs of BAT given changes made as per the first limitation.

Additional limitations were identified but were not considered to be key limitations.

- **Costs related to thiamine testing were included in the sponsor's base case.** The sponsor assumed that patients receiving fedratinib would undergo periodic thiamine testing, consistent with the Health Canada–approved product monograph.[2] The cost of thiamine testing was included in the sponsor's base case; however, the clinical experts consulted by CADTH indicated that thiamine testing is not uniformly reimbursed by the public health care payer across Canadian jurisdictions and may be paid out-of-pocket by patients.
  - The cost of thiamine testing was removed in the CADTH reanalysis of the BIA.

CADTH Reanalyses of the BIA

CADTH revised the sponsor's base case by changing the composition of the BAT treatment group, incorporating JAKi treatment discontinuation, removing clinical trials as a comparator, and removing the cost of thiamine testing (Table 22).

Table 22: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Composition of BAT	Include a proportion of patients on hydroxyurea, prednisone, danazol, busulfan, cytarabine, peginterferon alfa-2a, or watchful waiting; in the ruxolitinib-experienced subgroup, 50% of patients were assumed to continue to receive ruxolitinib as part of BAT.	BAT was assumed to be comprised of hydroxyurea (50%) and peginterferon (5%). The remaining patients were assumed to receive watchful waiting (no active treatment). Patients were assumed to discontinue ruxolitinib after a previous treatment failure. The annual cost of BAT in each subgroup was aligned with the CADTH base-case reanalysis of the economic evaluation ($1,735 per patient)
2. Discontinuation of JAKi treatment	Patients were assumed to remain on JAKi treatment for the duration of the BIA (156 weeks).	Patients were assumed to remain on JAKi treatment for 128.82 weeks.[a] Equivalent time to treatment discontinuation was assumed for fedratinib and ruxolitinib.
3. Clinical trials	[redacted]% of eligible patients were assumed to take part in clinical trials.	Clinical trials were removed as a comparator, with market shares adjusted accordingly.
4. Alignment of parameters in the CUA with the BIA.	No wastage.	5% wastage was assumed.
5. Thiamine testing	Cost of thiamine testing included.	Cost of thiamine testing excluded.
CADTH base case		1 + 2 + 3 + 4 + 5

BAT = best available therapy; BIA = budget impact analysis; JAKi = Janus Kinase inhibitor.

[a]Median time to treatment discontinuation employed in the sponsor's pharmacoeconomic submission (Weibull extrapolation of time to treatment discontinuation in JAKARTA).

Applying these changes increased the total 3-year budget impact for the JAKi-naive and ruxolitinib-experienced patient subgroups, as well as for the full Health Canada-indicated population (Table 23). Table 24 provides details of the CADTH reanalyses for the full Health Canada indication.

In the CADTH reanalysis, the 3-year budget impact of reimbursing fedratinib is estimated to be $4,622,039 ($4,916,720 including dispensing fees and markup) for the JAKi-naive patient subgroup and $38,577,552 ($40,446,233) for the ruxolitinib-experienced patient subgroup. The estimated budget impact for the full Health Canada indication is $43,199,591 ($45,362,953 including dispensing fees and markup) over the 3-year horizon.

Table 23: Summary of the CADTH Reanalyses of the BIA by Patient Subgroup

Analysis	3-year total	
	Drug costs only ($)	Dispensing fees and markup included ($)
Submitted base case		
JAKi-naive patients	4,165,648	4,288,810
Ruxolitinib-experienced patients	33,800,596	35,312,536
Full Health Canada indication	37,966,244	39,601,346
CADTH base case		
JAKi-naive patients	4,622,039	4,916,720
Ruxolitinib-experienced patients	38,577,552	40,446,233
Full Health Canada indication	43,199,591	45,362,953

BIA = budget impact analysis; JAKi = Janus kinase inhibitor.

Table 24: Summary of the CADTH Reanalyses of the BIA — Full Health Canada Indication

Stepped analysis	3-year total[a]	
	Drug costs only	Dispensing fees and markup included
Submitted base case	37,966,244	39,601,346
CADTH reanalysis 1	50,129,457	52,493,442
CADTH reanalysis 2	32,113,634	33,553,403
CADTH reanalysis 3	37,820,795	39,446,509
CADTH reanalysis 4	36,928,966	38,564,308
CADTH reanalysis 5	37,835,949	39,471,081
CADTH base case	43,199,591	45,362,953

BIA = budget impact analysis; JAKi = Janus kinase inhibitor.

[a]Combined JAKi-naive and ruxolitinib-experienced subgroups.

CADTH also conducted additional scenario analyses to address remaining uncertainty, using the CADTH base case. Results are provided in Table 25.

1. Assumed that thiamine testing would be reimbursed.
2. Assumed that patients would remain on JAKi inhibitors for the full duration of the BIA (156 weeks).
3. During consultation with clinical experts, they estimated that the number of patients with MF to be between 1,800 and 2,000. As such, CADTH conducted a scenario analysis assuming an increased prevalence of MF (0.0069%).
4. Health care payer perspective (i.e., inclusion of costs related to the treatment of adverse events (≥grade 3).

Table 25: Detailed Breakdown of the CADTH Reanalyses of the BIA

		Annual (drug costs only)[a]			3-year total[a]	
Stepped analysis	Scenario	Year 1	Year 2	Year 3	Drug costs only	Dispensing fees and markup included
Submitted base case	Reference	54,071,597	54,909,045	55,759,463	164,740,105	174,015,907
	New drug	64,570,962	67,526,342	70,609,044	202,706,349	213,617,253
	Budget impact	**10,499,365**	**12,617,298**	**14,849,581**	**37,966,244**	**39,601,346**
CADTH base case	Reference	48,052,756	48,796,986	24,690,096	121,539,838	128,000,897
	New drug	61,318,911	65,288,017	38,132,502	164,739,429	173,363,850
	Budget impact	**13,266,154**	**16,491,031**	**13,442,406**	**43,199,591**	**45,362,953**
CADTH scenario analysis 1: Thiamine testing reimbursed	Reference	48,052,756	48,796,986	24,690,096	121,539,838	127,999,887
	New drug	61,356,498	65,331,975	38,164,542	164,853,015	173,476,844
	Budget impact	**13,303,741**	**16,534,989**	**13,474,447**	**43,313,177**	**45,476,957**
CADTH scenario analysis 2: JAKi treatment duration 156 weeks	Reference	48,052,756	48,796,986	50,044,531	146,894,274	154,665,029
	New drug	61,318,911	65,288,017	69,158,416	195,765,343	205,893,964
	Budget impact	**13,266,154**	**16,491,031**	**19,113,885**	**48,871,070**	**51,228,935**
CADTH scenario analysis 3: Increased prevalence of MF	Reference	53,391,951	54,218,874	27,433,440	135,044,265	142,223,219
	New drug	68,132,123	72,542,241	42,369,447	183,043,810	192,626,500
	Budget impact	**14,740,171**	**18,323,367**	**14,936,007**	**47,999,546**	**50,403,281**
CADTH scenario analysis 4: Health care payer perspective	Reference	50,687,416	51,469,481	26,068,892	128,225,788	128,452,235
	New drug	64,602,834	68,756,905	40,236,704	173,596,442	173,863,689
	Budget impact	**13,915,418**	**17,287,423**	**14,167,812**	**45,370,654**	**45,411,454**

BIA = budget impact analysis; JAKi = Janus kinase inhibitor; MF = myelofibrosis.

[a]Combined JAKi-naive and ruxolitinib-experienced subgroups.