Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende fedratinib til behandling af myelofibrose

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet
2. Forhandlingsnotat fra Amgros
3. Ansøgers endelige ansøgning

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Virum, 27 March 2022.

To the Danish Medicines Council (DMC)

Bristol Myers Squibbs feedback on the draft of the assessment report for fedratinib for the treatment of disease-related splenomegaly or symptoms in adult patients with myelofibrosis (MF).

BMS appreciate the opportunity to provide feedback on the draft of the assessment report for fedratinib and at the same time use the possibility to clarify a few disagreements and question some assumptions.

The safety of fedratinib was evaluated in 608 patients who received more than 1 dose of fedratinib. Eight potential cases of encephalopathy, including Wernicke´s (WE) were reported, which is within the range of the reported prevalence of WE in the general population (ranging from 0.4% to 2.8%) (Galvin et al. 2010; EMA 2020). In addition to this, 7 out of the 8 subjects were taking fedratinib at 500 mg dose prior to the onset of the neurologic findings (EMA 2020; Harrison et al. 2017). All 8 potential WE cases were associated with pre-existing malnutrition and weight loss and/or significant nausea and vomiting that were not adequately controlled (Harrison et al. 2017; EMA 2020). The current recommended dose of fedratinib is 400 mg, and in contrast to earlier fedratinib studies such as JAKARTA, mitigation strategies for gastrointestinal (GI) events and thiamine levels have been developed and are included in fedratinib SmPC (EMA 2021a).
Treatment with JAK inhibitors such as ruxolitinib and fedratinib is associated with side effects and the lack of head-to-head comparison renders safety profile comparison difficult (EMA 2021a, 2021b). The decision to start a specific treatment is always associated with a careful and thorough assessment of the risk versus the benefit for each individual patient. Therefore, treatment with fedratinib is not expected to expose MF patients to an unnecessary risk and we find the wording very unfortunate in the following sentence on page 34 of the DMC assessment report: *"Ruxolitinib er ikke forbundet med risiko for Wernickes encefalopati, og det kan derfor være en bekymring, om* ***patienterne påføres en unødvendig, om end lille, risiko*** *for denne alvorlige bivirkning ved behandling med fedratinib."*

Infections are a major complication and cause of death in MF patients and is therefore of particular interest during safety profile review (EMA 2020). It is acknowledged, that infections including viral reactivation are a potential risk with JAK inhibitors and that caution in regards to potential risk of severe infection based on the class effect is required (EMA 2020). Nevertheless, BMS wishes to highlight, that the conclusion of the DMC about infection related to fedratinib are not in accordance with the conclusion from the European Medicines Agency (EMA 2020). Indeed, in the European public assessment report (EPAR), it is indicated that the frequency of subjects with TEAEs (all grades and SAEs) in JAKARTA up to cycle 6 in the infections and infestations SOC was comparable between fedratinib arms and placebo (EMA 2020). [redacted]. No increase in severe infections and virus zoster infections were found compared to placebo (EMA 2020). As a result, infection is not included in the section 4.4 Special Warmings and Precautions for Use in fedratinib SmPC (EMA

2021a). Further fedratinib is a selective JAK2 inhibitor with a limited impact on JAK1, which is involved in antiviral responses through Type I interferon signaling (EMA 2020). Post-marketing experience is essential to provide complementary and long-term safety information and BMS highly encourage reporting of adverse events (AEs) to ensure the safety of the patients treated with their products.

The DMC estimates, that 25% of the patients, who start treatment with fedratinib will switch to ruxolitinib to avoid the specific gastrointestinal side effects while maintaining the effect of the treatment. No rational for the chosen percentage is provided and BMS cannot relate that number to available data. In the JAKARTA study, 6.3% of the patients (6/96 patients) in the 400 mg fedratinib arm permanently discontinued treatment due to GI AEs (EMA 2020). In the 400 mg fedratinib arm, [redacted]. In the FREEDOM study, where mitigation strategies for GI events have been implemented, no patients had a treatment-related GI AE that required fedratinib dose modification or discontinuation after a median duration of treatment of 28.3 weeks (Gupta et al. 2021). Further, most of the GI AEs occurred in the first cycle of treatment in FREEDOM (Figure 1) and all the reported AEs of nausea, diarrhea and vomiting were of grade 1/2 (Gupta et al. 2021). Those data indicate that these events can be prevented or mitigated by early implementation of GI prophylaxis, which is included in the DMC´s health economic calculation. BMS disagree that 25 % of the patients will switch to ruxolitinib due to GI AEs and we look forward to offering a new treatment alternative to the MF patients in Denmark.

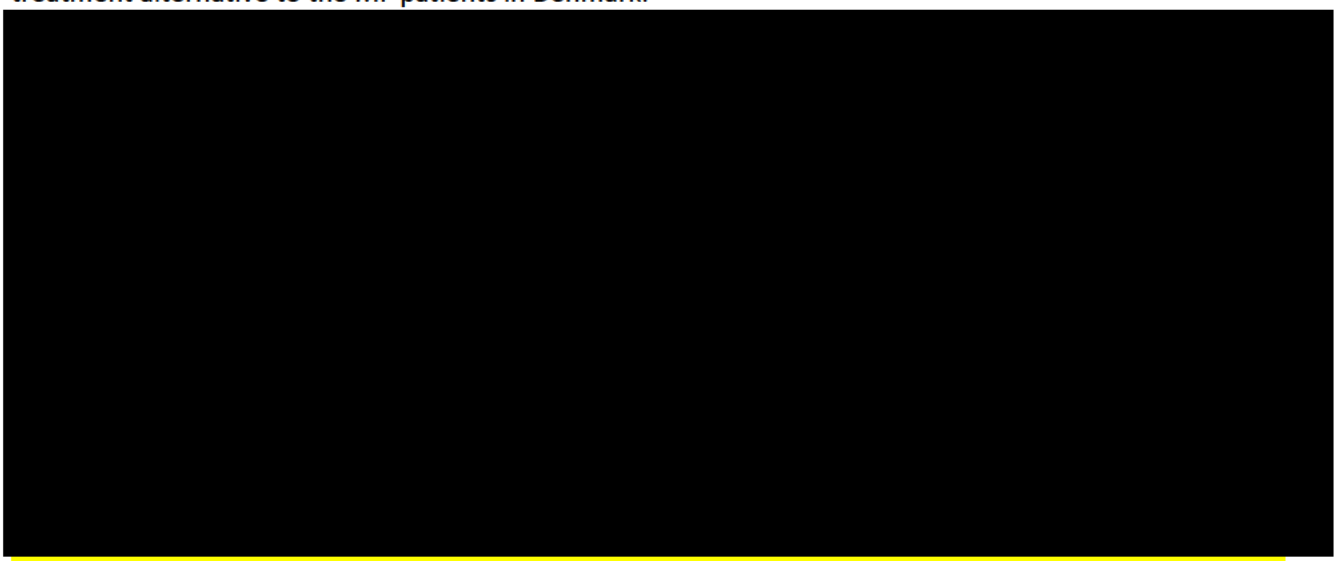

Figure 1. Frequency of nausea, vomiting, and diarrhea by treatment cycle in FREEDOM. (Gupta et al. 2021)

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28.03.2022

MGK/CAF/SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	20.04.2022
Leverandør	Bristol Myers Squibb
Lægemiddel	Inrebic (fedratinib)
Ansøgt indikation	Til behandling af myelofibrose med sygdomsrelateret splenomegali (forstørret milt) eller sygdomsrelaterede symptomer.

Forhandlingsresultat

Amgros har opnået følgende pris på Inrebic (fedratinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Inrebic (fedratinib)	100mg/400mg dagligt	120 stk. hårde kapsler	33.188,88	[redacted]	[redacted]

Prisen er **betinget** af en anbefaling af Medicinrådet.

[redacted]

[redacted]

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Inrebic (fedratinib)	100mg / 400mg dagligt	120 stk.	[redacted]	12*	[redacted]
Jakavi (ruxolitinib)	15 mg / 30mg dagligt	56 stk.	[redacted]	13**	[redacted]

*12,175
**13,04

Status fra andre lande

Norge: Under vurdering.[1]
Sverige: Anbefales til mellemrisiko-2 eller højrisiko myelofibrose, og som ikke tidligere har været behandlet med Januskinas-hæmmere (JAK-hæmmere).[2]
England: Inrebic (fedratinib) er anbefalet af NICE gennem Cancer Drugs Fund til behandling af myelofibrose efter behandling med Jakavi (ruxolitinib).[3]

Konklusion

[redacted]

[redacted]

[1] https://nyemetoder.no/metoder/fedratinib-indikasjon-ii
[2] https://www.tlv.se/download/18.1c32a37617b4106947eeddd6/1630059062199/bes210827_inrebic.pdf
[3] https://www.nice.org.uk/guidance/ta756/chapter/1-Recommendations

Medicinrådet

Application for the assessment of fedratinib (Inrebic®) for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis

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1 Basic information

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Overview of the pharmaceutical	
Proprietary name	Inrebic®
Generic name	Fedratinib
Marketing authorisation holder in Denmark	Celgene ApS (Denmark) C/O Bristol-Myers Squibb Danmark Hummeltoftevej 49 2830 Virum
ATC code	L01XE57
Pharmacotherapeutic group	Antineoplastic agents, protein kinase inhibitors
Active substance(s)	Fedratinib
Pharmaceutical form(s)	Capsule, hard
Mechanism of action	Fedratinib is an oral selective JAK inhibitor with activity against wild-type and mutationally activated Janus-associated kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). Fedratinib selectively inhibits JAK2, with higher inhibitory activity for JAK2 over family members JAK1, JAK3, and tyrosine kinase 2 (TYK2). Fedratinib reduced JAK2-mediated phosphorylation of signal transducer and activator of transcription (STAT 3/5) proteins and inhibited malignant cell proliferation in vitro and in vivo.[1]
Dosage regimen	The recommended dose is 400 mg fedratinib, administered as 4 × 100 mg capsules taken once daily. Fedratinib should be taken with food, preferably in the morning. Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.[1,2]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis that have been treated with ruxolitinib or who are JAK inhibitor naïve.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Prophylactic antiemetics based on local practice for the first 8 weeks of treatment and continued thereafter as clinically indicated is recommended.[1]
Packaging – types, sizes/number of units, and concentrations	100 mg, 120 capsules per cardboard carton.[1]
Orphan drug designation	Granted orphan drug designation from the European Medicines Agency (EMA) in 2010, which was maintained in 2020.

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2 Abbreviations

Abbreviation	Expansion
AE	adverse event
AIC	Akaike information criterion
ALT	alanine transaminase
AML	acute myeloid leukaemia
ASCT	allogeneic stem cell transplant
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
BAT	best available therapy
BIC	Bayesian information criterion
BL	baseline
BMS	Bristol-Myers Squibb
CI	confidence interval
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
DKK	Danish krone
DSKMS	Danish Study Group for Chronic Myeloid Diseases
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EMA	European Medicines Agency
EOC3	end of Cycle 3
EOC6	end of Cycle 6
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30
EOT	end of treatment
EPAR	European Public Assessment Report
EQ-5D-3L	3-level EQ-5D
ET	essential thrombocythaemia
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FEDR	fedratinib
FLT3	FMS-like tyrosine kinase 3
GHS	global health status
GI	gastrointestinal
Hb	haemoglobin
HR	hazard ratio
HRQoL	health-related quality of life
HSC	haematopoietic stem cell

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Abbreviation	Expansion
HTA	health technology assessment
IFNa	interferon alpha
IMP	Investigational Medicinal Product
IPSS	International Prognostic Scoring System
IRC	Independent Review Committee
ITC	indirect treatment comparison
ITT	intent-to-treat
IVRS	interactive voice response system
IWG-MRT	International Working Group for Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
KM	Kaplan-Meier
LOCF	last observation carried forward
MAIC	matching-adjusted indirect comparison
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MF-SAF	Myelofibrosis Symptom Assessment Form
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MPN-U	myeloproliferative neoplasm unclassifiable
MRI	magnetic resonance imaging
N/A	not applicable
NA	not assessed
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NoMA	Norwegian Medicines Agency
NR	not reported
OS	overall survival
PBO	placebo
PD	progressive disease
PFS	progression-free survival
PI-3K	phosphatidylinositol-3'-kinase
PMF	primary myelofibrosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	performance status
PV	polycythaemia vera
QD	once daily
QoL	quality of life

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Abbreviation	Expansion
RBC	red blood cell
RCT	randomised controlled trial
RD	risk difference
RR	response rate
RR25	spleen response rate of ≥ 25% spleen volume reduction
RSR	relative survival ratio
RUX	ruxolitinib
SAE	serious adverse event
SD	standard deviation
SLR	systematic literature review
SmPC	summary of product characteristics
STAT	signal transducer and activator of transcription
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
TSS	total symptom score
TTD	time to treatment discontinuation
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WHO	World Health Organization

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3 Tables and figures

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4 Summary

4.1 Indication

Fedratinib is indicated for the treatment of disease-related splenomegaly or symptoms in adults with primary myelofibrosis (PMF), post-polycythaemia vera (PV) myelofibrosis (MF) or post-essential thrombocythaemia (ET) MF who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.[1]

This indication received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 10 December 2020, marketing authorisation on 8 February 2021, and orphan drug designation from the European Medicines Agency (EMA) in 2010, which was maintained in 2020.[2,3] The focus of this submission is fedratinib for the treatment of patients who are JAK inhibitor naïve as an alternative treatment option to ruxolitinib. For information, a similar approach has been adopted in Sweden where the Dental and Pharmaceutical Benefits Agency, TLV, on August 26th, 2021 decided to reimburse fedratinib for patients with intermediate-2 or high-risk myelofibrosis who are JAK inhibitor naïve.[4]

4.2 Disease overview

Myelofibrosis is a rare and life-threatening myeloproliferative neoplasm (MPN), a bone marrow disorder with a high symptom burden. Myelofibrosis is characterised by bone marrow fibrosis, enlarged spleen (splenomegaly), constitutional symptoms (including fatigue and night sweats), and severe anaemia, and results in shortened survival.[5,6] It can either present de novo as PMF or after previously diagnosed PV and ET (post-PV MF and post-ET MF, respectively [i.e., secondary MF]).[7-9] Most patients with MF have an activating mutation of the JAK/signal transducer and activator of transcription (STAT) signalling pathway that leads to cell proliferation, inhibition of cell death, and clonal expansion of myeloproliferative malignant cells.[10,11]

There are limited epidemiological data on MF due to its low incidence and poor prognosis.[12] Myelofibrosis affects 0.4 per 100,000 people in European countries.[13] The disease predominantly affects older people (median age at PMF diagnosis in Denmark was 74 years in 2019)[14-16] but can occur at any age (range, 16-93 years).[17] From 2015 to 2019, 302 patients were diagnosed with PMF in Denmark, resulting in a mean incidence of 60.4 per year.[16] Five-year survival for PMF in Denmark is estimated to be approximately 55%.[16]

4.3 Current management and unmet need

Management of MF is complex and challenging, with limited treatment options. Allogeneic stem cell transplant (ASCT) is the only curative treatment, but most patients are ineligible due to age and comorbidities. For ASCT-ineligible patients, available therapies aim to relieve symptoms, reduce an enlarged spleen, improve blood cell counts, and potentially prevent disease progression.[18,19]

Until the approval of fedratinib, the oral JAK1/2 inhibitor ruxolitinib (approved centrally in the European Union [EU] in 2012) was the only treatment for MF for the treatment of disease-related splenomegaly or symptoms in adults with PMF, post-PV MF, or post-ET MF.[20] Ruxolitinib has been the standard first-line treatment in Denmark since April 2014 for patients with MF and highly symptomatic splenomegaly and/or constitutional symptoms and in patients with post-ET or post-PV MF.[21,22] Ruxolitinib is taken twice daily, and the recommended starting dose (5-20 mg) is based on platelet counts.[20]

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4.4 Fedratinib

Fedratinib is a selective oral JAK2 kinase inhibitor. The recommended dose of fedratinib is 400 mg taken once daily. Fedratinib provides a new treatment option for patients with MF as an alternative JAK inhibitor to ruxolitinib.

4.4.1 Clinical evidence

The efficacy and safety profile of fedratinib in patients with MF who are JAK inhibitor naïve has been demonstrated in the phase 3 placebo-controlled pivotal trial, JAKARTA.[1,3,23,24] In JAKARTA, fedratinib demonstrated clinically and statistically meaningful reductions in spleen volume and symptom burden versus placebo in JAK-inhibitor–naïve patients (intent-to-treat [ITT] population)[1,3,23,24]:

- A spleen volume reduction (SVR) of ≥ 35.0% at the end of Cycle 6 (EOC6) confirmed 4 weeks later was achieved in 36.5% of patients treated with 400 mg fedratinib versus 1.0% in the placebo arm (primary endpoint). Without the requirement of confirmation 4 weeks later, 46.9% of patients achieved SVR ≥ 35% at EOC6.[1,3]
- 40.4% of patients treated with 400 mg fedratinib achieved ≥ 50% reduction in total symptom score (TSS) versus 8.6% in the placebo arm.[1]
- Fedratinib was associated with improved health-related quality of life (HRQoL); the difference in mean change from baseline at the EOC6 in EQ-5D-3L health utility was clinically meaningful in favour of fedratinib. The proportion of patients having a clinically meaningful improvement in EQ-5D-3L health utility at the EOC6 was significantly higher in the fedratinib group than in the placebo group.[25]

In the absence of head-to-head evidence of fedratinib versus ruxolitinib, an indirect treatment comparison (ITC) was conducted using data from the JAKARTA, the COMFORT-I,[26] and the COMFORT-II[27] trials with ruxolitinib. Regardless of the ITC methodology used, fedratinib consistently demonstrated comparable spleen and symptom responses, with similar rates of grade 3 or 4 adverse events (AEs) versus ruxolitinib. Overall, because most efficacy and safety outcomes in the ITC were numerically in favour of fedratinib, the conclusion of noninferior efficacy of fedratinib can be considered an appropriate, if not a conservative, approach.

[redacted]

Evidence from JAKARTA 2 in the post-ruxolitinib setting demonstrated that fedratinib 400 mg once daily can provide clinically meaningful reductions in splenomegaly and symptoms in patients who are refractory/resistant or intolerant of ruxolitinib.[29]

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4.4.2 Economic evidence

A cost-minimisation analysis was conducted for fedratinib versus ruxolitinib; the choice of analysis was based on the clinical claim of at least noninferior efficacy and at least noninferior safety, based on the results of ITC and the dialogue meeting between Bristol-Myers Squibb (BMS) and the Medicines Council. Since both therapies are initiated in specialised secondary care and are administered orally, no differences in drug initiation and administration are anticipated and no major differences in routine management are expected. As such, cost-minimisation results were based on a comparison of drug acquisition costs and some specific monitoring costs. When considered at list price, fedratinib is not cost-saving in comparison to ruxolitinib over a treatment course in any scenarios tested. However, because the analysis should be based on the negotiated net prices, the results shown in this submission are not relevant to the decision-making process regarding reimbursement of fedratinib in Denmark.

Because most efficacy outcomes in the ITC were numerically in favour of fedratinib and had similar safety in terms of frequency of grade 3 or 4 AEs, cost-minimisation may be considered an appropriate, and likely a conservative, modelling approach.

4.5 Conclusion

Fedratinib has at least noninferior efficacy compared with ruxolitinib, the only approved therapy currently available for the treatment of disease-related splenomegaly or symptoms for MF in Denmark.

Fedratinib is an effective JAK2 inhibitor that will provide clinicians with an additional treatment option for patients with MF and disease-related splenomegaly or symptoms.

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5 The patient population, the intervention, and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Disease background

Myelofibrosis is a rare haematological disorder characterised by abnormal cytopenias, bone marrow fibrosis, extramedullary haematopoiesis, and shortened survival. The symptom burden of MF is substantial and includes enlarged spleen (splenomegaly), constitutional symptoms (including fatigue and night sweats), and severe anaemia.[5,6] Myelofibrosis can either present de novo as PMF or following previously diagnosed PV and ET (post-PV MF and post-ET MF, respectively [i.e., secondary MF]) (Figure 1).[7-9] For the purpose of this document, "myelofibrosis" (or "MF") refers to PMF, post-PV MF, and post-ET MF. Approximately 70% of patients develop de novo PMF rather than progressing from ET or PV.[30]

Figure 1. Major type of Philadelphia-negative myeloproliferative disorders

HSC = haematopoietic stem cell.
Source: Celgene-BMS data on file (2021)[31]

The abnormal proliferation of pluripotent haematopoietic stem cells releases inflammatory cytokines and growth factors in the bone marrow, leading to marrow fibrosis. Progressive fibrosis results in release of malignant stem cells into the circulation and extramedullary haematopoiesis, manifesting primarily as splenomegaly. Extramedullary haematopoiesis is not able to fully compensate for the loss of production of blood cells in the bone marrow; as a result, patients experience cytopenias (most commonly anaemia and thrombocytopenia). Myelofibrosis may also undergo transformation to acute myeloid leukaemia (AML),[32] resulting in a very poor prognosis.[33] The frequency of leukemic transformation varies based on MPN subtype. It is most common in PMF, with approximately 10%-20% at 10 years.[34] Risk factors for leukaemic transformation in the first 5 years of diagnosis included male sex, increased circulating blasts mutations, very high-risk karyotype, moderate or severe anaemia, constitutional symptoms, and age (≥ 70 years), in a cohort of 1,306 patients with PMF.[35] In a Swedish cohort, transformation to AML during 3-year follow-up was 47.6% in patients with MF.[36]

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Myelofibrosis is diagnosed and stratified by risk using one of the following scoring systems: the International Prognostic Scoring System (IPSS),[37] the Dynamic International Prognostic Scoring System (DIPSS),[38] or DIPSS-Plus[32] (Table 1).[39] These classify patients into 1 of 4 risk groups used for prognosis and treatment decision-making (low, intermediate-1, intermediate-2, and high risk) based on factors such as age, presence of constitutional symptoms, and haematological parameters. Of MF cases, 70% are in intermediate-2 and high-risk DIPSS-Plus categories and have median survivals of 2.9 and 1.3 years, respectively.[32]

Table 1. Prognostic scoring systems IPSS, DIPSS, and DIPSS-Plus

Scoring system	To be used	Prognostic factors	Risk score	Risk score and median survival (months)
IPSS[37]	At diagnosis	Age > 65 years	1	▪ Low risk (score 0), median survival 135 months ▪ Int-1 risk (score 1), 95 months ▪ Int-2 risk (score 2), 48 months ▪ High risk (score ≥ 3), 27 months
		Anaemia (Hb < 10 g/dL)	1	
		Leukocyte count > 25 × 10^9/L	1	
		Circulating blasts ≥ 1 %	1	
		Constitutional symptoms (fever, excessive sweats, weight loss)	1	
DIPSS[38]	During follow-up	Age > 65 years	1	▪ Low risk (score 0), not reached ▪ Int-1 risk (score 1-2), 170 months ▪ Int-2 risk (score 3-4), 48 months ▪ High risk (score 5-6), 18 months
		Anaemia (Hb< 10 g/dL)	2	
		Leukocyte count > 25 × 10^9/L	1	
		Circulating blasts ≥ 1 %	1	
		Constitutional symptoms (fever, excessive sweats, weight loss)	1	
DIPSS-Plus[a,32]	During follow-up	DIPSS low risk	0	▪ Low risk (score 0), 185 months ▪ Int-1 risk (score 1), 78 months ▪ Int-2 risk (score 2-3), 35 months ▪ High risk (score ≥ 4), 16 months
		DIPSS intermediate-1	1	
		DIPSS intermediate-2	2	
		DIPSS high risk	3	
		RBC transfusion dependent	1	
		Unfavourable karyotype[b]	1	
		Platelet count < 100 × 10^9/L	1	

DIPSS = Dynamic International Prognostic Scoring System; Hb = haemoglobin; Int = intermediate; IPSS = International Prognostic Scoring System; RBC = red blood cell.

[a] Calculate first the DIPSS score, and then add the score for transfusion dependency, cytogenetics, and thrombocytopenia to calculate the final DIPSS-Plus score.

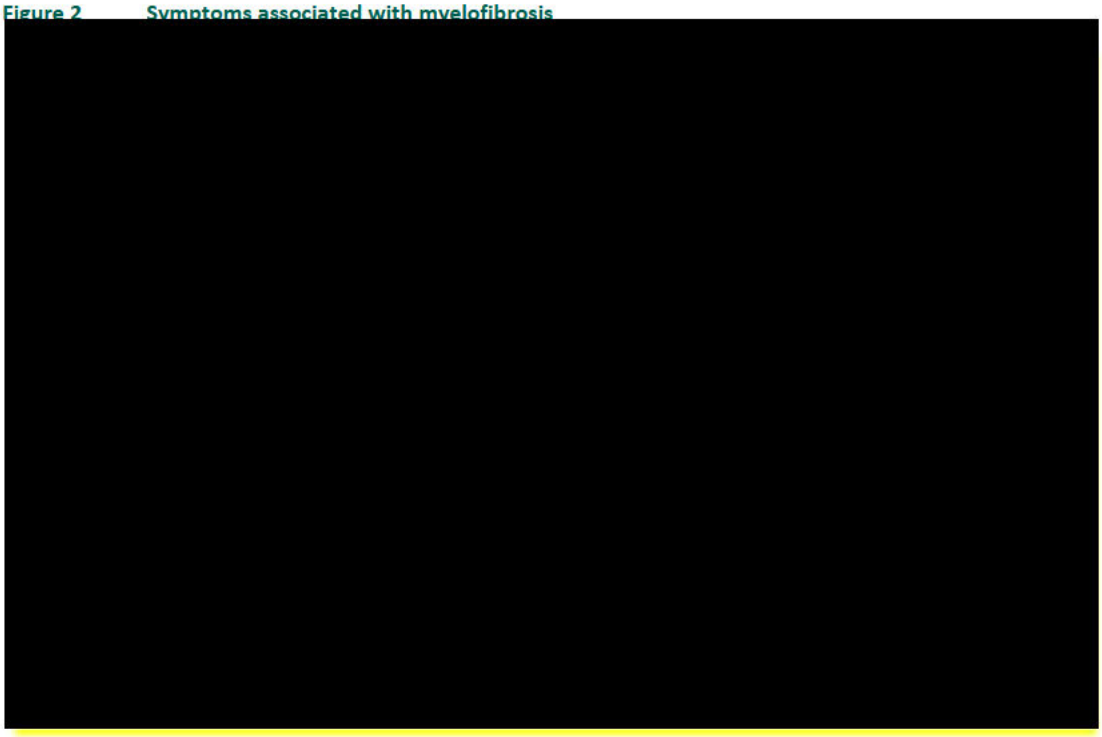
[b] Prognostic unfavourable karyotype: complex karyotype or sole or 2 abnormalities including +8, –7/7q-, i(17q), –5/5q-, inv(3), 12p-, or 11q23 rearrangement.

Source: Nordic MPN Study Group (2017)[21]

The symptom burden of MF has a significant detrimental impact on patients' HRQoL. The impact of MF on a patient's physical functioning and fatigue is comparable to that of metastatic cancer, as measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30).[40] Myelofibrosis is associated with debilitating symptoms that worsen as the disease progresses.[5,6] The main clinical manifestations are splenomegaly, present in over 80% of patients[37]; symptoms associated with cytopenias (e.g., anaemia, 35% of patients; neutropenia, 10%)[37]; and constitutional symptoms (night sweats, fever, and weight

loss, present in approximately 30% of patients[37]; fatigue present in > 80% of patients)[5] resulting from abnormal cytokine production (Figure 2).[5,6]

Figure 2 Symptoms associated with myelofibrosis



TSS = total symptom score.
Adapted from Devendra et al. (2017)[41]; Finazzi et al. (2012)[42]; Kander et al. (2015)[43]; Mesa et al. (2016)[14]; Polverelli et al. (2015)[44]

5.1.2 Epidemiology of myelofibrosis in Denmark

5.1.2.1 Incidence and prevalence

Myelofibrosis is a rare disease, and there are limited data on epidemiology and treatment patterns. Myelofibrosis affects 0.4 per 100,000 people in European countries.[13] A systematic review of publications and registry data regarding the incidence of MF in European countries found the incidence rate of MF ranged between 0.1 and 1.0 per 100,000.[13] Published prevalence data are limited and difficult to determine, mainly due to the scarcity of reliable and consistent reporting of data combined with limitations of incidence estimates.[12] Brochmann et al. (2017)[45] reported 4,704 patients (diagnosed between 1977 and March 2013) were living with MPN in Denmark in 2013.

Approximately 445 to 651 people are diagnosed with MPN in Denmark each year.[16] Between 2010 and 2019, 5,469 MPN cases were reported to the Danish Database for Chronic Myeloma Proliferative Neoplasms.[16] From 2015-2019, a total of 302 patients were diagnosed with MF,[16] which is a mean of 60.4 per year. The median age at diagnosis of MF was 74.4 years in 2019.[16]

Table 2 reports the incidence of MF in Denmark. It was not possible to obtain global or Danish prevalence data over time.

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Table 2. Incidence and prevalence of myelofibrosis in Denmark (2015-2019)

Year	2015	2016	2017	2018	2019
Incidence in Denmark	79	75	59	51	38[a]
Prevalence in Denmark	NR	NR	NR	NR	NR
Global prevalence[b]	NR	NR	NR	NR	NR

NR = not reported; WHO = World Health Organization.

[a] Lower incidence compared with previous years was suggested to be related to under-registration as well as possible diagnosis uncertainties in connection with the WHO 2016 classification.

[b] For small patient groups, also describe the worldwide prevalence.

Source: Danish Haematological Society (2020)[16]

5.1.2.2 Mortality and survival rates

Myelofibrosis reduces life expectancy, although overall survival (OS) from diagnosis varies considerably between individuals depending on their risk profile.[46] Figure 3 reports the survival curve for subtypes of MPN in Denmark over an 8-year period. Survival decreases over time, regardless of MPN subtype. Excluding patients with unclassified myeloproliferative disease, PMF has the worse survival of the MPN subgroups, with 5-year survival estimated to be approximately 55%.[16]

Figure 3. Kaplan-Meier survival curve for subtypes of myeloproliferative neoplasm

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Source: Danish Haematological Society (2020)[16]

Mortality data for Denmark is similar to that of other Nordic countries and the United States (US). Hultcrantz et al. (2012)[46] reported survival in patients with MPNs diagnosed in Sweden from 1973-2008. The 5-year relative survival ratio for PMF was 0.39 (95% confidence interval [CI], 0.35-0.43) (Figure 4, Table 3).

Figure 4. Cumulative relative survival among patients with myeloproliferative neoplasms in Sweden, stratified by subtype

ET = essential thrombocythaemia; MPN-U = myeloproliferative neoplasm unclassifiable; PMF = primary myelofibrosis; PV = polycythaemia vera; RSR = relative survival ratio.

Source: Hultcrantz et al. (2012)[46]

Table 3. Cumulative relative survival among patients with myeloproliferative neoplasms in Sweden, stratified by subtype from 1973-2008

	1-year RSR	5-year RSR	10-year RSR	15-year RSR	20-year RSR
PV (95% CI)	0.95 (0.94-0.96)	0.83 (0.81-0.84)	0.64 (0.62-0.67)	0.47 (0.44-0.50)	0.32 (0.29-0.35)
ET (95% CI)	0.92 (0.90-0.93)	0.80 (0.78-0.82)	0.68 (0.64-0.71)	0.52 (0.48-0.57)	0.44 (0.37-0.51)
PMF (95% CI)	0.76 (0.73-0.79)	0.39 (0.35-0.43)	0.21 (0.18-0.25)	0.11 (0.08-0.15)	0.06 (0.04-0.09)
MPN-U (95% CI)	0.87 (0.85-0.89)	0.63 (0.59-0.66)	0.49 (0.44-0.53)	0.39 (0.32-0.47)	

CI = confidence interval; ET = essential thrombocythaemia; MPN-U = myeloproliferative neoplasm unclassifiable; PMF = primary myelofibrosis; PV = polycythaemia vera; RSR = relative survival ratio.

Source: Hultcrantz et al. (2012)[46]

Digitising data from Roaldsnes et al. (2017)[47] the median OS for MF in Norway is 39.9 months (95% CI, 33.2-45.2 months). Median survival was lower in males (34.1 months; 95% CI, 27.0-44.1 months) than in females (41.0 months; 95% CI, 34.1-56.1 months) (Figure 5).

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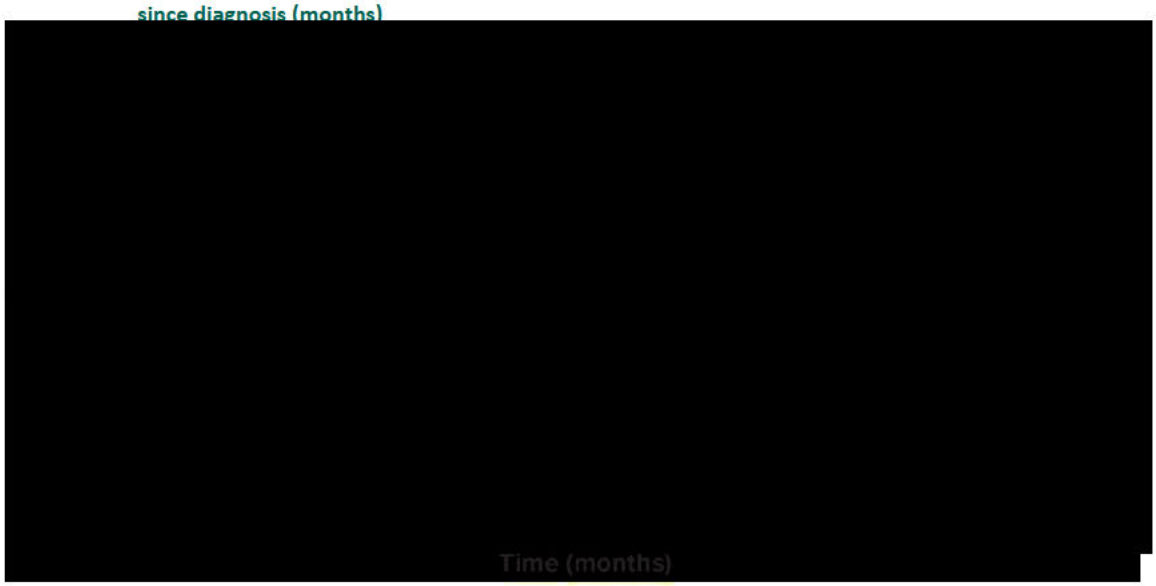
Figure 5. Kaplan-Meier survival curve for myelofibrosis in Norway by gender during the period 1993-2012: time to death since diagnosis (months)



Source: Calculated from Roaldsnes et al. (2017)[47]

Patients in the US with MF have a median OS of 6 years from diagnosis, which decreases in patients with a higher risk disease.[32] Using DIPSS-Plus, approximately 70% of patients with PMF in a US database study were shown to be at intermediate-2 and high-risk categories, with median OS of 2.9 and 1.3 years, respectively.[32] Using IPSS, median OS of patients from 7 European centres ranged from 11.2 years in low-risk patients to 2.2 years in high-risk patients (Figure 6).[37]

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Figure 6. Survival probability in primary myelofibrosis by IPSS score

CI = confidence interval; IPSS = International Prognostic Scoring System.
Source: Cervantes et al. (2009)[37]

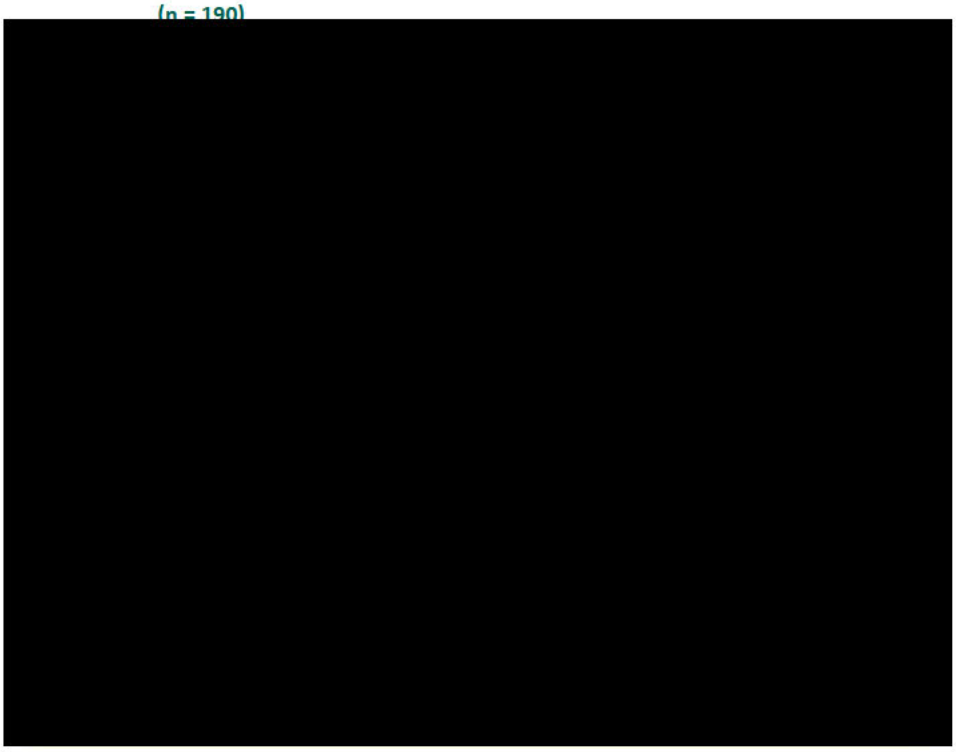
A modelling study estimated lost survival for patients with PMF compared with the general population in 5 European countries (Germany, France, Italy, Spain, and the United Kingdom).[48] Using data from a large cohort (n = 368) of patients with PMF diagnosed between 1996 and 2007, the study estimated that the mean (median) survival loss due to PMF was 9.6 (10.7) years, representing a relative survival loss of 45% compared with the general population. Overall, 81% of patients were estimated to experience life-year loss, which was more pronounced in males (mean, 11.3 years vs. 6.8 years for females), younger patients (< 65 years, 14.3 years; > 65 years, 4.9 years), and in patients with IPSS intermediate-2/high-risk disease (15.4 years vs. 4.8 years in patients with low/intermediate-1 disease).

Premature death often results from MF-associated complications, rather than MF per se. For example, in a study of 1,131 patients with PMF diagnosed from 1980-2007 at 7 centres from Europe, leukaemic transformation was the most frequent known cause of death, accounting for 17% of cases.[37] Other known causes of death were: disease progression without leukaemia (10%); thrombosis and cardiovascular complications (7%); infections (6%); and bleeding 3%, portal hypertension, and second neoplasia (2% each).

Schain et al. (2019)[49] reported survival estimates in 190 Swedish and Norwegian patients with MF (Norway: n = 89; Sweden: n = 101) who received ruxolitinib from a retrospective cohort study. Patients were identified from the

National Cancer Registries (Norway: 2002-2016; Sweden: 2001-2015) who had ≥ 1 record of ruxolitinib in the Prescribed Drug Registries (2013-2017). Results showed 1 and 4 year relative (to the general population) survival were 0.80 (95% CI, 0.74-0.86) and 0.52 (95% CI, 0.42-0.64), respectively (Figure 7). Loss in life expectancy was 11 years and excess mortality rate ratios were greater in patients aged > 70 versus < 60 years (3.16; 95% CI, 1.34-7.40).[49]

Figure 7. Relative survival from ruxolitinib treatment initiation in patients with myelofibrosis in Sweden and Norway (n = 190)



Source: Schain et al. (2019)[49]

5.1.3 Patient populations relevant for this application

Fedratinib is positioned as an alternative treatment option to ruxolitinib in adults with PMF, post-PV MF, or post-ET MF who are JAK inhibitor naïve. In the current clinical pathway of care, ruxolitinib is the only JAK inhibitor treatment available, for which 28% of patients had ≥ 35% SVR at week 48 (primary endpoint) and 32% at week 24 (secondary endpoint).[27,50] Ruxolitinib is the first-line treatment for patients with highly symptomatic splenomegaly and /or constitutional symptoms.[21] For patients older than 60 years who are not candidates for ruxolitinib or ASCT, hydroxyurea is recommended as first-line cytoreductive therapy.[21] In the case of a hyperproliferative phase of the disease and low fibrosis, pegylated interferon alpha (IFNa) may be considered as a first-line treatment option for younger patients as well as older patients (> 60 years) with good performance status (PS) and without contraindications for that treatment.[21] In this context, fedratinib would be expected to provide clinicians and patients an additional treatment option with at least equivalent efficacy to ruxolitinib, and as such would be used as an alternative to ruxolitinib in the same population of patients.

As noted earlier in this submission, published prevalence data for Denmark are limited and difficult to determine. Therefore, the expected eligible population for fedratinib was calculated using incidence and clinical input. Between 2015 and 2019, 302 patients were diagnosed with MF in Denmark,[16] giving a mean of 60.4 per year. It is anticipated

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that 42 patients will require treatment at diagnosis; of the 42, 30% will require a JAK inhibitor as their first-line treatment. Of the patients who require hydroxyurea and/or IFNa as first-line treatment, approximately 70% will receive a JAK inhibitor as a second-line treatment (Table 4).

Table 4. Eligible patient calculations

Population	No. of patients	Calculation	Source
Mean number of patients diagnosed with MF in Denmark each year	60	Mean taken from 5-year incidence data	Danish Haematological Society (2020)[16]
ASCT	6	10% of 60	Assumption based on clinical input
No symptoms at diagnosis	18	30% of 60	Assumption based on clinical input
Number of patients needing treatment within one year after diagnosis	14	75% of 18	Assumption based on clinical input
Number of patients requiring treatment at diagnosis	36	60% of 60	National Quality Register for Myeloproliferative Neoplasias (MPN) (2021)[51]
Total number of patients requiring treatment at diagnosis and not eligible for ASCT	50	83% of 60	Assumption based on clinical input 50 = 36 + 14
Number of patients requiring hydroxyurea and/or IFNa as first-line treatment	35	70% of 50	Assumption based on clinical input
Number of patients requiring a JAK inhibitor as first-line treatment	15	30% of 50	Assumption based on clinical input
Number of patients requiring a JAK inhibitor as a second-line treatment following treatment with hydroxyurea and/or IFNa	25	70% of 35	Assumption based on clinical input
Number of patients eligible for fedratinib treatment	40	100% of 15 (number of patients requiring a JAK inhibitor as first-line treatment) plus 100% of 25 (number of patients requiring a JAK inhibitor as a second-line treatment following treatment with hydroxyurea and/or IFNa)	Assumption based on clinical input

ASCT = allogeneic stem cell transplant; IFNa = interferon alpha; JAK = Janus kinase; MF = myelofibrosis.

The expected eligible patient population for fedratinib in Denmark was calculated based on this estimate and clinical expert feedback (Table 5). It is anticipated that a total of 40 patients with MF who also are JAK inhibitor naïve in Denmark are projected to be eligible to receive fedratinib in the first year, with the assumption that incidence stays the same over the time horizon of the analysis. Due to assumption of clinical equivalence between fedratinib and ruxolitinib, total life-years from the Norwegian Medicines Agency (NoMA) preferred extrapolation of ruxolitinib survival is used to inform mean survival of fedratinib patients.[52] Based on this, given a mean survival of 5.43 years, it is

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anticipated that the eligible patient population will rise to approximately 200 by year 5. Eligible patient numbers will continue to rise before plateauing at approximately 240 from year 6 onwards.

Table 5. Estimated number of patients eligible for treatment in Denmark

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	40	80	120	160	200

5.1.4 Subgroup of patients who are expected to have a different efficacy and safety than anticipated for the entire population

No difference in efficacy or safety in any subgroup of patients is anticipated for treatment with fedratinib when compared with the indicated population of patients with MF currently treated with ruxolitinib.

Patients with platelet counts ≥ 50 × 10^9/L were included in both the JAKARTA and the JAKARTA 2 studies. The efficacy and safety of fedratinib in the subgroup of patients with low platelet counts (50-100 × 10^9/L) were investigated in both trials, and baseline platelet counts did not seem to affect spleen volume or symptom response rates (RRs) with fedratinib 400 mg daily, with a manageable safety profile.[29] The recommended starting dose of fedratinib is 400 mg daily and does not require modification based on baseline platelet counts compared with ruxolitinib.[1,20]

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

In Denmark, the Danish Study Group for Chronic Myeloid Diseases (DSKMS) recommendations for the treatment of PMF were published in March 2013.[53] The Nordic MPN Study Group have also published treatment guidelines for ET, PV, and PMF.[21] Diagnosis of MPN is based on the World Health Organization (WHO) diagnostic criteria: mandatory investigations x-ray of the thorax, electrocardiogram, bone marrow biopsy, and blood tests.[53]

Recommendations are based on IPSS, DIPSS, and the presence of symptoms. Figure 8 outlines the treatment pathway; ruxolitinib is the first-line treatment for patients with highly symptomatic splenomegaly and/or constitutional symptoms and in patients with post-ET or post-PV MF.[21] Patients who are not a candidate for ruxolitinib or ASCT, with intermediate-1 risk disease, and with low-risk disease requiring therapy for MF-associated splenomegaly, hydroxyurea is recommended.[21] In the case of a hyperproliferative phase of the disease and low fibrosis, pegylated IFNa may be considered as a first-line treatment option for younger patients as well as older patients (> 60 years) with good PS and without contraindications for that treatment.[21] In this context, fedratinib would be expected to provide clinicians and patients an additional treatment option with at least equivalent efficacy to ruxolitinib, and as such would be used as an alternative to ruxolitinib in the same population of patients.

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Figure 8. Treatment pathway in Denmark

IFNa = interferon alpha; MF = myelofibrosis.
Source: Danish Study Group for Chronic Myeloid Diseases[53]

5.2.2 Rational for the selected patient population

Fedratinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF, post-PV MF, or post-ET MF who are JAK inhibitor naïve or have been treated with ruxolitinib. The current submission is for the JAK-inhibitor–naïve population and is supported by data from the randomised phase 3 study JAKARTA, while the wider indication for ruxolitinib-treated patients is supported by evidence from the single-arm phase 2 study JAKARTA 2. The early study termination did not influence the assessment of spleen RR at EOC6 in JAKARTA.[3] Nonresponder imputation for missing data at EOC6 was used for the reanalysis of the primary endpoint in JAKARTA 2 (in 21 of 97 patients, the primary endpoint was missing due to early study termination only), leading to a conservative estimate of the spleen RR of 30.9%, with the most conservative estimate being 22.7%, considering 8 patients achieving a response after dose up-titration as nonresponders.[3] While the conclusion in the European Public Assessment Report (EPAR) indicates that efficacy data robustly show a clinically relevant reduction in spleen volume using a dose of 400 mg in both pivotal fedratinib studies,[3] a more precise determination of the magnitude of fedratinib clinical benefit in the post-ruxolitinib setting is expected to be necessary in the context of some national reimbursement processes.

Further, there is no standard of care for patients with MF for whom ruxolitinib has failed or who are intolerant to ruxolitinib. Thus, in contrast to the JAK-inhibitor–naïve population, there is uncertainty in how to evaluate the benefit of fedratinib in patients with prior treatment with ruxolitinib in regards of the highly individualised treatment received. These different uncertainties could be mitigated by the ongoing randomised phase 3 controlled trial

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FREEDOM 2 (FEDR-MF-002; NCT03952039) in which fedratinib 400 mg once daily is being compared with best available therapy (BAT) in the post-ruxolitinib setting (estimated study completion date: 24 August 2024).[54] Finally, in the Danish Medicines Agency's method guide for assessment of new drugs (version 1.2), data from randomised controlled trials (RCTs) are indicated as the preferred source of efficacy data.

Based on the above rationale, the focus of this submission is fedratinib for the treatment of patients who are JAK inhibitor naïve as an alternative treatment option to ruxolitinib. Since April 2014, ruxolitinib has been the only JAK inhibitor approved as standard of care for patients with MF and highly symptomatic splenomegaly and/or constitutional symptoms.[22] Most efficacy outcomes in the ITC were numerically in favour of fedratinib and had similar safety in terms of frequency of grade 3 or 4 AEs, suggesting that fedratinib is a relevant alternative to ruxolitinib and supporting cost-minimisation as an appropriate, if not a conservative, modelling approach. A similar approach has been adopted in Sweden resulting in a decision by the Dental and Pharmaceutical Benefits Agency, TLV, on 26 August 2021 to reimburse fedratinib for patients with intermediate-2 or high-risk myelofibrosis who are JAK inhibitor naïve.[4]

5.2.3 Choice of comparator(s)

Ruxolitinib is the only relevant comparator for this submission based on Danish clinical practice and guidelines, as described in Section 5.2.1.[53] Based on current treatment guidelines and overlapping indications between fedratinib and ruxolitinib, the introduction of fedratinib is not expected to change the distribution of current treatment options other than providing an alternative JAK inhibitor to ruxolitinib.

In Denmark, ASCT is the only potentially curative treatment for MF,[21] but it is only suitable for patients who are fit enough to undergo such treatment associated with high morbidity and mortality.[55] In Denmark, ASCT is an option in transplantable patients categorised as either intermediate-2 or high risk or for intermediate-1 with high red blood cell (RBC) transfusion needs or high-risk mutations (according to DIPSS or IPSS).[53]

Patients not eligible for ASCT are treated with symptomatic therapies. Ruxolitinib is the only approved JAK inhibitor and used as the standard treatment in patients with MF in Denmark.[53] As described in Section 5.3.2 (proposed place in the treatment pathway), fedratinib would provide an additional JAK inhibitor for clinicians to use in the treatment of MF with disease-related splenomegaly or symptoms as an alternative to ruxolitinib.

5.2.4 Description of the comparator(s)

Ruxolitinib is indicated for disease-related splenomegaly or symptoms in adults with PMF, post-PV MF, or post-ET MF.[20] Ruxolitinib is also indicated for the treatment of adults with PV who are resistant to or intolerant of hydroxyurea, but it was not recommended as standard treatment in Denmark by KRIS.[20,22] Table 6 summarises the use of ruxolitinib as indicated.

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Table 6. Description of ruxolitinib

Generic name(s) (ATC code)	Ruxolitinib L01XE18
Mode of action	Ruxolitinib is a selective inhibitor of JAK1 and JAK2. These enable the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. MF and PV are associated with dysregulated JAK1 and JAK2 signalling. This dysregulation includes high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies.
Pharmaceutical form	Tablet
Posology	Starting dose: ▪ Myelofibrosis: based on platelet counts: – 20 mg twice daily for patients with a platelet count of > 200,000/mm^3 – 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 – 10 mg twice daily for patients with a platelet count between 75,000/mm^3 and 100,000/mm^3 – 5 mg twice daily for patients with a platelet count of 50,000/mm^3 to less than 75,000/mm^3 ▪ Polycythaemia vera: 10 mg given orally twice daily ▪ There is limited information to recommend a starting dose for patients with a low platelet count. The maximum recommended starting dose in these patients is 5 mg twice daily, and the patients should be titrated cautiously. Dose modifications are permitted based on platelet counts. The maximum dose permitted is 25 mg twice daily.
Method of administration	Oral twice daily
Dosing	Available in 5 mg, 10 mg, 15 mg, and 20 mg tablets
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Treatment should continue until the patient no longer derives benefit or treatment should be discontinued for platelet counts < 50,000/mm^3 or absolute neutrophil counts < 500/mm^3
Necessary monitoring, both during administration and during the treatment period	More frequent monitoring of haematology parameters and of clinical signs and symptoms of drug-related adverse drug reactions is recommended for patients with renal impairment, myelosuppression, and infections. Also see additional tests or investigations.
Additional tests or investigations	A complete blood cell count, including a white blood cell count differential, should be carried out prior to starting ruxolitinib and should be monitored every 2-4 weeks until ruxolitinib doses are stabilised.
Packaging	Pack of 56 tablets.

ATC = Anatomical Therapeutic Chemical Classification System; JAK = Janus kinase; PV = polycythaemia vera; STAT = signal transducer and activator of transcription.

Source: Jakavi SmPC (2021)[20]

5.3 The intervention

The indication for fedratinib is for disease-related splenomegaly or symptoms in adults with PMF, post-PV MF, or post-ET MF that have been treated with ruxolitinib or who are JAK inhibitor naïve.[1] Table 7 summarises the use of fedratinib as indicated. Full details of the prescribing information for fedratinib are available from the summary of product characteristics (SmPC) for Inrebic (see Appendix K).

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Table 7. Description of fedratinib

Generic name(s) (ATC code)	Fedratinib (L01XE57)
Mode of action	Fedratinib is an oral selective JAK inhibitor with activity against wild-type and mutationally activated JAK2 and FLT3. Most patients with MF have a mutation that results in constitutive activation of the JAK/STAT signalling pathway.[10,11] Activation of this pathway results in cell proliferation, inhibition of cell death, and clonal expansion of myeloproliferative malignant cells. Fedratinib selectively inhibits JAK2, with higher inhibitory activity for JAK2 over family members JAK1, JAK3, and tyrosine kinase 2 (TYK2).[1,56] Fedratinib is a more selective inhibitor of JAK2 than ruxolitinib, which inhibits both subtypes: JAK1 and JAK2. Abnormal activation of JAK2 is associated with MPNs, including primary MF, ET, and PV. In human cell lines expressing mutationally active JAK2, fedratinib reduced phosphorylation of STAT proteins, inhibited cell proliferation, and induced apoptotic cell death.[1] In mouse models of JAK2-driven myeloproliferative disease, fedratinib blocked phosphorylation of STAT 3/5 and improved survival, white blood cell counts, haematocrit, splenomegaly, and bone marrow fibrosis.[1]
Pharmaceutical form	Capsule, hard
Posology	400 mg fedratinib (four 100 mg capsules) taken once daily. Fedratinib can be taken with or without food.
Method of administration	Oral
Dosing	
Should the pharmaceutical be administered with other medicines?	No
Treatment duration	Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity. Fedratinib should be discontinued in patients who are unable to tolerate a dose of 200 mg daily.[1]
Necessary monitoring, both during administration and during the treatment period	Thiamine levels in patients should be assessed before starting treatment with fedratinib and during treatment as clinically indicated (e.g., each month for the first 3 months and every 3 months thereafter). Fedratinib treatment should not be started in patients with thiamine deficiency.
Additional tests or investigations	Prophylactic antiemetics based on local practice for the first 8 weeks of treatment and continued thereafter as clinically indicated is recommended.[1]
Packaging	Pack of 120 capsules of 100 mg each

ATC = Anatomical Therapeutic Chemical Classification System; ET = essential thrombocythaemia; FLT3 = FMS-like tyrosine kinase 3; JAK = Janus kinase; MF = myelofibrosis; MPN = myeloproliferative neoplasm; PV = polycythaemia vera; STAT = signal transducer and activator of transcription; TYK2 = tyrosine kinase 2.

5.3.1 Fedratinib: mode of action

Fedratinib is an oral selective JAK inhibitor with activity against wild-type and mutationally activated JAK2 and FMS-like tyrosine kinase 3 (FLT3). Most patients with MF have a mutation that results in constitutive activation of the JAK/STAT signalling pathway.[10,11] Activation of this pathway results in cell proliferation, inhibition of cell death, and clonal expansion of myeloproliferative malignant cells (Figure 9).

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Figure 9. The role of JAK2 in signal transduction through the JAK/STAT, PI-3K, and MAPK pathways

JAK = Janus kinase; MAPK = mitogen-activated protein kinase; PI-3K = phosphatidylinositol-3′-kinase; STAT = signal transducer and activator of transcription.
Source: Vainchenker et al. (2018)[57]

Fedratinib selectively inhibits JAK2, with higher inhibitory activity for JAK2 over family members JAK1, JAK3, and tyrosine kinase 2 (TYK2).[1,56] Fedratinib is a more selective inhibitor of JAK2 than ruxolitinib, which inhibits both subtypes: JAK1 and JAK2. Abnormal activation of JAK2 is associated with MPNs, including PMF, ET, and PV. In human cell lines expressing mutationally active JAK2, fedratinib reduced phosphorylation of STAT proteins, inhibited cell proliferation and induced apoptotic cell death.[1] In mouse models of JAK2-driven myeloproliferative disease, fedratinib blocked phosphorylation of STAT 3/5 and improved survival, white blood cell counts, haematocrit, splenomegaly, and bone marrow fibrosis.[1] Fedratinib also has activity against FLT3.[1]

5.3.2 Fedratinib: position in the treatment pathway

The current clinical treatment pathway for patients with MF in Denmark is shown in Figure 10 and is based on Nordic and national clinical guidelines as well as clinical input. The proposed place of fedratinib in the Danish pathway is indicated.[21,53]

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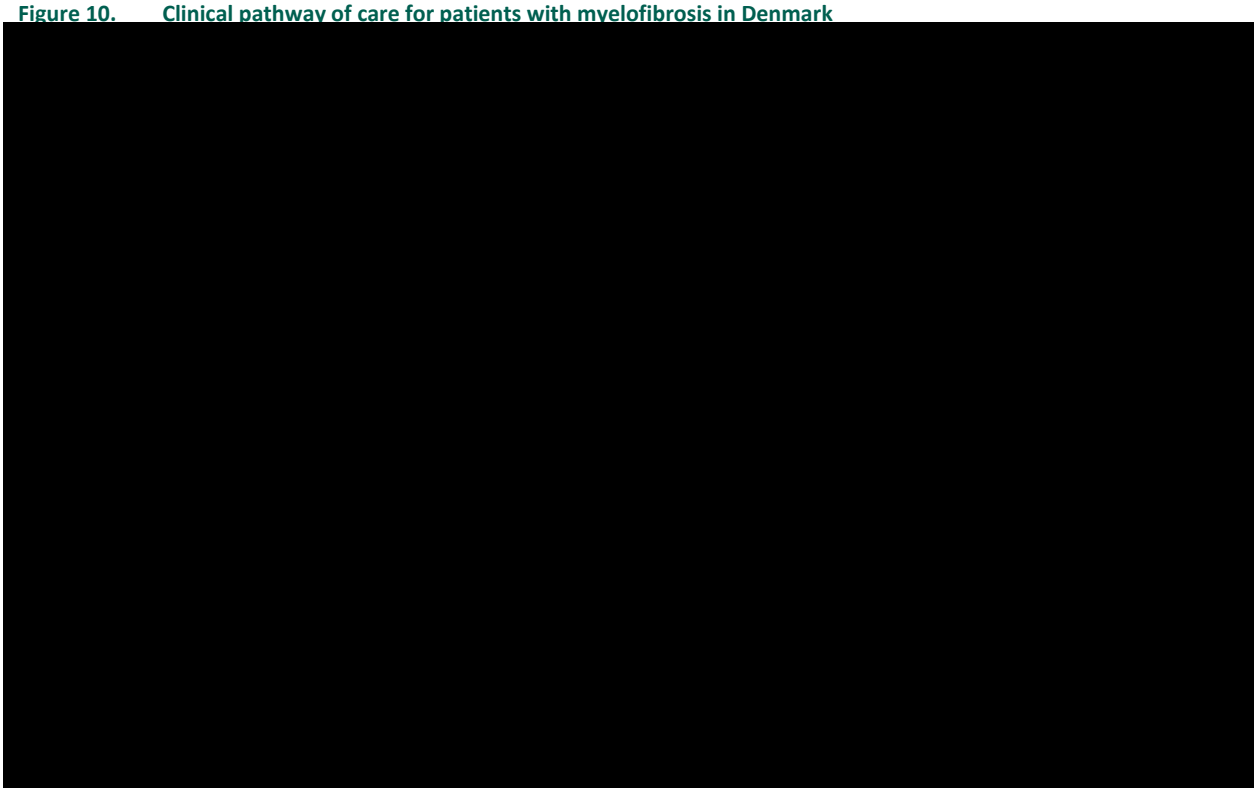
Figure 10. Clinical pathway of care for patients with myelofibrosis in Denmark



IFNa = interferon alpha; MF = myelofibrosis.
Adapted from the Danish Study Group for Chronic Myeloid Diseases[53]

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted for primary intervention trials from RCTs, non-RCTs, and real-world evidence, including retrospective and prospective observational studies related to treating patients with MF. The overall SLR on MF was performed in 4 parts, which included the original SLR, SLR Update 1, SLR Update 2, and SLR Update 3 conducted in 2018, 2019, 2020, and 2021, respectively. Brief methodology details are provided below:

- The first part (original SLR) was conducted to retrieve the evidence published up to 20 August 2018. The second part (SLR Update 1) was to update the original SLR with systematic searches of any published literature from 1 August 2018 to 3 October 2019, using the same key terms as those used in the original SLR. Similarly, SLR Update 2 searches were conducted on 13 February 2020 as the third part of this SLR, which included data evidence between 1 October 2019 to 13 February 2020. The searches for current SLR Update 3 (fourth part) were conducted on 20 April 2021.
- It was possible to split the results from the SLR into studies that focussed on patients with or without prior JAK inhibitor exposure. The focus of this submission is fedratinib for the treatment of patients who are JAK inhibitor naïve as an alternative treatment option to ruxolitinib. Therefore, the intervention and comparator studies included in this submission relate to the JAK-inhibitor–naïve population, with the exception of JAKARTA 2, a phase 2 trial investigating the safety and efficacy of fedratinib in patients previously treated with ruxolitinib, which is included as supportive evidence.[58]

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A detailed overview of the whole SLR methodology and search results are provided in Appendix A. Potentially relevant publications were reviewed and assessed to collate a final set of studies to form the main body of the clinical evidence. To determine the final set of studies eligible for review, explicit inclusion and/or exclusion criteria were applied to the literature search results. The inclusion and exclusion criteria for clinical studies are specified in Table A-14 in Appendix A. A PRISMA diagram for the JAK-inhibitor–naïve population can be found in Appendix A.3. A total of 12 RCTs from 88 publications, including 1 clinical study report, were included. Of the 12 studies, the SLR identified 1 key study that included the intervention in the population relevant to the scope of this submission:

- The phase 3 trial, JAKARTA, investigated the safety and efficacy of fedratinib in the ruxolitinib-naïve population[23]

The SLR identified 1 additional study assessing fedratinib, a phase 2 open-label randomised trial assessing the safety, pharmacokinetics, and pharmacodynamics of fedratinib administered once daily at 3 doses (300, 400, and 500 mg) in patients with MF.[59]

As previously stated, JAKARTA 2, a phase 2 trial investigating the safety and efficacy of fedratinib in patients previously treated with ruxolitinib, is included as supportive evidence. The evidence base to support the clinical efficacy of fedratinib reflects the licensed indication.

The clinical SLR identified 10 unique RCTs for comparator therapies. As outlined in Section 5.2.3, ruxolitinib is the only relevant comparator for this submission based on Danish clinical practice and guidelines; therefore, only 2 of the 10 studies were of relevance to the scope of this submission. For completeness, all 10 studies are listed in Table 8; however, only trials assessing ruxolitinib are reported further.

6.2 List of relevant studies

Table 8 presents the relevant studies included in this assessment; all trials of nonrelevant comparators are considered not applicable. For detailed information about included studies, refer to Appendix B.

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Table 8. Relevant studies included in the assessment

Drug	Author	Trial name	NCT number	Phase	Dates of study	Used in comparison of
Fedratinib	Pardanani et al. (2015)[23]	JAKARTA	NCT01437787	3	December 2011 to June 2014	Fedratinib vs. placebo for patients with intermediate-2 or high-risk primary MF, post-PV MF, or post-ET MF with splenomegaly
	Harrison et al. (2017)[58]	JAKARTA 2	NCT01523171	2	April 2012 to April 2014	Not applicable
	Pardanani et al. (2015)[59]	NA	NCT01420770	2	NR	Fedratinib in patients with intermediate-2 or high-risk MF
Busulfan-fludarabine	Patriarca et al. (2019)[60]	GITMO-MF2010	NCT01814475	2	July 2011 to December 2016	Not applicable
Pegylated interferon alfa-2b	Knudsen et al. (2018)[61]	DALIAH	NCT01387763	3	January 2012 to December 2020	Not applicable
	NCT01758588[54]	NA	NCT01758588	2	January 2013 to June 2017	Not applicable
Momelotinib	Mesa et al. (2017)[62]	SIMPLIFY-1	NCT01969838	3	December 2013 to May 2019	Not applicable
Pacritinib	Mesa et al. (2017)[63]	PERSIST-1	NCT01773187	3	January 2013 to April 2016	Not applicable
Ruxolitinib	Verstovsek et al. (2012)[26]	COMFORT-I	NCT00952289	3	August 2009 to October 2015	Ruxolitinib versus placebo in patients diagnosed with MF
Ruxolitinib	Harrison et al. (2012)[27]	COMFORT-II	NCT00934544	3	July 2019 to March 2015	Ruxolitinib versus best available therapy, as selected by the investigator in patients with primary MF, post-PV MF, or post-ET MF
Pomalidomide	Tefferi et al. (2017)[64]	RESUME	NCT01178281	3	September 2010 to May 2018	Not applicable
Pomalidomide	Tefferi et al. (2009)[65]	NA	NCT00463385	2	April 2007 to December 2013	Not applicable
Thalidomide	Abgrall et al. (2006)[66]	NA	NR	2b	NR	Not applicable

ET = essential thrombocythaemia; MF = myelofibrosis; NA = not applicable; NCT = National Clinical Trial; NR = not reported; PV = polycythaemia vera.

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6.3 Planned and ongoing studies assessing fedratinib

Two multicentre phase 3 trials are ongoing assessing fedratinib in patients with MF.

The FREEDOM trial (NCT03755518)[67] is a multicentre, single-arm, open-label, phase 3b trial investigating the efficacy and safety of fedratinib 400 mg once daily in patients with intermediate-risk or high-risk (DIPSS criteria) MF who have previously received ruxolitinib.[68] Fedratinib therapy will be continued until disease progression or unacceptable toxicity. The objectives include evaluation of spleen response, TSS response, and safety. Efficacy assessments will be performed for up to 12 months.

The FREEDOM 2 trial (NCT03952039)[69] is a multicentre open-label phase 3 trial that will randomise patients with intermediate-risk or high-risk (DIPSS criteria) MF who have previously received ruxolitinib to receive fedratinib or BAT (to include any investigator-selected treatment but cannot include ASCT or investigational agents) in a ratio of 2:1.[70] Therapy will be continued in both groups until disease progression or unacceptable toxicity. The primary objective is to compare spleen response; other assessments will include TSS response, HRQoL, and safety. Efficacy assessments will be performed for up to 24 months.

7 Efficacy and safety

7.1 Efficacy and safety of fedratinib compared with placebo in ruxolitinib-naïve patients

7.1.1 Relevant studies

JAKARTA (NCT01437787) is a randomised, double-blind, placebo-controlled, phase 3 trial that compares 400 mg or 500 mg fedratinib versus placebo in patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly. Data for this trial were initially published in 2015.[23] A revised analysis addresses possible bias resulting from early termination of the study and is described here based on data published in peer-reviewed articles, the EPAR,[3] and the Inrebic SmPC[1] and supplemented when necessary by the Clinical Study Report.[71]

Table 9 presents details of the JAKARTA methodology; further details on design, endpoints, and statistical analysis are described in Sections 7.1.1.1 to 7.1.1.3.

For detailed study characteristics refer to Appendix B. For baseline characteristics of patients included in each study refer to Appendix C.

Table 9. JAKARTA: summary of trial methodology

Key publications	▪ Pardanani et al. (2015)[23] ▪ EMA (2020)[3] ▪ Pardanani et al. (2020)[72] ▪ Mesa et al. (2020)[73] ▪ Mesa et al. (2020)[74] ▪ Inrebic SmPC (2021)[1] ▪ Talpaz and Kiladjian (2021)[24] ▪ Mesa et al. (2021)[75]
Sample size (n)	289
Study design	A phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study
Location	Multicentre: includes 94 active sites in 24 countries in Europe (2 sites in Sweden), Asia, Africa, North America, and South America

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Patient population	Patients with primary or secondary (post-PV or post-ET) MF.
Intervention(s)	▪ Fedratinib 400 mg once daily (n = 96) ▪ Fedratinib 500 mg once daily (n = 97) ▪ Patients with platelet count ≥ 50,000/µL were enrolled for both doses
Comparator(s)	Placebo (n = 96)
Follow-up period	The follow-up time for the duration of response was subject to extensive censoring due to early termination of the study and ranged from 0 to 18.2 months for the 400 mg arm and 0 to 19.7 months for the 500 mg arm, respectively
Is the study used in the health economic model?	N/A as cost-minimisation analysis was conducted, no outcomes from the study were used in the model, but efficacy and safety outcomes were included in the ITC (see Section 7.2)
Reasons for use/nonuse of the study in model	A cost-minimisation approach was conducted for fedratinib versus ruxolitinib based on the clinical equivalence shown in the ITC (see Section 7.2)
Primary endpoints reported	▪ Proportion of patients with ≥ 35% SVR at the EOC6 *and* confirmed 4 weeks later by MRI/CT.
Other outcomes reported include results	▪ Symptom RR using the modified MF-SAF: – Symptom RR: defined as the proportion of patients with ≥ 50% reduction in the TSS from baseline to the EOC6. Baseline TSS was the TSS value the week before randomisation or the week before an on-treatment assessment – TSS: Defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MF-SAF. ▪ OS ▪ PFS ▪ Spleen RR of ≥ 25% SVR at the EOC6 and confirmed 4 weeks later ▪ Duration of spleen response
Subgroups	▪ On demographic/ baseline characteristics for RR, OS, and PFS

CT = computed tomography; EMA = European Medicines Agency; EOC6 = end of Cycle 6; ET = essential thrombocythaemia; ITC = indirect treatment comparison; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; N/A = not applicable; OS = overall survival; PFS = progression-free survival; PV = polycythaemia vera; RR = response rate; SVR = spleen volume reduction; TSS = total symptom score.

Sources: Clinicaltrials.gov NCT01437787 (2016)[76]; Celgene-BMS data on file (2020)[28]; Pardanani et al. (2015)[23]; EMA (2020)[3]; Inrebic SmPC (2021)[1]

7.1.1.1 JAKARTA: study design

The primary objective of JAKARTA was to evaluate the efficacy of daily oral doses of 400 mg or 500 mg of fedratinib, compared with placebo in the reduction of spleen volume as determined by magnetic resonance imaging (MRI) (or computed tomography [CT] scan in patients with contraindications for MRI) and confirmed 4 weeks later. Patients were randomised (1:1:1) to receive fedratinib 400 mg, 500 mg, or placebo once daily for at least 6 consecutive 28-day cycles and until disease progression, relapse, or excess toxicity (Figure 11). Placebo was used as the control because ruxolitinib was not approved or widely accepted as the standard of care at the time of design of the trial. Crossover from placebo to fedratinib was permitted after Cycle 6, and completion of imaging assessments and fulfilment of protocol-specified criteria was completed earlier if the patient experienced progressive disease (PD). Crossover patients were randomised 1:1 to either fedratinib dose. The study was conducted at 94 sites in 24 countries and enrolled patients between December 2011 and September 2012. All patients discontinued treatment in the study in November 2013.

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Figure 11. JAKARTA: trial design

ECOG PS = Eastern Cooperative Oncology Group performance status; ET = essential thrombocytopenia; IWG-MRT = International Working Group for Myeloproliferative Neoplasms Research and Treatment; MF = myelofibrosis; PV = polycythaemia vera; QD = once daily; WHO = World Health Organization.

[a] Based on the approval of fedratinib 400 mg once daily dose. Moving forward, the slides will only show data for the fedratinib 400 mg treatment arm.

[b] One patient in the placebo group was randomised but died before taking the first dose of medication.

Adapted from Pardanani et al. (2015)[23]

7.1.1.2 JAKARTA: endpoints

The primary objective of JAKARTA was to assess the efficacy of daily oral doses of 400 mg or 500 mg of fedratinib compared with placebo in the reduction of spleen volume as determined by MRI (or CT scan in patients with contraindications for MRI).

The primary endpoint of JAKARTA is proportion of patients with ≥ 35% SVR at the EOC6 and confirmed 4 weeks later by MRI/CT.

Secondary endpoints are as follows:

- Symptom RR using the modified Myelofibrosis Symptom Assessment Form (MF-SAF):
  - Symptom RR: defined as the proportion of patients with ≥ 50% reduction in the TSS from baseline to the EOC6. Baseline TSS was the TSS value the week before randomisation or the week before an on-treatment assessment
  - TSS: Defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MF-SAF
- OS
- Progression-free survival (PFS)
- Spleen RR of ≥ 25% SVR (RR25) at the EOC6 and confirmed 4 weeks later
- Duration of spleen response
- Clinical and laboratory events graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

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Exploratory endpoints include the following:

- Change in HRQoL and utility using the EQ-5D-3L questionnaire
- The full list of the JAKARTA endpoints is available in the study protocol, which is available on the *JAMA Oncology* website in Supplement 1 of Pardanani et al. (2015)[77]

7.1.1.3 JAKARTA: statistical testing

Table 10 provides a summary of the planned statistical analyses in JAKARTA.

Table 10. JAKARTA: summary of the statistical analyses

Study	JAKARTA
Hypothesis objective	To evaluate the efficacy of daily doses of 400 or 500 mg of fedratinib compared with placebo on the SVR as determined by MRI.
Statistical analysis	Analysis of the primary endpoint ▪ A chi-squared test will be performed to compare each dose to the placebo at a 2-sided 2.5% alpha level. The RRs and 95% CI will be provided for each group as well as for the difference in RRs and 97.5% CI of the difference for each dose to placebo.
Sample size, power calculation	Spleen RR (primary endpoint): ▪ To maintain a 5% alpha level of the primary analyses, a 2.5% alpha was allocated to the comparison of each of the fedratinib 400 and 500 mg arm with the placebo control. Assuming the RR was 30% in either fedratinib arm and 5% in the placebo arm, 63 patients per arm would provide 90% power at a 2-sided 2.5% alpha level. Assuming there was approximately a 15% dropout rate, the RR would be 26% in either fedratinib arm and 4.3% in the placebo arm in the ITT population. Thus, 75 patients per study arm (total 225 patients) were planned to be randomised. OS (secondary endpoint): ▪ Assuming an exponential OS and a median in the placebo arm of 30 months, 84 pair-wise deaths (i.e., a total target of 84 deaths between the placebo arm and the 400 or 500 mg fedratinib arms) would provide 80% power to detect an HR of 0.5. The primary OS analysis would occur after a total of approximately 126 deaths. PFS (secondary endpoint): ▪ Assuming an exponential PFS and a median of 25 months in the placebo arm, then the number of events observed with the same study duration would provide > 95% power for PFS to detect a HR of 0.4. Study duration (final OS and PFS analyses): ▪ The planned study duration was approximately 55 months (4.6 years) based on the power for OS. Assuming the accrual required 9 months (25 patients per month), a 55-month study duration provided an average follow-up of 50.5 months (assuming 9.0 months for accrual could provide an average of 4.5 months follow-up).
Data management and patient withdrawals	A patient who permanently discontinued from the study treatment was followed as specified in the protocol. After permanent discontinuation of study treatment, a patient was assessed using the procedure normally planned for the end-of-treatment visit. All permanent discontinuations from study treatment were recorded in the appropriate electronic case report form after confirmation of permanent discontinuation.
Missing data	In general, no imputation is planned for missing data. The following approaches are default methods for missing data handling. Some exploratory analyses can be planned with different strategies for treating missing outcomes. ▪ Categorical data at baseline will be summarised for each treatment group using counts (n) and percentages (%). The number of patients with missing data may be mentioned but will not be included in the denominator for the calculation of percentages unless otherwise specified. ▪ Efficacy response variable: When a proportion is calculated for a binary response variable (e.g., RR), the denominator is based on the total number of patients in the analysis population used for the summary. There can be 3 observations: Yes, No, and/or Missing. For the patients with Missing outcomes, the default rule is that the patients will be treated as "no events."

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Study	JAKARTA
	▪ Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only. However, the number of patients with missing observations will be provided. ▪ Time to event data: Missing outcomes due to different reasons will be handled using different censoring rules. The censoring rules are specified as part of the definition of the analysis variables. ▪ Incomplete date of death: – If the day of death date is missing, it will be imputed to the first day of the month, except if the date of patient's last contact is the same month as death date. In this case, the death date will be imputed to the date of last contact + 1 day. – If the day and month of death date are missing, date of death will be imputed to 1 January of the year, except if date of patient's last contact is the same year as death date. In this case, the death date will be imputed to the date of last contact + 1 day. ▪ Incomplete date of first further therapy: if the day of first further therapy date is missing, the date will be imputed to the first day of the month. ▪ TEAE: Missing data will not be imputed. When any information is missing, the TEAE will be determined by the following conservative principle: an AE will be considered a TEAE if it cannot be confirmed that the event is not a TEAE due to missing data.

AE = adverse event; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; MRI = magnetic resonance imaging; OS = overall survival; PFS = progression-free survival; RR = response rate; SVR = spleen volume reduction; TEAE = treatment-emergent adverse event.

Sources: Celgene-BMS data on file (2018)[71]; EMA (2020)[3]; Pardanani et al. (2015)[77]

Randomised patients included any patient who had been allocated to a randomised treatment regardless of whether the treatment kit was used or not.[77]

Efficacy populations[3]

- The ITT population included all randomised patients who signed informed consent. The ITT population was the primary analysis population for all efficacy parameters. All analyses using this population were based on the treatment assigned by the interactive voice response system (IVRS).
- The 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 first 3 treatment cycles. All analyses using this population were based on the treatment actually received.
- The Symptom Analysis Population (modified MF-SAF) included ITT patients evaluable at baseline (for symptom assessment). Patients without a baseline TSS > 0 were considered nonevaluable for the symptom RR analysis. All analyses using this population were based on the treatment assigned by IVRS.
- The Bone Marrow Fibrosis Population included patients evaluable at baseline and with a post-baseline assessment evaluable according to central review, and who had received a minimum of 50% of the targeted dose for 3 cycles. Patients evaluable at baseline were those with bone marrow fibrosis grade > 0 by central review at baseline. All analyses using this population were based on the treatment assigned by IVRS.

Safety populations[3]

- The All Treated Population consisted of the subset of the ITT population that took at least 1 dose of study drug (even if partial). This population was used for analysis of exposure and safety data before crossover. All analyses using this population were based on the treatment actually received. Randomised patients for whom it was unclear whether they took the study drug were included in the Safety Population as randomised.

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- The Crossover Safety Population included all patients from the placebo arm who crossed over to receive fedratinib.

7.1.2 Efficacy and safety: results per study

7.1.2.1 JAKARTA: primary outcome—spleen response rate (≥ 35% SVR) at EOC6 confirmed 4 weeks later

The study met the primary endpoint of spleen RR at the EOC6, which had to be confirmed 4 weeks later, in contrast to clinical trials investigating ruxolitinib. For the ITT population, the spleen RR at the EOC6 and confirmed weeks later was 36.5% (95% CI, 26.8%-46.1%) in the 400 mg arm and 40.2% (95% CI, 30.4%-50.0%) in the 500 mg arm compared with 1.0% (95% CI, 0%-3.1%) in the placebo arm (Table 11). Both active treatment arms showed clinically meaningful and statistically significant differences compared with placebo ($P < 0.0001$, 2-sided at a significance level = 0.025 for each comparison).

Table 11. JAKARTA: spleen response rate (≥ 35% SVR) at EOC6 confirmed 4 weeks later (primary endpoint) and at EOC6 (intent-to-treat population)

		Fedratinib	
Response	**Placebo (n = 96)**	**400 mg (n = 96)**	**500 mg (n = 97)**
EOC6, confirmed 4 weeks later			
n (%)	1 (1.0)	35 (36.5)	39 (40.2)
95% CI[a]	0.0-3.1	26.8-46.1	30.4-50.0
Difference	—	35.42	39.16
P value[b]	—	< 0.0001	< 0.0001
97.5% CI of difference[a]	—	24.2-46.7	27.8-50.6
EOC6			
n (%)	1 (1.0)	45 (46.9)	48 (49.5)
95% CI[c]	0.0-3.1	36.9-56.9	39.5-59.4
Difference	—	45.83	48.44
P value[b]	—	< 0.0001	< 0.0001
97.5% CI of difference[c]	—	34.2-57.5	36.8-60.1

CI = confidence interval; EOC6 = end of Cycle 6; RR = response rate; SVR = spleen volume reduction.

[a] A chi-square test was performed to compare the RR at each dose to the placebo RR at a 2-sided 2.5% alpha level. The RRs and 95% CIs were provided for each arm as well as for the difference in RRs and 97.5% CIs of the difference for each dose to placebo. Confidence intervals were calculated using normal approximation.

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

[c] The mean and 95% CIs were provided for each arm. The 97.5% CIs of difference for each dose to placebo were calculated.

Source: EMA (2020)[3]

A total of 96.0% of patients (72 of 75) in the 400 mg fedratinib group had a reduction in spleen volume at the EOC6 while three-fourths of patients (75.9% [44 of 58]) in the placebo group had an increase in spleen volume at the same timepoint (Figure 12).[3]

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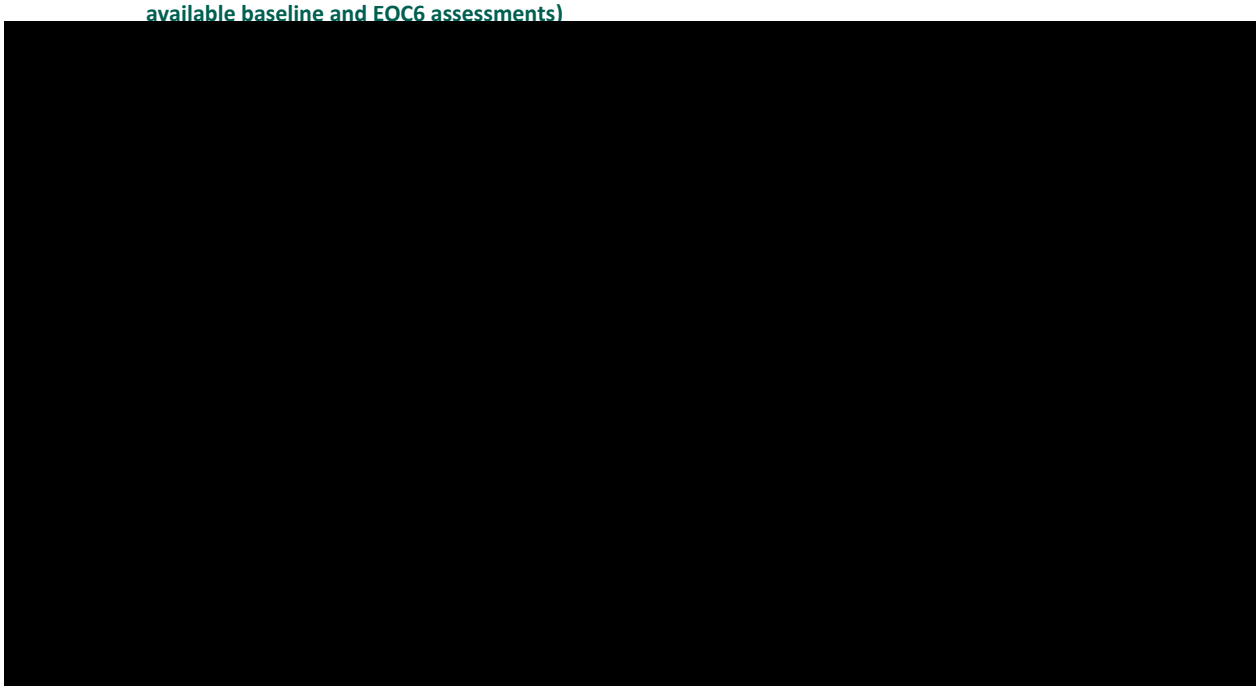
Figure 12. JAKARTA: percentage change in spleen volume from baseline at EOC6 (intent-to-treat population with available baseline and EOC6 assessments)



EOC6 = end of Cycle 6.

[a] Patients with available percentage change in spleen volume at EOC6.

Sources: EMA (2020)[3]; Pardanani et al. (2021)[78]

7.1.2.2 JAKARTA: secondary outcomes measures

The study met its key secondary endpoint, symptom RR (using the modified MF-SAF), defined as a ≥ 50% improvement from baseline in TSS. Patients completed the modified MF-SAF v2.0, which assesses 6 key MF symptoms (pruritus, night sweats, bone/muscle pain, early satiety, pain under ribs on the left side, and abdominal discomfort). The modified MF-SAF v2.0 was completed at baseline, during the first 6 treatment cycles, and at EOC6. The Symptom Analysis Population included 259 patients, which consisted of the ITT patients evaluable at baseline (for symptom assessment) and with TSS > 0 (patients without a baseline TSS > 0 were considered nonevaluable due to no place for symptom reduction); this differed from the ITT population with nonmissing baseline TSS, which included patients with baseline TSS = 0. The proportion of patients in the Symptom Analysis Population who had ≥ 50% reduction in TSS from baseline to EOC6 was 8.6% (95% CI, 2.5%-14.8%) in the placebo arm, 40.4% (95% CI, 30.3%-50.6%) in the 400 mg arm, and 34.8% (95% CI, 24.9%-44.7%) in the 500 mg arm (Table 12).

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Table 12. JAKARTA: symptom response rate (≥ 50% reduction in total symptom score) at EOC6—patients in the Symptom Analysis Population

		Fedratinib	
Response at EOC6	Placebo (n = 81)	400 mg (n = 89)	500 mg (n = 89)
n (%)	7 (8.6)	36 (40.4)	31 (34.8)
95% CI[a]	2.5-14.8	30.3-50.6	24.9-44.7
Difference	—	31.81	26.19
P value[b]	—	< 0.0001	< 0.0001
97.5 % CI of difference[a]		18.2-45.4	12.9-39.5

CI = confidence interval; EOC6 = end of Cycle 6; MF-SAF = Myelofibrosis Symptom Assessment Form; RR = response rate; TSS = total symptom score.

[a] A chi-square test was performed to compare each dose with placebo at a 2-sided 2.5% alpha level. The symptom RR (proportion of patients with ≥ 50% reduction in the TSS from baseline to the end of Cycle 6) and 95% CIs were provided for each arm as well as for the difference in proportions and 97.5% CIs of the difference for each dose to placebo.

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

Note: The TSS was defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the MF-SAF: night sweats, pruritus (itching), abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. Nonmissing baseline TSS includes patients with baseline TSS = 0.

Sources: EMA (2020)[3]; Celgene-BMS data on file (2018)[71]

Figure 13 summarises the percentage change in modified MF-SAF TSS at the EOC6 for patients in the placebo (n = 49) and 400 mg fedratinib (n = 71) arms.

Figure 13 JAKARTA: percentage change in total symptom score from baseline at EOC6 MF-SAF

BL = baseline; EOC6 = end of Cycle 6; MF-SAF = Myelofibrosis Symptom Assessment Form; TSS = total symptom score.
Note: The MF-SAF-evaluable population included all patients with a valid TSS at baseline, defined as available daily TSS for ≥ 5 of the 7 days in the week before Cycle 1 day 1 (C1D1).
Source: Mesa et al. (2021)[75]

The RR25 (i.e., proportion of patients who have a ≥ 25% reduction in volume of spleen size) at the EOC6 confirmed 4 weeks later for the ITT population was [redacted] in the placebo arm, [redacted] in the fedratinib 400 mg arm, and [redacted] in the fedratinib 500 mg arm

(Table 13). [redacted]).[71] RR25 at EOC6 without confirmation at week 4 was 2.1% (95% CI, 0%-4.9%) in the placebo arm, 56.3% (95% CI, 46.3%-66.2%) in the fedratinib 400 mg arm, and 56.7% (95% CI, 46.8%-66.6%) in the fedratinib 500 mg arm (Table 13).[3]

Table 13. JAKARTA: spleen response rate (≥ 25% SVR) at EOC6 confirmed 4 weeks later (intent-to-treat population) and at EOC6

		Fedratinib	
Response	**Placebo (n = 96)**	**400 mg (n = 96)**	**500 mg (n = 97)**
EOC6, confirmed 4 weeks later			
n (%)	[redacted]	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]
P value[a]	[redacted]	[redacted]	[redacted]
97.5% CI of difference[a]	[redacted]	[redacted]	[redacted]
EOC6			
n (%)	2 (2.1)	54 (56.3)	55 (56.7)
95% CI[b]	0-4.9	46.3-66.2	46.8-66.6

CI = confidence interval; CT = computed tomography; EOC6 = end of Cycle 6; MRI = magnetic resonance imaging; RR25 = spleen response rate of ≥ 25% spleen volume reduction; SVR = spleen volume reduction.

[a] A chi-square test was performed similar to the main analysis of RR25 regardless if a patient had a confirmatory MRI/CT at 4 weeks after the end of Cycle 6 that was a ≥ 25% reduction from baseline to confirm the response at the end of Cycle 6. Patients without an MRI/CT at the end of Cycle 6 and patients who had progressive disease before the end of Cycle 6 were considered nonresponders.

[b] Percentage change from baseline at the end of Cycle 6 in spleen volume was summarised. The mean and 95% CIs were provided for each arm. The 97.5% CIs of difference for each dose to placebo were calculated.

Sources: Celgene-BMS data on file (2018)[71]; EMA (2020)[3]

The duration of spleen response was defined for patients who achieved Independent Review Committee (IRC)–assessed spleen response (i.e., having ≥ 35% SVR) at any time during treatment or during the period before crossover for the placebo arm (i.e., responders). The duration of spleen response was calculated as the time from the date of the first IRC-assessed response to the date of subsequent IRC-assessed PD or death, whichever was earlier. Due to early termination of the study, and subsequent extensive censoring, Kaplan-Meier (KM) analysis was used to estimate duration of spleen response. Patients without subsequent IRC-assessed PD or death were censored at the last assessment date.[3]

One placebo patient had IRC-assessed spleen response before crossover (Table 14). The ITT population included 54 and 57 IRC-assessed spleen responders in the 400 and 500 mg arms, respectively. Based on KM estimates, the median duration of spleen response in the fedratinib arms was 18.2 and 19.7 months, respectively. It is recognised that 11.1% of responders (6 of 54) and 14.0% (8 of 57) in the 400 and 500 mg arms, respectively, progressed or died during the study. The 1 responder in the placebo arm had the first response before end of Cycle 3 [EOC3]) and then crossed over to receive fedratinib 500 mg at EOC6. After receiving fedratinib, further SVR was observed; consequently, this placebo crossover patient did not have a PD/death event throughout the study, and thus was censored at 16.7 months (Figure 14). The follow-up time for the duration of response was subject to extensive censoring due to early termination of the study and ranged from 0 to 18.2 months for the 400 mg arm and 0 to 19.7 months for the 500 mg arm, respectively.[3] The

most common reason for discontinuation of fedratinib was study termination (63.5%) and for placebo was crossover to fedratinib (74%).[78]

Table 14. JAKARTA: Kaplan-Meier analysis of duration of spleen response (intent-to-treat population)

		Fedratinib	
Response	Placebo (n = 96)	400 mg (n = 96)	500 mg (n = 97)
Number of patients assessed	1	54	57
Events, n (%)	0 (0.0)	6 (11.1)	8 (14.0)
Number of censored patients, n (%)	1 (100.0)	48 (88.9)	49 (86.0)
Duration of spleen response (months)			
25% quartile (95% CI)	N/A	18.2 (10.2-18.2)	16.0 (11.7-19.7)
Median (95% CI)	N/A	18.2 (N/A)	19.7 (16.0-19.7)
75% quartile (95% CI)	N/A	18.2 (N/A)	19.7 (N/A)

CI = confidence interval; IRC = Independent Review Committee; N/A = not applicable; PD = progressive disease.

Note: Duration of spleen response was defined as the time from the date of the first IRC-assessed response (≥ 35% spleen volume reduction) to the date of subsequent IRC-assessed PD or death, whichever was earlier. In the absence of subsequent PD (IRC assessment) or death, the duration of spleen response was censored at the date of the last valid assessment.

Source: EMA (2020)[3]; Celgene-BMS data on file (2018)[71]

Figure 14. JAKARTA: Kaplan-Meier plots of duration of spleen response (intent-to-treat population)

Note: Duration of spleen response was defined as the time from the date of the first IRC-assessed response (≥ 35% spleen volume reduction) to the date of subsequent IRC-assessed PD or death, whichever was earlier. In the absence of subsequent PD (IRC assessment) or death, the duration of spleen response was censored at the date of the last valid assessment.

Source: Celgene-BMS data on file (2018)[71]

Progression-free survival was defined as the time from randomisation to disease progression or death; KM curves were used to estimate PFS. In patients who did not reach disease progression or death, PFS was censored at the date of the last valid assessment. The PFS results for patients in the placebo arm included time after crossover to fedratinib. As mentioned previously, the study was terminated early; therefore, survival follow-up ceased. Ongoing patients were censored at the time of the study termination.[79]

At the time of study termination, survival follow-up was stopped for 74 patients (77%) in the 400 mg fedratinib arm and 65 (68%) randomised to placebo. The median PFS was significantly longer (HR, 0.42; 95% CI, 0.23-0.76; $P = 0.004$) in the fedratinib (23.2 months) arm compared with placebo (17.5 months), with 1-year PFS rates at 83% (fedratinib) and 67% (placebo) (Figure 15).[79]

Figure 15. JAKARTA: progression-free survival

CI = confidence interval; HR = hazard ratio; FEDR = fedratinib; PBO = placebo.
Source: Harrison et al. (2021)[79]

Overall survival was defined as the time from randomisation to death. Kaplan-Meier curves were used to estimate OS. The OS results for patients in the placebo arm included time after crossover to fedratinib. As mentioned previously, the study was terminated early; therefore, survival follow-up ceased and ongoing patients were censored at the time of the study termination.[79] Figure 16 presents OS results. The median OS was not reached in either treatment arm (HR, 0.57; 95% CI, 0.30-1.10; $P = 0.094$). At 12 months, survival rates were 92% in the fedratinib arm and 86% in the placebo arm. At 18 months, survival rates in the fedratinib and placebo arms were 87% and 80%, respectively.[79]

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Figure 16. JAKARTA: overall survival (intent-to-treat population)

CI = confidence interval; HR = hazard ratio; FEDR = fedratinib; PBO = placebo.
Source: Harrison et al. (2021)[79]

7.1.2.3 JAKARTA: key exploratory outcome measures

Exploratory outcome measures assessed change in HRQoL and utility using the EQ-5D-3L questionnaire. Patients completed the modified MF-SAF v2.0 at baseline, during the first 6 treatment cycles, and at EOC6. A key secondary endpoint was symptom RR defined as a ≥ 50% improvement from baseline in TSS, which is reported in Section 7.1.2.2.[75]

Figure 17 and Figure 18 show the changes from baseline in EQ-5D-3L health utility and visual analogue scale (VAS) scores for individual patients at EOC6. The baseline mean EQ-5D-3L health utility index was 0.70 for fedratinib and 0.72 for placebo. At EOC6, there was a statistically significant difference in patients achieving a clinically meaningful improvement from baseline favouring the fedratinib arm (23.2% vs. 6.5%; *P* = 0.002).[75]

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Figure 17. JAKARTA: EQ-5D-3L health utility

BL = baseline; EQ-5D-3L = 3-level EQ-5D.
Source: Mesa et al. (2021)[75]

Figure 18. JAKARTA: EQ-5D-3L VAS

BL = baseline; EQ-5D-3L = 3-level EQ-5D; VAS = visual analogue scale.
Source: Mesa et al. (2021)[75]

7.1.2.4 JAKARTA: safety results

Safety data were analysed for the placebo-controlled period (i.e., up to the EOC6) and for the entire study duration.

Median duration of exposure was 62.1 weeks for patients receiving 400 mg fedratinib, 59.7 weeks for the fedratinib 500 mg arm, and 24 weeks in the placebo arm in which patients were treated for 6 months or until

disease progression after which patients were allowed to cross over to active treatment.[3] The mean relative dose intensity was 92.8% for the fedratinib 400 mg arm, indicating most patients were able to receive the full fedratinib 400 mg dose[3] (Table 15). The median relative dose intensity up to 6 cycles was 98.8% for the fedratinib 400 mg arm and 93.0% in the fedratinib 500 mg arm.[3]

Table 15. JAKARTA: extent of exposure during the entire treatment duration

		Fedratinib	
Exposure	**Placebo[a] (n = 95)**	**400 mg (n = 96)**	**500 mg (n = 97)**
Number of cycles initiated			
Mean (SD)	5.0 (1.80)	13.2 (6.38)	11.6 (6.99)
Median (min, max)	6.0 (1.0, 11.0)	16.0 (1.0, 23.0)	14.0 (1.0, 22.0)
Duration of exposure (weeks)[b]			
Mean (SD)	19.8 (7.91)	52.0 (25.84)	46.4 (28.90)
Median (min, max)	24.0 (1.7, 43.7)	62.1 (1.00, 91.86)	59.7 (0.86, 89.00)
Cumulative dose (mg)			
Mean (SD)	N/A	134,610 (69,822.5)	139,695 (91,943.4)
Median (min, max)	N/A	153,050 (2,800, 257,200)	152,400 (2,400, 294,400)
Average daily dose (mg)			
Mean (SD)	N/A	371.3 (44.70)	429.6 (84.23)
Median (min, max)	N/A	395.1 (202.9, 400.0)	464.9 (96.0, 500.0)
Relative dose intensity (%)[c]			
Mean (SD)	N/A	92.8 (11.17)	85.9 (16.85)
Median (min, max)	N/A	98.8 (50.7, 100.0)	93.0 (19.2, 100.0)

max = maximum; min = minimum; N/A = not applicable; SD = standard deviation.

[a] Data for placebo patients who crossed over to fedratinib treatment are not counted after the date of crossover.

[b] Duration of exposure was calculated as ([last dose date-first dose date+ 1 day] ÷ 7). Last dose date was taken as the last dose date at the end of Cycle 6 or last dose date if before Cycle 6 for the first 6-cycle summary (or the day before the crossover) and the actual last dose date for the full treatment period summary.

[c] Relative dose intensity was calculated as (cumulative dose in milligrams) ÷ ([duration of exposure in weeks] × [planned dose intensity in milligrams/4 weeks]). The planned dose intensity was 11,200 mg/4 weeks for the 400 mg arm, and 14,000 mg/4 weeks for the 500 mg arm.

Source: EMA (2020)[3]

Most patients (≥ 93.7%) in each of the 3 treatment arms of the All Treated Population had at least 1 treatment-related adverse event (TEAE) during the entire treatment duration. Grade 3 or 4 TEAEs occurred in 30.5% of patients in the placebo arm, 70.8% in the fedratinib 400 mg arm, and 78.4% in the fedratinib 500 mg arm. Treatment-emergent AEs leading to permanent treatment discontinuation were 8.4%, 27.1%, and 36.1%, respectively, and TEAEs leading to dose reduction were 7.4%, 25.0%, and 45.4%.[3]

The frequencies of treatment-emergent serious adverse events (SAEs) during the entire treatment duration were 23.2% in the placebo arm, 38.5% in the fedratinib 400 mg arm, and 44.3% in the fedratinib 500 mg arm. Treatment-emergent AEs leading to death during the entire treatment duration were 6.3%, 5.2%, and 8.2%, respectively.[3] Table 16 presents the TEAEs associated with fedratinib in JAKARTA.

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Table 16. JAKARTA: safety overview (All Treated Population)

		Fedratinib	
Patients with ≥ 1 AE, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Any TEAE	89 (93.7)	96 (100.0)	95 (97.9)
Treatment-related TEAE	37 (38.9)	86 (89.6)	92 (94.8)
Grade 3 or 4 TEAE[a]	29 (30.5)	68 (70.8)	76 (78.4)
Treatment-related grade 3 or 4 TEAE	9 (9.5)	46 (47.9)	64 (66.0)
TEAE leading to death	6 (6.3)	5 (5.2)	8 (8.2)
Treatment-emergent SAE	22 (23.2)	37 (38.5)	43 (44.3)
Treatment-related treatment-emergent SAE	1 (1.1)	11 (11.5)	12 (12.4)
TEAE leading to permanent treatment discontinuation	8 (8.4)	26 (27.1)	35 (36.1)
TEAE leading to dose interruption	10 (10.5)	32 (33.3)	45 (46.4)
TEAE leading to dose reduction	7 (7.4)	24 (25.0)	44 (45.4)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: TEAEs were defined as AEs that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of the study drug.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Source: EMA (2020)[3]

Common adverse event data

In the fedratinib 400 mg arm, the most common nonhaematological TEAEs were gastrointestinal (GI) disorders, including diarrhoea in 68 patients (70.8%), nausea in 64 (66.7%), vomiting in 44 (45.8%), and abdominal pain in 15 (15.6%).[3] At the time JAKARTA was conducted, antiemetic prophylaxis was not required per study protocol[77]; this could explain the high incidence of nausea and vomiting, most of which was grade 1 and 2 (Table 17 and Table 18). Mitigation strategies to manage GI events were implemented in the ongoing studies FREEDOM and FREEDOM 2.[67] Other common nonhaematological TEAEs included fatigue in 24 patients (25.0%), muscle spasm in 15 (15.6%), and pain in the extremities in 12 (12.5%).[3]

The most common haematological TEAEs were anaemia in 53 patients (55.2%) and thrombocytopenia in 16 (16.7%).[3] Table 17 presents the common all-grade AEs reported in JAKARTA.

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Table 17. JAKARTA: all-grade treatment-emergent adverse events reported in ≥ 10% of patients

		Fedratinib	
Adverse event, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Patients with ≥ 1 AE	89 (93.7)	96 (100.0)	95 (97.9)
Diarrhoea	15 (15.8)	68 (70.8)	58 (59.8)
Nausea	15 (15.8)	64 (66.7)	51 (52.6)
Anaemia	13 (13.7)	53 (55.2)	47 (48.5)
Vomiting	5 (5.3)	44 (45.8)	54 (55.7)
Thrombocytopenia	8 (8.4)	16 (16.7)	22 (22.7)
Fatigue	9 (9.5)	24 (25.0)	14 (14.4)
Constipation	7 (7.4)	12 (12.5)	19 (19.6)
Abdominal pain	14 (14.7)	15 (15.6)	14 (14.4)
Cough	6 (6.3)	13 (13.5)	14 (14.4)
Dizziness	3 (3.2)	13 (13.5)	10 (10.3)
Headache	1 (1.1)	13 (13.5)	6 (6.2)
Dyspnoea	6 (6.3)	11 (11.5)	12 (12.4)
Asthenia	6 (6.3)	13 (13.5)	16 (16.5)
Pruritus	3 (3.2)	6 (6.3)	7 (7.2)
Oedema peripheral	8 (8.4)	14 (14.6)	9 (9.3)
Muscle spasms	1 (1.1)	15 (15.6)	8 (8.2)
Urinary tract infections	1 (1.1)	9 (9.4)	10 (10.3)
Pyrexia	3 (3.2)	7 (7.3)	6 (6.2)
Blood creatinine increased	1 (1.1)	11 (11.5)	17 (17.5)
Bone pain	2 (2.1)	12 (12.5)	8 (8.2)
Pain in extremity	4 (4.2)	12 (12.5)	3 (3.1)
ALT increased	1 (1.1)	12 (12.5)	9 (9.3)
Blood product transfusion dependent[b]	2 (2.1)	10 (10.4)	12 (12.4)
Decreased appetite	3 (3.2)	6 (6.3)	9 (9.3)
Weight decreased	5 (5.3)	5 (5.2)	12 (12.4)
Weight increased	4 (4.2)	12 (12.5)	8 (8.2)
AST increased	0 (0.0)	6 (6.3)	10 (10.3)
Hyperkalaemia	2 (2.1)	6 (6.3)	10 (10.3)
Neutropenia	0 (0.0)	6 (6.3)	12 (12.4)

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

[b] The AE of blood product transfusion dependent is based on investigator reporting, not by calculating the number of red blood cell transfusions per month based on the Gale et al. (2011)[80] definition.

Source: EMA (2020)[3]

Anaemia (44.8%) was the most commonly reported grade 3 or 4 TEAE and thrombocytopenia (11.5%) was the second most commonly reported TEAE in the fedratinib 400 mg arm. Table 18 presents the common grade 3 or 4 TEAEs reported in JAKARTA.

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Table 18. **JAKARTA: grade 3 or 4 treatment-emergent adverse events reported in ≥ 5% of patients during entire treatment duration**

		Fedratinib	
MedDRA system organ class preferred term, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Patients with ≥ 1 grade 3 or 4 TEAE	29 (30.5)	68 (70.8)	76 (78.4)
Blood and lymphatic system disorders	14 (14.7)	49 (51.0)	50 (51.5)
Anaemia	7 (7.4)	43 (44.8)	40 (41.2)
Thrombocytopenia	6 (6.3)	11 (11.5)	18 (18.6)
Neutropenia	0 (0.0)	4 (4.2)	10 (10.3)
Investigations	1 (1.1)	12 (12.5)	19 (19.6)
Lipase increased	1 (1.1)	4 (4.2)	7 (7.2)
Gastrointestinal disorders	5 (5.3)	11 (11.5)	24 (24.7)
Diarrhoea	0 (0.0)	5 (5.2)	5 (5.2)
Vomiting	0 (0.0)	3 (3.1)	9 (9.3)
Nausea	0 (0.0)	0 (0.0)	6 (6.2)
Metabolism and nutrition disorders	5 (5.3)	9 (9.4)	11 (11.3)
Hyperkalaemia	2 (2.1)	2 (2.1)	6 (6.2)
Cardiac disorders	5 (5.3)	13 (13.5)	8 (8.2)
Cardia failure	2 (2.1)	6 (6.3)	2 (2.1)
Infections and infestations	4 (4.2)	7 (7.3)	18 (18.6)
Pneumonia	1 (1.1)	2 (2.1)	5 (5.2)
General disorders and administration site conditions	3 (3.2)	8 (8.3)	12 (12.4)
Fatigue	0 (0.0)	7 (7.3)	7 (7.2)
Social circumstances	0 (0.0)	3 (3.1)	8 (8.2)
Blood product transfusion dependent[b]	0 (0.0)	3 (3.1)	8 (8.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

Note: AEs were coded using MedDRA Version 20.1 and were graded using NCI-CTCAE version 4.03. TEAEs were defined as AEs that developed, started, or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of the study drug. System organ classes are sorted in decreasing order of frequency for the fedratinib 400 mg column.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

[b] The AE of blood product transfusion dependent is based on investigator reporting, not by calculating the number of red blood cell transfusions per month based on the Gale et al. (2011)[80] definition.

Source: EMA (2020)[3]

Rates of discontinuation due to adverse event

Treatment-emergent AEs were observed in 100% (fedratinib) and 93.7% (placebo) of patients. Treatment-related AEs were reported in 89.6% of patients in the fedratinib group compared with 38.9% of patients in the placebo group, with just over half of those in the fedratinib group grade 3 or 4 in severity (fedratinib, 47.9%; placebo, 9.5%). Rates of discontinuation due to AEs were higher in the fedratinib group (fedratinib, 27.1%; placebo, 8.4%).[3]

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Adverse events leading to death

Table 19 presents the frequencies of TEAEs leading to death during the entire treatment duration. A total of 19 patients died across all study arms. Disease progression was reported as a TEAE leading to death in 2 patients (1 in the placebo arm and 1 in the fedratinib 500 mg arm).

Table 19. JAKARTA: treatment-emergent adverse events leading to death (All Treated Population)

		Fedratinib	
Primary system organ class preferred term, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Patients with ≥ 1 TEAE leading to death	6 (6.3)	5 (5.2)	8 (8.2)
General disorders and administration site conditions	1 (1.1)	1 (1.0)	1 (1.0)
Disease progression	1 (1.1)	0 (0.0)	1 (1.0)
Multiple organ dysfunction syndrome	0 (0.0)	1 (1.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (1.1)	3 (3.1)	0 (0.0)
Acute myeloid leukaemia	0 (0.0)	1 (1.0)	0 (0.0)
Acute leukaemia	0 (0.0)	1 (1.0)	0 (0.0)
Myelofibrosis	0 (0.0)	1 (1.0)	0 (0.0)
Transformation to acute myeloid leukaemia	1 (1.1)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (1.1)	2 (2.1)	2 (2.1)
Cardio-respiratory arrest	0 (0.0)	1 (1.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	1 (1.0)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (1.0)
Cardiac failure	0 (0.0)	0 (0.0)	1 (1.0)
Myocardial ischaemia	1 (1.1)	0 (0.0)	0 (0.0)
Infections and infestations	2 (2.1)	1 (1.0)	1 (1.0)
Sepsis	1 (1.1)	1 (1.1)	0 (0.0)
Pneumonia	1 (1.1)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (1.0)
Vascular disorders	0 (0.0)	1 (1.0)	0 (0.0)
Shock, haemorrhagic	0 (0.0)	1 (1.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (1.0)	1 (1.0)
Disseminated intravascular coagulation	0 (0.0)	1 (1.0)	0 (0.0)
Leukocytosis	0 (0.0)	0 (0.0)	1 (1.0)
Injury, poisoning, and procedural complications	1 (1.1)	1 (1.0)	0 (0.0)
Muscle rupture	0 (0.0)	1 (1.0)	0 (0.0)
Transfusion-related acute lung injury	1 (1.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	0 (0.0)	3 (3.1)
Respiratory failure	0 (0.0)	0 (0.0)	1 (1.0)
Pneumonitis	0 (0.0)	0 (0.0)	1 (1.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (1.0)

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Primary system organ class preferred term, n (%)	Placebo[a] (n = 95)	Fedratinib 400 mg (n = 96)	Fedratinib 500 mg (n = 97)
Gastrointestinal disorders	1 (1.1)	0 (0.0)	1 (1.0)
Ascites	1 (1.1)	0 (0.0)	0 (0.0)
Haematemesis	0 (0.0)	0 (0.0)	1 (1.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Notes: AEs were coded using MedDRA Version 20.1. TEAEs were defined as AEs that developed, started, or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of the study drug.

A patient could have multiple TEAEs leading to death.

System organ classes are sorted in decreasing order of frequency for the fedratinib 400 mg column.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Source: EMA (2020)[3]

Nonhaematological adverse events

Table 17 summarises the most frequently reported AEs during the placebo-controlled phase of the study. The most frequently reported nonhaematological AEs (> 45%) in the fedratinib group were GI AEs, namely diarrhoea, nausea, and vomiting; these AEs were reported in < 20% of patients in the placebo group. However, most GI events were mild or moderate in severity with the incidence of grade 3 or 4 GI-related AEs being 11.5% in the fedratinib group.[3] Furthermore, the incidence of GI toxicities decreased over time (Figure 19).[23] Gastrointestinal toxicities were generally managed with dose reductions or treatment interruptions (15% of patients in the fedratinib group) and only 7 patients discontinued therapy for GI toxicities.[23] At the time the JAKARTA study was conducted, antiemetic prophylaxis was not required per study protocol[77]; this could explain the high incidence of nausea and vomiting, most of which were grade 1 and 2 (Table 17 and Table 18). Mitigation strategies to manage GI events were implemented in the ongoing studies FREEDOM and FREEDOM 2.[67] Fatigue, muscle spasms, and pain in extremity were the only other nonhaematological AEs reported in ≥ 10% of patients receiving fedratinib. The only other grade 3 or 4 nonhaematological AE reported in ≥ 5% of patients was cardiac failure (6.3% in the fedratinib group vs. 2.1% in the placebo group).[3]

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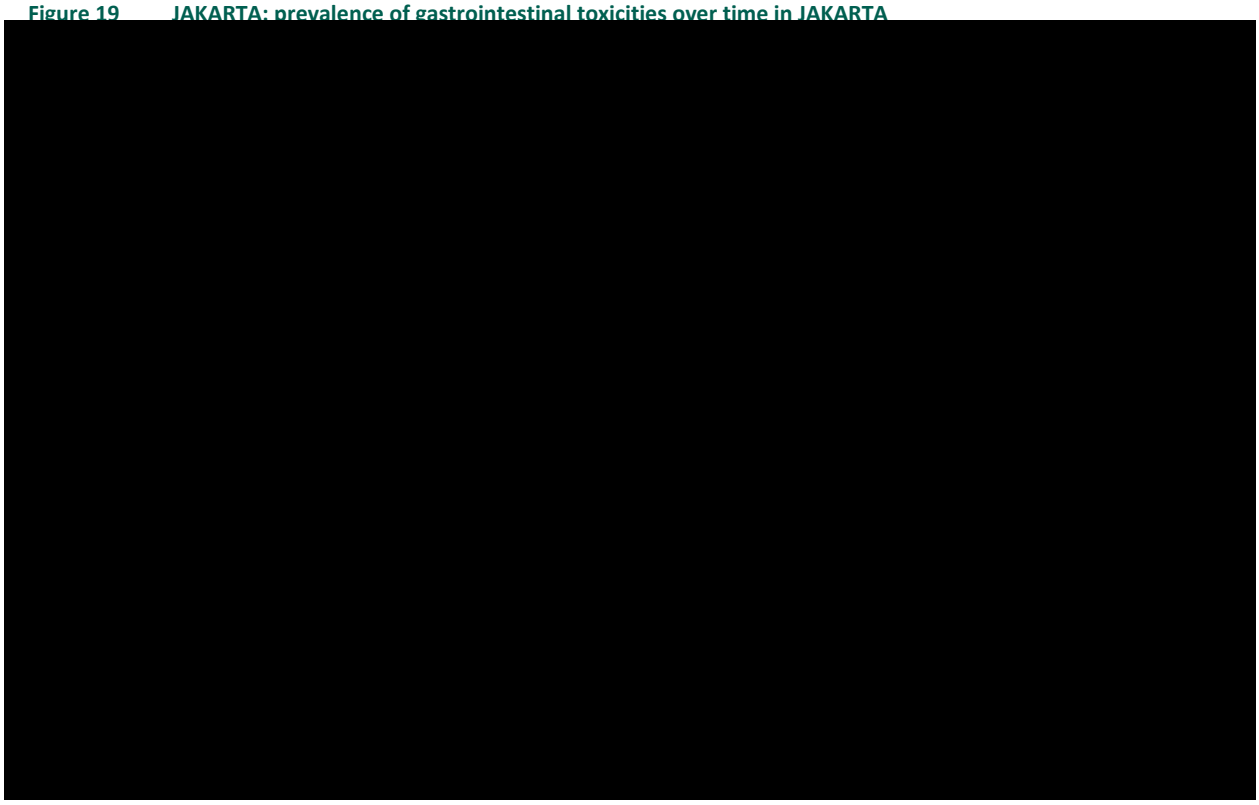
Figure 19 JAKARTA: prevalence of gastrointestinal toxicities over time in JAKARTA



Source: Pardanani et al. (2015)[23]

Unlike previous studies of fedratinib, the FREEDOM study (investigating fedratinib 400 mg once daily in patients with MF previously treated with ruxolitinib) prospectively required the following mitigation strategies to manage GI events[81,82]:

- Prophylactic and symptomatic use of anti-nausea, anti-vomiting, and anti-diarrhoeal treatments
- Fedratinib dosing modifications
- Administration of fedratinib with food

Preliminary safety data for the first 23 patients enrolled in the FREEDOM study have been presented and are summarised here. Median fedratinib treatment duration was 18.1 weeks (range, 1.6-47.9), and 10 patients (43%) had received > 6 fedratinib treatment cycles. The most common GI TEAEs were diarrhoea (n = 8), constipation (n = 8), vomiting (n = 4), and nausea (n = 3) (Figure 20). During fedratinib treatment, 14 patients (61%) received ondansetron and 7 patients (30%) received loperamide. Early data from the FREEDOM study suggest frequency and severity of GI events may be reduced via mitigation strategies.[81,82]

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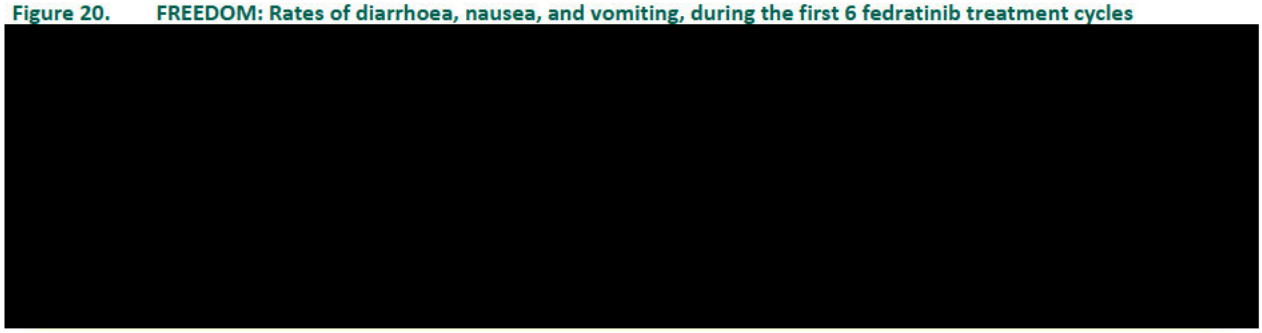
Figure 20. FREEDOM: Rates of diarrhoea, nausea, and vomiting, during the first 6 fedratinib treatment cycles



Note: Includes events with new onset in each cycle. All events of diarrhoea, nausea, and vomiting were grade 1 in severity.
Source: Gupta et al. (2020)[81]

Haematological adverse events

The only haematological AEs reported in ≥ 10% of patients in either group were anaemia and thrombocytopenia. Anaemia was reported in 40% of the fedratinib group (vs. 14% for placebo) and three-quarters of cases in the fedratinib group were grade 3 or 4 in severity. One patient discontinued fedratinib due to anaemia; 7 patients (7.3%) had dose interruptions/reductions for anaemia. The lowest haemoglobin levels were reached after 12 to 16 weeks on fedratinib, with partial recovery occurring from week 16 onwards. Out of 8 patients who were RBC transfusion dependent at baseline, 7 patients achieved transfusion independence during treatment with fedratinib, but 22 out of 88 patients who were RBC transfusion independent at baseline became dependent. The incidence of thrombocytopenia (any grade and grade 3 or 4) was similar in both groups (grade 3 or 4: fedratinib, 5%; placebo, 6%). In total, 2 patients discontinued fedratinib due to thrombocytopenia and 2 had dose reductions or treatment interruptions for management of thrombocytopenia.[71]

Over the entire study, the mean duration of exposure in patients initially randomised to receive fedratinib 400 mg was 52 weeks, and the mean relative dose intensity was 92.8%. Over the study period, 58% of patients in this group required ≥ 1 dose reduction and 23% had a treatment interruption of ≥ 7 days. The incidence of AEs in the fedratinib group over the entire study duration was consistent with that over the placebo-controlled period. Gastrointestinal-related AEs were the most frequently reported AEs, and the only other AEs (any grade) reported in > 20% of patients were anaemia (55%) and fatigue (25%). The only grade 3 or 4 AEs reported in ≥ 5% of patients were infections, diarrhoea, anaemia, thrombocytopenia, and cardiac failure. Adverse events leading to permanent discontinuation of fedratinib were thrombocytopenia (n = 4); cardiac failure (n = 3); and 2 each for the following AEs: anaemia, blood creatinine increased, diarrhoea, myocardial ischaemia, and nausea.[71]

Serious AEs occurred at a similar incidence in both groups over the placebo-controlled period. Serious AEs occurring in ≥ 2 patients were cardiac failure (n = 5), infections (n = 3), and anaemia (n = 2) in the fedratinib group, and infections (n = 5), cardiac failure and ascites (3 patients each), and pneumonia, splenic infarction, and transformation to AML (2 patients each) in the placebo group.[71]

There were 7 (7.3%) deaths on study in the fedratinib group and 12 (12.6%) in the placebo group during the placebo-controlled period. Progressive disease was the main cause in both groups (fedratinib, n = 4, 4.2%; placebo, n = 6, 6.3%) followed by AEs [fedratinib, n = 1, 1%, cardiogenic shock; placebo, n = 4, 4.2%, myocardial ischaemia, pneumonia, sepsis, and transfusion-related acute lung injury (1 patient each)]. There were also more deaths occurring within 30 days of the last dose of study drug in the placebo versus fedratinib group (fedratinib, n = 2; placebo, n = 6). Over the entire study period there were 15 deaths in the fedratinib 400 mg

group, 9 due to disease progression, 2 due to AEs (the additional AE was acute leukaemia) and 4 from other causes.[71]

JAKARTA: Safety overview

Over the entire treatment duration, all fedratinib-treated patients in the All Treated Population had ≥ 1 TEAE. The frequency of patients with events in the other categories of TEAEs (regardless of relationship to treatment) was lower in the 400 mg arm than in the 500 mg arm, with a between-arm difference of ≥ 5% for grade 3 or 4 TEAEs (70.8% vs. 78.4%), treatment-emergent SAEs (38.5% vs. 44.3%), TEAEs leading to permanent treatment discontinuation (27.1% vs. 36.1%), and TEAEs leading to dose reduction (25.0% vs. 45.4%) or dose interruption (33.3% vs. 46.4%).[3]

7.2 Efficacy and safety of fedratinib compared with ruxolitinib patients

7.2.1 Indirect treatment comparison analyses of efficacy and safety

As there is no head-to-head evidence comparing fedratinib with ruxolitinib, the comparative efficacy and safety of fedratinib and ruxolitinib in patients with MF who had no prior exposure to JAK inhibitor treatment cannot be directly inferred from a trial. Therefore, comparative evidence needs to be calculated using an anchored ITC. The following sections outline the methodology and results. For further details, please see Appendix F.[28]

7.2.1.1 Methodology

A feasibility assessment assessed the evidence base that resulted from the clinical SLR and additional screening, in terms of study design and PICO criteria,[83] to determine the comparability of the studies identified for analyses. Indirect methods are generally considered acceptable if applied with consideration of the basic assumptions of homogeneity and consistency.[84]

When using an anchored ITC, only imbalances in patient characteristics that are treatment-effect modifiers require statistical adjustment, as imbalances in prognostic factors across studies should not bias findings from anchored ITCs.[85]

7.2.1.2 Statistical analysis

A detailed description of statistical analysis for the ITC is reported in Section 3.3 of Appendix F. An anchored ITC was performed mainly using Bucher methods to assess the risk difference (RD) and 95% CI of ≥ 35% SVR from baseline to week 24 for fedratinib versus ruxolitinib.[86] An anchored matched-adjusted ITC (MAIC) was also performed to statistically adjust for imbalances in patient characteristics considered to be treatment-effect modifiers (treatment effect differs within the subgroups for a particular covariate).

To identify treatment-effect modifiers, characteristics that were reported for the comparator in the COMFORT trials and collected in the JAKARTA study were identified. A logistic regression analysis was performed for each endpoint (SVR and TSS reduction) using JAKARTA data (fedratinib 400 mg and placebo arms only), which included an interaction term for randomised treatment and each baseline characteristic being investigated for treatment-effect modification. 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 were considered to indicate that a variable could be a treatment-effect modifier. In the absence of known treatment-effect modifiers in the literature, the JAKARTA study was considered the best source of evidence for identifying potential treatment effect modifiers. Potential treatment-effect modification was identified for treatment-by-subgroup p-values < 0.1. The cut-off of

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0.1 was chosen arbitrarily to capture potentially important characteristics, while acknowledging the data were not collected with the statistical power of these tests in mind. Table 20 presents the subgroup analysis for SVR. Each variable in the table was dichotomised and the risk differences were presented for each of the 2 subgroups (category 1 and category 2). For example, for age, category 1 refers to the subgroup of patients with age ≤ 65 years and category 2 refers to age > 65 years; for Eastern Cooperative Oncology Group (ECOG) PS, category 1 refers to the subgroup of patients with ECOG PS ≥ 1 and category 2 to ECOG PS 0 (the order of x versus y defines whether the subgroup is category 1 or category 2). Penalised logistic regression was used to deal with instances of complete or quasi-complete separation. No treatment-effect modifiers were identified for TSS reduction, and therefore the Bucher ITC was considered appropriate for this outcome. However, the following variables were identified as potential treatment-effect modifiers for SVR:

- JAK2 status: Patients with JAK2 mutation seem to respond better to JAK2 inhibitor treatment than the wild type. Therefore, JAK2 status could be a potential treatment-effect modifier this variable was also identified as being imbalanced across the JAKARTA, COMFORT-I, and COMFORT-II. MAIC was used to address this imbalance.
- Constitutional symptoms: Patients with severe constitutional symptoms are expected to have a greater response as compared to those with no symptoms or mild symptoms and therefore could be a potential treatment-effect modifier, but this baseline characteristic was not reported for the COMFORT-I study. COMFORT-II reported constitutional symptoms, but these were not included in the COMFORT-II–only analyses for consistency with the primary analysis and in addition the proportion of patients having constitutional symptoms at baseline were similar across JAKARTA and COMFORT-II. Therefore, although considered a treatment effect modifier, no adjustment were needed in the indirect comparison. If anything, no adjustment is considered a conservative approach from the perspective of fedratinib as the difference relative to the control arm is smaller in JAKARTA than in COMFORT-II.

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Table 20. JAKARTA subgroup analyses for SVR

Variable	RD[a] (95% CI) subgroup category 1	RD[a] (95% CI) subgroup category 2	Interaction *P* value[b]
Age (≤ 65 vs. > 65 years)	49.2 (36.6-61.7)	40.9 (24.1-57.7)	0.450
ECOG PS (≥ 1 vs. 0)	47.5 (34.0-61.1)	43.9 (28.7-59.1)	0.908
Race (White vs. non-White)	50.0 (19.0-81.0)	45.4 (34.6-56.2)	0.483
Sex (female vs. male)	64.3 (49.8-78.8)	31.5 (18.5-44.6)	0.182
Weight (≤ median vs. > median)	58.1 (43.4-72.9)	36.9 (22.8-51.0)	0.204
Haemoglobin (≤ 10 vs. > 10 g/dL)	48.5 (31.4-65.5)	43.9 (31.0-56.9)	0.452
LDH (≤ 5 vs. > 5 ULN)	48.1 (36.7-59.5)	38.9 (14.4-61.4)	0.568
Platelet count (< 100 vs. ≥ 100 × 10^9/L)	38.5 (12.0-64.9)	47.5 (36.4-58.6)	0.701
WBC count (< 25 vs. ≥ 25 × 10^9/L)	49.1 (37.3-61.0)	34.8 (15.3-54.2)	0.874
Transfusion dependence (no vs. yes)	48.9 (38.2-59.6)	12.5 (–10.4 to 35.4)	0.175
Blast count (< 1% vs. ≥ 1%)	47.6 (32.5-62.7)	44.2 (30.1-58.2)	0.520
Fibrosis grade (1 or 2 vs. 3)[c]	37.2 (21.8-52.5)	51.0 (37.0-65.0)	0.543
JAK2 mutation status (negative vs. positive)	30.2 (12.3-48.1)	54.8 (42.5-67.2)	0.098
Spleen size > 10 cm (no vs. yes)	42.9 (24.5-61.2)	47.1 (34.9-59.3)	0.936
Spleen volume (≤ median vs. > median)	54.3 (40.0-68.7)	39.6 (25.1-54.1)	0.351
Constitutional symptoms (no vs. yes)	26.6 (6.4-46.8)	52.1 (40.6-63.5)	0.059

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; JAK2 = Janus kinase 2; LDH = lactate dehydrogenase; RD = risk difference; SVR = spleen volume reduction; ULN = upper limit of normal; WBC = white blood cell.

Note: Endpoint was defined as the proportion of patients achieving ≥ 35% SVR from baseline to end of Cycle 6 (week 24).

[a] RD for fedratinib versus placebo.

[b] *P* values for the interaction term < 0.1 were indicative of a variable being a treatment-effect modifier.

[c] Four patients in JAKARTA had fibrosis grade 0 (1 in the fedratinib arm and 3 in the placebo arm). The patient in the fedratinib arm had an SVR, and no patients in the placebo arm had an SVR.

Source: Tang et al. (2020)[86]

There were differences in ECOG PS between the trials, as COMFORT-I and II included patients with ECOG PS of 3, whereas JAKARTA did not include this group. However, this was not considered problematic because there were very few patients in the COMFORT studies with ECOG PS of 3 (2.3% in COMFORT-I and 0.9% in COMFORT-II) and the *P* value for the interaction term in the logistic regression analysis was 0.908, suggesting this was not an effect modifier.

Therefore, MAICs were used to explore the potential impact of JAK2 mutation status on the results, where individual fedratinib-treated patients were assigned statistical weights that adjust for their over- or underrepresentation relative to that observed in each comparative evidence source. The MAIC used a method of moments to estimate weights to allow a propensity score logistic regression model to be estimated without individual patient data for the comparative evidence sources. The model was estimated based on individual patient data available for the fedratinib-treated patients and published summary data available for the comparative evidence sources. Weighted logistic regression models were fitted to derive an adjusted RD for fedratinib versus placebo, and the adjusted RD was then used in a Bucher ITC.

Please see Section 9.5 in Appendix F for a detailed description of the weight diagnostics and effective sample size for MAIC analyses.

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7.2.1.3 Method of synthesis

An SLR of existing evidence followed by an ITC was conducted to support the understanding of the comparative efficacy and safety of fedratinib and ruxolitinib in this patient population. As described in Section 6.1, a clinical SLR was performed (searches completed on April 2021) to identify all relevant clinical information from RCTs, single-arm trials and real-world evidence related to the treatment of patients with MF. The overall SLR on MF was performed in 4 parts: the original SLR (inception to August 2018), SLR Update 1 (1 August 2018 to 4 October 2019), SLR Update 2 (1 September 2019 to 29 February 2020), and SLR Update 3 (29 February 2020 to 20 April 2021). The ITC was conducted after the SLR Update 2, and the SLR Update 3 did not identify any new relevant studies pertaining to the ITC; therefore, an updated ITC was not required. The SLR identified 5 studies that investigated either fedratinib or ruxolitinib in a patient population that had not received prior JAK inhibitor treatment:

- JAKARTA[23]:
  - A phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of fedratinib (400 mg and 500 mg) in patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly.
- Study NCT01420770[87]:
  - A phase 2, randomised, open-label, dose-ranging study of the efficacy and safety of fedratinib in 31 patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly.
  - Patients were randomised to receive either 300 mg, 400 mg, or 500 mg of fedratinib.
  - The primary endpoint was the percentage change in spleen volume at 12 weeks (EOC3) relative to baseline.
- COMFORT-I[26]:
  - A phase 3, randomised, double-blind, placebo-controlled trial conducted in sites in the US, Australia, and Canada.
  - Patients had intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF and a platelet count of ≥ 100 × 10^9/L.
  - The primary endpoint was the proportion of patients with a ≥ 35% reduction in spleen volume from baseline to week 24; no confirmation of response was reported.
- COMFORT-II[27]:
  - A phase 3, randomised, open-label, BAT-controlled trial conducted in Europe.
  - Patients had intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF and a platelet count of ≥ 100 × 10^9/L.
  - The primary endpoint was the proportion of patients with a ≥ 35% reduction in spleen volume from baseline to week 48; no confirmation of response was reported.
- SIMPLIFY-1[62]:
  - A phase 3, randomised, double-blind, active-controlled trial evaluating momelotinib versus ruxolitinib.
  - Momelotinib is not currently approved by the EMA for the treatment of MF and therefore is not a comparator of interest.
  - The primary endpoint of this study was the percentage of patients achieving a reduction of ≥ 35% in spleen volume from baseline at week 24.

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Three of the 5 studies identified in the clinical SLR have common comparator control arms to perform an anchored ITC:

- JAKARTA (control arm: placebo)
- COMFORT-I (control arm: placebo)
- COMFORT-II (control arm: BAT)

The BAT arm of COMFORT-II is assumed to be a common comparator to placebo, based on the findings of Mesa et al.[88] The paper compared baseline characteristics, spleen volume and spleen length response, patient-reported outcomes, and AEs of the COMFORT-I and COMFORT-II control arms; it concluded that non–JAK inhibitor therapies provide little improvement in splenomegaly, symptoms, or QoL compared with placebo.[88] Study NCT01420770 and the SIMPLIFY-1 study did not have a common comparator arm that could be used to perform an anchored indirect comparison of fedratinib with ruxolitinib. The SIMPLIFY-I and NCT01420770 studies were therefore not considered for the full feasibility assessment.

Overall network

Figure 21 presents the overall network for the JAKARTA, COMFORT-I, and COMFORT-II studies. The overall network assumes that the response in the placebo and BAT arms of COMFORT-I and COMFORT-II is the same, as was concluded in the paper by Mesa et al.[88]

Figure 21. Overall network

BAT = best available therapy.
Source: Celgene-BMS data on file (2020)[28]

Study design

Table 21 summarises the key aspects of the JAKARTA, COMFORT-I, and COMFORT-II trial designs. JAKARTA, COMFORT-I, and COMFORT-II were all phase 3 RCTs. JAKARTA and COMFORT-I were both double-blind, placebo-controlled studies, whereas COMFORT-II was an open-label and BAT-controlled trial. Of the patients in the COMFORT-II BAT arm, 67% received an active treatment and the most commonly received treatments were antineoplastic agents. Patients in the ruxolitinib arms of COMFORT-I and COMFORT-II received different doses

of ruxolitinib based on baseline platelet count, whereas in JAKARTA, different doses of fedratinib were investigated in different arms.[28]

The main differences in inclusion/exclusion criteria of the 2 ruxolitinib studies compared with the JAKARTA study were:

- Patients in COMFORT-I were resistant or refractory to, intolerant of, or not a candidate for available therapy and patients in COMFORT-II were not candidates for stem cell transplantation
- COMFORT-I and COMFORT-II allowed patients with an ECOG PS of 3 at baseline
- COMFORT-I and COMFORT-II only allowed patients with a baseline platelet count of ≥ 100 × 10^9/L

Even though patients in the COMFORT-I study were resistant or refractory to, or intolerant of, or not a candidate for available therapy, at the time the COMFORT-I study was started, there were very few options for available therapies.

The inclusion of ECOG PS 3 patients in the COMFORT-I and COMFORT-II trials is not considered problematic because there were very few patients in the COMFORT studies with ECOG PS 3 (7 patients [2.3%] in COMFORT-I and 2 [0.9%] in COMFORT-II).

Table 21. Summary of study design in JAKARTA, COMFORT-I, and COMFORT-II

	JAKARTA	COMFORT-I	COMFORT-II
Phase	3	3	3
Design	RCT	RCT	RCT
Intervention (n)	▪ Fedratinib 400 mg once daily (96) ▪ Fedratinib 500 mg once daily (97) (patients with platelet count ≥ 50,000/µL were enrolled for both doses)	Ruxolitinib twice daily (155) ▪ 20 mg dose – baseline platelet count > 200,000/µL ▪ 15 mg dose – baseline platelet count between 100,000/µL and 200,000/µL	Ruxolitinib twice daily (146) ▪ 20 mg dose – baseline platelet count > 200,000/µL ▪ 15 mg dose – baseline platelet count between 100,000/µL and 200,000/µL
Comparator (n)	Placebo (96)	Placebo (154)	BAT[a] (73)
Location	Multicentre[b]	US, Canada, and Australia	56 sites in 9 EU countries
Method of randomisation	1:1:1 ratio with no stratification	1:1 ratio with no stratification	2:1 ratio stratified by prognostic score at enrolment
Crossover	Yes, as per the protocol[c]	Yes, as per the protocol[d]	Yes, as per the protocol[e]
Key inclusion/exclusion criteria			
Treatment line	No previous JAK2 inhibitor treatment (73.4% of patients received prior MF therapy - hydroxycarbamide was the most frequently used prior MF therapy among all patients [71.9% in the fedratinib 400 mg arm and 56.3% in the placebo arm])[f]	No previous JAK inhibitor treatment, resistant or refractory to/intolerant of/not a candidate for available therapy (67.1% and 56.5% of patients had previous hydroxycarbamide in the ruxolitinib and placebo arms, respectively)	No previous JAK inhibitor treatment, not a candidate for stem cell transplantation (in the ruxolitinib arm, 75% of patients had previous hydroxycarbamide and 0% radiotherapy, and in the BAT arm, 68% of patients had previous hydroxycarbamide and 5% radiotherapy)
Platelet count	≥ 50 × 10^9/L	≥ 100 × 10^9/L	≥ 100 × 10^9/L
Diagnosis	PMF, post-PV MF or post-ET MF	PMF, post-PV MF or post-ET MF	PMF, post-PV MF or post-ET MF
IPSS[g] score ≥ 2	Yes	Yes	Yes

	JAKARTA	COMFORT-I	COMFORT-II
ECOG PS	0, 1, or 2	0, 1, 2, or 3	0, 1, 2, or 3
Palpable spleen ≥ 5 cm	Yes	Yes	Yes

BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = essential thrombocythaemia; EU = European Union; IPSS = International Prognostic Scoring System; JAK = Janus kinase; JAK2 = Janus kinase 2; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythaemia vera; RCT = randomised controlled trial; US = United States.

[a] 67% of patients in the COMFORT-II BAT arm received at least 1 active treatment that included antineoplastic agents (37 patients [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%]).

[b] Includes 94 active sites across 24 countries (Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan [Province of China], the United Kingdom, and the US).

[c] In JAKARTA, 71 patients from the placebo arm were re-randomised to one of the fedratinib arms at crossover (10 before the end of Cycle 6).[3]

[d] In COMFORT-I, 111 patients crossed over to ruxolitinib (median time to crossover of 41 weeks).[89]

[e] In COMFORT-II, 45 patients crossed over to ruxolitinib (median time to crossover of 66 weeks).[89]

[f] Prior myelofibrosis therapies included: antineoplastic agents including hydroxycarbamide (186 patients [64.4%]), an immunomodulatory agent including interferon (54 patients [18.7%]), corticosteroids (22 patients [10.4%]), platelet-reducing agent (19 patients [9%]), other (12 patients [5.7%]), hormone (8 patients [3.8%]), and haematopoietic agent (1 patient [0.5%]).

[g] IPSS score calculation – 1 point for each of the following criteria: age > 65 years, white blood cell count > 25 × 10^9/L, haemoglobin < 10 g/dL, peripheral blood blasts ≥ 1%, constitutional symptoms (weight loss and/or unexplained fever or excessive sweats).

Sources: Harrison et al. (2012)[27]; EMA (2020)[3]; Verstovsek et al. (2012)[26]

All 3 RCTs allowed crossover from the control arm to the interventional arm but, as can be seen in Table 22, definitions for crossover differed slightly among the 3 studies. The criteria for crossover for the COMFORT-I and COMFORT-II trials specified that patients must have experienced an increase (≥ 25%) in spleen volume from baseline and nadir, respectively. Similarly, the JAKARTA statistical analysis plan specified that patients could cross over from the control arm to the interventional arm after disease progression. In the JAKARTA study, disease progression was defined as an increase in spleen volume of ≥ 25% compared with baseline, leukaemic transformation, or an increase in peripheral blood blast percentage of ≥ 20%. Despite the different definitions of crossover across the 3 studies, for both efficacy outcomes (SVR and TSS reduction), the statistical analysis of JAKARTA, COMFORT-I, and COMFORT-II specified that patients who crossed over after disease progression were considered to be nonresponders. As such, the fact that patients in the control arm had subsequently received the intervention is not likely to bias the comparison of these endpoints between arms of these trials.[28]

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Table 22. Definitions of crossover in JAKARTA, COMFORT-I, and COMFORT-II

	JAKARTA	COMFORT-I	COMFORT-II
Definition of crossover	Placebo patients were re-randomised to receive 400 mg or 500 mg of fedratinib at EOC6 or at the time of progressive disease prior to EOC6. Progressive disease was defined as: ▪ Enlargement of spleen volume by MRI (or CT scan in patients with contraindications for MRI) of ≥ 25% compared with baseline value ▪ Leukaemic transformation, confirmed by a bone marrow blast count of ≥ 20% or the occurrence of a granulocytic sarcoma (chloroma) ▪ An increase in peripheral blood blast percentage of ≥ 20% that persists for at least 1 week	Up to week 24, crossover from placebo to ruxolitinib required both symptom worsening and a ≥ 25% spleen volume increase from baseline. After week 24, crossover from placebo to ruxolitinib required ≥ 25% spleen volume increase from baseline.	At any time, crossover from BAT to ruxolitinib was permitted if criteria for disease progression were met. Progression was defined as a ≥ 25% increase in spleen volume from on-study nadir (which could include the baseline volume) or splenectomy.

BAT = best available therapy; CT = computed tomography; EOC6 = end of Cycle 6; MRI = magnetic resonance imaging.
Sources: Harrison et al. (2012)[27]; EMA (2020)[3]; Pardanani et al. (2015)[23]; Verstovsek et al. (2012)[26]; Celgene-BMS data on file (2020)[28]

Primary and secondary endpoints

Table 23 summarises the primary and secondary endpoints of the JAKARTA, COMFORT-I, and COMFORT-II studies.

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Table 23. Primary and secondary endpoints of JAKARTA, COMFORT-I, and COMFORT-II

	JAKARTA	COMFORT-I	COMFORT-II
Primary	Proportion of patients with ≥ 35% SVR at the EOC6 and confirmed 4 weeks later by MRI/CT	Proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to week 24 as measured by MRI/CT	Proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 48, assessed by MRI/CT
Secondary	▪ Symptom RR using the modified MF-SAF: – Symptom RR: defined as the proportion of patients with ≥ 50% reduction in the TSS from baseline to the EOC6. Baseline TSS was the TSS value the week before randomisation or the week before an on-treatment assessment – TSS: Defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MF-SAF. ▪ OS ▪ PFS ▪ Spleen RR of ≥ 25% SVR at the EOC6 and confirmed 4 weeks later ▪ Duration of spleen response	▪ Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume among patients initially randomised to receive ruxolitinib ▪ Proportion of patients who had a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the modified MF-SAF v2.0 diary ▪ Change in TSS from baseline to Week 24 as measured by the modified MF-SAF v2.0 diary ▪ OS	▪ Proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24, assessed by MRI/CT ▪ Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume and less than 25% above the on-study nadir ▪ Time to achieve a first ≥ 35% reduction in spleen volume from baseline ▪ PFS ▪ Leukaemia-free survival ▪ OS ▪ Transfusion dependency/independency ▪ Change in bone marrow histomorphology ▪ HRQoL assessments using EORTC QLQ-C30 and FACT

CT = computed tomography; EOC6 = end of Cycle 6; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FACT = Functional Assessment of Cancer Therapy; HRQoL = health-related quality of life; MF-SAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; OS = overall survival; PFS = progression-free survival; RR = response rate; SVR = spleen volume reduction; TSS = total symptom score.

Note: Safety was an endpoint in the COMFORT-I and COMFORT-II studies, however, safety was not specifically stated as a secondary endpoint in the existing publications.

Sources: Harrison et al. (2012)[27]; EMA (2020)[3]; Verstovsek et al. (2012)[26]; Celgene-BMS data on file (2020)[28]

Spleen volume reduction was the primary endpoint for the JAKARTA, COMFORT-I, and COMFORT-II studies; however, the primary endpoint differed in the following ways:

- The JAKARTA study included a confirmation of response 4 weeks after the EOC6 measurement, whereas the COMFORT-I and COMFORT-II studies did not include a confirmation.
- The COMFORT-II study had the proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 48, whereas JAKARTA and COMFORT-I measured the primary endpoint at week 24.

Although there were differences in the primary endpoints of the JAKARTA, COMFORT-I, and COMFORT-II studies, the COMFORT-II study also reported the proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 24, and the JAKARTA study also reported a ≥ 35% reduction from baseline in spleen volume at week 24, regardless of confirmation. In terms of the endpoint definition, it was therefore possible to compare like-for-like the proportion of patients achieving a ≥ 35% reduction in volume of spleen at week 24 as assessed by MRI or CT scan and by independent review.

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The secondary endpoint in JAKARTA (proportion of patients who had a ≥ 50% reduction in TSS from baseline to the end of week 24), was also reported for the COMFORT-I study, but not the COMFORT-II study. The key similarities and differences in the calculation of the TSS in JAKARTA and COMFORT-I are summarised in Table 24. Both the JAKARTA and COMFORT-I studies used the modified MF-SAF to analyse TSS, although the COMFORT-I study used version 2 of the modified MF-SAF, which includes an extra question to assess inactivity. In both studies, the MF-SAF diary was completed each day, and TSS at baseline was calculated as the mean TSS from the 7 days prior to baseline. In both JAKARTA and COMFORT-I, patients with missing baseline TSS were not included in the analyses. Furthermore, patients in JAKARTA with a baseline TSS of 0 were not included in the Symptom Analysis Population. Patients in JAKARTA had to have had a TSS for 5 out of the 7 days prior to baseline, otherwise the baseline TSS was considered missing. Patients in COMFORT-I had to have had a TSS for 4 out of the 7 days prior to baseline. In JAKARTA, the week 24 TSS was the mean TSS of the 7 days prior to the EOC6 (24 weeks), and patients must have had a TSS for 5 out of the 7 days; however, in COMFORT-I, the week 24 TSS was the mean TSS of the 28 days prior to the week 24 visit, and patients had to have had a TSS for at least 20 days out of 28. For both outcomes (SVR and TSS reduction), the statistical analysis of JAKARTA, COMFORT-I, and COMFORT-II specified that patients who crossed over after disease progression were considered nonresponders.[28]

Owing to the clinical hold placed on all studies conducted under the investigational new drug application, including the JAKARTA study, data for OS and PFS were not collected from this point. Therefore, the PFS and OS data that are available are not robust or suitable for comparison and are not included in these analyses.[28]

Table 24. Comparison of total symptom score outcomes in JAKARTA and COMFORT-I

	JAKARTA	COMFORT-I
MF-SAF version	Modified MF-SAF version 1	Modified MF-SAF version 2
MF-SAF items	6 items: ▪ Night sweats ▪ Itching (pruritus) ▪ Abdominal discomfort ▪ Filling up quickly when you eat (early satiety) ▪ Pain under ribs on left side	Bone or muscle pain 7 items: ▪ Night sweats ▪ Itching (pruritus) ▪ Abdominal discomfort ▪ Feeling of fullness (early satiety) ▪ Pain under ribs on left side ▪ Bone or muscle pain ▪ Inactivity
MF-SAF items used to calculate TSS	All 6 items	6 items – not including the inactivity item
Baseline TSS calculation	Mean of the daily TSS for 7 days prior to dosing at baseline	Mean of the daily scores through the 7-day baseline period
EOC6/week 24 TSS calculation	Mean of the daily TSS for 7 days during the last week of Cycle 6	Mean TSS of 28 days prior to the week 24 visit

EOC6 = end of Cycle 6; MF-SAF = Myelofibrosis Symptom Assessment Form; TSS = total symptom score.
Sources: Harrison et al. (2012)[27]; EMA (2020)[3]; Verstovsek et al. (2012)[26]; Celgene-BMS data on file (2020)[28]

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7.2.1.4 Results from indirect comparison

Spleen volume reduction

The baseline characteristics before and after matching the JAKARTA ITT and low platelet count populations to the COMFORT-I and -II populations, along with effective sample sizes, are presented in Table 25. Further detail of the approach to weighting and MAIC are provided in the NMA report.[28] Table 26 presents the ITC results for the proportion of patients achieving a ≥ 35% SVR from baseline to week 24.

In the network meta-analysis (NMA) that included both the COMFORT-I and COMFORT-II trials, fedratinib 400 mg had a comparable proportion of patients with ≥ 35% SVR as ruxolitinib (RD, 11.0%; 95% CI, −1.4% to 23.4%). When comparing to the COMFORT-I population, fedratinib had a comparable proportion of patients with ≥ 35% SVR as ruxolitinib (RD, 6.2%; 95% CI, −7.4% to 19.8%). When comparing to the COMFORT-II population, fedratinib had a 15.5% (95% CI, 2.1%-29.0%) greater proportion of patients with a ≥ 35% SVR than ruxolitinib.[86]

The MAIC analyses, which adjusted for the imbalance in the JAK2 mutation status of patients (mutant vs. wild-type vs. unknown) across the 3 studies, showed that fedratinib 400 mg had a significantly greater proportion of patients with ≥ 35% SVR than ruxolitinib (RD, 14.7%; 95% CI, 2.4%-27.1%).[86]

Table 25. Baseline characteristics before and after matching the JAKARTA ITT population to the COMFORT-I and COMFORT-II populations

Population	N/ESS	% JAK2: mutant	% JAK2: wild type	% JAK2: missing
JAKARTA ITT population				
COMFORT-I	N = 309	76.4	21.7	1.9
JAKARTA before matching	N = 192	63.0	32.3	4.7
JAKARTA after matching	[redacted]	[redacted]	[redacted]	[redacted]
COMFORT-II	N = 219	72.6	25.1	2.3
JAKARTA before matching	N = 192	63.0	32.3	4.7
JAKARTA after matching	[redacted]	[redacted]	[redacted]	[redacted]
JAKARTA ITT population with platelet count ≥ 100 × 10^9/L				
COMFORT-I	N = 309	76.4	21.7	1.9
JAKARTA before matching	[redacted]	[redacted]	[redacted]	[redacted]
JAKARTA after matching	[redacted]	[redacted]	[redacted]	[redacted]
COMFORT-II	N = 219	72.6	25.1	2.3
JAKARTA before matching	[redacted]	[redacted]	[redacted]	[redacted]
JAKARTA after matching	[redacted]	[redacted]	[redacted]	[redacted]

ESS = effective sample size; ITT = intent to treat; JAK2 = Janus kinase 2; N = sample size.

Source: Celgene-BMS data on file (2020)[28]

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Table 26. Fedratinib 400 mg versus ruxolitinib: indirect treatment comparison results for the SVR endpoint

		JAKARTA		COMFORT-I		COMFORT-II	
Outcome	**Analysis performed**	**PBO**	**400 mg FEDR**	**PBO**	**RUX**	**BAT**	**RUX**
≥ 35% SVR from baseline to week 24 (JAKARTA ITT population and no confirmation of response 4 weeks later)	No analysis performed (absolute responses)	1.0% (n = 1; N = 96)	46.9% (n = 45; N = 96)	0.7% (n = 1; N = 153)	41.9% (n = 65; N = 155)	0% (n = 0; N = 72)	31.9% (n = 46; N = 144)
	Bucher ITC			Δ 400 mg FEDR–RUX [95% CI]: 4.6% [–8.3 to 17.4]		Δ 400 mg FEDR–RUX [95% CI]: 13.9% [1.2-26.6]	
	MAIC using Bucher methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 7.9% [–5.2 to 20.9]		Δ 400 mg FEDR–RUX [95% CI]: 16.3% [3.5-29.0]	
	Frequentist NMA			Δ 400 mg FEDR–RUX [95% CI]: 9.4% [–2.2 to 20.9]			
	MAIC using frequentist NMA methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 12.3% [0.6-24.0]			
≥ 35% SVR from baseline to week 24 (subgroup of the JAKARTA ITT population with platelet counts ≥ 100 × 10^9/L and no confirmation of response 4 weeks later)	No analysis performed (absolute responses)	[redacted]	[redacted]	0.7% (n = 1; N = 153)	41.9% (n = 65; N = 155)	0% (n = 0; N = 72)	31.9% (n = 46; N = 144)
	Bucher ITC			Δ 400 mg FEDR–RUX [95% CI]: 6.2% [–7.4 to 19.8]		Δ 400 mg FEDR–RUX [95% CI]: 15.5% [2.1-29.0]	
	MAIC using Bucher methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 10.4% [–3.2 to 24.1]		Δ 400 mg FEDR–RUX [95% CI]: 18.5% [5.1-31.9]	
	Frequentist NMA			Δ 400 mg FEDR–RUX [95% CI]: 11.0% [–1.4 to 23.4]			
	MAIC using frequentist NMA methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 14.7% [2.4-27.1]			

BAT = best available therapy; CI = confidence interval; FEDR = fedratinib; ITC = indirect treatment comparison; ITT = intent-to-treat; JAK2 = Janus kinase 2; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; PBO = placebo; Δ 400 mg FEDR–RUX = risk difference between fedratinib and ruxolitinib; RUX = ruxolitinib; SVR = spleen volume reduction.

[a] Adjustment made for JAK2 status at baseline.

Sources: Celgene-BMS data on file (2020)[28]; Tang et al. (2020)[86]

Total symptom score reduction

The ITC results for the outcome of the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to week 24 are presented in Table 27. The Bucher ITC was used because no effect modifiers were identified for this outcome, suggesting an MAIC was not required (see Section 7.2.1.2).

For the TSS reduction endpoint, 2 populations from JAKARTA were compared with the COMFORT-I results (note that TSS reduction results were not reported for the COMFORT-II study):

- ITT with nonmissing TSS at baseline
- Subgroup of the ITT population with a platelet count of ≥ 100 × 10^9/L and nonmissing TSS at baseline

The results discussed here are for the ITCs made with the subgroup of the JAKARTA patients with a platelet count of ≥ 100 × 10^9/L, because the results for the 2 JAKARTA populations did not differ greatly. [redacted]

Table 27. Fedratinib 400 mg versus ruxolitinib: indirect treatment comparison results for the total symptom score reduction endpoint

Outcome	Analysis performed	JAKARTA		COMFORT-I		COMFORT-II	
		PBO	400 mg FEDR	PBO	RUX	BAT	RUX
≥ 50% reduction in TSS from baseline to week 24 (ITT population with nonmissing baseline TSS)	No analysis performed (absolute responses)	[redacted]	[redacted]	5.3% (n = 8; N = 152)	45.9% (n = 68; N = 148)	NR	NR
	Bucher ITC			[redacted]		N/A	
≥ 50% reduction in TSS from baseline to week 24 (subgroup of the JAKARTA ITT population with platelet counts ≥ 100 × 10^9/L and nonmissing baseline TSS)	N/A (absolute responses)	[redacted]	[redacted]	5.3% (n = 8; N = 152)	45.9% (n = 68; N = 148)	N/A	N/A
	Bucher ITC			[redacted]		N/A	

BAT = best available therapy; CI = confidence interval; FEDR = fedratinib; ITC = indirect treatment comparison; ITT = intent-to-treat; N/A = not applicable; NR = not reported; PBO = placebo; Δ 400 mg FEDR–RUX = risk difference between fedratinib and ruxolitinib; RUX = ruxolitinib; TSS = total symptom score.

Source: Celgene-BMS data on file (2020)[28]

Indirect treatment comparison: summary of indirect treatment comparison efficacy results

As a head-to-head trial was not available, an ITC was performed to compare the efficacy and safety of fedratinib with ruxolitinib. The results of this ITC suggest that fedratinib is associated with [redacted] The difference was approximately [redacted] when considering comparison with results from both COMFORT-I and COMFORT-II and was [redacted] for the ITT population from JAKARTA and when considering the subgroup of patients with a platelet count of ≥ 100 × 10^9/L. The comparison of TSS responses for JAKARTA and COMFORT-I, however, suggested that [redacted]. Overall, as most efficacy outcomes in the ITC were [redacted]

7.2.1.5 Descriptive comparison: safety analysis

As there is no head-to-head evidence comparing fedratinib with ruxolitinib, the comparative safety of fedratinib and ruxolitinib in patients with MF who had no prior exposure to JAK inhibitor treatment cannot be directly inferred from a trial. However, descriptive comparative evidence was reported in the ITC. Methodology and efficacy results of the ITC are detailed in Section 7.2.1. To report the same timepoints (up to 6 cycles) across the studies included in the descriptive comparative safety results, the results do not cover safety data for the whole treatment duration. Safety data reported above for JAKARTA (see Section 7.1.2.4) and JAKARTA 2 (see Section 7.3.2.5) are reported for the whole treatment duration and should be considered separately to this descriptive comparative analysis.

Treatment-emergent adverse events

The descriptive comparative results for the percentage of patients in JAKARTA, COMFORT-I, and COMFORT-II who experienced AEs are presented in Table 28.

Both the JAKARTA and COMFORT-I studies reported AEs for the primary analyses at 24 weeks, prior to crossover. The COMFORT-II study also reported AEs for the primary analyses, which was at 48 weeks. Adverse events for fedratinib-treated patients and ruxolitinib-treated patients were therefore compared using the JAKARTA and COMFORT-I studies.

Overall, results of the descriptive analysis of JAKARTA and COMFORT-I suggested a similar safety profile in terms of frequency for grade 3 or 4 AEs fedratinib and ruxolitinib. Where reported, the percentages of ruxolitinib-treated patients in COMFORT-II who experienced certain AEs (Table 28) were similar to the percentages for ruxolitinib-treated patients in COMFORT-I.

Results suggests that fedratinib is associated a higher incidence of any grade GI toxicities compared with ruxolitinib. Noteworthy differences (chosen to be ≥ 10%) between fedratinib-treated patients and ruxolitinib-treated patients in the JAKARTA and COMFORT-I studies were as follows:

- Diarrhoea (any grade): there were more fedratinib-treated patients who experienced diarrhoea
- Nausea (any grade): there were more fedratinib-treated patients who experienced nausea
- Vomiting (any grade): there were more fedratinib-treated patients who experienced vomiting

At the time the JAKARTA study was conducted, antiemetic prophylaxis was not provided to patients, which could explain the increased incidence of nausea and vomiting.

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Table 28. Adverse events

Adverse event, %	JAKARTA: 24 weeks		COMFORT-I: 24 weeks		COMFORT-II: 48 weeks	
	PBO (n = 95)	400 mg FEDR (n = 96)	PBO (n = 151)	RUX (n = 155)	BAT (n = 73)	RUX (n = 146)
Deaths due to AEs	6.3	1.0	7.3	5.8	5.5	4.1
SAEs	23.2	20.8	35.1	27.7	28.8	30.1
Grade 3 or 4 AEs	30.5	52.1	44.4	47.1	24.7	41.8
Discontinuation due to AEs	8.4	13.5	10.6	11.0	5.5	8.2
Any AEs	93.7	99.0	98.0	97.4	90.4	99.3
Haematological AEs						
Anaemia (grade 3 or 4)	24.2[a]	41.7[a]	19.2[a]	45.2[a]	31	42
Thrombocytopenia (grade 3 or 4)	9.5[a]	11.4[a]	1.3[a]	12.9[a]	7	8
Nonhaematological AEs						
Bruising (any grade)	NR	NR	9.3	18.7	NR	NR
Bruising (grade 3 or 4)	NR	NR	0	0	NR	NR
Dizziness (any grade)	3.2	8.3	6.6	14.8	NR	NR
Dizziness (grade 3 or 4)	0	0	0	0.6	NR	NR
Headache (any grade)	1.1	9.4	5.3	14.8	4	10
Headache (grade 3 or 4)	0	0	0	0	0	1
Diarrhoea (any grade)	15.8	65.6	21.2	23.2	12	23
Diarrhoea (grade 3 or 4)	0	5.2	0	1.9	0	1
Nausea (any grade)	14.7	61.5	19.2	14.8	7	13
Nausea (grade 3 or 4)	0	0	0.7	0	0	1
Vomiting (any grade)	5.3	38.5	9.9	12.3	NR	NR
Vomiting (grade 3 or 4)	0	3.1	0.7	0.6	NR	NR
Bleeding events						
≥ Grade 3 bleeding events	0	2.1	2.0[b]	2.6[b]	NR[b]	NR[b]
Infections						
Urinary tract infection (any grade)	1.1	6.3	5.3	9.0	NR	NR
Herpes zoster (any grade)	1.1	1.0	0.7	1.9	NR	NR

AE = adverse event; BAT = best available therapy; FEDR = fedratinib; NR = not reported; PBO = placebo; RUX = ruxolitinib; SAE = serious adverse event.

[a] Derived based on laboratory values.

[b] For the COMFORT-I and COMFORT-II studies combined, percentages of patients experiencing grade 3+ bleeding events in the ruxolitinib arms and control arms were 4.7% and 3.1%, respectively.

Sources: Celgene-BMS data on file (2020)[28]; NICE (2015)[89]; Jakafi PI [90]

7.3 Supportive evidence: efficacy and safety of fedratinib in patients with myelofibrosis previously treated with ruxolitinib

7.3.1 Relevant studies

JAKARTA 2 was a phase 2, multicentre, open-label, single-arm study that evaluated the efficacy of a once daily, 400 mg dose of fedratinib in 97 patients previously treated with ruxolitinib.[58] The study included adults aged ≥ 18 years with a current diagnosis of intermediate-1 with symptoms, intermediate-2, or high-risk PMF, post-PV MF or post-ET MF. Risk categorisation was carried out using the IPSS or DIPSS in patients enrolled after Protocol Amendment 3.

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Patients included in JAKARTA 2 were defined as resistant or intolerant to ruxolitinib by investigator assessment.[58] Resistance to ruxolitinib was recorded as either an absence of response, disease progression (increase in spleen size during ruxolitinib treatment), or loss of response at any time during ruxolitinib treatment. Ruxolitinib intolerance was recorded as haematological toxicity (anaemia, thrombocytopenia, other) or nonhaematological toxicity. Patients had to have received ruxolitinib treatment for ≥ 14 days and have discontinued ruxolitinib for ≥ 14 days prior to receiving fedratinib.

Table 29. JAKARTA 2: summary of trial methodology

Key publications	▪ Pardanani et al. (2015)[59] ▪ JAKARTA 2 trial results[58] ▪ Updated analysis using stringent criteria for ruxolitinib failure[29]
Sample size (n)	97
Study design	A phase 2, multicentre, open-label, single-arm study
Location	United States, Austria, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, United Kingdom
Patient population	Patients previously treated with ruxolitinib and with a current diagnosis of intermediate-1 with symptoms, intermediate-2, or high-risk primary MF, post-PV MF or post-ET MF
Intervention(s)	400 mg fedratinib
Comparator(s)	None
Follow-up period	Follow-up ranged from 0 to 13.4 months
Is the study used in the health economic model?	No
Reasons for use/nonuse of the study in model	A cost-minimisation analysis was conducted for ruxolitinib-naïve patients only.
Primary endpoints reported	RR, defined as the proportion of patients who have a ≥ 35% reduction from baseline in volume of spleen at EOC6 as measured by MRI (or CT scan in patients with contraindications for MRI)
Other outcomes reported include results	Secondary efficacy assessments: ▪ Spleen RR, defined as the proportion of patients with a ≥ 35% SVR at EOC3, relative to baseline, as measured by MRI/CT scan ▪ Duration of spleen response as measured by MRI/CT ▪ Spleen volume and percentage change of spleen volume at EOC3 and EOC6 from baseline as measured by MRI/CT ▪ Proportion of patients with a ≥ 50% reduction in spleen size by palpation at EOC6, relative to baseline ▪ Symptom RR, defined as the proportion of patients with ≥ 50% reduction in the TSS at EOC6 relative to baseline Key exploratory assessments: ▪ OS, defined as the proportion of patients alive at the time of final analysis ▪ Change in HRQoL using EORTC QLQ-C30 V3.0
Subgroups	Analyses of spleen volume reduction and symptom RR were measured in pre-planned subgroups of: ▪ Demographic factors and baseline disease characteristics ▪ Platelet count at baseline (< 100×10^9/L or ≥ 100×10^9/L) ▪ Patients resistant versus intolerant to ruxolitinib

CT = computed tomography; EOC3 = end of Cycle 3; EOC6 = end of Cycle 6; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; ET = essential thrombocythaemia; HRQoL = health-related quality of life; MF = myelofibrosis; MRI = magnetic resonance imaging; OS = overall survival; PV = polycythaemia vera; RR = response rate; SVR = spleen volume reduction; TSS = total symptom score.

Sources: Harrison et al. (2017)[58]; Harrison et al. (2020)[29]; Clinicaltrials.gov NCT01523171 (2016)[91]

7.3.1.1 JAKARTA 2: study design

The primary objective of JAKARTA 2 was to assess the efficacy of once daily dose of 400 mg of fedratinib (with dose escalation up to 600 mg permitted)[58] in patients previously treated with ruxolitinib and with a current diagnosis of intermediate-1 with symptoms, intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF based on the reduction of spleen volume at the end of 6 treatment cycles.[91]

The JAKARTA 2 trial design consisted of a screening period of up to 28 days, followed by a treatment phase of six 28-day cycles of fedratinib (24 weeks) and a follow-up visit (approximately 30 days following the last dose of fedratinib).[58] Patients could remain on fedratinib until disease progression or unacceptable toxicity (Figure 22).

Figure 22. JAKARTA 2: study design

BL = baseline; C = cycle; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; ET = essential thrombocythaemia; Int = intermediate; MF = myelofibrosis; MRI = magnetic resonance imaging; PV = polycythaemia vera; QD = once daily.

* Permitted dose escalation is 400-600 mg/day (dose up-titration permitted if < 50% reduction in spleen size by palpation at the end of Cycles 2 and 4).

† Baseline occurred within 14 days of the first fedratinib dose.

Source: Harrison et al. (2019)[92]

7.3.1.2 JAKARTA 2: endpoints

The primary outcome measure in JAKARTA 2 was spleen response, defined as the proportion of patients with a ≥ 35% SVR from baseline at the EOC6.[58] This was measured using MRI or CT and assessed by blinded central review. Splenomegaly is the main physical feature of MF and the cause of many symptoms associated with the disease. As such, SVR is a key treatment goal in MF.

The EMA approved the use of 400 mg fedratinib once daily, excluding any patients who had dose escalation up to 600 mg. Therefore, the primary endpoint for the EMA label was conducted to account for patients who only received 400 mg once daily of fedratinib.

Secondary outcomes measured in JAKARTA 2 include[29,58]:

- Spleen RR (≥ 35% SVR) at EOC3
- Duration of spleen response

- Percentage change of spleen volume at EOC3 and EOC6
- Proportion of patients with a ≥ 50% reduction in palpable spleen length from baseline to EOC6
- Symptom RR (≥ 50% reduction in TSS) at EOC6

Patient-reported outcomes were measured using the MF-SAF as an indicator of the effect of fedratinib on symptoms of MF and patients' symptom RRs.[29] The EORTC QLQ-C30 was also measured as an exploratory endpoint to capture changes in patients' HRQoL over time. This included measurements of changes to global domains of EORTC QLQ-C30, as well as functional and symptom domains specific to MF.[3]

Other clinically relevant exploratory measures included OS and subgroup analyses of the efficacy of fedratinib in patients based on demographic factors and baseline disease characteristics, platelet count at baseline, and patients resistant versus intolerant to ruxolitinib.[29,58,79]

The safety of fedratinib was assessed by measuring the incidence of TEAE and changes from baseline in clinical laboratory parameters and vital signs.[29]

7.3.1.3 JAKARTA 2: statistical testing

The primary objective of JAKARTA 2 was to determine efficacy of fedratinib with regards to the reduction of spleen volume.[58] Assuming 25% of patients achieved the primary endpoint of ≥ 35% reduction in spleen volume from baseline, 70 evaluable patients were required to provide at least 90% power (at a 1-sided 2.5% α level) to test the null hypothesis of ≥ 10% of patients achieving the primary endpoint.[58]

The primary analysis of JAKARTA 2 was conducted in the per-protocol population (n = 83), defined as patients with evaluable baseline and at least one post-baseline MRI/CT scan of spleen volume (EOC3 or EOC6)[58] and no important protocol deviations that could impact the efficacy outcome.[3] In patients who did not reach EOC6 owing to the clinical hold, missing data were accounted for using the last observation carried forward method.

The ITT population comprised all 97 patients enrolled in the study and provided the largest sample size and statistically robust source for evaluations of efficacy in JAKARTA 2. A reanalysis of JAKARTA 2 data was conducted to confirm the efficacy of fedratinib in subsets of enrolled patients who met new stringent definitions of ruxolitinib relapsed, refractory, or intolerant (Figure 23).[29] This reanalysis established that the efficacy of fedratinib is consistent, regardless of the relapse or refractory criteria applied.

To determine the treatment effect of fedratinib on clinically important subpopulations, prespecified subgroup analyses were conducted. These included subgroup analyses of patients with a platelet count of between ≥ 50 × 10^9/L and < 100 × 10^9/L or ≥ 100 × 10^9/L at baseline, and patients resistant and intolerant to ruxolitinib.[3,58,92]

A summary of the statistical analyses in JAKARTA 2 is provided in Table 30.

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Table 30. JAKARTA 2: summary of statistical analyses

Trial number (acronym)	NCT01523171 (JAKARTA 2)
Hypothesis objective	Fedratinib will improve spleen volume reduction in patients with MF that have been previously treated with ruxolitinib.
Statistical analysis	Spleen responses were measured using MRI/CT and continuous variables were summarised using descriptive statistics (i.e., n, mean, median, SD, min, max). A 1-sided significance level of α = 2.5% was used for hypothesis testing. Chi-squared testing was not performed due to the early termination of the study.
Sample size, power calculation	Assuming 25% of patients achieved the primary endpoint of a ≥ 35% reduction in spleen volume from baseline, 70 evaluable patients were required to provide at least 90% power to test the null hypothesis of ≥ 10% of patients achieving the primary endpoint. Based on the COMFORT-I study results, ~ 60% of patients receiving ruxolitinib were nonresponders. Therefore, 60% of 70 evaluable patients were required to provide 80% power to test a spleen response rate ≤ 10% for the subgroup of patients who did not reach the primary endpoint of spleen response during the ruxolitinib studies.
Data management, patient withdrawals	In the original analysis, the LOCF method was used to account for patients who did not meet EOC6 due to the clinical hold. In the updated analyses presented in this submission (full ITT population and reanalysis populations), LOCF was not applied. A patient without a Cycle 6 assessment was considered a nonresponder. The CSR provides efficacy results in ITT and per-protocol populations with and without LOCF.

CSR = clinical study report; CT = computed tomography; EOC6 = end of Cycle 6; ITT = intent-to-treat; LOCF = last observation carried forward; max = maximum; MF = myelofibrosis; min = minimum; MRI = magnetic resonance imaging; n = number of observations; SD = standard deviation.

Sources: Harrison et al. (2017)[58]; EMA (2020)[3]

All patients in JAKARTA 2 discontinued study treatment: 63 (65%) owing to the early termination of the study, 18 (19%) owing to AEs, 6 (6%) owing to patient decision, 3 (3%) owing to disease progression, and 7 (7%) owing to patient's death.[29,58]

7.3.1.4 JAKARTA 2: reanalysis

JAKARTA 2 was initiated shortly after the approval of ruxolitinib; therefore, the criteria for defining ruxolitinib resistance or intolerance were not yet well defined.[3] Patients in the original protocol were classified as resistant or intolerant to ruxolitinib per the investigators' assessments. A reanalysis of the efficacy of fedratinib in JAKARTA 2 was performed on patients determined to be relapsed or refractory or intolerant to ruxolitinib, based on criteria recommended by MF experts from the US and EU at an advisory board meeting in April 2018 and later discussed with health authorities.[93]

These more stringent definitions of ruxolitinib failure are presented in Table 31. The criteria are currently being used in ongoing studies of MF in patients who have been treated with ruxolitinib. Patients enrolled in the study were reclassified as relapsed/refractory or intolerant if they met at least one of the criteria in Table 31.

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Table 31. JAKARTA 2: ruxolitinib failure criteria

ITT population (n = 97)	Ruxolitinib failure cohort (n = 79)
Ruxolitinib treatment for ≥ 14 days and resistant or intolerant to ruxolitinib per investigator discretion: ▪ Resistant: no response or stable disease, evidence of disease progression, or loss of response ▪ Intolerant: discontinuation due to unacceptable toxicity	Relapsed: < 30% reduction in spleen size (or < 10% reduction in spleen volume) at the end of ruxolitinib treatment compared with baseline after an initial response. Patients must have had treatment with ruxolitinib for ≥ 3 months. Response to ruxolitinib is defined as: ▪ ≥ 50% reduction in spleen size for baseline spleen > 10 cm, ▪ Nonpalpable spleen for baseline spleen between 5 and 10 cm, ▪ Not eligible for spleen response for baseline spleen < 5 cm, or ▪ ≥ 35% reduction in spleen volume from baseline.
	Refractory: < 30% reduction in spleen size (or < 10% reduction in spleen volume) at the end of ruxolitinib treatment compared with baseline and failure to meet criteria for response during ruxolitinib treatment. Patients must have had treatment with ruxolitinib for ≥ 3 months.
	Intolerant: ruxolitinib treatment for ≥ 28 days complicated by the development of RBC transfusion requirement (≥ 2 units per month for 2 months); or grade ≥ 3 thrombocytopenia, anaemia, haematoma, and/or haemorrhage while receiving ruxolitinib

ITT = intent-to-treat; RBC = red blood cell; SVR = spleen volume reduction.
Note: Criteria for ruxolitinib failure were accepted by MF experts from the United States and European Union at a meeting in April 2018 with the study sponsor. The sponsors also reviewed the proposed criteria with relevant regulatory authorities.
Source: Harrison et al. (2019)[92]

This analysis split patients into 2 populations: the Stringent Criteria Cohort comprising 79 patients who met at least one criterion from the stringent definitions for ruxolitinib relapsed, refractory, or intolerant; and the sensitivity cohort comprising 66 patients who received 6 fedratinib treatment cycles or discontinued before EOC6 for reasons other than "study terminated by sponsor."[92] The aim of the sensitivity cohort analysis is to estimate fedratinib response without the impact of the clinical hold.

A consort diagram depicting how these criteria were applied to the ITT population to generate ruxolitinib Stringent Criteria and Sensitivity Cohorts is provided in Figure 23.

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Figure 23. JAKARTA 2: CONSORT diagram (reanalysis)

CONSORT = Consolidated Standards of Reporting Trials; ITT = intent-to-treat.
* 1 patient was categorised as "Other: Lack of efficacy."
Source: Harrison et al. (2019)[92]

7.3.2 Efficacy and safety: results per study

7.3.2.1 JAKARTA 2: primary outcome: spleen response rate (≥ 35% SVR) at EOC6

Treatment with fedratinib is associated with a significant spleen RR; in the EMA label, 22.7% of patients achieved the primary outcome of spleen RR defined as ≥ 35% SVR at EOC6.[1] Similarly, in the ITT population, 31% of patients achieving ≥ 35% SVR at EOC6, which the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consider an appropriate threshold for response in patients with MF.[29,94] These results were consistent in the intermediate-2/high-risk (based on DIPSS as described in Table 1) subpopulation, for which 33.3% of patients (95% CI, 22%-45%) achieved ≥ 35% SVR at EOC6.[3]

Results from the reanalysis, which applied more stringent criteria of ruxolitinib relapse and intolerance to the ITT population, found results were concordant with the ITT population; with 30% of Stringent Criteria Cohort patients demonstrating ≥ 35% SVR at EOC6 (95% CI, 21%-42%).[29] When removing patients who were directly impacted by the clinical hold (i.e., the sensitivity cohort), 36% of patients demonstrated SVR at EOC6 (95% CI, 25%-49%).

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Table 32. JAKARTA 2: spleen response rates at EOC6 (≥ 35% SVR)

	Fedratinib 400 mg						
	ITT population (n = 97)	Int-1[a,b] patients (n = 16)	Int-2[a] patients (n = 47)	High-risk patients[a] (n = 34)	Reanalysis: Stringent Criteria Cohort[c] (n = 79)	Reanalysis: Sensitivity Cohort[d] (n = 66)	EMA label (n = 97)
n (%)	30 (31)	3 (18.8)	18 (38.3)	9 (26.5)	24 (30)	24 (36)	22 (22.7)
95% CI	22-41	4.0-45.6	24.5-53.6	12.9-44.4	21-42	25-49	15-32

CI = confidence interval; EMA = European Medicines Agency; EOC6 = end of Cycle 6; Int = intermediate; ITT = intent-to-treat; SVR = spleen volume reduction.

[a] Based on the Dynamic International Prognostic Scoring System as described in Table 1.

[b] Patients with intermediate-1 disease had to have constitutional symptoms.

[c] Reanalysis of ITT data in the ruxolitinib failure cohort defined using new stringent definitions of ruxolitinib relapsed/refractory.

[d] The sensitivity cohort estimates fedratinib response without the impact of the clinical hold.

Sources: Harrison et al. (2020)[29]; EMA (2020)[3]

7.3.2.2 JAKARTA 2: secondary outcome measures

JAKARTA 2: spleen response rate (≥ 35% SVR) at EOC3

Treatment with fedratinib is associated with almost half of patients achieving ≥ 35% SVR at EOC3, which the IWG-MRT and ELN regard as a lasting benefit qualifying a response.[29,94]

The proportion of patients with ≥ 35% SVR at EOC3 were 40% (95% CI, 30%-51%) in the ITT population, 43% (95% CI, 32%-55%) in the Stringent Criteria Cohort, and 41% (95% CI, 29%-54%) in the sensitivity cohort.[29]

JAKARTA 2: duration of spleen response

Treatment with fedratinib is associated with most patients achieving a duration of response longer than 9 months, although this outcome measure required extensive censoring due to early termination.[29]

For the duration of response analysis, responders were all patients who at any time achieved ≥ 35% SVR from baseline: this included 47 patients in JAKARTA 2 (Figure 24).[29] Based on KM estimates, only 25% of patients had a duration of response of less than 9.4 months and the median duration was not reached. Median spleen volume response duration was also not reached (95% CI, 7.2 months-not reached) in both the Stringent Criteria Cohort (n = 41 responders) and the sensitivity cohort (n = 34 responders).

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Figure 24. JAKARTA 2: Kaplan-Meier plot of duration of spleen response, ≥ 35 SVR at any time on study treatment (intent-to-treat population)

SVR = spleen volume reduction.

Note: Patients at risk are shown along the horizontal axis. The duration of spleen response was calculated from the first date of spleen response (i.e., ≥ 35% SVR from baseline) to the first date of disease progression (i.e., ≥ 25% spleen volume increase from baseline) or death, whichever was earlier.

Source: Harrison et al. (2020)[29]

JAKARTA 2: percentage change of spleen volume at EOC6

Treatment with fedratinib is associated with most patients achieving a reduction in spleen volume, with an average reduction of one-third.[29] In the ITT population, the median percentage changes in spleen volume were and −38.0% at EOC6 (range, −73% to 115%).[3,29,95]

When considering individual changes in spleen volume for patients with measurements at baseline and EOC6, all patients except 1 in the ITT population showed a reduction in volume.[29] In the Stringent Criteria Cohort, all patients showed a SVR (Figure 25).

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Figure 25. JAKARTA 2: waterfall plot of individual changes in spleen volume from baseline to EOC6 (intent-to-treat and Stringent Criteria Cohort)

BL = baseline; EOC6 = end of Cycle 6; ITT = intent-to-treat.
Source: Harrison et al. (2020)[29]

JAKARTA 2: spleen response rate by palpation at EOC6

Spleen RR by palpation was defined as the proportion of patients with ≥ 50% reduction in spleen size.[29] In the ITT population of JAKARTA 2, treatment with fedratinib was associated with considerable reductions in spleen size, with almost one-third of patients treated achieving ≥ 50% reduction in size, which the IWG-MRT and ELN consider a clinically meaningful response in patients with MF.[29,94] In the ITT population, the proportion of patients with ≥ 50% reduction in spleen size was 31% at EOC6. The proportions of patients with ≥ 50% reduction in spleen size using the Stringent Criteria Cohort and sensitivity analysis were 30% and 36%, respectively (Table 33).[29,95]

Of note, the patients that demonstrated ≥ 35% SVR at EOC6 were the same patients who demonstrated ≥ 50% reduction in spleen size at EOC6. This supports previous literature that suggests these outcomes are highly consistent or equivalent.[96-98]

Table 33. JAKARTA 2: spleen response rate by palpation (≥ 50% reduction in spleen size) at EOC6

Response	ITT population (n = 97)	Stringent Criteria Cohort (n = 79)	Sensitivity Analysis Cohort (n = 66)
n (%)	30 (31)	24 (30)	24 (36)

ITT = intent-to-treat.
Note: Spleen size was measured by palpation (i.e., length in cm).
Sources: Harrison et al. (2020)[29]

Results in the Stringent Criteria Cohort and sensitivity cohort were consistent with the ITT population, with reduction in spleen size of ≥ 50% at EOC6 observed in 24 (30%) and 24 (36%) patients, respectively.[29]

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JAKARTA 2: symptom response rate (≥ 50% reduction in total symptom score) at EOC6

The analyses of symptom RRs were performed using the MF-SAF Analysis Population, defined as patients with an evaluable baseline assessment of modified MF-SAF TSS, and at least one post-baseline evaluable assessment.[3] Symptom RRs were defined as the proportion of patients with ≥ 50% reduction in TSS from baseline to EOC6.

Treatment with fedratinib was associated with considerable symptom relief, with most evaluable patients having demonstrated an improvement in TSS and more than a quarter achieving the clinically meaningful threshold for response of ≥ 50% reduction.[29,94] The proportion of patients in the MF-SAF Analysis Population with a ≥ 50% reduction in TSS at EOC6 was 27% (95% CI, 18%-37%). Among patients with evaluable TSS data at baseline and EOC6, 82% reported some decrease in symptom severity with fedratinib.

Symptom RRs in the Stringent Criteria and Sensitivity Cohorts supported results for the ITT population.[29] At EOC6, symptom RRs were 27% (95% CI, 17%-39%) and 32% (95% CI, 21%-45%), respectively (Table 34). In the EMA label (400 mg), 21.5% (95% CI, 13.7%-31.2%) of patients had a symptom response.[3]

Table 34. JAKARTA 2: symptom response rates at EOC6 (≥ 50% total symptom score)

	Fedratinib 400 mg			
≥ 50% reduction in TSS at EOC6	All enrolled (n = 90)	Int-2/high-risk patients[a]	Reanalysis: Stringent Criteria Cohort[b] (n = 74)	Reanalysis: Sensitivity Cohort[c] (n = 62)
MF-SAF				
n (%)[d]	24 (27)	NA	20 (27)	20 (32)
95% CI	18-37	NA	17-39	21-45

CI = confidence interval; EOC6 = end of Cycle 6; Int = intermediate; ITT = intent-to-treat; MF-SAF = Myelofibrosis Symptom Assessment Form; NA = not assessed; TSS = total symptom score.

[a] ITT population of JAKARTA 2 minus the 16 Int-1 patients.

[b] Reanalysis of ITT data in the ruxolitinib failure cohort defined using new stringent definitions of ruxolitinib relapsed/refractory.

[c] The sensitivity cohort estimates fedratinib response without the impact of the clinical hold.

[d] Includes patients with evaluable baseline and ≥ 1 post-baseline MF-SAF assessment.

Sources: Harrison et al. (2020)[29]; Celgene-BMS data on file (2020)[99]

JAKARTA 2: total symptom score by key symptoms

All key symptoms assessed in the MF-SAF Analysis Population in JAKARTA 2 showed an improvement at EOC6 in half of the evaluable patients, with median percentage changes of[3]:

- −83% in pain under ribs on left side
- −76% in night sweats
- −51% in early satiety
- −46% in abdominal discomfort
- −44% in pruritus
- −22% in bone or muscle pain

These results indicate that treatment with fedratinib is associated with relief of many of the constitutional symptoms of MF.

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7.3.2.3 JAKARTA 2: key exploratory outcome measures

JAKARTA 2: spleen or symptom response rate at EOC6

Spleen or symptom RR is defined as the number of patients achieving either ≥ 35% SVR or ≥ 50% reduction in TSS. At EOC6 in JAKARTA 2, in patients with evaluable TSS data at baseline and EOC6, treatment with fedratinib was associated with a decrease in symptom severity (Figure 26).[29]

Figure 26. JAKARTA 2: waterfall plot of individual changes from baseline in symptom score, in patients with assessments at baseline and EOC6

BL = baseline; EOC6 = end of Cycle 6; ITT = intent-to-treat; MF-SAF = Myelofibrosis Symptom Assessment Form.
Source: Harrison et al. (2020)[29]

JAKARTA 2: EORTC QLQ-C30

EORTC QLQ-C30 analyses were undertaken in the EORTC QLQ-C30 analysis population (n = 90), defined as all treated patients who had a baseline and ≥ 1 post-baseline assessment of the QLQ-C30 questionnaire.[3]

Treatment with fedratinib was associated with improvements in HRQoL, with patients having demonstrated post-baseline improvements in global QoL, physical functioning, fatigue, pain, and appetite loss. For all other functional and symptom domains, HRQoL was maintained over the 6-cycle treatment except for nausea and vomiting, which worsened.[100]

The QLQ-C30 is a widely used cancer-specific instrument made up of functional domains (for which a higher score indicates a better HRQoL) and symptom domains (for which a lower score indicates a better HRQoL).[101] At EOC6, mean changes from baseline in QLQ-C30 functional domain scores were as follows[100]:

- Global Health Status QoL: 11.1
- Physical functioning domain: 10.8
- Role functioning domain: 9.2

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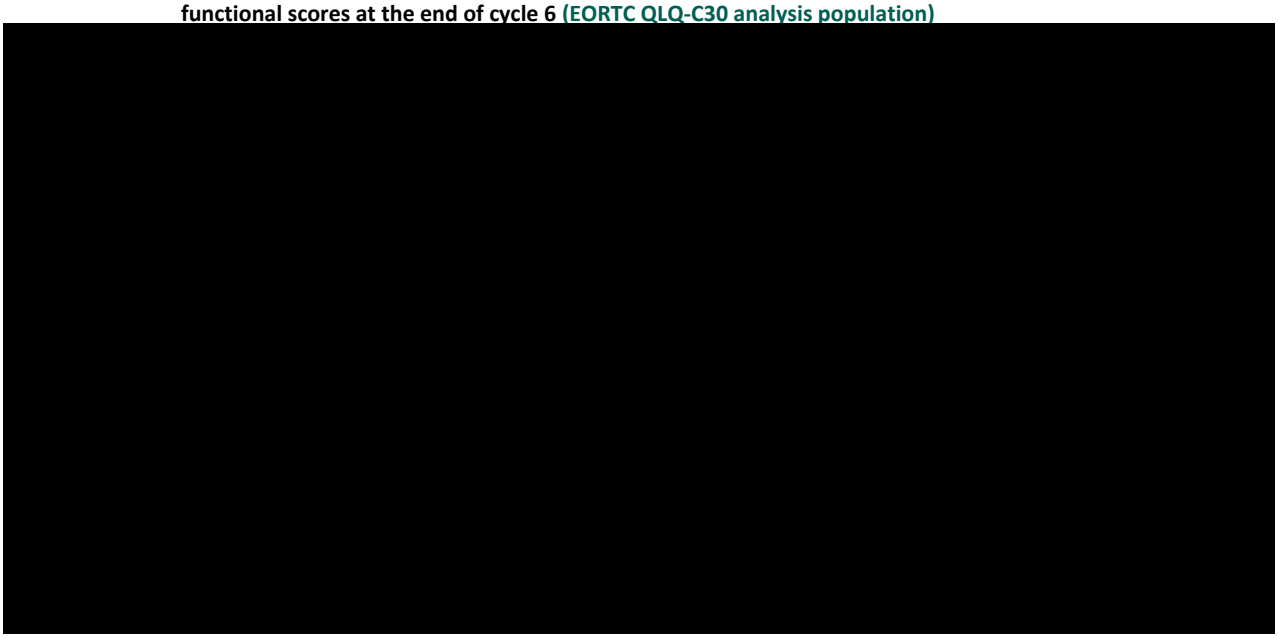
- Social functioning domain: 9.4

For symptom domain scores, considerable improvements in mean change in QLQ-C30 score from baseline to EOC6 were observed for appetite loss (−20.4), insomnia (−18.1), dyspnoea (−13.2), fatigue (−14.5), and pain (−10.9).[100]

The rates of clinically meaningful changes at EOC6 in EORTC QLQ-C30 functional and symptom scores are presented in Figure 27 and Figure 28, respectively. Clinically meaningful improvement and deterioration in each domain were defined as a ≥ 10-point increase and decrease, respectively, from baseline. A change from baseline of < 10 points was considered no change.

Figure 27. JAKARTA 2: Responder analyses of clinically meaningful changes from baseline in EORTC QLQ-C30 functional scores at the end of cycle 6 (EORTC QLQ-C30 analysis population)



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS = global health status; QoL = quality of life.
Source: Harrison et al. (2021)[100]

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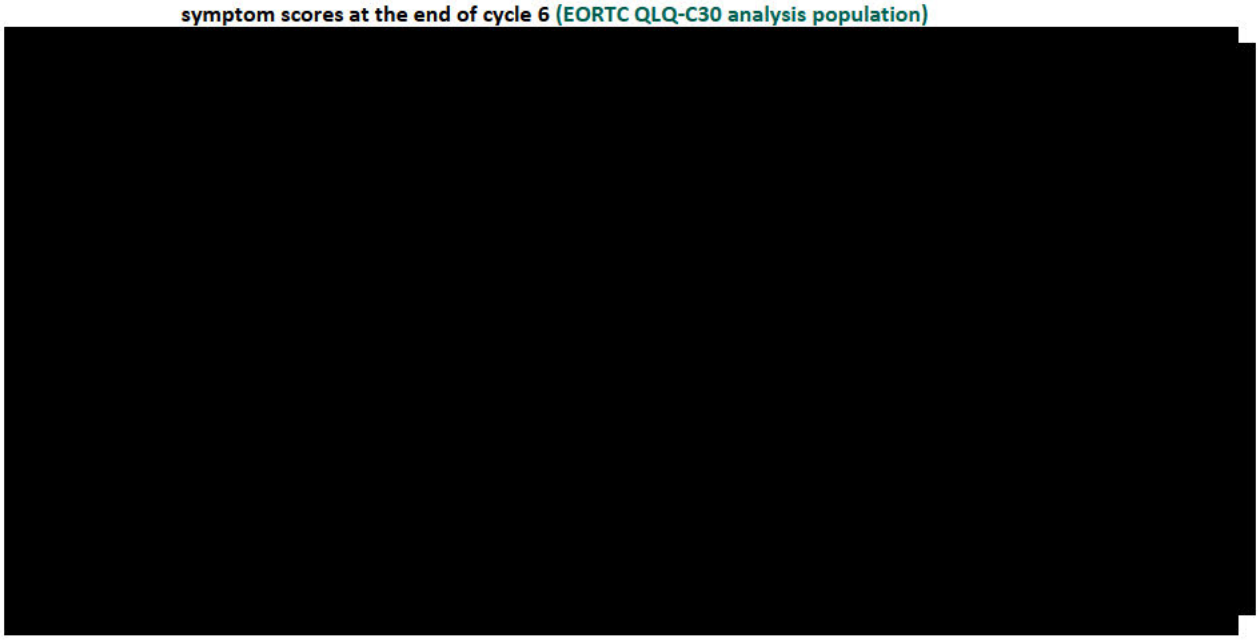
Figure 28. JAKARTA 2: Responder analyses of clinically meaningful changes from baseline in EORTC QLQ-C30 symptom scores at the end of cycle 6 (EORTC QLQ-C30 analysis population)



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.
Source: Harrison et al. (2021)[100]

7.3.2.4 JAKARTA 2: subgroup analysis

Subgroup analyses were carried out to determine the treatment effect of fedratinib on clinically important subpopulations. These analyses included spleen RR (≥ 35% SVR) by baseline demographic and disease characteristics, as well as in subgroups of patients with a platelet count of between ≥ 50 × 10^9/L and < 100 × 10^9/L or ≥ 100 × 10^9/L at baseline and patients resistant or intolerant to ruxolitinib (Table 35).[3]

Overall, results of the subgroup analyses of spleen RR and symptom RR were consistent across baseline demographic and disease characteristics subgroups, supporting the robustness of the results of the primary analysis.[3]

Irrespective of the baseline platelet count at baseline, fedratinib showed clinical benefit in terms of spleen RR and symptom RR (Table 35).[3,29]

Table 35. JAKARTA 2: efficacy of fedratinib 400 mg by platelet count at baseline

	Platelet count at baseline	
Efficacy	**≥ 50 × 10^9/L to < 100 × 10^9/L (n = 33)**	**≥ 100 × 10^9/L (n = 64)**
≥ 35% SVR at EOC6[a]		
ITT population, n (%)	12 (36.4)	18 (28.1)
95% CI[b]	20.0-52.8	17.1-39.1

CI = confidence interval; CT = computed tomography; EOC6 = end of Cycle 6; ITT = intent-to-treat; MRI = magnetic resonance imaging; SVR = spleen volume reduction.

[a] Spleen volume was measured by MRI/CT scan and reviewed in a blinded fashion by a central imaging laboratory.

[b] CI estimated using Clopper–Pearson Exact method.

Sources: Harrison et al. (2020)[29]; EMA (2020)[3]

Similarly, fedratinib showed clinical benefit in terms of spleen RR, irrespective of ruxolitinib status (resistant vs. intolerant) at baseline (Table 36).[29,95]

Table 36. JAKARTA 2: efficacy of fedratinib 400 mg in patients resistant or intolerant to ruxolitinib at baseline

	ITT population (n = 97)		Stringent Criteria Cohort (n = 79)		Sensitivity Analysis Cohort (n = 66)	
Efficacy	Resistant[a] (n = 64)	Intolerant[a] (n = 32)	Relapsed/ refractory[b] (n = 65)	Intolerant[b] (n = 14)	Relapsed/ refractory[b] (n = 56)	Intolerant[b] (n = 10)
≥ 35% SVR at EOC6						
n (%)	21 (33)	9 (28)	20 (31)	4 (29)	20 (36)	4 (40)
95% CI	22-46	14-47	20-43	8-58	23-50	12-74

CI = confidence interval; EOC6 = end of Cycle 6; ITT = intent-to-treat; SVR = spleen volume reduction.

[a] Per enrolling investigator. One patient was classified as "Other: lack of efficacy."

[b] Relapsed/refractory or intolerant per updated stringent criteria.

Sources: Harrison et al. (2020)[29]

7.3.2.5 JAKARTA 2: safety results

The safety analyses were performed in the All Treated Population; defined as enrolled patients who took at least 1 dose (even if partial) of study medication (n = 97).[3] The median number of treatment cycles was 6 (interquartile range, 3.9-8.9).[58] Fourteen (14.4%) patients received more than 12 cycles. Treatment was discontinued due to early study termination in 63 (65%) patients. The remainder of patients discontinued study treatment due to AEs (19%), disease progression (6%), patient decision (3%), or other reasons (7%). Thirty-eight (39%) patients had at least 1 dose reduction, 13 (13%) had 2 dose reductions, and 4 (4%) had more than 2 dose reductions. A total of 25 (25.8%) patients had a dose interruption for at least 7 consecutive days.

Table 37 summarises the treatment exposure in JAKARTA 2.

Table 37. JAKARTA 2: fedratinib exposure (Safety Population)

Fedratinib exposure	Fedratinib 400 mg (n = 97)
Cycles administered	
Mean (SD)	7.3 (4.43)
Median (min, max)	6.0 (1.0, 20.0)
Duration of exposure[a] (weeks)	
Mean (SD)	28.1 (17.80)
Median (min, max)	24.4 (0.7, 79.4)
Average daily dose (mg)	
Mean (SD)	384.5 (82.55)
Median (min, max)	400.0 (158.5, 554.9)
Relative dose intensity,[b] %	
Mean (SD)	96.1 (20.64)
Cumulative dose, mg	
Mean (SD)	77,915 (56,648.3)
Median (min, max)	59,600 (2,000, 251,300)

max = maximum; min = minimum; SD = standard deviation.

[a] Duration of exposure was calculated as ([last dose date – first dose date + 1 day] ÷ 7). Last dose date was taken as the last dose date at the end of Cycle 6 or last dose date if before Cycle 6 for the first 6-cycle summary and the actual last dose date for the full treatment period summary.

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[b] Relative dose intensity was calculated as (cumulative dose in milligrams) ÷ ([duration of exposure in weeks] × [planned dose intensity in milligrams/4 weeks]). The planned dose intensity was 11,200 mg/4 weeks for the 400 mg arm and 14,000 mg/4 weeks for the 500 mg arm.

Source: EMA (2020)[3]

All 97 patients had at least 1 TEAE of any grade.[29] Grade 3 or 4 TEAEs were reported by 61 patients (63.0%). Treatment-emergent SAEs were reported by 33 patients (34%). Seven patients (7%) had a TEAE that led to death during treatment or follow-up: in 4 cases, the cause of death was determined to be due to disease progression, and the other 3 cases were due to a TEAE considered not related to study treatment. Treatment-emergent AEs leading to treatment discontinuation occurred in 19 patients (19.6%) and TEAEs leading to dose interruption and reduction occurred in 26 patients (26.8%) and 35 patients (36.1%), respectively.[3,29]

An overview of the TEAEs associated with fedratinib in JAKARTA 2 is provided in Table 38.

Table 38. JAKARTA 2: safety overview (All Treated Population)

Adverse event, n (%)	Fedratinib 400 mg (n = 97)
TEAE	97 (100.0)
Treatment-related TEAE	88 (90.7)
Grade 3 or 4 TEAE	61 (62.9)
Treatment-related grade 3 or 4 TEAE	50 (51.5)
TEAE leading to death	7 (7.2)
Treatment-related TEAE leading to death	0 (0.0)
Treatment-emergent SAE	33 (34.0)
Treatment-related treatment-emergent SAE	11 (11.3)
TEAE leading to permanent treatment discontinuation	19 (19.6)
TEAE leading to dose interruption	26 (26.8)
TEAE leading to dose reduction	35 (36.1)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Data are for patients with ≥ 1 TEAE.

Sources: EMA (2020)[3]; Harrison et al. (2020)[29]

Common adverse event data

The most common nonhaematological TEAEs were GI disorders including diarrhoea in 60 (62%) patients, nausea in 54 (56%) patients, vomiting in 40 (41%) patients, constipation in 20 (21%) patients, and abdominal pain in 12 (12%) patients.[3] Other common nonhaematological TEAEs in other system order classes included pruritus in 17 (17.5%) patients, fatigue in 15 (15.5%) patients, cough and headache in 13 (13%) patients each, urinary tract infection and dyspnoea in 12 (12%) patients each, and dizziness in 11 (11%) patients.

The most common haematological TEAEs were anaemia in 47 (48%) patients and thrombocytopenia in 26 patients (27%).[58] Grade 3 or 4 anaemia was reported in 37 patients (38%) and thrombocytopenia in 21 (22%).

A summary of the common AEs reported in JAKARTA 2 is presented in Table 39.

Table 39. JAKARTA 2: common adverse events (All Treated Population)

Adverse event, n (%)	Fedratinib 400 mg (n = 97)	
	Grades 1-2	Grades 3-4
Haematological adverse events		
Anaemia	10 (10)	37 (38)
Thrombocytopenia	5 (5)	21 (22)
Lymphopenia	1 (1)	3 (3)
Nonhaematological adverse events		
Diarrhoea	56 (58)	4 (4)
Nausea	54 (56)	0 (0)
Vomiting	40 (41)	0 (0)
Constipation	19 (20)	1 (1)
Pruritus	16 (16)	0 (0)
Fatigue	13 (13)	2 (2)
Headache	12 (12)	1 (1)
Cough	13 (13)	0 (0)
Urinary tract infection	12 (12)	0 (0)
Dyspnoea	11 (11)	1 (1)
Dizziness	11 (11)	0 (0)
Abdominal pain	7 (7)	2 (2)
Alanine aminotransferase increased	3 (3)	3 (3)
Pneumonia	3 (3)	2 (2)
Hyperlipasaemia	1 (1)	3 (3)
Hyperuricaemia	2 (2)	2 (2)
Dehydration	1 (1)	2 (2)
Tumour lysis syndrome	0 (0)	2 (2)
Cardiac failure	1 (1)	2 (2)
Amylase increased	1 (1)	2 (2)
Blood bilirubin increased	0 (0)	2 (2)
Cardiac failure	1 (1)	2 (2)
Respiratory failure	0 (0)	0 (0)
Splenic rupture	0 (0)	0 (0)

Notes: Shown are any grade event occurring in more than 10% of patients and grade 3-4 events occurring in more than 1 patient.

Sources: Harrison et al. (2017)[58]; Harrison et al. (2020)[29]

Treatment-emergent serious adverse events

Treatment-emergent SAEs were reported in 33 patients (34%).[3,58] The most common SAE was cardiac disorders, reported in 6 patients (6.2%). Pneumonia was reported in 4 patients (4.1%), pleural effusion in 3 (3.1%), and fall in 2 (2.1%).

Eleven patients (11.3%) had SAEs considered treatment related.[3] Pneumonia was the only treatment-related SAE reported in more than 1 patient and occurred in 2 patients.

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Adverse events leading to treatment discontinuation

Treatment-emergent AEs leading to treatment discontinuation occurred in 19 patients (19.6%), of whom 11 (11.3%) had a grade 3 or 4 event.[3,29] The most common reason for treatment discontinuation was grade 3 or 4 thrombocytopenia, which occurred in 2 patients. One patient had disease transformation to AML, which was considered an AE, but the reason for discontinuation was recorded as disease progression.

One case of grade 3 encephalopathy was reported, but it was subsequently determined by an independent expert safety panel to be related to hepatic encephalopathy and inconsistent with Wernicke's encephalopathy.[58] The event resolved within 1 week after discontinuation of fedratinib treatment.

Adverse events leading to death

Seven (7%) patients died during treatment in JAKARTA 2, but none of the deaths was deemed to be related to fedratinib.[29] Three patients died due to fatal TEAEs of pneumonia, shock, and cardio-respiratory arrest. The 4 other patients died due to disease progression as the main cause of death.

A summary of TEAEs leading to death is provided in Table 40.

Table 40. JAKARTA 2: treatment-emergent adverse events leading to death (Safety Population)

System organ class preferred term, n (%)	Fedratinib 400 mg (n = 97)
Patients with at least 1 TEAE leading to death	**7 (7.2)**
General disorders and administration site conditions	**2 (2.1)**
Disease progression[b]	1 (1.0)
General physical health deterioration	1 (1.0)
Infections and infestations	**2 (2.1)**
Pneumonia	1 (1.0)
Sepsis	1 (1.0)
Cardiac disorders	**1 (1.0)**
Cardio-respiratory arrest	1 (1.0)
Neoplasms; benign, malignant, and unspecified (including cysts and polyps)	**1 (1.0)**
Acute myeloid leukaemia	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	**1 (1.0)**
Respiratory failure	1 (1.0)
Vascular disorders	**1 (1.0)**
Shock	1 (1.0)

TEAE = treatment-emergent adverse event.
Source: EMA (2020)[3]

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JAKARTA 2: safety overview

The most common TEAEs observed in JAKARTA 2 were consistent with the known safety profile of fedratinib, could be managed with dose modifications, and were not a frequent reason for discontinuation of fedratinib.

The most frequent grade 3 or 4 events in this study were anaemia and thrombocytopenia.[3] Given that the patients in the study tended to have advanced disease, were heavily pretreated, and had higher rates of baseline anaemia and thrombocytopenia, this finding is not unexpected. Additionally, as the JAK/STAT pathway modulates haematopoiesis, it may potentially be a contributing factor to cytopenias. The 3 fatal TEAEs (pneumonia, cardio-respiratory arrest, and shock) were not considered to be related to fedratinib treatment.[29]

Analysis of the signs and symptoms that may be associated with events of Wernicke's encephalopathy in JAKARTA 2 were not suggestive of any confirmed cases. Increased clinical awareness of the potential for developing Wernicke's encephalopathy and routine thiamine monitoring, with thiamine replacement as appropriate, sufficiently minimises the risk of developing this AE.

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8 Health economic analysis

8.1 Cost-minimisation analysis

As presented in Section 7.2.1.4, the result of the ITC shows that fedratinib has at least noninferior efficacy and at least noninferior safety compared with ruxolitinib. Both therapies are also JAK inhibitors and are initiated in specialised secondary care. Further, both drugs are administered orally, without any anticipated differences in drug initiation, monitoring, or routine management as a result.

Based on the premise of clinical equivalence, a cost-minimisation analysis was deemed the most appropriate for comparing fedratinib to ruxolitinib from the perspective of the Danish healthcare system for patients being treated for disease-related splenomegaly or symptoms in adults with PMF, post-PV MF, or post-ET MF who are JAK inhibitor naïve or have been treated with ruxolitinib.

8.2 Summary of analysis

The base-case cost-minimisation analysis was based on drug acquisition costs and monitoring costs, such as testing for thiamine deficiency. The rationale for only including these costs was, as previously pointed out, that neither administration nor side-effects would be assumed to differ between treatments. Regular testing for thiamine deficiency is required alongside fedratinib treatment, though clinicians may prefer to test prior to treatment initiation and then provide prophylactic thiamine supplementation. As such, initial thiamine test cost and prophylactic supplementation is included in the base-case analysis. Additional monitoring costs were also included, based on the prescribing information of both products. Both treatments are given orally without differences in administration and, as shown in Section 7.2.1.5, the ITC safety outcome supports the claim of at least noninferior safety of fedratinib compared with ruxolitinib.[28] Both the JAKARTA and COMFORT-I studies reported AEs for the primary analyses at 24 weeks, prior to cross over. The COMFORT-II study also reported AEs for the primary analyses, which was at 48 weeks. Therefore, AEs for patients treated with fedratinib and patients treated with ruxolitinib were compared using the JAKARTA and COMFORT-I studies. Where reported, the percentages of patients treated with ruxolitinib in COMFORT-II who experienced certain AEs were similar to the percentages for patients treated with ruxolitinib in COMFORT-I. Therefore, because the type and occurrence of AEs were similar between the treatments, AE costs were not considered in the cost-minimisation analysis. The cost of managing diarrhoea, nausea, and vomiting events with prophylactic use of loperamide is included as a scenario.

A summary of the rationale for cost-minimisation approach is shown in Table 41. A working version of cost-minimisation analysis is presented in the form of an Excel file.

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Table 41. Key assumptions and components of the cost-minimisation approach

Component	Claim or assumption
Effectiveness	Effectiveness is assumed to be at least noninferior, as presented in Section 7.2.1.5.
Safety	Safety is assumed to be at least noninferior.
Equi-effective doses	Both drugs are administered orally Fedratinib 400 mg once daily Ruxolitinib is based on starting dose: ▪ 20 mg twice daily for patients with a platelet count of > 200,000/mm^3 ▪ 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 ▪ 10 mg twice daily for patients with a platelet count between 75,000/mm^3 and 100,000/mm^3 ▪ 5 mg twice daily for patients with a platelet count of 50,000/mm^3 to less than 75,000/mm^3 Dosing is in line with the respective European marketing authorisations for patients with myelofibrosis.
Direct medicine costs	As per Danish Medicines Council guideline, the drug acquisition costs are based on pharmacy selling price.
Indirect costs	Assumed to be equivalent for both fedratinib and ruxolitinib

8.3 Resource use and costs

Table 42 presents drug acquisition costs for relevant comparators. The recommended dose of fedratinib is 400 mg once daily. Ruxolitinib is taken twice daily, and the recommended starting dose (5-20 mg) is based on platelet counts.[20] However, as pointed out in Section 5.1.4, there is limited information available on the starting dose for ruxolitinib in patients with low platelet counts, so treatment should be titrated cautiously.

Table 42. Drug acquisition prices

Drug	Strength per unit	Units per pack	Cost per pack (DKK)[a]	Total dose per day	Drug cost per day (DKK)	Drug cost per 28 days (DKK)
Fedratinib	100 mg	120	34,035.23	400 mg	1,134.51	31,766.21
	100 mg	120	34,035.23	200 mg[c]	567.25	15,883.11
Ruxolitinib[b]	5 mg	56	12,734.40	10 mg	454.80	12,734.40
	10 mg	56	25,468.79	20 mg	909.60	25,468.79
	15 mg	56	25,468.79	30 mg	909.60	25,468.79
	20 mg	56	25,468.79	40 mg	909.60	25,468.79

[a] Pharmacy selling prices.

[b] The total dose per day is 10-40 mg depending on the platelet count.

[c] 200 mg dose to be used in conjunction with concomitant CYP3A4 inhibitor treatment.

It has not been possible to identify data to inform the proportions of patients prescribed ruxolitinib who are receiving each dose based on their platelet count from the literature. Given the differences in cost per day dependent on dose used, these data are needed to estimate the average cost per patient for ruxolitinib. Therefore, the observed median dosage of 30 mg per day was used in the base case,[52] which corresponds with the label dose for patients with a platelet count > 100,000/mm^3 because the 30-mg and 40-mg formulations are priced equivalently. This could be viewed as a conservative assumption, as it excludes the additional cost of dose escalation using the 5-mg tablets of ruxolitinib.

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It is stated in the product information for fedratinib that the dose may be reduced to 200 mg per day if used in conjunction with concomitant CYP3A4 inhibitor therapy. There is an option in the model to include a proportion of patients on this regimen, and the impact on cost is explored in scenario analyses.

8.3.1 Duration of therapy

To calculate overall treatment costs for patients with MF, published treatment discontinuation data for ruxolitinib were used for both fedratinib and ruxolitinib. Treatment discontinuation was assumed to be similar for fedratinib due to the similar efficacy, mode of action, administration, and tolerability of the treatments.

Study termination of JAKARTA was the most common reason for discontinuing fedratinib in the trial, resulting in the time to treatment discontinuation (TTD) data being immature from the JAKARTA study.[3] This immaturity is also confirmed by survival extrapolations conducted based on the JAKARTA trial data. As can be seen from Table 43, all distributions resulted in Akaike information criterion (AIC) and Bayesian information criterion (BIC) values within rule of thumbs reported as no difference in statistical fit.[102,103] It is therefore difficult to use the fit statistics as guidance for model selection in this case. Similarly, as can be seen in Figure 29, all distributions also had a good visual fit to the KM data from the trial. However, the long-term extrapolations result in a large variation of long-term TTD.

Table 43. Statistical fit of parametric functions to time to treatment discontinuation data

Distribution	AIC	BIC
Exponential	515.6	518.2
Log-logistic	516.4	521.6
Gompertz	516.7	521.9
Log-normal	516.8	521.9
Generalised gamma	518.4	526.1

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 29. Survival extrapolation of JAKARTA time to treatment discontinuation

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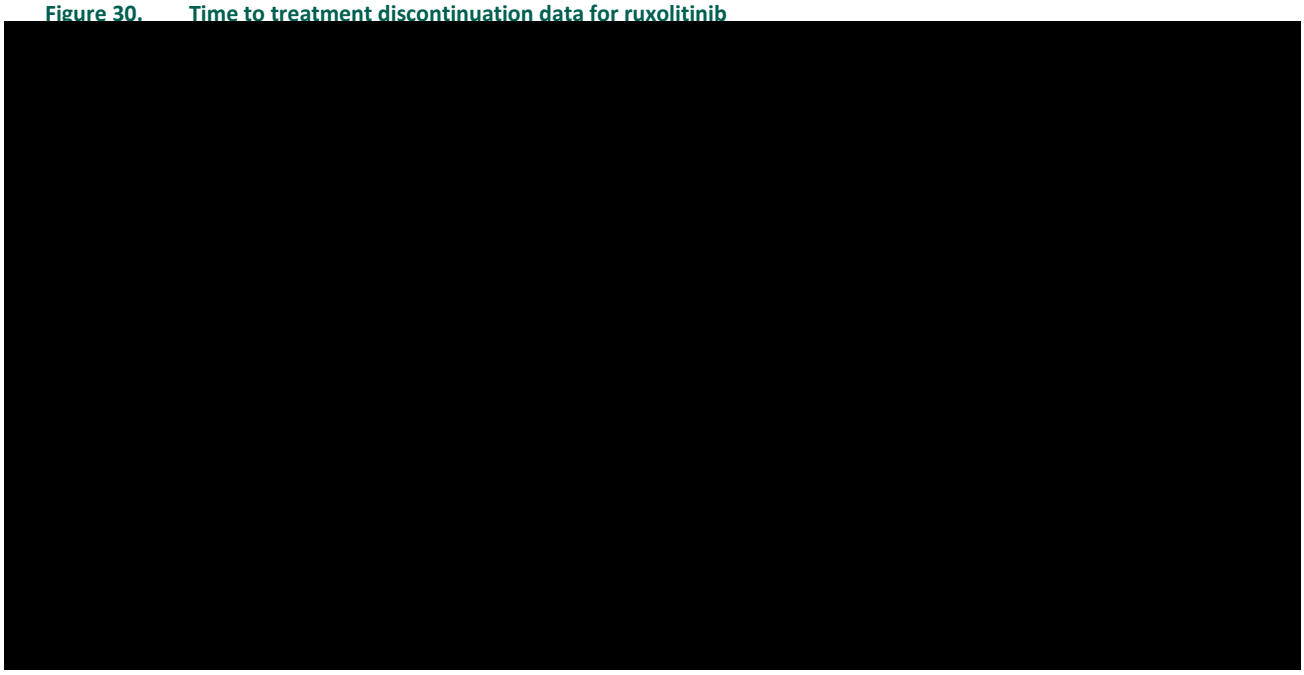
KM = Kaplan-Meier.

More mature 5-year TTD data for ruxolitinib are available in the recent ruxolitinib assessment by the NoMA.[52] In the ruxolitinib assessment by the NoMA, parametric survival analysis was conducted on the 5-year TTD data. The agency's preferred analysis used the generalised gamma distribution to extrapolate TTD and the company-preferred analysis used the Gompertz distribution.[52]

These data are the most mature publicly available data for treatment discontinuation of a JAK inhibitor and would be applicable to both arms, given the premise of equivalence. Thus, for the current analysis, these data were digitised and used to estimate mean duration of treatment (Figure 30). The generalised gamma curve was used in the base case, which results in a mean duration of treatment of 4.07 years. The use of the Gompertz distribution is explored in scenario analyses, which results in a mean duration of treatment of 3.62 years. In a further scenario, an analysis using the extrapolated data from the JAKARTA trial for fedratinib and the digitised data for ruxolitinib were investigated. In this scenario, the generalised gamma distribution was used for both treatments.

Figure 30. Time to treatment discontinuation data for ruxolitinib



8.3.2 Adverse event costs

The ITC safety outcome supports the claim of at least noninferior safety of fedratinib compared with ruxolitinib,[28] especially for the grade 3 and 4 adverse that would be events requiring medical treatments and thus cost. Both the JAKARTA and COMFORT-I studies reported AEs for the primary analyses at 24 weeks, prior to cross over. The COMFORT-II study reported AEs for the primary analyses, which was at 48 weeks. Therefore, AEs for fedratinib-treated patients and ruxolitinib-treated patients were compared using the JAKARTA and COMFORT-I studies given same timepoint for reporting. Where reported, the percentages of ruxolitinib-treated patients in JAKARTA who experienced certain AEs were similar to the percentages for fedratinib-treated patients in COMFORT-I in most AE categories. Therefore, AE costs were not considered in the base-case cost-minimisation analysis.

Nordic clinicians that have been consulted agreed that fedratinib and ruxolitinib could be considered equivalent, but also noted that a slightly higher proportion of patients in the JAKARTA trial had experienced any grade GI AEs such as diarrhoea, nausea, and vomiting. The clinicians have stated that this could be managed

with the prophylactic use of, for example, loperamide in patients experiencing such events. Anti-diarrhoeal prophylaxis was not given in the JAKARTA trial, so it is likely that, if this were provided in clinical practice, rates of such AEs would be lower.[104] No data are available on proportion of patients treated with loperamide alongside fedratinib or the duration of loperamide therapy. Therefore, a scenario is presented in which all fedratinib patients are assumed to be treated with the maximum dose of prophylactic loperamide for the management of acute diarrhoea (8 mg per day) for the duration of their treatment with fedratinib. This scenario should, however, be seen as a highly conservative scenario, as not all patients experienced GI AEs in the trial and the side effects were not persistent throughout the full duration of the trial.

8.3.3 Monitoring costs

The prescribing information for fedratinib recommends regular testing of blood cell count, liver function, blood urea, and creatinine. The unit costs of these tests were identified from Danish sources: DKK 49.15 for complete blood cell count,[105] DKK 15 for liver function test,[106] DKK 29 for blood urea test,[107] and DKK 29 for creatinine test.[107] Testing is assumed to take place at initiation of treatment followed by one of each test annually. The prescribing information for ruxolitinib recommends that blood cell counts should be monitored every 2 to 4 weeks until the dose of ruxolitinib is stabilised. Therefore, it is assumed that blood cell counts for patients on ruxolitinib are monitored every 3 weeks for a total of 12 weeks.

One specific additional cost that has been included related to the monitoring of fedratinib treatment is the testing of thiamine levels. Patients with thiamine deficiency should not be treated with fedratinib until thiamine has been repleted to normal levels. Therefore, patients on fedratinib treatment should be tested for thiamine deficiency at regular intervals in accordance with the prescribing information.[1] It is assumed that thiamine testing and treatment will not add substantially to the physician monitoring burden, so only the cost of the thiamine test is included in the analysis.

Based on Nordic clinical input, patients with suspicion of thiamine deficiency being treated with ruxolitinib would be treated with thiamine supplementation. This treatment would be initiated without prior testing because testing is not specifically requested in the ruxolitinib prescribing information and the treatment is safe and has a low cost. The costs of initial thiamine testing and subsequent prophylactic thiamine supplementation (but without continued thiamine testing) are included for fedratinib, based on conversations with clinicians, suggesting that prophylactic treatment would be preferred to regular testing. A scenario has been included for testing of thiamine levels at 4-week intervals for the first 12 weeks, followed by 12-week intervals for the duration of fedratinib therapy according to the prescribing information.[1] This scenario did not include prophylactic thiamine supplementation, as it is anticipated that the cost would be applicable to a similar proportion of fedratinib and ruxolitinib patients. The cost of a thiamine test in Denmark was identified from 2 separate laboratory facilities, covering 2 different regions, and the average of these costs is used in the analysis, which equates to DKK 496.50.[106,107]

The option to include monitoring costs in the form of outpatient visits is included in the model. Within this scenario analysis, it is assumed that patients on fedratinib and patients on ruxolitinib would both require a 30-minute outpatient visit each month. These assumptions can be adjusted within the model. The 30-minute outpatient visit is costed as DKK 451.95 (consultation with a specialist).

8.3.4 Indirect costs

Because both drugs are given orally, no administration cost was taken in account. The difference in cost of travel to collect prescriptions was assumed to be minimal and was therefore not included in this analysis.

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8.4 Results

8.4.1 Base-case results

As presented earlier, no differences in treatment initiation, administration, or indirect costs have been identified between ruxolitinib and fedratinib, meaning that only drug costs and monitoring costs have been included in the base case of this cost-minimisation analysis.

The results presented here are based on the list price of fedratinib in Denmark and are presented for completeness only. Given that we anticipate price negotiations will be conducted following this submission, the results shown below are not relevant to the decision-making process regarding reimbursement of fedratinib in Denmark.

Results of the cost-minimisation analysis are shown for both fedratinib and ruxolitinib in Table 44. This results in a cost difference associated with fedratinib of DKK 333,568 in the base case, based on a mean treatment duration of 4.07 years.

Table 44. Base-case overview

Comparator	Total cost (DKK)	Difference (DKK)
Fedratinib	1,680,362	
Ruxolitinib	1,346,793	333,568

8.5 Sensitivity analyses

Table 45 presents the scenario analyses conducted as part of the cost-minimisation analysis. Scenario 1 uses the company-preferred Gompertz TTD distribution from the NoMA assessment of ruxolitinib to model treatment discontinuation for both fedratinib and ruxolitinib. Scenario 2 uses TTD data from the JAKARTA trial to model treatment discontinuation for fedratinib (shown in Figure 29) and models ruxolitinib TTD based on the 5-year data from the NoMA assessment of ruxolitinib as in the base case. Generalised gamma distribution is selected for both ruxolitinib and fedratinib so that a consistent functional form is used for both data sets. Scenario 3 includes the cost of the maximum dose (8 mg per day) of acute anti-diarrhoeal prophylaxis with loperamide for all patients on fedratinib treatment, for the entire duration of treatment. In scenario 4, the thiamine test cost is applied throughout the duration of fedratinib treatment and thiamine supplementation is not included. In scenario 5, monitoring costs are included for both arms assuming 1 visit per month and each visit lasting 30 minutes. In scenario 6, 10% of patients receive 200 mg fedratinib plus CYP3A4 inhibitors

As presented in Table 45, in all scenarios tested, the cost difference is lower or very similar to the base case, and the base case is thereby a conservative estimate.

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Table 45. Results of scenario analyses

Scenario		Model setting altered from base case	Description	Comparator	Total cost (DKK)	Difference (DKK)
0	Base-case analysis	None	Base-case model settings	Fedratinib	1,680,362	
				Ruxolitinib	1,346,793	333,568
1	Gompertz distribution	TTD distribution for both comparators	Company-preferred Gompertz TTD distribution	Fedratinib	1,497,979	
				Ruxolitinib	1,200,588	297,391
2	Fedratinib TTD extrapolation	TTD distribution for fedratinib	Generalised gamma distribution from JAKARTA to model fedratinib TTD	Fedratinib	1,433,690	
				Ruxolitinib	1,346,793	86,897
3	Anti-diarrhoeal prophylaxis	Include anti-diarrhoeal prophylaxis cost	Include anti-diarrhoeal prophylaxis cost	Fedratinib	1,682,020	
				Ruxolitinib	1,346,793	335,227
4	Thiamine testing throughout treatment	Thiamine testing	Thiamine testing throughout treatment	Fedratinib	1,689,607	
				Ruxolitinib	1,346,793	342,814
5	Monitoring costs	Include monitoring costs for both arms	Include monitoring costs for both arms	Fedratinib	1,691,388	
				Ruxolitinib	1,357,820	333,568
6	Fedratinib dosing scenario	Proportion of patients receiving 200 mg fedratinib plus CYP3A4 inhibitors	10% of patients receiving 200 mg fedratinib plus CYP3A4 inhibitors	Fedratinib	1,596,691	
				Ruxolitinib	1,346,793	249,898

TTD = time to treatment discontinuation.

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9 Budget-impact analysis

Table 46 and Table 47 show the number of patients anticipated to be treated with fedratinib and ruxolitinib over the next 5 years, with and without the introduction of fedratinib. These patient numbers are generated using an anticipated uptake of fedratinib of 15% in year 1 and 50% from year 2 to year 5, applied to the eligible patient numbers presented in Table 5.

Table 48 and Table 49 show the anticipated expenditure per patient per year of fedratinib and ruxolitinib, based on the base-case settings of the cost-minimisation analysis presented in Section 8.

Table 50 shows the anticipated budget impact of introducing fedratinib at list price over the next 5 years. It is important to note that price negotiations are anticipated, and this estimate of budget impact is subject to change following these negotiations.

9.1 Number of patients

Table 46. Number of patients expected to be treated over the next 5-year period: if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Fedratinib	6	40	60	80	100
Ruxolitinib	34	40	60	80	100
Total number of patients	40	80	120	160	200

Table 47. Number of patients expected to be treated over the next 5-year period: if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Fedratinib	0	0	0	0	0
Ruxolitinib	40	80	120	160	200
Total number of patients	40	80	120	160	200

9.2 Expenditure per patient

Table 48. Costs (DKK) per patient per year: if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Fedratinib	413,965	413,346	413,346	413,346	413,346
Ruxolitinib	331,540	331,094	331,094	331,094	331,094

Table 49. Costs (DKK) per patient per year: if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Fedratinib	0	0	0	0	0
Ruxolitinib	331,540	331,094	331,094	331,094	331,094

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9.3 Budget impact

Table 50. Expected budget impact of recommending the pharmaceutical for the current indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	13,756,144	29,777,611	44,666,417	59,555,222	74,444,028
Of which: drug costs	13,734,970	29,762,202	44,643,304	59,524,405	74,405,506
Of which: monitoring costs	21,174	15,409	23,113	30,818	38,522
Minus: the pharmaceutical under consideration is NOT recommended	13,261,595	26,487,542	39,731,312	52,975,083	66,218,854
Of which: drug costs	13,243,771	26,487,542	39,731,312	52,975,083	66,218,854
Of which: monitoring costs	17,824	0	0	0	0
Budget impact of the recommendation	494,549	3,290,070	4,935,104	6,580,139	8,225,174

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10 Discussion

Summary

- The clinical and economic evidence in this application strongly supports the case for at least noninferior efficacy, with similar rates of AEs and lower costs of fedratinib than with ruxolitinib, the only other JAK inhibitor available for use in MF in Denmark.
- If adopted, fedratinib would provide clinicians with an additional treatment option for this difficult to treat population, including patients who are intolerant of ruxolitinib, such as those with low platelet counts.

10.1 Interpretations and conclusions of the clinical evidence

The approval of fedratinib is based on one pivotal trial that enrolled 289 patients with MF who were JAK inhibitor naïve (JAKARTA). The submission also includes one additional study (JAKARTA 2), a phase 2 trial, investigating the safety and efficacy of fedratinib in patients previously treated with ruxolitinib, which is included as supportive evidence. Results of both studies are likely to be generalisable to the anticipated population in Denmark: patients with MF who have not previously received a JAK inhibitor or who are intolerant of ruxolitinib, in line with the label. Both studies included patients from Europe, with JAKARTA including 2 sites in Sweden. Both studies used SVR35 (blinded independent central review–assessed by MRI or CT) as the primary endpoint, which is recognised as clinically relevant by clinical input and used as a primary endpoint in pivotal trials for emerging therapies (e.g., pacritinib, momelotinib, CPI-610). As per ELN guidelines, achieving SVR35 or TSS50 classifies a patient as a responder, corroborating that both types of response are important in MF. In JAKARTA and JAKARTA 2, fedratinib showed robust spleen and symptom responses in patients with MF. Although long-term efficacy and safety data for fedratinib are lacking, phase 3 trials are ongoing and BMS/Celgene are committed to continued real-world data collection.

10.1.1 Strengths and limitations of the clinical evidence

As a head-to-head trial was not available, an ITC was performed to compare the efficacy and safety of fedratinib with ruxolitinib, the standard JAK inhibitor used in the treatment of disease-related splenomegaly or symptoms for MF in Denmark, as confirmed by clinical input. The results of this ITC suggest that fedratinib is associated with a higher SVR rate compared with ruxolitinib. The difference was approximately 10% when considering comparison with results from both COMFORT-I and COMFORT-II, and was similar for the ITT population from JAKARTA and when considering the subgroup of patients with a platelet count of $\geq 100 \times 10^9$/L. The comparison of TSS responses for JAKARTA and COMFORT-I, however, suggested that more patients receiving ruxolitinib achieve a ≥ 50% reduction in TSS from baseline at 24 weeks. Overall, as most efficacy and safety outcomes in the ITC were numerically in favour of fedratinib, the conclusion of noninferior efficacy of fedratinib can be considered conservative.

10.1.2 JAKARTA

JAKARTA was a placebo-controlled trial; however, at study initiation, there were no approved active comparators, necessitating this trial design. Note that BAT, the comparator used in other pivotal trials in MF such as the ruxolitinib pivotal trial, COMFORT-II, is considered to be comparable to placebo, as demonstrated in an analysis of data for the control groups of COMFORT-I and -II.[88]

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The study has a number of limitations. The study was designed to include a 24-week placebo-controlled phase, after which patients from the placebo group could crossover to receive either fedratinib dose. Because of the Food and Drug Administration hold, all studies with fedratinib were terminated in November 2013. As only 10 patients crossed over before the EOC6, the placebo-controlled phase provides a robust assessment of the short-term efficacy and safety of fedratinib.

10.1.3 Indirect treatment comparison

The ITC of fedratinib versus ruxolitinib used the best quality evidence available to inform the network and was based on a comprehensive and robust SLR. A total of 188 potentially relevant studies (15 RCTs and 173 non-RCTs) were identified from the SLR for inclusion in the ITC. Only 3 of these studies (JAKARTA, COMFORT-I, and COMFORT-II) fulfilled the criteria to support the ITC of fedratinib with ruxolitinib for the endpoints of SVR and/or TSS reduction in patients who were JAK inhibitor naïve and passed the feasibility assessment. Bucher (TSS) and MAIC (SVR) represent the most appropriate and well-accepted methodologies when a common treatment comparator is available and treatment-effect modifiers need to be controlled for, or are assumed to be comparable across variables that differ between trials, respectively.[108]

The ITC had some limitations. Analyses were post hoc and were not powered to detect a statistical difference. The feasibility assessment identified several differences in study design, inclusion/exclusion criteria, baseline characteristics, and endpoint definitions that could potentially introduce bias into the analyses. The analyses including both the COMFORT-I and COMFORT-II studies relied on the assumption that the SVR response and the TSS response in the placebo and BAT arms are the same. This was based on a previous analysis of the COMFORT-I and COMFORT-II trials, which concluded that non–JAK inhibitor therapies provided little improvement in splenomegaly, symptoms, or QoL as compared with placebo.[88] In addition, COMFORT-I and COMFORT-II only enrolled patients with a baseline platelet count of ≥ 100 × 10^9/L, whereas JAKARTA included patients with a baseline platelet count of ≥ 50 × 10^9/L. As well as the ITT analyses, a subgroup of JAKARTA patients with a platelet count of ≥ 100 × 10^9/L was compared with the COMFORT-I and COMFORT-II studies for the SVR and TSS outcomes. Although this allowed for a more like-for-like comparison based on platelet counts, subgrouping the JAKARTA patients did not preserve the randomisation of the JAKARTA study because the study was not stratified by platelet count.

For the SVR outcome, the MAIC and simulated treatment comparison analyses were adjusted for JAK2 mutation status; however, these analyses were limited by not being able to also adjust for constitutional symptoms at baseline (yes or no), which were also identified as a potential treatment-effect modifier. Constitutional symptoms were not reported for the COMFORT-I study; therefore, any adjusted analyses for SVR could not include this variable. For TSS, a difference in the calculation of TSS at 24 weeks was identified across the JAKARTA and COMFORT-I studies. Despite this difference, it was considered that the ITC could still provide a useful insight into the comparative reduction in symptoms provided by the 2 treatments. Finally, the lack of symptom data in COMFORT-II may have influenced the study findings. However, the resulting sample size would be too small to derive conclusive results if analyses were adjusted for all variables. Regardless of the ITC methodology used, fedratinib consistently demonstrated comparable spleen and symptom responses versus ruxolitinib.

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10.1.4 JAKARTA 2

JAKARTA 2 is generally considered a high-quality study, being conducted in accordance with the ethical principles of Good Clinical Practice according to the International Council for Harmonisation guidelines.[58]

A panel of independent central readers evaluated the MRI/CT imaging scans and were blinded to reduce the potential bias in the evaluation process.[58] As this was a single-arm study, there was no risk of bias with regards to comparative evaluation. However, the single-arm design was unable to provide direct comparative evidence.

Potential bias may have resulted from the early termination of the fedratinib programme.[58] In particular, 65% of the patients in JAKARTA 2 discontinued treatment due to the early termination of the study. This meant that many patients had missing data at EOC6, and additional analyses were undertaken to address this limitation. This included the last observation carried forward method in the per-protocol population conducted in the original analyses, which presented a less conservative analysis that provided superior results compared with the reanalyses for the efficacy of fedratinib in JAKARTA 2.

10.2 Interpretation and conclusions of economic evidence

The cost-minimisation results were based on a comparison of drug acquisition costs and thiamine deficiency test costs for fedratinib, showing that, when based on list price for fedratinib, fedratinib is not cost-saving in comparison to ruxolitinib (increase in cost of DKK 333,568 per patient). However, given that we anticipate price negotiations will be conducted following this submission, the results shown in this submission are not relevant to the decision-making process regarding reimbursement of fedratinib in Denmark.

Because most efficacy outcomes in the ITC were numerically in favour of fedratinib and had a similar safety profile in terms of frequency of grade 3 or 4 AEs, cost-minimisation may be considered to be an appropriate modelling approach.

10.2.1 Strengths and limitations of the economic evaluation

The cost-minimisation analysis was based on a number of assumptions. The model was based on an ITC, which confirmed equivalence between ruxolitinib and fedratinib. In the base case, the TTD was modelled based on mature data for ruxolitinib. Assumptions were made around the frequency of patient monitoring, though these costs were minor compared with drug-acquisitions costs. There was a lack of data around the distribution of ruxolitinib doses given based on platelet count of patients with MF in Denmark. Therefore, the observed median dosage of 30 mg per day was used in the base case. A number of scenarios were tested, which confirmed that results were robust, and the interpretation of the results in all scenarios was similar to the base case.

11 List of experts

Because of impartiality concerns, no clinicians have been consulted formally “for the record” for this application submission. Input has been collected during the dialogue meeting with the chairman of the Medicines Council expert committee and in informal discussions with clinical experts in Denmark and Sweden. The Medicines Council is encouraged to validate the clinical input provided in this application with the expert committee.

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Appendix A. Literature search for efficacy and safety of intervention and comparator(s)

Please find attached the full SLR report, which should be treated as confidential information.

Clinical SLR Update
in MF_Report_v1.0_1

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Appendix A.1 Databases

Table A-1. Databases included in the literature search

		Original SLR			SLR Update 1			SLR Update 2			SLR Update 3		
Database	Platform	Relevant period for the search	Date of Search	Hits	Relevant period for the search	Date of Search	Hits	Relevant period for the search	Date of Search	Hits	Relevant period for the search	Date of Search	Hits
MEDLINE and Embase	embase.com	Up to 20 Aug 2018	20 Aug 2018	3,059	1 Aug 2018 to 3 Oct 2019	3 Oct 2018	336	1 Sep 2019 to 13 Feb 2020	13 Feb 2020	261	1 Feb 2020 to 20 Apr 2021	20 Apr 2021	493
MEDLINE In-Process	pubmed.com			44			48			37			44
Cochrane Central	onlinelibrary .wiley.com			668			43			33			57
Cochrane DARE	onlinelibrary .wiley.com			11			0			0			493
Total				3,782			427			331			594
Grand total													5,134

SLR = systematic literature review.

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Appendix A.2 Search strategy

Appendix A.2.1 Original SLR (20 August 2018)

Appendix A.2.1.1 MEDLINE and Embase: Embase.com

Table A-2. MEDLINE and Embase search for clinical SLR, 20 August 2018

#	Query	Hits
1	'myelofibrosis'/exp	9,035
2	myelofibros*:ab,ti OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti) OR (('bone marrow' OR agnogen*) NEAR/2 fibros*):ab,ti) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti) OR 'primary mf':ab,ti	10,071
3	'myeloid metaplasia'/exp	4,828
4	myelosclerosis:ab,ti OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti)	12,252
5	'myeloproliferative disorder'/de	9,501
6	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	1,944,587
7	'clinical study'/de OR 'clinical article'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti OR 'medical record review'/exp OR 'intervention study'/exp OR 'open study'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'cross-sectional study'/exp OR 'major clinical study'/mj OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'observational study'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	6,051,014
8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case study'/exp OR 'editorial'/exp OR 'case report'/exp	4,394,117
9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	4,804,215
10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	2,277,357
11	#1 OR #2 OR #3 OR #4 OR #5	26,062
12	#8 OR #9 OR #10	11,425,061
13	'fedratinib'/exp OR 'pacritinib'/exp OR 'ruxolitinib'/exp OR 'thalidomide'/exp OR 'pomalidomide'/exp OR 'hydroxyurea'/exp OR 'lenalidomide'/exp OR 'momelotinib'/exp OR 'recombinant erythropoietin'/exp OR 'danazol'/exp OR 'interferon'/exp OR 'dna methyltransferase inhibitor'/exp OR azacitidine:ab,ti OR decitabine:ab,ti OR flucytosine:ab,ti OR guadecitabine:ab,ti OR zebularine:ab,ti OR darbepoetin*:ab,ti OR epoetin*:ab,ti OR 'anagrelide'/exp OR 'cytarabine'/exp OR 'melphalan'/exp OR 'mercaptopurine'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'tioguanine'/exp OR fedratinib:ab,ti OR pacritinib:ab,ti OR ruxolitinib:ab,ti OR jakavi:ab,ti OR jakafi:ab,ti OR thalidomide:ab,ti OR pomalidomide:ab,ti OR hydroxyurea:ab,ti OR 'hydroxy urea':ab,ti OR 'hydroxy-urea':ab,ti OR lenalidomide:ab,ti OR azacytidine:ab,ti OR cytarabine:ab,ti OR melphalan:ab,ti OR mercaptopurine:ab,ti OR momelotinib:ab,ti OR danazol:ab,ti OR interferon*:ab,ti OR anagrelide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR tioguanine:ab,ti OR	997,408

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#	Query	Hits
	thioguanine:ab,ti OR 'allo-sct':ab,ti OR 'allo sct':ab,ti OR 'allogeneic stem cell transplantation'/exp OR 'autologous stem cell transplantation'/exp OR 'hematopoietic stem cell transplantation'/exp OR asct:ab,ti OR hsct:ab,ti	
14	(#6 OR #7) AND #11 AND #13	3,369
15	#14 NOT #12	967
16	**#14 NOT #12 AND [english]/lim**	**3,059**

Appendix A.2.1.2 Cochrane Library: Wiley Interscience

Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Interscience

Table A-3. Cochrane search for all study designs, 20 August 2018

#	Query	Hits
#1	MeSH descriptor: [Primary Myelofibrosis] explode all trees	81
#2	myelofibros*:ab,ti,kw OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti,kw) OR (((“bone marrow” OR agnogen*) NEAR/2 fibros*):ab,ti,kw) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti,kw) OR “primary mf”:ab,ti,kw (Word variations have been searched)	417
#3	MeSH descriptor: [Myeloproliferative Disorders] explode all trees	668
#4	myelosclerosis:ab,ti,kw OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti,kw)	299
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)	1,101
#6	(azacitidine OR decitabine OR flucytosine OR guadecitabine OR zebularine OR darbepoetin* OR epoetin* OR anagrelide OR cytarabine OR melphalan OR mercaptopurine OR prednisolone OR prednisone OR tioguanine OR fedratinib OR pacritinib OR ruxolitinib OR jakavi OR jakafi OR thalidomide OR pomalidomide OR hydroxyurea OR “hydroxy urea” OR “hydroxy-urea” OR lenalidomide OR azacytidine OR cytarabine OR melphalan OR mercaptopurine OR momelotinib OR danazol OR interferon* OR anagrelide OR prednisolone OR prednisone OR tioguanine OR thioguanine OR ASCT OR “allo-sct” OR “allo SCT” OR “stem cell transplant*” OR HSCT OR SCT):ab,ti,kw (Word variations have been searched)	40,337
#7	**#5 AND #6 in Cochrane Reviews, Trials, Clinical Answers (Word variations have been searched)**	**679**

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Appendix A.2.1.3 MEDLINE In-process: PubMed.com

Table A-4. MEDLINE In-process search for all study designs, 20 August 2018

#	Query	Hits
1	Search "Primary Myelofibrosis"[MeSH Terms]	5,917
2	Search (myelofibrosis[Title/Abstract] OR mielofibrosis[Title/Abstract] OR osteomyelofibrosis[Title/Abstract] OR "primary mf"[Title/Abstract] OR "myeloid metaplasia"[Title/Abstract] OR myelosclerosis[Title/Abstract] OR "myeloproliferative disorder"[Title/Abstract] OR "myeloproliferative disorders"[Title/Abstract] OR "bone marrow fibrosis"[Title/Abstract])	10,625
3	Search (agnogenic[Title/Abstract] AND metaplasia[Title/Abstract])	372
4	Search (agnogenic[Title/Abstract] AND fibrosis[Title/Abstract])	74
5	Search ((nonleukemia[Title/Abstract] OR nonleukaemia[Title/Abstract] OR aleukemia[Title/Abstract] OR aleukaemia[Title/Abstract] OR agnogenic[Title/Abstract]) AND myelosis[Title/Abstract])	10
6	Search ("myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative neoplasm"[Title/Abstract] OR "myeloproliferative neoplasms"[Title/Abstract] OR "myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative carcinoma"[Title/Abstract] OR "myeloproliferative malignant"[Title/Abstract] OR "myeloproliferative malignancy"[Title/Abstract] OR "myeloproliferative malignancies"[Title/Abstract] OR "myeloproliferative tumor"[Title/Abstract] OR "myeloproliferative tumour"[Title/Abstract])	3,150
7	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6)	13,800
8	Search ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))	449,534
10	Search (azacitidine[Title/Abstract] OR decitabine[Title/Abstract] OR flucytosine[Title/Abstract] OR guadecitabine[Title/Abstract] OR zebularine[Title/Abstract] OR darbepoetin[Title/Abstract] OR epoetin[Title/Abstract] OR anagrelide[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR fedratinib[Title/Abstract] OR pacritinib[Title/Abstract] OR ruxolitinib[Title/Abstract] OR jakavi[Title/Abstract] OR jakafi[Title/Abstract] OR thalidomide[Title/Abstract] OR pomalidomide[Title/Abstract] OR hydroxyurea[Title/Abstract] OR â€œhydroxy ureaâ€[Title/Abstract] OR â€œhydroxy-ureaâ€[Title/Abstract] OR lenalidomide[Title/Abstract] OR azacytidine[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR momelotinib[Title/Abstract] OR danazol[Title/Abstract] OR interferon[Title/Abstract] OR anagrelide[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR thioguanine[Title/Abstract] OR ASCT[Title/Abstract] OR "allo-sct"[Title/Abstract] OR "allo SCT"[Title/Abstract] OR "stem cell transplant"[Title/Abstract] OR HSCT[Title/Abstract] OR SCT[Title/Abstract])	256,423
11	**Search (#7 AND #8 AND #10)**	**44**

Appendix A.2.2 SLR Update 1 (3 October 2018)

Appendix A.2.2.1 MEDLINE and Embase: Embase.com

Table A-5. MEDLINE and Embase search for clinical SLR, 3 October 2018

#	Query	Hits
1	'myelofibrosis'/exp	9,822
2	myelofibros*:ab,ti OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti) OR (('bone marrow' OR agnogen*) NEAR/2 fibros*):ab,ti) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti) OR 'primary mf':ab,ti	10,981
3	'myeloid metaplasia'/exp	5,241
4	myelosclerosis:ab,ti OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti)	13,635
5	'myeloproliferative disorder'/de	9,862

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#	Query	Hits
6	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	2,146,253
7	'clinical study'/de OR 'clinical article'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti OR 'medical record review'/exp OR 'intervention study'/exp OR 'open study'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'cross-sectional study'/exp OR 'major clinical study'/mj OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'observational study'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	6,781,125
8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case study'/exp OR 'editorial'/exp OR 'case report'/exp	4,753,580
9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,331,327
10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	2,435,101
11	#1 OR #2 OR #3 OR #4 OR #5	28,395
12	#8 OR #9 OR #10	12,237,088
13	'fedratinib'/exp OR 'pacritinib'/exp OR 'ruxolitinib'/exp OR 'thalidomide'/exp OR 'pomalidomide'/exp OR 'hydroxyurea'/exp OR 'lenalidomide'/exp OR 'momelotinib'/exp OR 'recombinant erythropoietin'/exp OR 'danazol'/exp OR 'interferon'/exp OR 'dna methyltransferase inhibitor'/exp OR azacitidine:ab,ti OR decitabine:ab,ti OR flucytosine:ab,ti OR guadecitabine:ab,ti OR zebularine:ab,ti OR darbepoetin*:ab,ti OR epoetin*:ab,ti OR 'anagrelide'/exp OR 'cytarabine'/exp OR 'melphalan'/exp OR 'mercaptopurine'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'tioguanine'/exp OR fedratinib:ab,ti OR pacritinib:ab,ti OR ruxolitinib:ab,ti OR jakavi:ab,ti OR jakafi:ab,ti OR thalidomide:ab,ti OR pomalidomide:ab,ti OR hydroxyurea:ab,ti OR 'hydroxy urea':ab,ti OR 'hydroxy-urea':ab,ti OR lenalidomide:ab,ti OR azacytidine:ab,ti OR cytarabine:ab,ti OR melphalan:ab,ti OR mercaptopurine:ab,ti OR momelotinib:ab,ti OR danazol:ab,ti OR interferon*:ab,ti OR anagrelide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR tioguanine:ab,ti OR thioguanine:ab,ti OR 'allo-sct':ab,ti OR 'allo sct':ab,ti OR 'allogeneic stem cell transplantation'/exp OR 'autologous stem cell transplantation'/exp OR 'hematopoietic stem cell transplantation'/exp OR asct:ab,ti OR hsct:ab,ti	1,070,898
14	(#6 OR #7) AND #11 AND #13	5,028
15	#14 NOT #12	3,448
16	#14 NOT #12 AND [english]/lim	3,357
17	**#14 NOT #12 AND [english]/lim AND [1-8-2018]/sd NOT [3-10-2019]/sd**	**336**

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Appendix A.2.2.2 Cochrane Library: Wiley Interscience

Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Interscience

Table A-6. Cochrane search for all study designs, 3 October 2018

#	Query	Hits
#1	MeSH descriptor: [Primary Myelofibrosis] explode all trees	89
#2	myelofibros*:ab,ti,kw OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti,kw) OR ((("bone marrow" OR agnogen*) NEAR/2 fibros*):ab,ti,kw) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti,kw) OR "primary mf":ab,ti,kw (Word variations have been searched)	467
#3	MeSH descriptor: [Myeloproliferative Disorders] explode all trees	704
#4	myelosclerosis:ab,ti,kw OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti,kw)	376
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)	1,229
#6	(azacitidine OR decitabine OR flucytosine OR guadecitabine OR zebularine OR darbepoetin* OR epoetin* OR anagrelide OR cytarabine OR melphalan OR mercaptopurine OR prednisolone OR prednisone OR tioguanine OR fedratinib OR pacritinib OR ruxolitinib OR jakavi OR jakafi OR thalidomide OR pomalidomide OR hydroxyurea OR "hydroxy urea" OR "hydroxy-urea" OR lenalidomide OR azacytidine OR cytarabine OR melphalan OR mercaptopurine OR momelotinib OR danazol OR interferon* OR anagrelide OR prednisolone OR prednisone OR tioguanine OR thioguanine OR ASCT OR "allo-sct" OR "allo SCT" OR "stem cell transplant*" OR HSCT OR SCT):ab,ti,kw (Word variations have been searched)	43,320
#8	**#5 AND #6 in Cochrane Reviews, Trials, Clinical Answers (Word variations have been searched)**	**679**
#9	**#8 with Publication Year from 2018 to 2019, in Trials**	**43**
#10	**#8 with Cochrane Library publication date from Jan 2018 to Dec 2019, in Cochrane Reviews and Clinical Answers**	**0**

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Appendix A.2.2.3 MEDLINE In-process: PubMed.com

Table A-7. MEDLINE In-process search for all study designs, 3 October 2018

#	Query	Hits
1	Search "Primary Myelofibrosis"[MeSH Terms]	6185
2	Search (myelofibrosis[Title/Abstract] OR mielofibrosis[Title/Abstract] OR osteomyelofibrosis[Title/Abstract] OR "primary mf"[Title/Abstract] OR "myeloid metaplasia"[Title/Abstract] OR myelosclerosis[Title/Abstract] OR "myeloproliferative disorder"[Title/Abstract] OR "myeloproliferative disorders"[Title/Abstract] OR "bone marrow fibrosis"[Title/Abstract])	11,112
3	Search (agnogenic[Title/Abstract] AND metaplasia[Title/Abstract])	372
4	Search (agnogenic[Title/Abstract] AND fibrosis[Title/Abstract])	74
5	Search ((nonleukemia[Title/Abstract] OR nonleukaemia[Title/Abstract] OR aleukemia[Title/Abstract] OR aleukaemia[Title/Abstract] OR agnogenic[Title/Abstract]) AND myelosis[Title/Abstract])	10
6	Search ("myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative neoplasm"[Title/Abstract] OR "myeloproliferative neoplasms"[Title/Abstract] OR "myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative carcinoma"[Title/Abstract] OR "myeloproliferative malignant"[Title/Abstract] OR "myeloproliferative malignancy"[Title/Abstract] OR "myeloproliferative malignancies"[Title/Abstract] OR "myeloproliferative tumor"[Title/Abstract] OR "myeloproliferative tumour"[Title/Abstract])	3,607
7	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6)	14,601
8	Search ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))	3,21,210
9	Search (azacitidine[Title/Abstract] OR decitabine[Title/Abstract] OR flucytosine[Title/Abstract] OR guadecitabine[Title/Abstract] OR zebularine[Title/Abstract] OR darbepoetin[Title/Abstract] OR epoetin[Title/Abstract] OR anagrelide[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR fedratinib[Title/Abstract] OR pacritinib[Title/Abstract] OR ruxolitinib[Title/Abstract] OR jakavi[Title/Abstract] OR jakafi[Title/Abstract] OR thalidomide[Title/Abstract] OR pomalidomide[Title/Abstract] OR hydroxyurea[Title/Abstract] OR â€œhydroxy ureaâ€[Title/Abstract] OR â€œhydroxy-ureaâ€[Title/Abstract] OR lenalidomide[Title/Abstract] OR azacytidine[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR momelotinib[Title/Abstract] OR danazol[Title/Abstract] OR interferon[Title/Abstract] OR anagrelide[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR thioguanine[Title/Abstract] OR ASCT[Title/Abstract] OR "allo-sct"[Title/Abstract] OR "allo SCT"[Title/Abstract] OR "stem cell transplant"[Title/Abstract] OR HSCT[Title/Abstract] OR SCT[Title/Abstract])	2,69,013
10	**Search (#7 AND #8 AND #10)**	**48**

Appendix A.2.3 SLR Update 2 (13 February 2020)

Appendix A.2.3.1 MEDLINE and Embase: Embase.com

Table A-8. MEDLINE and Embase search for clinical SLR, 13 February 2020

#	Query	Hits
1	'myelofibrosis'/exp	10,123
2	myelofibros*:ab,ti OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti) OR (('bone marrow' OR agnogen*) NEAR/2 fibros*):ab,ti) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti) OR 'primary mf':ab,ti	11,381
3	'myeloid metaplasia'/exp	5,415
4	myelosclerosis:ab,ti OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti)	14,197

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#	Query	Hits
5	'myeloproliferative disorder'/de	9,985
6	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	21,94,497
7	'clinical study'/de OR 'clinical article'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti OR 'medical record review'/exp OR 'intervention study'/exp OR 'open study'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'cross-sectional study'/exp OR 'major clinical study'/mj OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'observational study'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	70,02,446
8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case study'/exp OR 'editorial'/exp OR 'case report'/exp	48,43,078
9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	53,97,339
10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	24,74,297
11	#1 OR #2 OR #3 OR #4 OR #5	29,281
12	#8 OR #9 OR #10	1,24,28,883
13	'fedratinib'/exp OR 'pacritinib'/exp OR 'ruxolitinib'/exp OR 'thalidomide'/exp OR 'pomalidomide'/exp OR 'hydroxyurea'/exp OR 'lenalidomide'/exp OR 'momelotinib'/exp OR 'recombinant erythropoietin'/exp OR 'danazol'/exp OR 'interferon'/exp OR 'dna methyltransferase inhibitor'/exp OR azacitidine:ab,ti OR decitabine:ab,ti OR flucytosine:ab,ti OR guadecitabine:ab,ti OR zebularine:ab,ti OR darbepoetin*:ab,ti OR epoetin*:ab,ti OR 'anagrelide'/exp OR 'cytarabine'/exp OR 'melphalan'/exp OR 'mercaptopurine'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'tioguanine'/exp OR fedratinib:ab,ti OR pacritinib:ab,ti OR ruxolitinib:ab,ti OR jakavi:ab,ti OR jakafi:ab,ti OR thalidomide:ab,ti OR pomalidomide:ab,ti OR hydroxyurea:ab,ti OR 'hydroxy urea':ab,ti OR 'hydroxy-urea':ab,ti OR lenalidomide:ab,ti OR azacytidine:ab,ti OR cytarabine:ab,ti OR melphalan:ab,ti OR mercaptopurine:ab,ti OR momelotinib:ab,ti OR danazol:ab,ti OR interferon*:ab,ti OR anagrelide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR tioguanine:ab,ti OR thioguanine:ab,ti OR 'allo-sct':ab,ti OR 'allo sct':ab,ti OR 'allogeneic stem cell transplantation'/exp OR 'autologous stem cell transplantation'/exp OR 'hematopoietic stem cell transplantation'/exp OR asct:ab,ti OR hsct:ab,ti	10,93,935
14	(#6 OR #7) AND #11 AND #13	5,359
15	#14 NOT #12	3,653
16	#14 NOT #12 AND [english]/lim	3,562
17	**#14 NOT #12 AND [english]/lim AND [1-9-2019]/sd NOT [29-2-2020]/sd**	**261**

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Appendix A.2.3.2 Cochrane Library: Wiley Interscience

Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Interscience

Table A-9. Cochrane search for all study designs, 13 February 2020

#	Query	Hits
#1	MeSH descriptor: [Primary Myelofibrosis] explode all trees	101
#2	myelofibros*:ab,ti,kw OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti,kw) OR ((("bone marrow" OR agnogen*) NEAR/2 fibros*):ab,ti,kw) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti,kw) OR "primary mf":ab,ti,kw (Word variations have been searched)	522
#3	MeSH descriptor: [Myeloproliferative Disorders] explode all trees	82
#4	myelosclerosis:ab,ti,kw OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti,kw)	479
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)	797
#6	(azacitidine OR decitabine OR flucytosine OR guadecitabine OR zebularine OR darbepoetin* OR epoetin* OR anagrelide OR cytarabine OR melphalan OR mercaptopurine OR prednisolone OR prednisone OR tioguanine OR fedratinib OR pacritinib OR ruxolitinib OR jakavi OR jakafi OR thalidomide OR pomalidomide OR hydroxyurea OR "hydroxy urea" OR "hydroxy-urea" OR lenalidomide OR azacytidine OR cytarabine OR melphalan OR mercaptopurine OR momelotinib OR danazol OR interferon* OR anagrelide OR prednisolone OR prednisone OR tioguanine OR thioguanine OR ASCT OR "allo-sct" OR "allo SCT" OR "stem cell transplant*" OR HSCT OR SCT):ab,ti,kw (Word variations have been searched)	49,161
#8	**#5 AND #6 in Cochrane Reviews, Trials, Clinical Answers (Word variations have been searched)**	**544**
#9	**#8 with Publication Year from 2018 to 2019, in Trials**	**33**
#10	**#8 with Cochrane Library publication date from Jan 2018 to Dec 2019, in Cochrane Reviews and Clinical Answers**	**0**

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Appendix A.2.3.3 MEDLINE In-process: PubMed.com

Table A-10. MEDLINE In-process search for all study designs, 13 February 2020

#	Query	Hits
1	Search "Primary Myelofibrosis"[MeSH Terms]	6,261
2	Search (myelofibrosis[Title/Abstract] OR mielofibrosis[Title/Abstract] OR osteomyelofibrosis[Title/Abstract] OR "primary mf"[Title/Abstract] OR "myeloid metaplasia"[Title/Abstract] OR myelosclerosis[Title/Abstract] OR "myeloproliferative disorder"[Title/Abstract] OR "myeloproliferative disorders"[Title/Abstract] OR "bone marrow fibrosis"[Title/Abstract])	11,261
3	Search (agnogenic[Title/Abstract] AND metaplasia[Title/Abstract])	372
4	Search (agnogenic[Title/Abstract] AND fibrosis[Title/Abstract])	74
5	Search ((nonleukemia[Title/Abstract] OR nonleukaemia[Title/Abstract] OR aleukemia[Title/Abstract] OR aleukaemia[Title/Abstract] OR agnogenic[Title/Abstract]) AND myelosis[Title/Abstract])	10
6	Search ("myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative neoplasm"[Title/Abstract] OR "myeloproliferative neoplasms"[Title/Abstract] OR "myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative carcinoma"[Title/Abstract] OR "myeloproliferative malignant"[Title/Abstract] OR "myeloproliferative malignancy"[Title/Abstract] OR "myeloproliferative malignancies"[Title/Abstract] OR "myeloproliferative tumor"[Title/Abstract] OR "myeloproliferative tumour"[Title/Abstract])	3,789
7	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6)	14,867
8	Search ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))	3,11,372
9	Search (azacitidine[Title/Abstract] OR decitabine[Title/Abstract] OR flucytosine[Title/Abstract] OR guadecitabine[Title/Abstract] OR zebularine[Title/Abstract] OR darbepoetin[Title/Abstract] OR epoetin[Title/Abstract] OR anagrelide[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR fedratinib[Title/Abstract] OR pacritinib[Title/Abstract] OR ruxolitinib[Title/Abstract] OR jakavi[Title/Abstract] OR jakafi[Title/Abstract] OR thalidomide[Title/Abstract] OR pomalidomide[Title/Abstract] OR hydroxyurea[Title/Abstract] OR â€œhydroxy ureaâ€[Title/Abstract] OR â€œhydroxy-ureaâ€[Title/Abstract] OR lenalidomide[Title/Abstract] OR azacytidine[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR momelotinib[Title/Abstract] OR danazol[Title/Abstract] OR interferon[Title/Abstract] OR anagrelide[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR thioguanine[Title/Abstract] OR ASCT[Title/Abstract] OR "allo-sct"[Title/Abstract] OR "allo SCT"[Title/Abstract] OR "stem cell transplant"[Title/Abstract] OR HSCT[Title/Abstract] OR SCT[Title/Abstract])	2,73,300
10	**Search (#7 AND #8 AND #10)**	**37**

Appendix A.2.4 SLR Update 3 (20 April 2021)

Appendix A.2.4.1 MEDLINE and Embase: Embase.com

Table A-11. MEDLINE and Embase search for clinical SLR, 20 April 2021

#	Query	Hits
1	'myelofibrosis'/exp	10,938
2	myelofibros*:ab,ti OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti) OR (('bone marrow' OR agnogen*) NEAR/2 fibros*):ab,ti) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti) OR 'primary mf':ab,ti	12,331
3	'myeloid metaplasia'/exp	5,758
4	myelosclerosis:ab,ti OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti)	15,521

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#	Query	Hits
5	'myeloproliferative disorder'/de	10,300
6	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	23,75008
7	'clinical study'/de OR 'clinical article'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti OR 'medical record review'/exp OR 'intervention study'/exp OR 'open study'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'cross-sectional study'/exp OR 'major clinical study'/mj OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'observational study'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	78,21,940
8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case study'/exp OR 'editorial'/exp OR 'case report'/exp	51,74,740
9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	55,98,441
10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	26,30,263
11	#1 OR #2 OR #3 OR #4 OR #5	31,569
12	#8 OR #9 OR #10	1,31,05,581
13	'fedratinib'/exp OR 'pacritinib'/exp OR 'ruxolitinib'/exp OR 'thalidomide'/exp OR 'pomalidomide'/exp OR 'hydroxyurea'/exp OR 'lenalidomide'/exp OR 'momelotinib'/exp OR 'recombinant erythropoietin'/exp OR 'danazol'/exp OR 'interferon'/exp OR 'dna methyltransferase inhibitor'/exp OR azacitidine:ab,ti OR decitabine:ab,ti OR flucytosine:ab,ti OR guadecitabine:ab,ti OR zebularine:ab,ti OR darbepoetin*:ab,ti OR epoetin*:ab,ti OR 'anagrelide'/exp OR 'cytarabine'/exp OR 'melphalan'/exp OR 'mercaptopurine'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'tioguanine'/exp OR fedratinib:ab,ti OR pacritinib:ab,ti OR ruxolitinib:ab,ti OR jakavi:ab,ti OR jakafi:ab,ti OR thalidomide:ab,ti OR pomalidomide:ab,ti OR hydroxyurea:ab,ti OR 'hydroxy urea':ab,ti OR 'hydroxy-urea':ab,ti OR lenalidomide:ab,ti OR azacytidine:ab,ti OR cytarabine:ab,ti OR melphalan:ab,ti OR mercaptopurine:ab,ti OR momelotinib:ab,ti OR danazol:ab,ti OR interferon*:ab,ti OR anagrelide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR tioguanine:ab,ti OR thioguanine:ab,ti OR 'allo-sct':ab,ti OR 'allo sct':ab,ti OR 'allogeneic stem cell transplantation'/exp OR 'autologous stem cell transplantation'/exp OR 'hematopoietic stem cell transplantation'/exp OR asct:ab,ti OR hsct:ab,ti	11,82,415
14	(#6 OR #7) AND #11 AND #13	6,182
15	#14 NOT #12	4,119
16	#14 NOT #12 AND [english]/lim	4,025
17	'navitoclax'/exp OR 'navitoclax':ab,ti OR 'navitoclax dihydrochloride':ab,ti	1,802
18	(#6 OR #7) AND #11 AND #18	24
19	#18 NOT #12	9
20	#18 NOT #12 AND [english]/lim	9
21	#14 NOT #12 AND [english]/lim AND [1-2-2020]/sd NOT [15-4-2021]/sd	490
22	**#20 OR #21**	**493**

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Appendix A.2.4.2 Cochrane Library: Wiley Interscience

Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Interscience

Table A-12. Cochrane search for all study designs, 20 April 2021

#	Query	Hits
#1	MeSH descriptor: [Primary Myelofibrosis] explode all trees	118
#2	myelofibros*:ab,ti,kw OR mielofibros*:ab,ti OR osteomyelofibros*:ab,ti OR (((myeloid* OR agnogen*) NEAR/2 metaplas*):ab,ti,kw) OR ((("bone marrow" OR agnogen*) NEAR/2 fibros*):ab,ti,kw) OR (((nonleukem* OR nonleukaem* OR aleukem* OR aleukaem* OR agnogen*) NEAR/2 myelos*):ab,ti,kw) OR "primary mf":ab,ti,kw (Word variations have been searched)	540
#3	MeSH descriptor: [Myeloproliferative Disorders] explode all trees	74
#4	myelosclerosis:ab,ti,kw OR ((myeloproliferative NEAR/2 (disorder* OR neoplasm* OR cancer* OR carcinoma* OR malginan* OR tumor* OR tumour*)):ab,ti,kw)	479
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)	815
#6	(azacitidine OR decitabine OR flucytosine OR guadecitabine OR zebularine OR darbepoetin* OR epoetin* OR anagrelide OR cytarabine OR melphalan OR mercaptopurine OR prednisolone OR prednisone OR tioguanine OR fedratinib OR pacritinib OR ruxolitinib OR jakavi OR jakafi OR thalidomide OR pomalidomide OR hydroxyurea OR "hydroxy urea" OR "hydroxy-urea" OR lenalidomide OR azacytidine OR cytarabine OR melphalan OR mercaptopurine OR momelotinib OR danazol OR interferon* OR anagrelide OR prednisolone OR prednisone OR tioguanine OR thioguanine OR ASCT OR "allo-sct" OR "allo SCT" OR "stem cell transplant*" OR HSCT OR SCT):ab,ti,kw (Word variations have been searched)	46,673
#7	navitoclax:ab,ti,kw or "navitoclax dihydrochloride":ab,ti,kw	19
#8	#5 AND #6 in Cochrane Reviews, Trials, Clinical Answers (Word variations have been searched)	541
#9	#5 AND #7	6
#10	#8 with Publication Year from Feb 2020 to Apr 2021, in Trials	53
#11	**#9 OR #10 with Publication Year from Feb 2020 to Apr 2021, in Trials**	**57**
#12	**#8 with Cochrane Library publication date from Feb 2020 to Apr 2021, in Cochrane Reviews and Clinical Answers**	**0**

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Appendix A.2.4.3 MEDLINE In-process: PubMed.com

Table A-13. MEDLINE In-process search for all study designs, 21 April 2021

#	Query	Hits
1	Search "Primary Myelofibrosis"[MeSH Terms]	6,488
2	Search (myelofibrosis[Title/Abstract] OR mielofibrosis[Title/Abstract] OR osteomyelofibrosis[Title/Abstract] OR "primary mf"[Title/Abstract] OR "myeloid metaplasia"[Title/Abstract] OR myelosclerosis[Title/Abstract] OR "myeloproliferative disorder"[Title/Abstract] OR "myeloproliferative disorders"[Title/Abstract] OR "bone marrow fibrosis"[Title/Abstract])	11,826
3	Search (agnogenic[Title/Abstract] AND metaplasia[Title/Abstract])	373
4	Search (agnogenic[Title/Abstract] AND fibrosis[Title/Abstract])	77
5	Search ((nonleukemia[Title/Abstract] OR nonleukaemia[Title/Abstract] OR aleukemia[Title/Abstract] OR aleukaemia[Title/Abstract] OR agnogenic[Title/Abstract]) AND myelosis[Title/Abstract])	10
6	Search ("myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative neoplasm"[Title/Abstract] OR "myeloproliferative neoplasms"[Title/Abstract] OR "myeloproliferative cancer"[Title/Abstract] OR "myeloproliferative carcinoma"[Title/Abstract] OR "myeloproliferative malignant"[Title/Abstract] OR "myeloproliferative malignancy"[Title/Abstract] OR "myeloproliferative malignancies"[Title/Abstract] OR "myeloproliferative tumor"[Title/Abstract] OR "myeloproliferative tumour"[Title/Abstract])	4,478
7	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6)	15,886
8	Search ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))	3,72,806
9	(navitoclax[Title/Abstract] OR "navitoclax dihydrochloride"[Title/Abstract] OR azacitidine[Title/Abstract] OR decitabine[Title/Abstract] OR flucytosine[Title/Abstract] OR guadecitabine[Title/Abstract] OR zebularine[Title/Abstract] OR darbepoetin[Title/Abstract] OR epoetin[Title/Abstract] OR anagrelide[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR fedratinib[Title/Abstract] OR pacritinib[Title/Abstract] OR ruxolitinib[Title/Abstract] OR jakavi[Title/Abstract] OR jakafi[Title/Abstract] OR thalidomide[Title/Abstract] OR pomalidomide[Title/Abstract] OR hydroxyurea[Title/Abstract] OR â€œhydroxy ureaâ€[Title/Abstract] OR â€œhydroxy-ureaâ€[Title/Abstract] OR lenalidomide[Title/Abstract] OR azacytidine[Title/Abstract] OR cytarabine[Title/Abstract] OR melphalan[Title/Abstract] OR mercaptopurine[Title/Abstract] OR momelotinib[Title/Abstract] OR danazol[Title/Abstract] OR interferon[Title/Abstract] OR anagrelide[Title/Abstract] OR prednisolone[Title/Abstract] OR prednisone[Title/Abstract] OR tioguanine[Title/Abstract] OR thioguanine[Title/Abstract] OR ASCT[Title/Abstract] OR "allo-sct"[Title/Abstract] OR "allo SCT"[Title/Abstract] OR "stem cell transplant"[Title/Abstract] OR HSCT[Title/Abstract] OR SCT[Title/Abstract])	2,90,339
10	Search (#7 AND #8 AND #10)	44

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Appendix A.3 Study selection criteria

Table A-14 presents the Inclusion and exclusion criteria for clinical studies **Error! Reference source not found.**.

Table A-14. Inclusion and exclusion criteria for the clinical systematic literature review

Category	Inclusion criteria	Exclusion criteria
Population	▪ Adult patients ▪ Patients with intermediate-1, intermediate-2, and high-risk myelofibrosis (including primary, PPV-MF, or PET-MF), or myelofibrosis of indeterminate/undescribed risk	▪ Patients with low-risk myelofibrosis ▪ Healthy volunteers ▪ Children only (< 18 years)
Interventions	▪ 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 (such as ASCT) ▪ Navitoclax	▪ Studies assessing interventions not on the list
Comparators	▪ Placebo ▪ Best supportive care ▪ Any other pharmacological agents ▪ Splenectomy ▪ Non-pharmacological interventions (such as ASCT)	▪ No restrictions
Outcomes	The data extraction was done in the Excel-based extraction template shared and agreed with BMS (previously Celgene). Some of the outcomes were: ▪ Spleen volume ▪ Total symptom score (from any instrument) ▪ Overall survival ▪ Progression-free survival ▪ Leukaemia-free survival ▪ Patient-reported outcomes ▪ Safety	▪ Pharmacokinetics ▪ Economic outcomes

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Category	Inclusion criteria	Exclusion criteria
	▪ Tolerability ▪ **Subgroups** – Age – Region – Baseline platelet counts – Patients with/without prior JAK inhibitor exposure – Primary/secondary myelofibrosis – Prognostic score (intermediate-1, intermediate-2, high-risk/intermediate-2, high-risk)	
Study type	▪ RCTs ▪ Clinical trials (non-RCTs and single arm) ▪ Prospective observational studies ▪ Retrospective studies ▪ Cross-sectional studies ▪ Systematic reviews[a]	▪ Letters, comments, and editorials ▪ Non-systematic reviews ▪ Case reports and case series ▪ Preclinical trials and animal experiments ▪ Publications with redundant information
Time limit	▪ Original SLR: data inception to August 2018 ▪ SLR update 1: 1 August 2018 to 4 October 2019 ▪ SLR update 2: 1 September 2019 to 29 February 2020 ▪ SLR update 3: 29 February 2020 to 20 April 2021	▪ No limit
Language	▪ English only	▪ Non-English

ASCT = allogenic stem cell transplant; JAK = Janus kinase; MF = myelofibrosis; PET = post-essential thrombocythemia; PPV = post-polycythaemia vera; RCT = randomised controlled trial; SLR = systematic literature review.

[a] Systematic reviews were included and flagged for bibliography searches.

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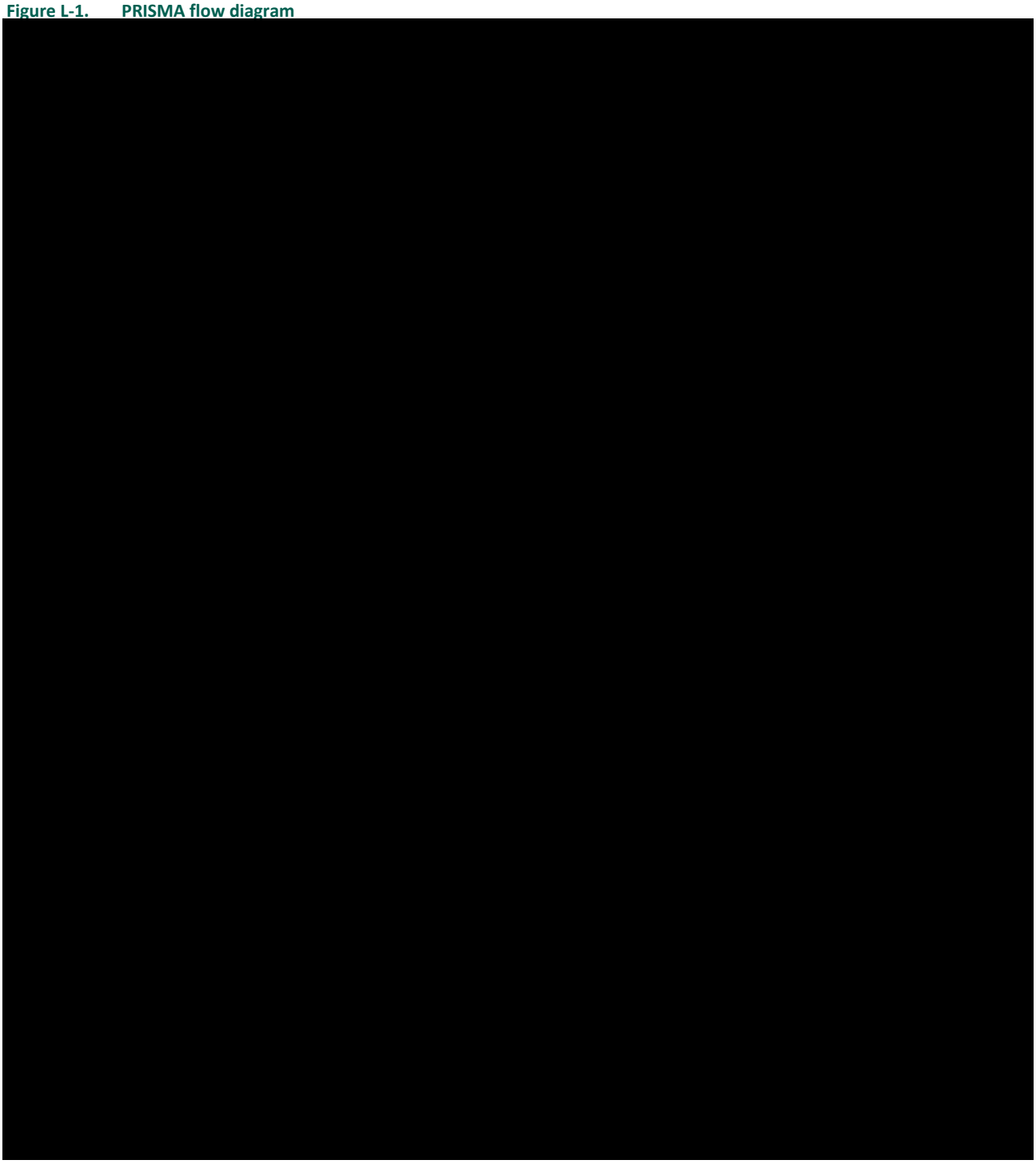
Appendix A.4 PRISMA

Figure L-1. PRISMA flow diagram



ASCT = allogeneic stem cell transplant; CSR = clinical study report; JAK = Janus kinase; MF = myelofibrosis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial; SLR = systematic literature review.

[a] The CSR included is a JAKARTA phase 3 trial.

[b] Daver et al. was extracted in both the RCT and non-RCT searches due to randomised and nonrandomised data type.

[c] The CSR included is a JAKARTA-2 phase 2 trial.

[d] 19 studies from 22 publication assessing ASCT were not extracted. However, they were included as evidence base in the current SLR update in line with the inclusion criteria.

Source: Moher et al. (2009)[109]

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Appendix B. Main characteristics of included studies

Table B-1. JAKARTA

Trial name: JAKARTA	NCT number: NCT01437787
Objective	To evaluate the efficacy of daily doses of 400 or 500 mg of fedratinib compared with placebo on the SVR as determined by MRI.
Publications – title, author, journal, year	Pardanani A, Harrison C, Cortes JE, Cervantes F, Mesa RA, Milligan D, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. JAMA Oncol. 2015 Aug;1(5):643-51. doi:10.1001/jamaoncol.2015.1590. Celgene-BMS data on file. Clinical study report. JAKARTA trial. 13 December 2018.
Study type and design	A randomised, double-blind, placebo-controlled, phase 3 trial. Enrolled patients were randomly assigned 1:1:1 via an interactive voice response system. Eligible patients in the placebo arm were allowed to cross over to receive treatment with either 400 or 500 mg of fedratinib after a second 1:1 randomisation in either of the following 2 scenarios: ▪ When a patient had completed the first 6 cycles of treatment and had completed EOC6 imaging assessments or ▪ When a patient had PD (based on the protocol-defined criteria) before completing the first 6 cycles of treatment The investigators, patients, sponsor, and other personnel responsible for the study conduct and data analyses were blinded to treatment assignment.
Sample size (n)	289
Main inclusion and exclusion criteria	Inclusion criteria[76]: ▪ Diagnosis of primary MF or post-PV MF or post-ET MF, according to the 2008 World Health Organization and IWG-MRT criteria. ▪ MF classified as high-risk or intermediate-risk level 2, as defined by modified IWG-MRT criteria (IPSS). ▪ Enlarged spleen, palpable at least 5 cm below costal margin. ▪ At least 18 years of age. ▪ ECOG performance status of 0, 1, or 2 at study entry. ▪ The following laboratory values within 14 days prior to the initiation of IMP or placebo: – Absolute neutrophil count ≥ 1.0 x 10^9/L – Platelet count ≥ 50 x 10^9/L – Serum creatinine ≤ 1.5 x upper limit of normal (ULN) – Serum amylase and lipase ≤ 1.5 x ULN Exclusion criteria[76]: ▪ Splenectomy. ▪ Any chemotherapy (e.g., hydroxyurea), immunomodulatory drug therapy (e.g., thalidomide, interferon alpha), Anagrelide, immunosuppressive therapy, corticosteroids > 10 mg/day prednisone or equivalent, or growth factor treatment (e.g., erythropoietin), or hormones (e.g., androgens, danazol) within 14 days prior to initiation of IMP or placebo; darbepoetin use within 28 days prior to initiation of IMP or placebo. Patients who have had exposure to hydroxyurea (e.g., Hydrea) in the past may be enrolled in the study as long as it has not been administered within 14 days prior to initiation of IMP or placebo. ▪ Major surgery within 28 days or radiation within 6 months prior to initiation of IMP or placebo. ▪ Prior treatment with a Janus kinase 2 (JAK2) inhibitor. ▪ Known active (acute or chronic) hepatitis A, B, or C; and hepatitis B and C carriers. ▪ AST or ALT ≥ 2.5 × ULN. ▪ Total bilirubin: – Exclude if ≥ 3.0 × ULN

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Trial name: JAKARTA	NCT number: NCT01437787
	– Patients with total bilirubin between 1.5-3.0 × ULN must be excluded if the direct bilirubin fraction is ≥ 25% of the total – Prior history of chronic liver disease (e.g., chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, nonalcoholic steatohepatitis)
Intervention	▪ Fedratinib 400 mg once daily (n = 96) ▪ Fedratinib 500 mg once daily (n = 97)
Comparator(s)	Matched placebo once daily for at least 6 consecutive 4-week cycles (n = 96).
Follow-up time	The follow-up time for the duration of response was subject to extensive censoring due to early termination of the study and ranged from 0-18.2 months for the 400 mg arm and 0-19.7 months for the 500 mg arm, respectively.
Is the study used in the health economic model?	No A cost-minimisation analysis was conducted, no outcomes from the study were used in the model, but efficacy and safety outcomes were included in the ITC.
Primary, secondary, and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was the proportion of patients with ≥ 35% SVR at the EOC6 and confirmed 4 weeks later by MRI/CT. Secondary endpoints were symptom RR using the modified MF-SAF, spleen RR of ≥ 25% SVR at the EOC6 and confirmed 4 weeks later, duration of spleen response and clinical and laboratory events graded by the NCI-CTCAE v4.03. The exploratory analysis included analysis of OS and PFS. There was also an exploratory analysis of change in HRQoL and utility using the EQ-5D-3L questionnaire was also undertaken.
Method of analysis	The ITT population was the primary population for all efficacy parameters. Analysis of the primary endpoint used a chi-squared test to compare each dose to the placebo at a 2-sided 2.5% alpha level. The RRs and 95% CI were provided for each group as well as for the difference in RRs and 97.5% CI of the difference for each dose to placebo.
Subgroup analyses	▪ On demographic/ baseline characteristics for RR, OS, and PFS
Other relevant information	None

ALT = alanine transaminase; AST = aspartate transaminase; CI = confidence interval; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EOC6 = end of Cycle 6; EQ-5D-3L = 3-level EQ-5D; ET = essential thrombocythaemia; HRQoL = health-related quality of life; IMP = Investigational Medicinal Product; IPSS = International Prognostic Scoring System; ITC = indirect treatment comparison; ITT = intent-to-treat; IWG-MRT = International Working Group for Myelofibrosis Research and Treatment; JAK2 = Janus kinase 2; MF-SAF = Myelofibrosis Symptom Assessment Form; NCI = National Cancer Institute; NCT = National Clinical Trial; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PV = polycythaemia vera; RR = response rate; SVR = spleen volume reduction; ULN = upper limit of normal.

Sources: Pardanani et al. (2015)[23]; Celgene-BMS data on file (2018)[71]

Table B-2. Indirect treatment comparison

	JAKARTA	COMFORT-I	COMFORT-II
Objective	To evaluate the efficacy and safety of fedratinib therapy in patients with primary or secondary (post-PV or post-ET) MF	To evaluate the efficacy and safety of ruxolitinib in patients with intermediate-2 or high-risk myelofibrosis	To evaluate the efficacy and safety of ruxolitinib, compared with the BAT in patients with myelofibrosis
Publications – title, author, journal, year	Pardanani A, Harrison C, Cortes JE, Cervantes F, Mesa RA, Milligan D, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. JAMA Oncol. 2015 Aug;1(5):643-51. doi:10.1001/jamaoncol.2015.1590. Celgene-BMS data on file. Clinical study report. JAKARTA trial. 13 December 2018.	Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807. doi:10.1056/NEJMoa1110557.	Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012 Mar 1;366(9):787-98. doi:10.1056/NEJMoa1110556.
Study type and design	A phase 3, multicentre, randomised, double-blind, placebo-controlled, three-arm study	A phase 3, multicentre, randomised, double-blind, placebo-controlled trial	A phase 3, multicentre, randomised, double-blind, BAT-controlled trial
Sample size (n)	289	309	219
Main inclusion and exclusion criteria			
Treatment line	No previous JAK2 inhibitor treatment (73.4% of patients received prior MF therapy: hydroxycarbamide was the most frequently used prior MF therapy among all patients [71.9% in the fedratinib 400 mg arm and 56.3% in the placebo arm])[f]	No previous JAK inhibitor treatment, resistant or refractory to/intolerant of/not a candidate for available therapy (67.1% and 56.5% of patients had previous hydroxycarbamide in the ruxolitinib and placebo arms, respectively)	No previous JAK inhibitor treatment, not a candidate for stem cell transplantation (in the ruxolitinib arm, 75% of patients had previous hydroxycarbamide and 0% radiotherapy, and in the BAT arm, 68% of patients had previous hydroxycarbamide and 5% radiotherapy)
Platelet count	≥ 50 × 10^9/L	≥ 100 × 10^9/L	≥ 100 × 10^9/L
Diagnosis	PMF, post-PV MF or post-ET MF	PMF, post-PV MF or post-ET MF	PMF, post-PV MF or post-ET MF
IPSS[g] score ≥ 2	Yes	Yes	Yes
ECOG PS	0, 1, or 2	0, 1, 2, or 3	0, 1, 2, or 3
Palpable spleen ≥ 5 cm	Yes	Yes	Yes
Intervention (n)	▪ Fedratinib 400 mg once daily (96) ▪ Fedratinib 500 mg once daily (97) (patients with platelet count ≥ 50,000/µL were enrolled for both doses)	Ruxolitinib twice daily (155) ▪ 20 mg dose – baseline platelet count > 200,000/µL 15 mg dose – baseline platelet count between 100,000/µL and 200,000/µL	Ruxolitinib twice daily (146) ▪ 20 mg dose – baseline platelet count > 200,000/µL 15 mg dose – baseline platelet count between 100,000/µL and 200,000/µL
Comparator (n)	Placebo (96)	Placebo (154)	BAT[a] (73)

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	JAKARTA	COMFORT-I	COMFORT-II
Follow-up time	The follow-up time for the duration of response was subject to extensive censoring due to early termination of the study and ranged from 0-18.2 months for the 400 mg arm and 0-19.7 months for the 500 mg arm, respectively.	32 weeks	12 months
Is the study used in the health economic model?	No. A cost-minimisation analysis was conducted; no outcomes from the study were used in the model.	No. A cost-minimisation analysis was conducted; no outcomes from the study were used in the model.	No. A cost-minimisation analysis was conducted; no outcomes from the study were used in the model.
Study endpoints			
Primary	Proportion of patients with ≥ 35% SVR at the EOC6 *and* confirmed 4 weeks later MRI/CT	Proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to week 24 as measured by MRI/CT	Proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 48, assessed by MRI/CT
Secondary	▪ Symptom RR using the modified MF-SAF: – Symptom RR: defined as the proportion of patients with ≥ 50% reduction in the TSS from baseline to the EOC6. Baseline TSS was the TSS value the week before randomisation or the week before an on-treatment assessment – TSS: Defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MF-SAF ▪ OS ▪ PFS ▪ Spleen RR of ≥ 25% SVR at the EOC6 and confirmed 4 weeks later ▪ Duration of spleen response	▪ Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume among patients initially randomised to receive ruxolitinib ▪ Proportion of patients who had a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the modified MF-SAF v2.0 diary ▪ Change in TSS from baseline to Week 24 as measured by the modified MF-SAF v2.0 diary ▪ OS	▪ Proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24, assessed by MRI/CT ▪ Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume and less than 25% above the on-study nadir ▪ Time to achieve a first ≥ 35% reduction in spleen volume from baseline ▪ PFS ▪ Leukaemia-free survival ▪ OS ▪ Transfusion dependency/independency ▪ Change in bone marrow histomorphology ▪ HRQoL assessments using EORTC QLQ-C30 and FACT
Method of analysis	The ITT population was the primary population for all efficacy parameters. Analysis of the primary endpoint used a chi-squared test to compare each dose with the placebo at a 2-sided 2.5% alpha level. The RRs and 95% CI were provided for each group as well as for the difference in RRs and 97.5% CI of the difference for each dose to placebo.	Efficacy analyses were ITT analyses. Patients with missing baseline values were excluded from analysis comparing change from baseline. Kaplan-Meier method was used to estimate durability of spleen response and survival.	Efficacy analyses were ITT analyses with data from all patients who underwent randomisation. Comparisons were made using the exact Cochran–Mantel–Haenszel test, stratified according to prognostic category (intermediate-2 risk or high risk). Kaplan-Meier method was used to estimate survival and PFS.

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	JAKARTA	COMFORT-I	COMFORT-II
Subgroup analyses	On demographic/ baseline characteristics for RR, OS, and PFS	Post hoc analysis: ▪ JAK2 V617F mutation ▪ Myelofibrosis subtypes (PMF, post-PV myelofibrosis, and post-ET myelofibrosis)	Prespecified subgroups defined according to sex, myelofibrosis subtype, and prognostic category. Post hoc analysis based on JAK2 V617F mutation status.
Other relevant information	None	None	None

BAT = best available therapy; CI = confidence interval; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; EOC6 = end of Cycle 6; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; ET = essential thrombocythaemia; FACT = Functional Assessment of Cancer Therapy; HRQoL = health-related quality of life; IPSS = International Prognostic Scoring System; ITT = intent-to-treat; JAK = Janus kinase; JAK2 = Janus kinase 2; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; OS = overall survival; PFS = progression-free survival; PMF = primary myelofibrosis; PV = polycythaemia vera; RCT = randomised controlled trial; RR = response rate; SVR = spleen volume reduction; TSS = total symptom score; US = United States.

[a] 67% of patients in the COMFORT-II BAT arm received at least 1 active treatment, which included the following: antineoplastic agents (37 patients [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%]).

[b] Includes 94 active sites across 24 countries (Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan [Province of China], the United Kingdom, and the US).

[c] In JAKARTA, 71 patients from the placebo arm were re-randomised to one of the fedratinib arms at crossover (10 before EOC6).[71]

[d] In COMFORT-I, 111 patients crossed over to ruxolitinib (median time to crossover of 41 weeks).[89]

[e] In COMFORT-II, 45 patients crossed over to ruxolitinib (median time to crossover of 66 weeks).[89]

[f] Prior myelofibrosis therapies included the following: antineoplastic agents including hydroxycarbamide (186 patients [64.4%]), an immunomodulatory agent including interferon (54 patients [18.7%]), corticosteroids (22 patients [10.4%]), platelet-reducing agent (19 patients [9%]), other (12 patients [5.7%]), hormone (8 patients [3.8%]), and haematopoietic agent (1 patient [0.5%]).

[g] IPSS score calculation – 1 point for each of the following criteria: age > 65 years, white blood cell count > 25×10^9/L, haemoglobin < 10 g/dL, peripheral blood blasts ≥ 1%, constitutional symptoms (weight loss and/or unexplained fever or excessive sweats).

Sources: Harrison et al. (2012)[27]; Celgene-BMS data on file (2018)[71]; Verstovsek et al. (2012)[26]

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Table B-3. JAKARTA 2

Trial name: JAKARTA 2	NCT number: NCT01523171
Objective	Briefly state the overall objective of the study
Publications – title, author, journal, year	Harrison CN, Schaap N, Vannucchi AM, Kiladjian J-J, Tiu RV, Zachee P, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol. 2017 Jul;4(7):e317-e24. doi:10.1016/S2352-3026(17)30088-1. Harrison CN, Schaap N, Vannucchi AM, Kiladjian J-J, Jourdan E, Silver RT, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: an updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol. 2020 Jun;95(6):594-603. doi:http://dx.doi.org/10.1002/ajh.25777.
Study type and design	A phase 2, multicentre, open-label, single-arm study.
Sample size (n)	97
Main inclusion and exclusion criteria	Inclusion criteria: ▪ Diagnosis of PMF or post-PV MF or post-ET MF, according to the 2008 World Health Organization and IWG-MRT response criteria ▪ Patients who previously received ruxolitinib treatment for PMF or post-PV MF or post-ET MF or PV or ET for at least 14 days (exposure of < 14 days is allowed for patients who discontinued ruxolitinib due to intolerability or allergy) and discontinued the treatment for at least 14 days prior to the first dose of SAR302503 ▪ MF classified as intermediate-1 with symptoms, intermediate-2, or high risk by Dynamic International Prognostic Scoring System[38] ▪ Spleen ≥ 5 cm below costal margin as measured by palpation ▪ Male and female patients ≥ 18 years of age ▪ Signed written informed consent Exclusion criteria: ▪ Splenectomy ▪ ECOG performance status of > 2 before the first dose of SAR302503 at Cycle 1 Day 1 ▪ The following laboratory values within 14 days prior to the initiation of SAR302503: – Absolute neutrophil count < 1.0×10^9/L – Platelet count < 50×10^9/L – Serum creatinine > 1.5 × upper limit of normal (ULN) – Serum amylase and lipase > 1.5 × ULN ▪ Aspartate aminotransferase or alanine aminotransferase ≥ 2.5 × ULN ▪ Total bilirubin ≥ 3.0 × ULN ▪ Patients with total bilirubin between 1.5-3.0 × ULN must be excluded if the direct bilirubin fraction is ≥ 25% of the total ▪ Patients with known active (acute or chronic) hepatitis A, B, or C; and hepatitis B and C carriers ▪ Prior history of chronic liver disease (e.g., chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, nonalcoholic steatohepatitis) ▪ Patients with any other prior malignancies are not eligible, except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which patient has been disease-free for at least 5 years ▪ Any chemotherapy, immunomodulatory drug therapy (e.g., thalidomide, interferon alpha), Anagrelide, immunosuppressive therapy, corticosteroids > 10 mg/day prednisone or equivalent, or growth factor treatment (e.g., erythropoietin), or hormones (e.g., androgens, danazol) within 14 days prior to initiation of SAR302503; darbepoetin use within 28 days prior to initiation of SAR302503. The only chemotherapy allowed will be hydroxyurea within 1 day prior to initiation of SAR302503 ▪ Uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4), angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery bypass

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Trial name: JAKARTA 2	NCT number: NCT01523171
	graft surgery, transient ischaemic attack, or pulmonary embolism within 3 months prior to initiation of SAR302503
Intervention	400 mg fedratinib (n = 97)
Comparator(s)	None
Follow-up time	Follow-up ranged from 0 to 13.4 months
Is the study used in the health economic model?	No A cost-minimisation analysis was conducted for ruxolitinib-naïve patients only.
Primary, secondary, and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was RR. Secondary efficacy assessments included spleen RR, duration of spleen response, proportion of patients with a ≥ 50% reduction in spleen size by palpation at EOC6, relative to baseline and symptom RR, exploratory assessment of change in HRQoL using EORTC QLQ-C30 V3.0. **Other endpoints:** Analysis of OS have yet to be undertaken due to the short follow-up period and the early termination of the study.
Method of analysis	Spleen responses were measured using MRI/CT and continuous variables were summarised using descriptive statistics (i.e., n, mean, median, SD, min, max). A 1-sided significance level of α = 2.5% was used for hypothesis testing. Chi-squared testing was not performed due to the early termination of the study
Subgroup analyses	Analyses of spleen volume reduction and symptom RR were measured in pre-planned subgroups of: ▪ Demographic factors and baseline disease characteristics ▪ Platelet count at baseline (< 100×10^9/L or ≥ 100×10^9/L) ▪ Patients resistant versus intolerant to ruxolitinib
Other relevant information	None

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOC3 = end of Cycle 3; EOC6 = end of Cycle 6; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; ET = essential thrombocythaemia; HRQoL = health-related quality of life; IWG-MRT = International Working Group for Myelofibrosis Research and Treatment; MF = myelofibrosis; MRI = magnetic resonance imaging; OS = overall survival; PMF = primary myelofibrosis; PV = polycythaemia vera; RR = response rate; SD = standard deviation; ULN = upper limit of normal.

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Appendix C. Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Appendix C.1 JAKARTA

Appendix C.1.1 Baseline characteristics

Overall, the ITT population consisted of 58.8% men and 41.2% women; patients were mostly White (88.9%) and had a median age of 65.0 years. The proportion of patients who were ≤ 65 years of age was higher in the 400 mg arm (63.5%) than in the placebo and 500 mg arms (45.8% and 50.5%, respectively). Overall, 9.0% of the ITT population was older than 75 years. The highest proportion of patients in each of the 3 treatment arms lived in Western Europe (43.6% overall) and Eastern Europe (26.0% overall).

In general, demographic characteristics were well balanced across both treatment arms.

Table C-1. JAKARTA: baseline characteristics

	JAKARTA		
Variable	Fedratinib 400 mg (n = 96)	Fedratinib 500 mg (n = 97)	Placebo (n = 96)
Median age (range), years	63 (39-86)	65 (39-80)	66 (27-85)
Male, %	56.3	62.9	57.3
MF subtype, %			
Primary MF	64.6	64.9	60.4
Post-PV MF	25.0	25.8	28.1
Post-ET MF	10.4	9.3	11.5
IPSS risk status, %			
Intermediate-2	59.4	48.5	47.9
High	40.6	51.5	52.1
Previous hydroxyurea therapy, %	71.9	60.8	56.3
Median platelet count (range), $\times 10^9$/L	221 (31-1155)	241 (23-873)	187 (52-1075)
Median haemoglobin (range), g/dL	10.7 (4.8-16.8)	9.8 (5.0-17.4)	10.1 (4.5-17.1)
Median palpable spleen length (range), cm	16 (5-40)	14 (4-32)	17 (5-40)
Median spleen volume (range), cm^3	2,652 (316-6,430)	2,366 (388-8,244)	2,660 (662-7,911)
JAK V617F mutation status, %			
Positive	64.6	74.2	61.5
Negative	31.3	20.6	33.3
Missing	4.2	5.2	5.2
Median TSS (using modified MF-SAF)	15.3	16.0	12.4
ECOG PS score of 0, %	42.7	32.0	32.3
RBC transfusion dependence[a], n (%)			
Yes	6 (6.3)	8 (8.3)	5 (5.2)
No	90 (93.8)	88 (91.7)	92 (94.8)

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Variable	JAKARTA		
	Fedratinib 400 mg (n = 96)	Fedratinib 500 mg (n = 97)	Placebo (n = 96)
Fibrosis grade, n (%)			
0	1 (1.0)	3 (3.1)	3 (3.1)
1	7 (7.3)	11 (11.3)	2 (2.1)
2	36 (37.5)	34 (35.1)	40 (41.7)
3	49 (51.0)	45 (46.4)	47 (49.0)
Missing	3 (3.1)	4 (4.1)	4 (4.2)

ECOG PS = Eastern Cooperative Oncology Group performance status; ET = essential thrombocytopenia; IPSS = International Prognostic Scoring System; JAK = Janus kinase; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptom Assessment Form; PV = polycythaemia vera; RBC = red blood cell; TSS = total symptom score.

[a] Transfusion dependence was defined as receiving ≥ 2 units/month of RBCs over 3 months.

Sources: Pardanani et al. (2015)[23]; EMA (2020)[3]

Appendix C.1.2 Comparability of patients across studies

Not applicable.

Appendix C.1.3 Comparability of the study populations with Danish patients eligible for treatment

The incidence of MF is strongly related to age, with the highest incidence rates in older people; however, MF can occur at any age (range, 16-93 years).[17] The Danish Database for Chronic Myeloma Proliferative Neoplasms reported the median age of patients diagnosed in 2019 was 74.4 years, with 74.4% of patients being diagnosed aged ≥ 60 years and only 25.6% aged < 60 years at diagnosis.[16]

In the JAKARTA trial, the median age for patients was 65 years.[23] Although this is younger than the median age of people diagnosed with MF in Denmark, the other baseline characteristics are similar to the Danish population, as confirmed by clinical input. Therefore, the JAKARTA trial was deemed to be reflective of the general MF population.

Appendix C.2 Indirect treatment comparison

Appendix C.2.1 Baseline characteristics

Table C-2 presents baseline characteristics commonly reported for the JAKARTA, COMFORT-I, and COMFORT-II studies. Table C-3 presents standardised differences comparing characteristics pooled across treatment arms in these studies. Standardised differences of ≥ 10% were used to determine a between-group numerical imbalance.[28] Additionally, plots of the baseline characteristics can be found in Appendix C.2.1.1. In these plots, characteristics are also pooled across arms for each trial and 95% CIs are presented for proportions and means, where reported.[28]

Table C-2. Indirect treatment comparison: baseline characteristics

Variable	JAKARTA		COMFORT-I		COMFORT-II	
	FEDR 400 mg	PBO	RUX 15 mg and 20 mg	PBO	RUX 15 mg and 20 mg	BAT
n	96	96	155	154	146	73
Previous hydroxyurea use, n (%)	69 (71.9)	54 (56.3)	104 (67.1)	87 (56.5)	110 (75.3)	50 (68.5)

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Variable	JAKARTA		COMFORT-I		COMFORT-II	
	FEDR 400 mg	PBO	RUX 15 mg and 20 mg	PBO	RUX 15 mg and 20 mg	BAT
ECOG PS, n (%)						
0	41 (42.7)	31 (32.3)	47 (31.1)	38 (25.5)	58 (39.7)	26 (35.6)
1	47 (49.0)	56 (58.3)	87 (57.6)	82 (55.0)	77 (52.7)	37 (50.7)
2	8 (8.3)	8 (8.3)	14 (9.3)	25 (16.8)	10 (6.8)	9 (12.3)
3	NA	NA	3 (2.0)	4 (2.7)	1 (0.7)	1 (1.4)
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, 1,155.0)	187.0 (51.6, 1,075.0)	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)
Post-PV MF	24 (25.0)	27 (28.1)	50 (32.3)	47 (30.5)	48 (32.9)	20 (27.4)
Post-ET MF	10 (10.4)	11 (11.5)	35 (22.6)	22 (14.3)	21 (14.4)	14 (19.2)
Mean time since diagnosis, 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, n (%)						
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)
Mutant	62 (64.6)	59 (61.5)	113 (72.9)	123 (79.9)	110 (75.3)	49 (67.1)
Missing/unknown	4 (4.2)	5 (5.2)	2 (1.3)	4 (2.6)	1 (0.7)	4 (5.5)
Fibrosis grade, n (%)						
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, 6,430)	2,660.0 (662, 7,911)	2,597.7 (478.1, 7,461.8)	2,566.3 (521.0, 8,880.7)	2,407.6 (451.3, 7,765.6)	2,317.9 (728.5, 7,701.1)
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)
Male, n (%)	54 (56.3)	55 (57.3)	79 (51.0)	88 (57.1)	83 (56.8)	42 (57.5)
Race, %						
White	89.6	93.8	89.0	90.3	80.8	91.8
Asian	8.3	5.2	3.2	2.6	NR	NR
Black/African American	1.0	1.0	3.9	4.5	NR	NR
Other	1.0	0.0	3.9	2.6	0.0	1.4

Variable	JAKARTA		COMFORT-I		COMFORT-II	
	FEDR 400 mg	PBO	RUX 15 mg and 20 mg	PBO	RUX 15 mg and 20 mg	BAT
Unknown	NA	NA	NA	NA	19.2	6.8
Mean TSS[c] (SD)	17.56 (13.530) [n = 91]	14.72 (11.954) [n = 85]	18.2 (NR)	16.9 (NR)	N/A	N/A

BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = essential thrombocythaemia; FEDR = fedratinib; JAK2 = Janus kinase 2; max = maximum; min = minimum; MF = myelofibrosis; N/A = not applicable; NA = not assessed; NR = not reported; PBO = placebo; PMF = primary myelofibrosis; PV = polycythaemia vera; RUX = ruxolitinib; SD = standard deviation; 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.

Sources: Harrison et al. (2012)[27]; Celgene-BMS data on file (2018)[71]; Verstovsek et al. (2012)[26]; Celgene-BMS data on file (2020)[28]

Table C-3. Summary of baseline characteristics in JAKARTA, COMFORT-I and COMFORT-II and the corresponding standardized difference when compared with the JAKARTA study

Variable	Study				Standardised difference between JAKARTA and COMFORT-I	Standardised difference between JAKARTA and COMFORT-II	Standardised difference between JAKARTA and COMFORT-I and -II
	JAKARTA	COMFORT-I	COMFORT-II	COMFORT-I and -II pooled			
N	192	309	219	528			
Proportion of patients who received previous hydroxyurea	0.64	0.62	0.73	0.66	4.66	19.47	5.07
Proportion of patients with ECOG PS							
0	0.38	0.28	0.38	0.32	21.45	1.76	11.55
1	0.54	0.55	0.52	0.54	2.10	3.19	0.09
2	0.08	0.13	0.09	0.11	14.04	1.23	8.99
3	0.00	0.02	0.01	0.02	21.53	13.58	18.62
Missing	0.01	0.03	0.00	0.02	18.49	10.23	11.30
Proportion of patients with MF subtype							
PMF	0.63	0.50	0.53	0.51	25.73	19.39	23.09
Post-PV MF	0.27	0.31	0.31	0.31	10.66	9.92	10.35
Post-ET MF	0.11	0.22	0.16	0.20	30.18	14.82	24.03
Mean time since diagnosis, months (SD)	61.39 (11.09)	57.01 (8.23)	No SD for COMFORT-II	No SD for COMFORT-II	44.84	No SD for COMFORT-II	No SD for COMFORT-II
Proportion of patients with risk status							
Intermediate -2	0.54	0.38	0.51	0.43	31.40	5.93	20.67
High risk	0.46	0.61	0.49	0.56	30.04	5.93	19.90

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Variable	Study				Standardised difference between JAKARTA and COMFORT-I	Standardised difference between JAKARTA and COMFORT-II	Standardised difference between JAKARTA and COMFORT-I and -II
	JAKARTA	COMFORT-I	COMFORT-II	COMFORT-I and -II pooled			
Proportion of patients with JAK2 mutational profile							
Wild type	0.32	0.22	0.25	0.23	24.07	15.92	20.63
Mutant	0.63	0.76	0.73	0.75	29.37	20.62	25.68
Missing/ unknown	0.05	0.02	0.02	0.02	15.38	13.14	14.44
Proportion of patients with fibrosis grade							
0	0.02	0.01	0.02	0.02	9.08	1.37	4.28
1	0.05	0.10	0.11	0.11	21.62	23.51	22.41
2	0.40	0.37	0.37	0.37	5.54	4.40	5.07
3	0.50	0.44	0.42	0.43	12.02	15.15	13.32
Missing	0.04	0.08	0.06	0.07	17.84	10.74	15.01
Proportion of patients with spleen length > 10 cm	0.72	0.81	0.70	0.76	19.40	4.59	9.01
Proportion of males	0.57	0.54	0.57	0.55	5.49	0.62	2.96
Proportion of patients by race							
White	0.92	0.90	0.84	0.88	6.95	22.33	13.67
Asian	0.07	0.03	0.00	0.02	18.05	38.11	25.35
Black/ African American	0.01	0.04	0.00	0.02	19.90	14.51	10.84
Other	0.01	0.03	0.00	0.02	20.10	0.92	13.82
Unknown	0.00	0.00	0.15	0.06	0	59.57	36.51

ECOG PS = Eastern Cooperative Oncology Group performance status; ET = essential thrombocythaemia; JAK2 = Janus kinase 2; MF = myelofibrosis; PMF = primary myelofibrosis; PV= polycythaemia vera; SD = standard deviation.

Source: Celgene-BMS data on file (2020)[28]

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Appendix C.2.1.1 Baseline characteristic plots[28]

Figure C-2. Proportion of patients who received previous hydroxyurea

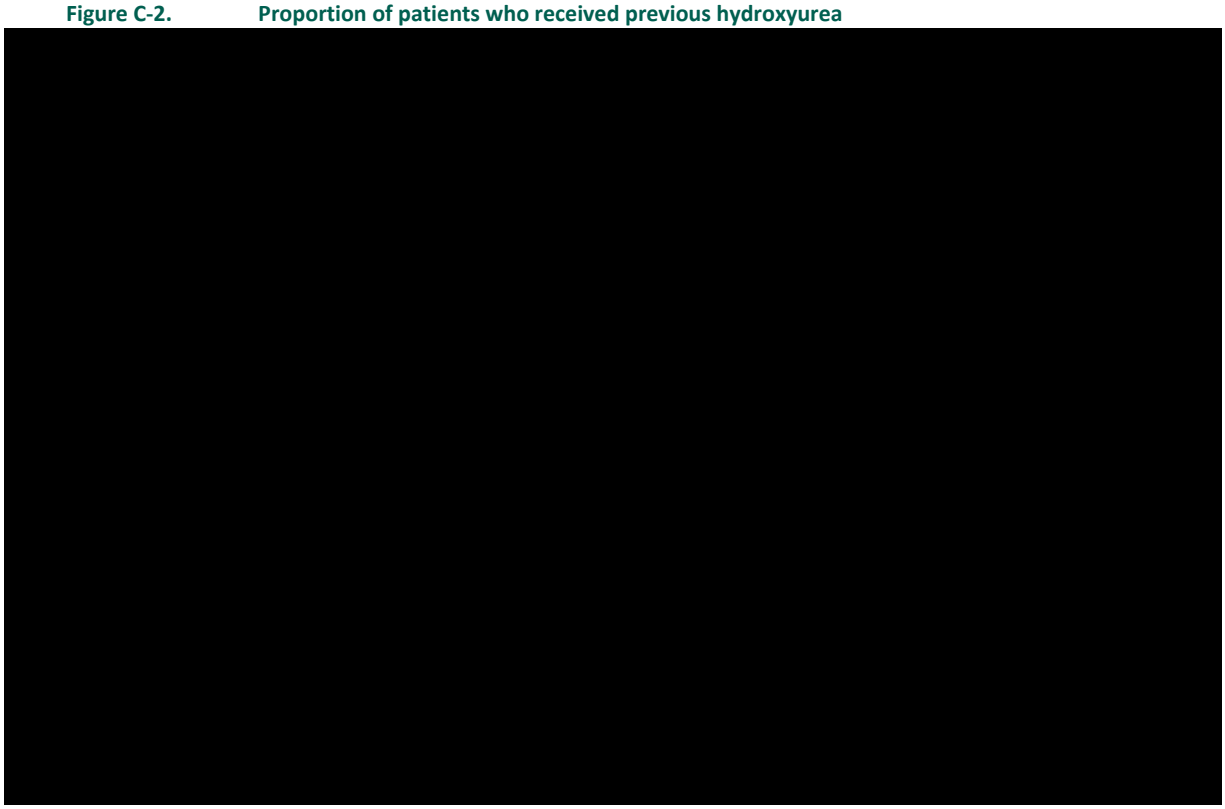

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Figure C-3. Proportion of patients with ECOG PS 0, 1, 2, and 3

ECOG PS = Eastern Cooperative Oncology Group performance status.

Figure C-4. Proportion of patients with primary myelofibrosis, post-essential thrombocythaemia myelofibrosis, and post-polycythaemia vera myelofibrosis

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ET = essential thrombocythaemia; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythaemia vera.

Note: no standard deviations were available for COMFORT-II and therefore CIs could not be calculated.

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Figure C-6. Proportion of patients with intermediate-2 or high-risk disease

Figure C-7. Proportion of patients with mutant or wild-type JAK2 mutational profile

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JAK2 = Janus kinase 2.

Figure C-8. Proportion of patients with fibrosis grade 0,1, 2, and 3

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Figure C-9. Mean spleen volume

Figure C-10. Proportion of patients with spleen length > 10 cm

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Figure C-11. Mean age

Figure C-12. Proportion of male patients

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Appendix C.2.2 Comparability of patients across studies

Differences in baseline characteristics were noted between studies. However, all characteristics that were unbalanced at baseline were subgroups analysed in JAKARTA and found to show consistent benefits for fedratinib over placebo. Thus, the differences in baseline patient characteristics were considered to be unlikely to be effect modifiers, making it feasible to perform an ITC using standard methodology.[28]

Appendix C.2.3 Comparability of the study populations with Danish patients eligible for treatment

The incidence of MF is strongly related to age, with the highest incidence rates in older people; however, MF can occur at any age (range, 16-93 years).[17] The Danish Database for Chronic Myeloma Proliferative Neoplasms reported the median age of patients diagnosed with MF in 2019 was 74.4 years, with 74.4% of patients being diagnosed at 60 years and older and only 25.6% diagnosed younger than 60 years.[16]

The median age across all studies included in the ITC ranged from 63.0 to 70.0 years. Although this is younger than the median age of people diagnosed with MF in Denmark, the other baseline characteristics are similar to the Danish population, as confirmed by clinical input. Therefore, the population in the ITC was deemed to be reflective of the general MF population.

Appendix C.3 JAKARTA 2

Appendix C.3.1 Baseline characteristics

The demographics and baseline disease characteristics in JAKARTA 2 are representative of a group of patients with advanced MF and a high disease burden, with most patients (79.4%) having received ≥ 2 prior anticancer therapies.[110]

Of patients enrolled in JAKARTA 2, there were comparable proportions of men (55%) and women (45%),[58] most patients were White (94.8%),[110] and the median age was 67 years.[58] The largest proportion of patients (55%) had been diagnosed with PMF, followed by post-PV (26%) and post-ET (20%).[58] At baseline, most patients had an ECOG PS of 0 (26.8%) or 1 (46.4%), while 23.7% of patients had an ECOG PS of 2.[110] Almost all patients (95.9%) had constitutional symptoms (night sweats, itching, abdominal discomfort, abdominal pain, early satiety, or bone pain) prior to starting treatment with fedratinib.[58] Patients had advanced disease at baseline, with a median baseline spleen volume of 2,894 mL – 14 times that of the normal spleen.[29]

The most frequent MF risk categories, as defined by IPSS or DIPSS following a protocol amendment, were intermediate-2 risk (48%) and high risk (35%), while intermediate-1 risk with symptoms (17%) was less frequent.[58]

A summary of the baseline characteristics in JAKARTA 2 is provided in Table C-4.

Table C-4. JAKARTA 2: Baseline characteristics (ITT population)

Variable	Patients (n = 97)
Median age, years (range)	67 (38-83)
Sex, n (%)	
Male	53 (55%)
Female	44 (45%)
Race, n (%)[a]	
White	92 (94.8%)

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Variable	Patients (n = 97)
Black	1 (1.0%)
Asian	4 (4.1%)
Median weight, kg (range)	73.0 (47.0-105.7)
Disease type, n (%)	
Primary MF	53 (55%)
Post-polycythaemia vera	25 (26%)
Post-essential thrombocythaemia	19 (20%)
Risk status, n (%)[b]	
Intermediate-1	16 (17%)
Intermediate-2	47 (49%)
High risk	34 (35%)
Median time since diagnosis, years (range)	4.1 (0.3-24.5)
JAK2 mutational profile, n (%)	
Wild-type	29 (30%)
Mutant	61 (63%)
Missing	7 (7%)
RBC transfusion dependence status, n (%)[c]	
Yes	14 (14%)
No	83 (86%)
Platelet count, n (%)	
$< 50 \times 10^9$/L	1 (1%)
$\geq 50 \times 10^9$/L to $< 100 \times 10^9$/L	32 (33%)
$\geq 100 \times 10^9$/L	64 (66%)
Haemoglobin level, n (%)	
< 10 g/dL	51 (53%)
≥ 10 g/dL	46 (47%)
ECOG, n (%)	
0	26 (26.8%)
1	45 (46.4%)
2	23 (23.7%)
Missing	3 (3.1%)
Constitutional symptoms[d]	
Yes	93 (95.9%)
No	4 (4.1%)
Median baseline spleen volume, mL (range)	2,894 (737-7,815)
Median baseline spleen size, cm (range)[e]	18 (5-36)

CSR = clinical study report; CT = computed tomography; DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; IPSS = International Prognostic Scoring System; ITT = intent-to-treat; JAK2 = Janus kinase 2; MF = myelofibrosis; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; MRI = magnetic resonance imaging; RBC = red blood cell.

Notes: Spleen volume was measured by MRI/CT scan and reviewed in a blinded fashion by a central imaging laboratory. Spleen size was measured by palpation (i.e., length in cm).

[a] The race categories in the electronic case report form were Caucasian/White, Black, Asian/Oriental and other. The race categories in this table were standardised for consistency across fedratinib CSRs. Race 'other' is not presented because there were no patients in the category.

[b] Risk category per IPSS or DIPSS for patients enrolled after Protocol Amendment 3.

[c] Receiving ≥ 2 units/month of RBC transfusions over 3 months prior to first dose.

[d] A patient had constitutional symptoms if any of the symptoms in the baseline MPN-SAF (night sweats, itching, abdominal discomfort, abdominal pain, early satiety, bone pain) had a value greater than zero.

[e] Below lower coastal region.

Sources: Harrison et al. (2017)[58]; Harrison et al. (2019)[92]; Harrison et al. (2020)[29]; JAKARTA 2 CSR[71]

Appendix C.3.2 Comparability of patients across studies

Not applicable.

Appendix C.3.3 Comparability of the study populations with Danish patients eligible for treatment

The Danish Database for Chronic Myeloma Proliferative Neoplasms reported the median age of patients diagnosed in 2019 was 74.4 years. In the JAKARTA trial, the median age for patients was 67 years. Although this is younger than the median age of people diagnosed with MF in Denmark, the other baseline characteristics are similar to the Nordic region population, as confirmed by clinical input. Therefore, the JAKARTA 2 trial was deemed to be reflective of the general MF population.

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Appendix D. Efficacy and safety results per study

Appendix D.1 Definition, validity, and clinical relevance of included outcome measures

Table D-1. Definition, validity, and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance	Study
Spleen RR	The proportion of patients with ≥ 35% SVR at EOC6 and confirmed 4 weeks later by MRI/CT.	Ruxolitinib was launched using SVR35 as the primary endpoint.[111] Pivotal trials for emerging therapies (e.g., pacritinib, momelotinib, CPI-610) include SVR35 as the primary endpoint.[112,113]	SVR35 as assessed by MRI or CT is included as the primary endpoint in all MF trials and is recognised as clinically relevant by health authorities and the Medical Society for Hematology. The IWG-MRT/ELN guideline response criteria state achieving SVR35 or TSS50 classifies a patient as a responder, corroborating that both types of response are important in MF.[94]	JAKARTA JAKARTA 2
Symptom RR	Symptom RR: defined as the proportion of patients with ≥ 50% reduction in the TSS from baseline to the EOC6. Baseline TSS was the TSS value the week before randomisation or the week before an on-treatment assessment. TSS: Defined as the average value of the daily total score, which was calculated as the sum of the daily scores of the 6 items of the modified MF-SAF. Change in TSS from baseline to week 24 as measured by the modified MF-SAF v2.0 diary.	The MF-SAF was developed specifically to assess symptoms in patients with MF and used data from an international internet-based survey in 458 patients.[114] A modified version of the MF-SAF (v2.0) includes 6 key symptoms (i.e., excluding fatigue) and was used in the fedratinib trials.	Symptom RR as assessed by TSS using the MF-SAF v2.0 diary was used in the COMFORT-I trial, which formed part of the clinical evidence used in support of ruxolitinib's approval for use in Denmark.	JAKARTA JAKARTA 2
OS	The time interval from the date of randomisation to the date of death due to any cause. In the absence of confirmation of death, OS was censored at the last date the patient was known to be alive.	OS is recognised as the gold standard measure of efficacy in oncology clinical trials and is required by drug regulatory agencies for the approval of new cancer treatments.[115,116] The advantages of using OS are as follows[116]: ▪ Easily and precisely measured ▪ Generally based on objective and quantitative assessment		JAKARTA
	The time interval from the date of first dose to the date of death due to any cause. In the absence of confirmation of death before the analysis cutoff date, OS was to be censored at the last date the patient was known to be alive, or at the study cutoff date, whichever was earlier.			JAKARTA 2

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Outcome measure	Definition	Validity	Clinical relevance	Study
PFS	The time interval from the date of randomisation to the date of the first investigator-assessed disease progression or the date of death due to any cause, whichever came first. In the absence of PD or death, PFS was censored at the date of the last valid assessment performed.	PFS is a recognised measure of patient benefit and is a suggested relevant outcome measure by drug regulatory agencies for the approval of new cancer treatments.[115,116] The advantages of using OS include are as follows[116]: ▪ Generally assessed earlier and with smaller sample size compared with survival studies ▪ Measurement of stable disease included ▪ Generally based on objective and quantitative assessment		JAKARTA
Duration of spleen response	The time from the date of the first response by IRC to the date of subsequent PD by IRC or death, whichever was earlier.	As per EMA guidance, data on duration of response should normally be reported in clinical trials of new cancer treatments.[115]		JAKARTA

CT = computed tomography; ELN = European LeukemiaNet; EMA = European Medicines Agency; EOC6 = end of Cycle 6; FDA = Food and Drug Administration; IRC = Independent Review Committee; IWG-MRT = International Working Group for Myeloproliferative Neoplasms Research and Treatment; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RR = response rate; SVR = spleen volume reduction; TSS = total symptom score.

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Appendix D.2 Results per study

Table D-2. Results of JAKARTA (NCT01437787)

Outcome	Study arm	n	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference[a]	95% CI	*P* value		
Spleen response rate (≥ 35% SVR) at EOC6	Fedratinib 400 mg	96	35 patients (36.5%) (26.8-46.1)	34.0%	3.9%-249.4%	0.0004	35.0	4.9-250.4	0.0004	The absolute values were obtained from the relative values.	Celgene-BMS data on file (2018)[71]
	Fedratinib 500 mg	97	39 patients (40.2%) (30.4-50.0)	37.6%	4.4%-274.3%	0.0003	38.6	5.4-275.3	0.0003		
	Placebo	96	1 patient (1.0%) (0.0-3.1)	NA	NA	NA		NA	NA		
Symptom response rate (≥ 50% reduction in total symptom score) at EOC6 – patients in the intent-to-treat population with nonmissing baseline total symptom score	Fedratinib 400 mg	89	36 patients (40.4%) (29.5-49.6)	30.5%	9.8%-74.6%	0.0001	4.6	2.1-9.7	0.0001	The absolute values were obtained from the relative values.	Celgene-BMS data on file (2018)[71]
	Fedratinib 500 mg	91	31 patients (34.1%) (24.3-43.8)	25.3%	7.2%-64.1%	0.0005	3.9	1.8-8.5	0.0005		
	Placebo	81	7 patients (8.6%) (2.4-14.1)	NA	NA	NA	NA	NA	NA		

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Outcome	Study arm	n	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference[a]	95% CI	*P* value		
Spleen response rate (≥ 25% SVR) at EOC6 confirmed 4 weeks later (intent-to-treat population)	Fedratinib 400 mg	96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The absolute values were obtained from the relative values.	Celgene-BMS data on file (2018)[71]
	Fedratinib 500 mg	97	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo	96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Duration of spleen response	Fedratinib 400 mg	54	6 patients (11.1%)	11.1%	NA	NA	NA	NA	NA	Descriptive statistics only.	Celgene-BMS data on file (2018)[71]
	Fedratinib 500 mg	57	8 patients (14.0%)	14%	NA	NA	NA	NA	NA		
	Placebo	1	0 patients (0.0%)	NA	NA	NA	NA	NA	NA		
Median PFS	Fedratinib 400 mg	96	23.2 (17.1-23.7) months	5.7	NA	NA	0.42	0.23-0.76	0.004	Cox proportional hazard ratios, log-rank 1-sided *P* value.	Harrison et al. (2021)[79]
	Placebo	96	17.5 (15.9-22.7) months	NA	NA	NA	NA	NA	NA		
12-month PFS	Fedratinib 400 mg	96	83%	16.7%	NA	NA	NA	NA	NA	Event-free probability estimates were obtained from KM survival estimates.	Harrison et al. (2021)[79]
	Placebo	96	67%	NA	NA	NA	NA	NA	NA		
Median OS	Fedratinib 400 mg	96	Not reached	NA	NA	NA	0.57	0.3-1.1	0.094	Cox proportional hazard ratios, log-rank 1-sided *P* value.	Harrison et al. (2021)[79]
	Placebo	96	Not reached	NA	NA	NA	NA	NA	NA		

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Outcome	Study arm	n	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference[a]	95% CI	*P* value		
12-month OS	Fedratinib 400 mg	96	92%	5.2%	NA	NA	NA	NA	NA	Event-free probability estimates were obtained from KM survival estimates.	Harrison et al. (2021)[79]
	Placebo	96	86%	NA	NA	NA	NA	NA	NA		
18-month OS	Fedratinib 400 mg	96	87%	7.3%	NA	NA	NA	NA	NA	Event-free probability estimates were obtained from KM survival estimates.	Harrison et al. (2021)[79]
	Placebo	96	80%	NA	NA	NA	NA	NA	NA		
EQ-5D-3L health utility	Fedratinib 400 mg	73		0.09	NA	NA	NA	NA	NA	Descriptive statistics only.	Mesa et al. (2021)[75]
	Placebo	56		NA	NA	NA	NA	NA	NA		
EQ-5D-3L VAS	Fedratinib 400 mg	69		7.10	NA	NA	NA	NA	NA	Descriptive statistics only.	Mesa et al. (2021)[75]
	Placebo	52		NA	NA	NA	NA	NA	NA		

CI = confidence interval; EOC6 = end of Cycle 6; EQ-5D-3L = 3-level EQ-5D; KM = Kaplan-Meier; NA = not applicable; OS = overall survival; PFS = progression-free survival; SVR = spleen volume reduction; VAS = visual analogue scale.

[a] Estimated relative risk calculated comparing 400 mg fedratinib arm versus placebo.

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Table D-3. Results of JAKARTA 2 (NCT01523171)

Outcome	Study analysis	n	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients with a ≥ 35% SVR from baseline at the EOC6	ITT	97	31% (22-41)	NA	NA	NA	NA	NA	NA	NA	Harrison et al. (2020)[29]; EMA (2020)[3]
	Stringent Criteria Cohort	79	30% (21-42)	NA	NA	NA	NA	NA	NA	NA	
	Sensitivity Cohort	66	36% (25-49)	NA	NA	NA	NA	NA	NA	NA	
	EMA label	97	22.7% (15-32)	NA	NA	NA	NA	NA	NA	NA	
Spleen RR (≥ 35% SVR) at EOC3	ITT	97	40 % (30-51)	NA	NA	NA	NA	NA	NA	NA	Harrison et al. (2020)[29]
	Stringent Criteria Cohort	79	43% (32-55)	NA	NA	NA	NA	NA	NA	NA	
	Sensitivity Cohort	66	41% (29-54)	NA	NA	NA	NA	NA	NA	NA	
Median percentage change in spleen volume at EOC6	ITT	NA	–38.0% (range, –73% to 115)	NA	NA	NA	NA	NA	NA	NA	Harrison et al. (2020)[29]
Proportion of patients with a ≥ 50% reduction in palpable spleen length from baseline to EOC6	ITT	97	31%	NA	NA	NA	NA	NA	NA	NA	Harrison et al. (2020)[29]
	Stringent Criteria Cohort	79	30%	NA	NA	NA	NA	NA	NA	NA	
	Sensitivity Cohort	66	36%	NA	NA	NA	NA	NA	NA	NA	
Symptom RR (≥ 50% reduction in TSS) at EOC6	All enrolled	90	27% (18-37)	NA	NA	NA	NA	NA	NA	NA	Harrison et al. (2020)[29]; EMA (2020)[3]
	Stringent Criteria Cohort	74	27% (17-39)	NA	NA	NA	NA	NA	NA	NA	
	Sensitivity Cohort	62	32% (21-45)	NA	NA	NA	NA	NA	NA	NA	

CI = confidence interval; EMA = European Medicines Agency; EOC3 = end of Cycle 3; EOC6 = end of Cycle 6; ITT = intent to treat; NA = not applicable; RR = response rate; SVR = spleen volume reduction; TSS = total symptom score.

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Table D-4. Results of COMFORT-I (NCT00952289)

Outcome	Study arm	n	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Patients with ≥ 35% reduction in spleen volume	RUX	155	41.9%	41.3%	5.2%-297.8%	0.0000	64.2	9-456.6	0.0000	The absolute values were obtained from the relative values.	Verstovsek et al. (2012)[26]
	PBO	153	0.7%	NA	NA	NA	NA	NA	NA		
Patients with ≥ 50% reduction in total symptom score	RUX	148	45.9%	40.7%	17.6%-87%	0.0000	8.7	4.3-17.5	0.0000	The absolute values were obtained from the relative values.	
	PBO	152	5.3%	NA	NA	NA	NA	NA	NA		

CI = confidence interval; NA = not applicable; PBO = placebo; RUX = ruxolitinib.

Table D-5. Results of COMFORT-II (NCT00934544)

Outcome	Study arm	n	Result	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Patients with ≥ 35% reduction in spleen volume	RUX	145	32.1%	31.4%	1.3%-512.4%	0.0066	46.8	2.9-749.1	0.0066	The absolute values were obtained from the relative values.	Harrison et al. (2012)[27]
	BAT	73	0.7%	NA	NA	NA	NA	NA	NA		

BAT = best available therapy; CI = confidence interval; NA = not applicable; RUX = ruxolitinib.

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Appendix E. Safety data for intervention and comparator(s)

All safety data for the respective studies and analysis are presented in the main body of this dossier in the following sections: JAKARTA, Section 7.1.2.4; ITC: Section 7.2.1.5; and JAKARTA 2, Section 7.3.2.5. The safety results are also provided here.

Appendix E.1.1 JAKARTA safety data

Safety data were analysed for the placebo-controlled period (i.e., up to the EOC6) and for the entire study duration. Median duration of exposure was 62.1 weeks for patients receiving 400 mg fedratinib, 59.7 weeks for the fedratinib 500 mg arm, and 24 weeks in the placebo arm in which patients were treated for 6 months or until disease progression, after which patients were allowed to cross over to active treatment.[3] The mean relative dose intensity was 92.8% for the fedratinib 400 mg arm, indicating most patients were able to receive the full fedratinib 400 mg dose[3] (Table E-1). The median relative dose intensity up to 6 cycles was 98.8% for the fedratinib 400 mg arm and 93.0% in the fedratinib 500 mg arm.[3]

Table E-1. JAKARTA: extent of exposure during the entire treatment duration

		Fedratinib	
Exposure	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Number of cycles initiated			
Mean (SD)	5.0 (1.80)	13.2 (6.38)	11.6 (6.99)
Median (min, max)	6.0 (1.0, 11.0)	16.0 (1.0, 23.0)	14.0 (1.0, 22.0)
Duration of exposure (weeks)[b]			
Mean (SD)	19.8 (7.91)	52.0 (25.84)	46.4 (28.90)
Median (min, max)	24.0 (1.7, 43.7)	62.1 (1.00, 91.86)	59.7 (0.86, 89.00)
Cumulative dose (mg)			
Mean (SD)	N/A	134,610 (69,822.5)	139,695 (91,943.4)
Median (min, max)	N/A	153,050 (2,800, 257,200)	152,400 (2,400, 294,400)
Average daily dose (mg)			
Mean (SD)	N/A	371.3 (44.70)	429.6 (84.23)
Median (min, max)	N/A	395.1 (202.9, 400.0)	464.9 (96.0, 500.0)
Relative dose intensity (%)[c]			
Mean (SD)	N/A	92.8 (11.17)	85.9 (16.85)
Median (min, max)	N/A	98.8 (50.7, 100.0)	93.0 (19.2, 100.0)

max = maximum; min = minimum; N/A = not applicable; SD = standard deviation.

[a] Data for placebo patients who crossed over to fedratinib treatment are not counted after the date of crossover.

[b] Duration of exposure was calculated as ([last dose date – first dose date + 1 day] ÷ 7). Last dose date was taken as the last dose date at the end of Cycle 6 or last dose date if before Cycle 6 for the first 6-cycle summary (or the day before the crossover) and the actual last dose date for the full treatment period summary.

[c] Relative dose intensity was calculated as (cumulative dose in milligrams) ÷ ([duration of exposure in weeks] × [planned dose intensity in milligrams/4 weeks]). The planned dose intensity was 11,200 mg/4 weeks for the 400 mg arm, and 14,000 mg/4 weeks for the 500 mg arm.

Source: EMA (2020)[3]

Most patients (≥ 93.7%) in each of the 3 treatment arms of the All Treated Population had at least 1 TEAE during the entire treatment duration. Grade 3 or 4 TEAEs occurred in 30.5% of patients in the placebo arm, 70.8% in the fedratinib 400 mg arm, and 78.4% in the fedratinib 500 mg arm. Treatment-emergent AEs leading

to permanent treatment discontinuation were 8.4%, 27.1%, and 36.1%, respectively, and TEAEs leading to dose reduction were 7.4%, 25.0%, and 45.4%.[3]

The frequencies of treatment-emergent SAEs during the entire treatment duration were 23.2% in the placebo arm, 38.5% in the fedratinib 400 mg arm, and 44.3% in the fedratinib 500 mg arm. Treatment-emergent AEs leading to death during the entire treatment duration were 6.3%, 5.2%, and 8.2%, respectively.[3] Table E-2 presents the TEAEs associated with fedratinib in JAKARTA.

Table E-2. JAKARTA: safety overview (All Treated Population)

		Fedratinib	
Patients with ≥ 1 AE, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Any TEAE	89 (93.7)	96 (100.0)	95 (97.9)
Treatment-related TEAE	37 (38.9)	86 (89.6)	92 (94.8)
Grade 3 or 4 TEAE	29 (30.5)	68 (70.8)	76 (78.4)
Treatment-related grade 3 or 4 TEAE	9 (9.5)	46 (47.9)	64 (66.0)
TEAE leading to death	6 (6.3)	5 (5.2)	8 (8.2)
Treatment-emergent SAE	22 (23.2)	37 (38.5)	43 (44.3)
Treatment-related treatment-emergent SAE	1 (1.1)	11 (11.5)	12 (12.4)
TEAE leading to permanent treatment discontinuation	8 (8.4)	26 (27.1)	35 (36.1)
TEAE leading to dose interruption	10 (10.5)	32 (33.3)	45 (46.4)
TEAE leading to dose reduction	7 (7.4)	24 (25.0)	44 (45.4)

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: TEAEs were defined as AEs that started or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of the study drug.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Source: EMA (2020)[3]

Appendix E.1.1.1 Common adverse event data

In the fedratinib 400 mg arm, the most common nonhaematological TEAEs were GI disorders, including diarrhoea in 68 patients (70.8%), nausea in 64 (66.7%), vomiting in 44 (45.8%), and abdominal pain in 15 (15.6%).[3] At the time JAKARTA was conducted, antiemetic prophylaxis was not required per study protocol[77]; this could explain the high incidence of nausea and vomiting, most of which was grade 1 and 2 (Table E-3 and Table E-4). Mitigation strategies to manage GI events were implemented in the ongoing studies FREEDOM and FREEDOM 2.[67] Other common nonhaematological TEAEs included fatigue in 24 patients (25.0%), muscle spasm in 15 (15.6%), and pain in the extremities in 12 (12.5%).[3]

The most common haematological TEAEs were anaemia in 53 patients (55.2%) and thrombocytopenia in 16 (16.7%).[3] Table E-3 presents the common all-grade AEs reported in JAKARTA.

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Table E-3. JAKARTA: all-grade treatment-emergent adverse events reported in ≥ 10% of patients

		Fedratinib	
AE, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Patients with ≥ 1 AE	89 (93.7)	96 (100.0)	95 (97.9)
Diarrhoea	15 (15.8)	68 (70.8)	58 (59.8)
Nausea	15 (15.8)	64 (66.7)	51 (52.6)
Anaemia	13 (13.7)	53 (55.2)	47 (48.5)
Vomiting	5 (5.3)	44 (45.8)	54 (55.7)
Thrombocytopenia	8 (8.4)	16 (16.7)	22 (22.7)
Fatigue	9 (9.5)	24 (25.0)	14 (14.4)
Constipation	7 (7.4)	12 (12.5)	19 (19.6)
Abdominal pain	14 (14.7)	15 (15.6)	14 (14.4)
Cough	6 (6.3)	13 (13.5)	14 (14.4)
Dizziness	3 (3.2)	13 (13.5)	10 (10.3)
Headache	1 (1.1)	13 (13.5)	6 (6.2)
Dyspnoea	6 (6.3)	11 (11.5)	12 (12.4)
Asthenia	6 (6.3)	13 (13.5)	16 (16.5)
Pruritus	3 (3.2)	6 (6.3)	7 (7.2)
Oedema peripheral	8 (8.4)	14 (14.6)	9 (9.3)
Muscle spasms	1 (1.1)	15 (15.6)	8 (8.2)
Urinary tract infections	1 (1.1)	9 (9.4)	10 (10.3)
Pyrexia	3 (3.2)	7 (7.3)	6 (6.2)
Blood creatinine increased	1 (1.1)	11 (11.5)	17 (17.5)
Bone pain	2 (2.1)	12 (12.5)	8 (8.2)
Pain in extremity	4 (4.2)	12 (12.5)	3 (3.1)
ALT increased	1 (1.1)	12 (12.5)	9 (9.3)
Blood product transfusion dependent[b]	2 (2.1)	10 (10.4)	12 (12.4)
Decreased appetite	3 (3.2)	6 (6.3)	9 (9.3)
Weight decreased	5 (5.3)	5 (5.2)	12 (12.4)
Weight increased	4 (4.2)	12 (12.5)	8 (8.2)
AST increased	0 (0.0)	6 (6.3)	10 (10.3)
Hyperkalaemia	2 (2.1)	6 (6.3)	10 (10.3)
Neutropenia	0 (0.0)	6 (6.3)	12 (12.4)

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

[b] The AE of blood product transfusion dependent is based on investigator reporting, not by calculating the number of red blood cell transfusions per month based on the Gale et al. (2011)[80] definition.

Source: EMA (2020)[3]

Anaemia (44.8%) was the most commonly reported grade 3 or 4 TEAE and thrombocytopenia (11.5%) was the second most commonly reported TEAE in the fedratinib 400 mg arm. Table E-4 presents the common grade 3 or 4 TEAEs reported in JAKARTA.

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Table E-4. JAKARTA: grade 3 or 4 treatment-emergent adverse events reported in ≥ 5% of patients during entire treatment duration

		Fedratinib	
MedDRA system organ class preferred term, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Patients with ≥ 1 grade 3 or 4 TEAE	29 (30.5)	68 (70.8)	76 (78.4)
Blood and lymphatic system disorders	14 (14.7)	49 (51.0)	50 (51.5)
Anaemia	7 (7.4)	43 (44.8)	40 (41.2)
Thrombocytopenia	6 (6.3)	11 (11.5)	18 (18.6)
Neutropenia	0 (0.0)	4 (4.2)	10 (10.3)
Investigations	1 (1.1)	12 (12.5)	19 (19.6)
Lipase increased	1 (1.1)	4 (4.2)	7 (7.2)
Gastrointestinal disorders	5 (5.3)	11 (11.5)	24 (24.7)
Diarrhoea	0 (0.0)	5 (5.2)	5 (5.2)
Vomiting	0 (0.0)	3 (3.1)	9 (9.3)
Nausea	0 (0.0)	0 (0.0)	6 (6.2)
Metabolism and nutrition disorders	5 (5.3)	9 (9.4)	11 (11.3)
Hyperkalaemia	2 (2.1)	2 (2.1)	6 (6.2)
Cardiac disorders	5 (5.3)	13 (13.5)	8 (8.2)
Cardia failure	2 (2.1)	6 (6.3)	2 (2.1)
Infections and infestations	4 (4.2)	7 (7.3)	18 (18.6)
Pneumonia	1 (1.1)	2 (2.1)	5 (5.2)
General disorders and administration site conditions	3 (3.2)	8 (8.3)	12 (12.4)
Fatigue	0 (0.0)	7 (7.3)	7 (7.2)
Social circumstances	0 (0.0)	3 (3.1)	8 (8.2)
Blood product transfusion dependent[b]	0 (0.0)	3 (3.1)	8 (8.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

Note: AEs were coded using MedDRA Version 20.1 and were graded using NCI-CTCAE version 4.03. TEAEs were defined as AEs that developed, started, or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of the study drug. System organ classes are sorted in decreasing order of frequency for the fedratinib 400 mg column.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

[b] The AE of blood product transfusion dependent is based on investigator reporting, not by calculating the number of red blood cell transfusions per month based on the Gale et al. (2011)[80] definition.

Source: EMA (2020)[3]

Rates of discontinuation due to adverse event

Treatment-emergent AEs were observed in 100% (fedratinib) and 93.7% (placebo) of patients. Treatment-related AEs were reported in 89.6% of patients in the fedratinib group compared with 38.9% of patients in the placebo group, with just over half of those in the fedratinib group being grade 3 or 4 in severity (fedratinib, 47.9%; placebo, 9.5%). Rates of discontinuation due to AEs were higher in the fedratinib group (fedratinib, 27.1%; placebo, 8.4%).[3]

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Adverse events leading to death

Table E-5 presents the frequencies of TEAEs leading to death during the entire treatment duration. A total of 19 patients died across all study arms. Disease progression was reported as a TEAE leading to death in 2 patients (1 in the placebo arm and 1 in the fedratinib 500 mg arm).

Table E-5. JAKARTA: treatment-emergent adverse events leading to death (All Treated Population)

		Fedratinib	
Primary system organ class preferred term, n (%)	Placebo[a] (n = 95)	400 mg (n = 96)	500 mg (n = 97)
Patients with ≥ 1 TEAE leading to death	6 (6.3)	5 (5.2)	8 (8.2)
General disorders and administration site conditions	1 (1.1)	1 (1.0)	1 (1.0)
Disease progression	1 (1.1)	0 (0.0)	1 (1.0)
Multiple organ dysfunction syndrome	0 (0.0)	1 (1.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (1.1)	3 (3.1)	0 (0.0)
Acute myeloid leukaemia	0 (0.0)	1 (1.0)	0 (0.0)
Acute leukaemia	0 (0.0)	1 (1.0)	0 (0.0)
Myelofibrosis	0 (0.0)	1 (1.0)	0 (0.0)
Transformation to acute myeloid leukaemia	1 (1.1)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (1.1)	2 (2.1)	2 (2.1)
Cardio-respiratory arrest	0 (0.0)	1 (1.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	1 (1.0)	0 (0.0)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (1.0)
Cardiac failure	0 (0.0)	0 (0.0)	1 (1.0)
Myocardial ischaemia	1 (1.1)	0 (0.0)	0 (0.0)
Infections and infestations	2 (2.1)	1 (1.0)	1 (1.0)
Sepsis	1 (1.1)	1 (1.1)	0 (0.0)
Pneumonia	1 (1.1)	0 (0.0)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (1.0)
Vascular disorders	0 (0.0)	1 (1.0)	0 (0.0)
Shock, haemorrhagic	0 (0.0)	1 (1.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (1.0)	1 (1.0)
Disseminated intravascular coagulation	0 (0.0)	1 (1.0)	0 (0.0)
Leukocytosis	0 (0.0)	0 (0.0)	1 (1.0)
Injury, poisoning, and procedural complications	1 (1.1)	1 (1.0)	0 (0.0)
Muscle rupture	0 (0.0)	1 (1.0)	0 (0.0)
Transfusion-related acute lung injury	1 (1.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	0 (0.0)	3 (3.1)
Respiratory failure	0 (0.0)	0 (0.0)	1 (1.0)
Pneumonitis	0 (0.0)	0 (0.0)	1 (1.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (1.0)
Gastrointestinal disorders	1 (1.1)	0 (0.0)	1 (1.0)
Ascites	1 (1.1)	0 (0.0)	0 (0.0)
Haematemesis	0 (0.0)	0 (0.0)	1 (1.0)

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AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Notes: AEs were coded using MedDRA Version 20.1. TEAEs were defined as AEs that developed, started, or worsened in severity on or after the date and time of the first study drug dose up to 30 days after the last dose of the study drug.

A patient could have multiple TEAEs leading to death.

System organ classes are sorted in decreasing order of frequency for the fedratinib 400 mg column.

[a] AEs for placebo patients who crossed over to fedratinib treatment are not included if they occurred on or after the date of crossover.

Source: EMA (2020)[3]

Nonhaematological adverse events

Table E-3 summarises the most frequently reported AEs during the placebo-controlled phase of the study. The most frequently reported nonhaematological AEs (> 45%) in the fedratinib group were GI AEs, namely diarrhoea, nausea, and vomiting; these AEs were reported in < 20% of patients in the placebo group. However, most GI events were mild or moderate in severity with the incidence of grade 3 or 4 GI-related AEs being 11.5% in the fedratinib group.[3] Furthermore, the incidence of GI toxicities decreased over time (Figure E-1).[23] Gastrointestinal toxicities were generally managed with dose reductions or treatment interruptions (15% of patients in the fedratinib group), and only 7 patients discontinued therapy for GI toxicities.[23] At the time the JAKARTA study was conducted, antiemetic prophylaxis was not required per study protocol[77]; this could explain the high incidence of nausea and vomiting, most of which were grade 1 and 2 (see Table E-3 and Table E-4). Mitigation strategies to manage GI events were implemented in the ongoing studies FREEDOM and FREEDOM 2.[67] Fatigue, muscle spasms, and pain in extremity were the only other nonhaematological AEs reported in ≥ 10% of patients receiving fedratinib. The only other grade 3 or 4 nonhaematological AE reported in ≥ 5% of patients was cardiac failure (6.3% in the fedratinib group vs. 2.1% in the placebo group).[3]

Source: Pardanani et al. (2015)[23]

Unlike previous studies of fedratinib, the FREEDOM study (investigating fedratinib 400 mg once daily in patients with MF previously treated with ruxolitinib) prospectively required the following mitigation strategies to manage GI events[81,82]:

- Prophylactic and symptomatic use of anti-nausea, anti-vomiting, and anti-diarrhoeal treatments
- Fedratinib dosing modifications
- Administration of fedratinib with food

Preliminary safety data for the first 23 patients enrolled in the FREEDOM study have been presented and are summarised here. Median fedratinib treatment duration was 18.1 weeks (range, 1.6-47.9 weeks), and 10 patients (43%) had received > 6 fedratinib treatment cycles. The most common GI TEAEs were diarrhoea (n = 8), constipation (n = 8), vomiting (n = 4), and nausea (n = 3) (Figure E-2). During fedratinib treatment, 14 patients (61%) received ondansetron and 7 patients (30%) received loperamide. Early data from the FREEDOM study suggest frequency and severity of GI events may be reduced via mitigation strategies.[81,82]

Note: Includes events with new onset in each cycle. All events of diarrhoea, nausea, and vomiting were grade 1 in severity.
Source: Gupta et al. (2020)[81]

Haematological adverse events

The only haematological AEs reported in ≥ 10% of patients in either group were anaemia and thrombocytopenia. Anaemia was reported in 40% of the fedratinib group (vs. 14% for placebo) and three-quarters of cases in the fedratinib group were grade 3 or 4 in severity. One patient discontinued fedratinib because of anaemia; 7 patients (7.3%) had dose interruptions/reductions for anaemia. The lowest haemoglobin levels were reached after 12 to 16 weeks on fedratinib, with partial recovery occurring from week 16 onwards. Of 8 patients who were RBC transfusion dependent at baseline, 7 patients achieved transfusion independence during treatment with fedratinib, but 22 of 88 patients who were RBC transfusion independent at baseline became dependent. The incidence of thrombocytopenia (any grade and grade 3 or 4) was similar in both groups (grade 3 or 4: fedratinib, 5%; placebo, 6%). In total, 2 patients discontinued fedratinib because of thrombocytopenia and 2 had dose reductions or treatment interruptions for management of thrombocytopenia.[71]

Over the entire study, the mean duration of exposure in patients initially randomised to receive fedratinib 400 mg was 52 weeks, and the mean relative dose intensity was 92.8%. Over the study period, 58% of patients in this group required ≥ 1 dose reduction and 23% had a treatment interruption of ≥ 7 days. The incidence of AEs in the fedratinib group over the entire study duration was consistent with that over the placebo-controlled period. Gastrointestinal-related AEs were the most frequently reported AEs, and the only other AEs (any grade) reported in > 20% of patients were anaemia (55%) and fatigue (25%). The only grade 3 or 4 AEs reported in ≥ 5% of patients were infections, diarrhoea, anaemia, thrombocytopenia, and cardiac failure. Adverse events

leading to permanent discontinuation of fedratinib were thrombocytopenia (n = 4); cardiac failure (n = 3); and 2 each for the following AEs: anaemia, blood creatinine increased, diarrhoea, myocardial ischaemia, and nausea.[71]

Serious AEs occurred at a similar incidence in both groups over the placebo-controlled period. Serious AEs occurring in ≥ 2 patients were cardiac failure (n = 5), infections (n = 3), and anaemia (n = 2) in the fedratinib group and infections (n = 5), cardiac failure and ascites (3 patients each), and pneumonia, splenic infarction, and transformation to AML (2 patients each) in the placebo group.[71]

There were 7 deaths (7.3%) on study in the fedratinib group and 12 (12.6%) in the placebo group during the placebo-controlled period. Progressive disease was the main cause in both groups (fedratinib, n = 4 [4.2%]; placebo, n = 6 [6.3%]) followed by AEs (fedratinib, n = 1 [1%], cardiogenic shock; placebo, n = 4 [4.2%], myocardial ischaemia, pneumonia, sepsis, and transfusion-related acute lung injury [1 patient each]). There were also more deaths occurring within 30 days of the last dose of study drug in the placebo versus fedratinib group (fedratinib, n = 2; placebo, n = 6). Over the entire study period there were 15 deaths in the fedratinib 400 mg group, 9 due to disease progression, 2 due to AEs (the additional AE was acute leukaemia), and 4 from other causes.[71]

Appendix E.1.2 Indirect treatment comparison safety data

Appendix E.1.2.1 Treatment-emergent adverse events

Table E-6 presents the descriptive comparative results for the percentage of patients in JAKARTA, COMFORT-I, and COMFORT-II who experienced AEsTable 28.

Both the JAKARTA and COMFORT-I studies reported AEs for the primary analyses at 24 weeks, prior to crossover. The COMFORT-II study also reported AEs for the primary analyses, which was at 48 weeks. Therefore, AEs for fedratinib-treated patients and ruxolitinib-treated patients were compared using the JAKARTA and COMFORT-I studies.

Overall, results of the descriptive analysis of JAKARTA and COMFORT-I suggested a similar safety profile in terms of frequency for grade 3 or 4 AEs between fedratinib and ruxolitinib. Where reported, the percentages of ruxolitinib-treated patients in COMFORT-II who experienced certain AEs (see Table 28) were similar to the percentages for ruxolitinib-treated patients in COMFORT-I.

Results suggest that fedratinib is associated a higher incidence of any-grade GI toxicities compared with ruxolitinib. Noteworthy differences (chosen to be ≥ 10%) between fedratinib-treated patients and ruxolitinib-treated patients in the JAKARTA and COMFORT-I studies were as follows:

- Diarrhoea (any grade): there were more fedratinib-treated patients who experienced diarrhoea
- Nausea (any grade): there were more fedratinib-treated patients who experienced nausea
- Vomiting (any grade): there were more fedratinib-treated patients who experienced vomiting

At the time the JAKARTA study was conducted, antiemetic prophylaxis was not provided to patients, which could explain the increased incidence of nausea and vomiting.

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Table E-6. Adverse events in JAKARTA, COMFORT-I, and COMFORT-II

AE, %	JAKARTA: 24 weeks		COMFORT-I: 24 weeks		COMFORT-II: 48 weeks	
	PBO (n = 95)	400 mg FEDR (n = 96)	PBO (n = 151)	RUX (n = 155)	BAT (n = 73)	RUX (n = 146)
Deaths due to AEs	6.3	1.0	7.3	5.8	5.5	4.1
SAEs	23.2	20.8	35.1	27.7	28.8	30.1
Grade 3 or 4 AEs	30.5	52.1	44.4	47.1	24.7	41.8
Discontinuation due to AEs	8.4	13.5	10.6	11.0	5.5	8.2
Any AEs	93.7	99.0	98.0	97.4	90.4	99.3
Haematological AEs						
Anaemia (grade 3 or 4)	24.2[a]	41.7[a]	19.2[a]	45.2[a]	31	42
Thrombocytopenia (grade 3 or 4)	9.5[a]	11.4[a]	1.3[a]	12.9[a]	7	8
Nonhaematological AEs						
Bruising (any grade)	NR	NR	9.3	18.7	NR	NR
Bruising (grade 3 or 4)	NR	NR	0	0	NR	NR
Dizziness (any grade)	3.2	8.3	6.6	14.8	NR	NR
Dizziness (grade 3 or 4)	0	0	0	0.6	NR	NR
Headache (any grade)	1.1	9.4	5.3	14.8	4	10
Headache (grade 3 or 4)	0	0	0	0	0	1
Diarrhoea (any grade)	15.8	65.6	21.2	23.2	12	23
Diarrhoea (grade 3 or 4)	0	5.2	0	1.9	0	1
Nausea (any grade)	14.7	61.5	19.2	14.8	7	13
Nausea (grade 3 or 4)	0	0	0.7	0	0	1
Vomiting (any grade)	5.3	38.5	9.9	12.3	NR	NR
Vomiting (grade 3 or 4)	0	3.1	0.7	0.6	NR	NR
Bleeding events						
≥ Grade 3 bleeding event	0	2.1	2.0[b]	2.6[b]	NR[b]	NR[b]
Infections						
Urinary tract infection (any grade)	1.1	6.3	5.3	9.0	NR	NR
Herpes zoster (any grade)	1.1	1.0	0.7	1.9	NR	NR

AE = adverse event; BAT = best available therapy; FEDR = fedratinib; NR = not reported; PBO = placebo; RUX = ruxolitinib; SAE = serious adverse event.

[a] Derived based on laboratory values.

[b] For the COMFORT-I and COMFORT-II studies combined, percentages of patients experiencing grade 3+ bleeding events in the ruxolitinib arms and control arms were 4.7% and 3.1%, respectively.

Sources: Celgene-BMS data on file (2020)[28]; NICE (2015)[89]; Jakafi PI (2018)[90]

Appendix E.1.3 JAKARTA 2 safety data

The safety analyses were performed in the All Treated Population, defined as enrolled patients who took at least 1 dose (even if partial) of study medication (n = 97).[3] The median number of treatment cycles was 6 (interquartile range, 3.9-8.9).[58] Fourteen patients (14.4%) received more than 12 cycles. Treatment was discontinued because of early study termination in 63 patients (65%). The remainder of patients discontinued study treatment because of AEs (19%), disease progression (6%), patient decision (3%), or other reasons (7%). Thirty-eight patients (39%) had at least 1 dose reduction, 13 (13%) had 2 dose reductions, and 4 (4%) had more than 2 dose reductions. A total of 25 patients (25.8%) had a dose interruption for at least 7 consecutive days.

Table E-7 summarises the treatment exposure in JAKARTA 2.

Table E-7. JAKARTA 2: fedratinib exposure (Safety Population)

Fedratinib exposure	Fedratinib 400 mg (n = 97)
Cycles administered	
Mean (SD)	7.3 (4.43)
Median (min, max)	6.0 (1.0, 20.0)
Duration of exposure[a] (weeks)	
Mean (SD)	28.1 (17.80)
Median (min, max)	24.4 (0.7, 79.4)
Average daily dose (mg)	
Mean (SD)	384.5 (82.55)
Median (min, max)	400.0 (158.5, 554.9)
Relative dose intensity,[b] %	
Mean (SD)	96.1 (20.64)
Cumulative dose, mg	
Mean (SD)	77,915 (56,648.3)
Median (min, max)	59,600 (2,000, 251,300)

max = maximum; min = minimum; SD = standard deviation.

[a] Duration of exposure was calculated as ([last dose date – first dose date + 1 day] ÷ 7). Last dose date was taken as the last dose date at the end of Cycle 6 or last dose date if before Cycle 6 for the first 6-cycle summary and the actual last dose date for the full treatment period summary.

[b] Relative dose intensity was calculated as (cumulative dose in milligrams) ÷ ([duration of exposure in weeks] × [planned dose intensity in milligrams/4 weeks]). The planned dose intensity was 11,200 mg/4 weeks for the 400 mg arm and 14,000 mg/4 weeks for the 500 mg arm.

Source: EMA (2020)[3]

All 97 patients had at least 1 TEAE of any grade.[29] Grade 3 or 4 TEAEs were reported by 61 patients (63.0%). Treatment-emergent SAEs were reported by 33 patients (34%). Seven patients (7%) had a TEAE that led to death during treatment or follow-up: in 4 cases, the cause of death was determined to be due to disease progression, and the other 3 cases were due to a TEAE considered not related to study treatment. Treatment-emergent AEs leading to treatment discontinuation occurred in 19 patients (19.6%), and TEAEs leading to dose interruption and reduction occurred in 26 patients (26.8%) and 35 patients (36.1%), respectively.[3,29]

Table E-8 presents an overview of the TEAEs associated with fedratinib in JAKARTA 2.

Table E-8. JAKARTA 2: safety overview (All Treated Population)

Adverse event, n (%)	Fedratinib 400 mg (n = 97)
TEAE	97 (100.0)
Treatment-related TEAE	88 (90.7)
Grade 3 or 4 TEAE	61 (62.9)
Treatment-related grade 3 or 4 TEAE	50 (51.5)
TEAE leading to death	7 (7.2)
Treatment-related TEAE leading to death	0 (0.0)
Treatment-emergent SAE	33 (34.0)
Treatment-related treatment-emergent SAE	11 (11.3)
TEAE leading to permanent treatment discontinuation	19 (19.6)
TEAE leading to dose interruption	26 (26.8)
TEAE leading to dose reduction	35 (36.1)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Data are for patients with ≥ 1 TEAE.
Sources: EMA (2020)[3]; Harrison et al. (2020)[29]

Appendix E.1.3.1 Common adverse event data

The most common nonhaematological TEAEs were GI disorders, including diarrhoea in 60 patients (62%), nausea in 54 (56%), vomiting in 40 (41%), constipation in 20 (21%), and abdominal pain in 12 (12%).[3] Other common nonhaematological TEAEs in other system order classes included pruritus in 17 patients (17.5%), fatigue in 15 (15.5%), cough and headache in 13 (13%) each, urinary tract infection and dyspnoea in 12 (12%) each, and dizziness in 11 (11%).

The most common haematological TEAEs were anaemia in 47 patients (48%) and thrombocytopenia in 26 (27%).[58] Grade 3 or 4 anaemia was reported in 37 patients (38%) and thrombocytopenia in 21 (22%).

Table E-9 summarises the common AEs reported in JAKARTA 2.

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Table E-9. JAKARTA 2: common adverse events (All Treated Population)

	Fedratinib 400 mg (n = 97)	
Adverse event, n (%)	**Grades 1-2**	**Grades 3-4**
Haematological adverse events		
Anaemia	10 (10)	37 (38)
Thrombocytopenia	5 (5)	21 (22)
Lymphopenia	1 (1)	3 (3)
Nonhaematological adverse events		
Diarrhoea	56 (58)	4 (4)
Nausea	54 (56)	0 (0)
Vomiting	40 (41)	0 (0)
Constipation	19 (20)	1 (1)
Pruritus	16 (16)	0 (0)
Fatigue	13 (13)	2 (2)
Headache	12 (12)	1 (1)
Cough	13 (13)	0 (0)
Urinary tract infection	12 (12)	0 (0)
Dyspnoea	11 (11)	1 (1)
Dizziness	11 (11)	0 (0)
Abdominal pain	7 (7)	2 (2)
Alanine aminotransferase increased	3 (3)	3 (3)
Pneumonia	3 (3)	2 (2)
Hyperlipasaemia	1 (1)	3 (3)
Hyperuricaemia	2 (2)	2 (2)
Dehydration	1 (1)	2 (2)
Tumour lysis syndrome	0 (0)	2 (2)
Cardiac failure	1 (1)	2 (2)
Amylase increased	1 (1)	2 (2)
Blood bilirubin increased	0 (0)	2 (2)
Cardiac failure	1 (1)	2 (2)
Respiratory failure	0 (0)	0 (0)
Splenic rupture	0 (0)	0 (0)

Notes: Shown are any grade event occurring in more than 10% of patients and grade 3-4 events occurring in more than 1 patient.

Sources: Harrison et al. (2017)[58]; Harrison et al. (2020)[29]

Appendix E.1.3.2 Treatment-emergent serious adverse events

Treatment-emergent SAEs were reported in 33 patients (34%).[3,58] The most common SAE was cardiac disorders, reported in 6 patients (6.2%). Pneumonia was reported in 4 patients (4.1%), pleural effusion in 3 (3.1%), and fall in 2 (2.1%).

Eleven patients (11.3%) had SAEs considered treatment related.[3] Pneumonia was the only treatment-related SAE reported in more than 1 patient and occurred in 2 patients.

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Appendix E.1.3.3 Adverse events leading to treatment discontinuation

Treatment-emergent AEs leading to treatment discontinuation occurred in 19 patients (19.6%), of whom 11 (11.3%) had a grade 3 or 4 event.[3,29] The most common reason for treatment discontinuation was grade 3 or 4 thrombocytopenia, which occurred in 2 patients. One patient had disease transformation to AML, which was considered an AE, but the reason for discontinuation was recorded as disease progression.

One case of grade 3 encephalopathy was reported, but it was subsequently determined by an independent expert safety panel to be related to hepatic encephalopathy and inconsistent with Wernicke's encephalopathy.[58] The event resolved within 1 week after discontinuation of fedratinib treatment.

Appendix E.1.3.4 Adverse events leading to death

Seven patients (7%) died during treatment in JAKARTA 2, but none of the deaths was deemed to be related to fedratinib.[29] Three patients died due to fatal TEAEs of pneumonia, shock, and cardiorespiratory arrest. The 4 other patients died due to disease progression as the main cause of death.

Table E-10 summarises TEAEs leading to death.

Table E-10. JAKARTA 2: treatment-emergent adverse events leading to death (Safety Population)

System organ class preferred term, n (%)	Fedratinib 400 mg (n = 97)
Patients with at least 1 TEAE leading to death	**7 (7.2)**
General disorders and administration site conditions	**2 (2.1)**
Disease progression	1 (1.0)
General physical health deterioration	1 (1.0)
Infections and infestations	**2 (2.1)**
Pneumonia	1 (1.0)
Sepsis	1 (1.0)
Cardiac disorders	**1 (1.0)**
Cardio-respiratory arrest	1 (1.0)
Neoplasms; benign, malignant, and unspecified (including cysts and polyps)	**1 (1.0)**
Acute myeloid leukaemia	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	**1 (1.0)**
Respiratory failure	1 (1.0)
Vascular disorders	**1 (1.0)**
Shock	1 (1.0)

TEAE = treatment-emergent adverse event.
Source: EMA (2020)[3]

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Appendix F. Comparative analysis of efficacy and safety

All indirect comparison results are presented in the main body of this dossier; please see links below. Please also find attached the full ITC report, which should be treated as confidential information.

- Indirect treatment comparison: Section 7.2.

Adobe Acrobat Document

Table F-1 summarises the results of the ITC.

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Table F-1. Meta-analysis of studies comparing fedratinib to ruxolitinib for patients with myelofibrosis

		JAKARTA		COMFORT-I		COMFORT-II	
Outcome	**Analysis performed**	**PBO**	**400 mg FEDR**	**PBO**	**RUX**	**BAT**	**RUX**
≥ 35% SVR from baseline to week 24 (JAKARTA ITT population and no confirmation of response 4 weeks later)	No analysis performed (absolute responses)	1.0% (n = 1; N = 96)	46.9% (n = 45; N = 96)	0.7% (n = 1; N = 153)	41.9% (n = 65; N = 155)	0% (n = 0; N = 72)	31.9% (n = 46; N = 144)
	Bucher ITC			Δ 400 mg FEDR–RUX [95% CI]: 4.6% [–8.3 to 17.4]		Δ 400 mg FEDR–RUX [95% CI]: 13.9% [1.2-26.6]	
	MAIC using Bucher methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 7.9% [–5.2 to 20.9]		Δ 400 mg FEDR–RUX [95% CI]: 16.3% [3.5-29.0]	
	Frequentist NMA			Δ 400 mg FEDR–RUX [95% CI]: 9.4% [–2.2 to 20.9]			
	MAIC using frequentist NMA methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 12.3% [0.6-24.0]			
≥ 35% SVR from baseline to week 24 (subgroup of the JAKARTA ITT population with platelet counts ≥ 100 × 10^9/L and no confirmation of response 4 weeks later)	No analysis performed (absolute responses)	[redacted]	[redacted]	0.7% (n = 1; N = 153)	41.9% (n = 65; N = 155)	0% (n = 0; N = 72)	31.9% (n = 46; N = 144)
	Bucher ITC			Δ 400 mg FEDR–RUX [95% CI]: 6.2% [–7.4 to 19.8]		Δ 400 mg FEDR–RUX [95% CI]: 15.5% [2.1-29.0]	
	MAIC using Bucher methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 10.4% [–3.2 to 24.1]		Δ 400 mg FEDR–RUX [95% CI]: 18.5% [5.1-31.9]	
	Frequentist NMA			Δ 400 mg FEDR–RUX [95% CI]: 11.0% [–1.4 to 23.4]			
	MAIC using frequentist NMA methodology[a]			Δ 400 mg FEDR–RUX [95% CI]: 14.7% [2.4-27.1]			
≥ 50% reduction in TSS from baseline to week 24 (ITT population with nonmissing baseline TSS)	No analysis performed (absolute responses)	[redacted]	[redacted]	5.3% (n = 8; N = 152	45.9% (n = 68; N = 148)	NR	NR
	Bucher ITC			[redacted]		N/A	

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Outcome	Analysis performed	JAKARTA		COMFORT-I		COMFORT-II	
		PBO	400 mg FEDR	PBO	RUX	BAT	RUX
≥ 50% reduction in TSS from baseline to week 24 (subgroup of the JAKARTA ITT population with platelet counts ≥ 100 × 10^9/L and nonmissing baseline TSS)	N/A (absolute responses)	[redacted]	[redacted]	5.3% (n = 8; N = 152)	45.9% (n = 68; N = 148)	N/A	N/A
	Bucher ITC			Δ [redacted]		N/A	

BAT = best available therapy; CI = confidence interval; FEDR = fedratinib; ITC = indirect treatment comparison; ITT = intent to treat; JAK2 = Janus kinase 2; MAIC = matching-adjusted indirect comparison; N/A = not applicable; NMA = network meta-analysis; NR = not reported; PBO = placebo; Δ 400 mg FEDR–RUX = risk difference between fedratinib and ruxolitinib; RUX = ruxolitinib; SVR = spleen volume reduction; TSS = total symptom score.

[a] Adjustment made for JAK2 status at baseline.

Source: Celgene-BMS data on file (2020)[28]

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Appendix G. Extrapolation

A description of the TTD extrapolations is provided in Section 8.3.1.[i]

Appendix H. Literature search for HRQoL data

Not applicable because HRQoL data are not used in economic evaluation due to the cost-minimisation approach.

Appendix I. Mapping of HRQoL data

Not applicable because a cost-minimisation approach was used.

Appendix J. Probabilistic sensitivity analyses

Probabilistic sensitivity analyses were not conducted because a cost-minimisation approach was used.

Appendix K. Fedratinib summary of product characteristics

Appendix_K_Inrebic EPAR SmPC.pdf

[i] https://medicinraadet.dk/media/tdandcfg/anvendelse-af-forloebsdata-i-sundhedsoekonomiske-analyser-vers-11_adlegacy.pdf

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Appendix L. List of 551 studies reviewed

Appendix_L_List of inclusion studies 55

Appendix M. List of 539 studies excluded

Appendix_M_List of excluded studies 53

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REQUEST OF ADDITIONAL DATA BY THE DANISH MEDICINES COUNCIL FOR THE ASSESSMENT OF FEDRATINIB FOR MYELOFIBROSIS ON 13 JANUARY 2022

Content

Question 1.

Is there additional data documenting the occurrence of gastrointestinal adverse events while using prophylactic treatment against diarrhea and nausea/vomiting at the same time?

The application includes data from the FREEDOM study, but this covers very few patients (data cut off March 2020) and the exact "mitigation strategies" are not very accurately described. The Expert Committee would like to request additional safety data from FREEDOM from a longer follow-up time including more patients, as well as a precise description of the mitigation strategies, including whether patients only received prophylactic treatment during a start-up phase or whether treatment was constant through the study? In addition, it is requested to provide information about how many cases of hospitalization related to gastrointestinal toxicity occurred.

FREEDOM: Updated results (data cutoff April 2021)

Gupta et al. have recently presented updated safety and tolerability results of fedratinib from the FREEDOM trial at ASH 2021 based on data cutoff of 9 April 2021 (Gupta et al. 2021). The objective of this analysis was to investigate the safety of fedratinib 400 mg once daily and the effectiveness of gastrointestinal (GI) and thiamine mitigation strategies in the FREEDOM study.

Compared to the prior data cutoff (26 March 2020; n= 23 patients), 11 additional patients were enrolled at data cutoff 9 April 2021, leading to a total of 34 patients (Figure 1) (Gupta et al. 2020; Gupta et al. 2021), of whom 18 has discontinued treatment. Reasons for treatment discontinuation in > 1 patient were lack of efficacy (n = 5), AEs (n=4; 1 was Treatment-related [G3 thrombocytopenia]), disease progression (n = 2), patient decision (n = 2), and to undergo transplant (n = 2).

Median fedratinib treatment duration was 28.3 (range, 1.6-101.3) weeks, and 14 (41%) patients completed > 12 cycles of fedratinib treatment. The median fedratinib daily dose was 400 mg/day (range, 298-400) (Gupta et al. 2021).

The frequency of GI AEs were substantially lower in FREEDOM than in previous clinical trials of fedratinib (Pardanani et al. 2021; Harrison et al. 2020). As observed in the JAKARTA studies, most GI AEs were grade 1/2 events. All Grade diarrhea, nausea and vomiting were reported in 35%, 26% and 18% of patients, respectively (Table 1) (Gupta et al. 2021). Grade 1/2 constipation occurred in 47% of patients, potentially related to more frequent use of GI-directed therapies such as ondansetron and loperamide. Grade 3/4 GI AEs were reported in 5 patients (15%), but none were nausea, vomiting, diarrhea or constipation. There were no treatment-related Grade 3/4 GI AEs reported in FREEDOM. No patient had a treatment-related GI AE that required fedratinib dose modification or treatment discontinuation (Gupta et al. 2021).

Table 1. Gastrointestinal AEs reported in > 10% of patients (all cause) in FREEDOM (April 2021).

	Fedratinib 400 mg/day (N = 34)	
n (%)	**All Grade**	**Grade 3-4**
Any GI AE	29 (85)	5 (15)[a]
Constipation	16 (47)	0
Diarrhea	12 (35)	0
Nausea	9 (26)	0
Abdominal pain	8 (24)	1 (3)
Vomiting	6 (18)	0

[a]Four patients had grade 3 to 4 GI AEs that were not included in this table: upper abdominal pain, ascites, gastric antral vascular ectasia, and gastric hemorrhage (n = 1 each).
AE, adverse event; GI, gastrointestinal. Table adapted from (Gupta et al. 2021).

As previously observed, GI AEs occurred mostly during the first cycle and then decreased in frequency in FREEDOM (Figure *2*) (Gupta et al. 2021; Pardanani et al. 2015). Common GI-directed comedications were ondansetron (n = 22 [65%]) and loperamide (n = 11 [32%]). Ondansetron was primarily administered prophylactically and loperamide for symptomatic treatment.

[redacted]

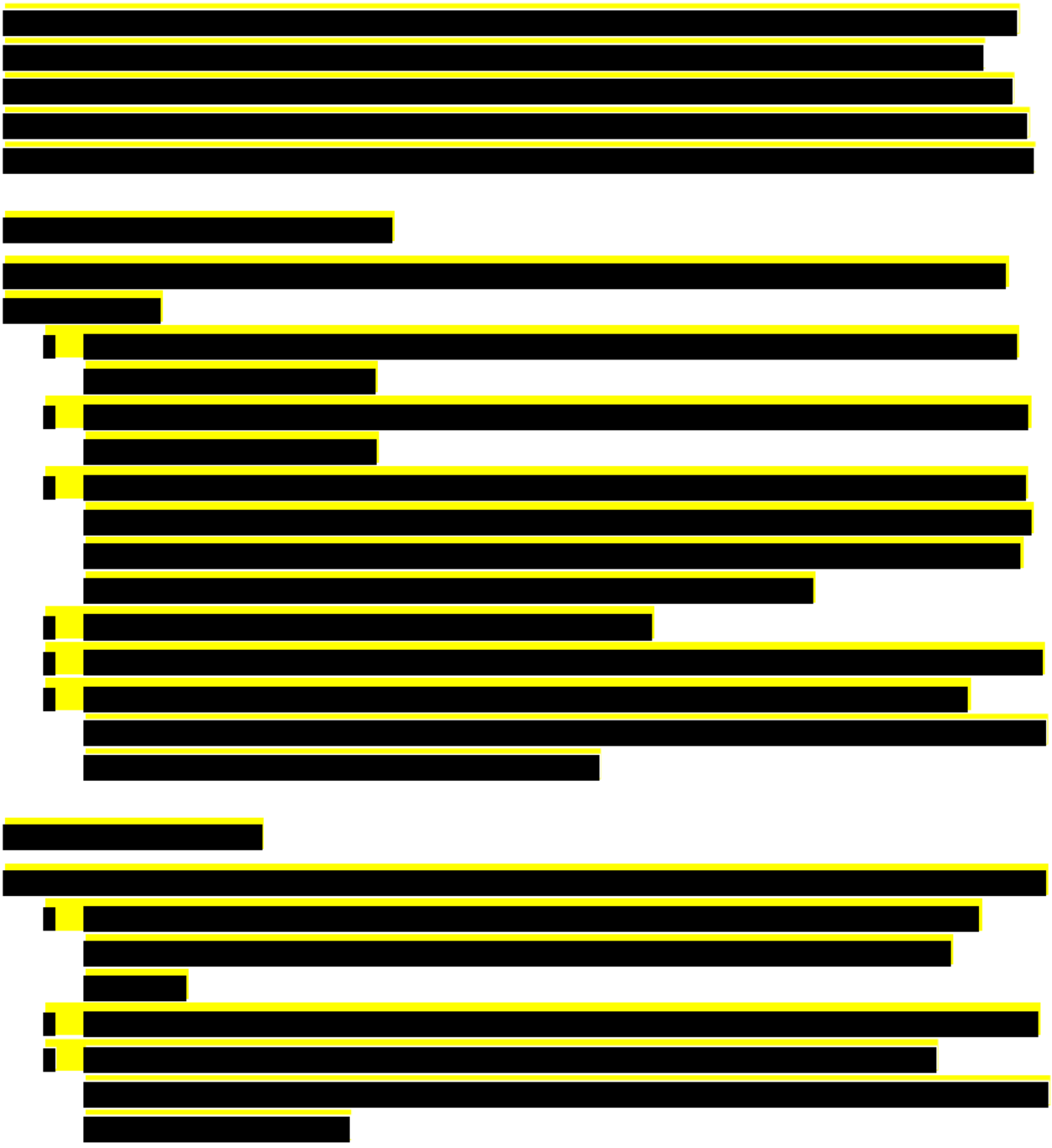
Figure 2. Frequency of nausea, vomiting and diarrhea in FREEDOM. Proportion of patients with reported diarrhea, vomiting, and nausea in the FREEDOM study over the first 6 cycles of fedratinib therapy Includes events with new onset in each cycle (data cutoff April 2021) (Gupta et al. 2021).

[redacted]

In conclusion, fedratinib was well tolerated. The frequency of GI AEs were substantially lower in FREEDOM compared to previous clinical trials investigating fedratinib, suggesting that the mitigation strategies, including GI prophylaxis and prompt treatment at the first onset of symptoms, can prevent or mitigate the GI events.

The section detailing the mitigation strategies and the management of GI AEs from the FREEDOM protocol is provided below.

Management of GI AEs in FREEDOM



[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

In Fedratinib Summary of Product Characteristics (SPC), the following recommendation specific for GI AEs is provided. In case of ≥ Grade 3 nausea, vomiting or diarrhea not responding to supportive measures within 48 hours, interrupt fedratinib dose until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose (EMA 2021a). We kindly refer to the SPC for the full recommendations about fedratinib dosing (EMA 2021a).

Concomitant antiemetic and antidiarrheal in JAKARTA and severity of GI AEs

In JAKARTA, no specific instructions for prophylactic antiemetic or symptomatic antidiarrheal treatment were given in the protocol. Concomitant medications were defined as any treatments received by the subject concomitantly to study treatment, from first study treatment intake to the last study treatment + 30 days. In the 400 mg fedratinib arm, [redacted]

Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
For the fedratinib 400 mg arm, only subjects initially randomized to this arm are included. For placebo subjects only data before crossover are included. AE, adverse event; GI, gastrointestinal. (BMS, Data on file).

Question 2. a)

The Expert Committee requests additional data to inform the possible cases of Wernicke's encephalopathy. Data from individual patients and how it could be excluded that fedratinib is associated with an increased risk of WE (or similar CNS disease).

Cases of encephalopathy, including Wernicke's

From the 608 fedratinib-exposed patients, 8 subjects (1.3%) with neurological signs or symptoms suggesting the diagnosis of potential Wernicke´s encephalopathy (WE) or other encephalopathy were identified (EMA 2020; Harrison et al. 2017). Of these patients, 6 had MF, 1 had polycythemia vera and 1 had metastatic head and neck cancer. Four of the subjects were from the Phase 3 pivotal study in MF (JAKARTA, EFC12153), and the other 4 subjects were enrolled in other fedratinib studies (Studies ARD11936, ARD12042, ARD12181 [JAKARTA2], and TES13519). An independent panel of experts evaluated demographics, full case report, clinical characteristics (including thiamine levels when available) and MRI scans (Figure *3*).

[redacted]

Median age was 69.1 years (IQR 67-71) and 7 out of the 8 subjects were female (Harrison et al. 2017). The time on fedratinib until symptoms was between two and thirteen 28-day cycles (EMA 2020). Seven out of the 8 subjects were taking fedratinib at 500 mg prior to the onset of the neurologic findings (doses were escalated in certain studies) (EMA 2020).

Of the 8 potential cases, only 1 case of WE was confirmed. One patient was determined to have experienced hepatic encephalopathy but not Wernicke's. Of the remaining six patients, there was no consensus reached between experts (EMA 2020). Additional information about the 8 potential cases of WE are provided in Table *4.* Pardanani et al. have published additional details for the 4 potential cases of WE identified in the JAKARTA study, which are found in eTable 6 of the JAMA Oncology 2015 publication (Pardanani et al. 2015).

Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment and dizziness except for 1 subject with head and neck cancer, brain metastasis, difficulty eating, and weight loss who had a fatal outcome (EMA 2020).

Based on the extensive review of the data in these 8 subjects, at most, 7 cases of encephalopathy (1.2%), including Wernicke's, occurred in > 600 subjects treated with fedratinib in MPN or solid tumor studies. The prevalence of WE in the general population is 0.4% to 2.8% based on typical brain lesions found on autopsy studies (Galvin et al. 2010). Further analysis of the data surrounding these events suggest that, while WE did occur in subjects treated with fedratinib, the subjects had predisposing factors that are known to lead to WE in any population. These potential cases had pre-existing malnutrition, weight loss, significant GI AEs that were not adequately controlled, or other risk factors that may have contributed to thiamine deficiency (Harrison et al. 2017). Except for one patient, the potential cases of WE were amongst others treated with thiamine supplementation (EMA 2020). Two patients recovered while continuing to take fedratinib and oral thiamine supplements, along with better control of their nausea and vomiting (Harrison et al. 2017).

FREEDOM trial and long-term safety cohort of fedratinib in patients with MF

Early termination of the trials investigating fedratinib has impacted data collection in regard to the long-term safety profile, including risk of neurological events. The longest follow-up for patients treated with fedratinib is from a phase I/II extension study (TED12015; NCT00724334) that followed and extended a 6-cycle dose-finding TED12037 (NCT00631462) study in patients with intermediate- or high-risk MF (Inrebic 2019; EMA 2020). Pardanani et al. reported long-term safety and tolerability of fedratinib in patients who received ≥24 fedratinib treatment cycles in TED12037 and TED12015 at 2 international congresses (Pardanani et al. 2020a). Fedratinib Long-term (LT) cohort comprised 28 patients (47% of all 59 enrolled patients) who received ≥24 cycles of fedratinib. Median treatment duration in the LT cohort was 46 cycles (range 25–72) and the median fedratinib dose overall was 462 mg/day (range 283–800). No suspected cases of WE were reported. Although 1 patient experienced a late grade 3/4 neurologic treatment-emergent AE in the phase 1/2 TED12015 extension study (a Grade 3 post-herpetic neuralgia at cycle 36), the event was not considered treatment-related and did not require fedratinib dose reduction or treatment interruption. (Pardanani et al. 2020a; Pardanani et al. 2020b).

In the FREEDOM trial, in which proactive mitigation strategies for thiamine level decreases and potential encephalopathy, including WE, were implemented, no cases of WE have been reported (data cutoff April 2021) (Gupta et al. 2021).

Question 2. b)

b) In this context, the Expert Committee would like any evidence that routine measurements of thiamin levels can prevent WE events (have similar event been observed in FREEDOM?), as well as an explanation of the frequency of monitoring, intervention limits and number of patients who received intervention (thiamin substitution or other) or were subjected to additional examinations in connection with thiamin measurements.

Wernicke's encephalopathy is a preventable and treatable condition if recognized early and if thiamine-replacement therapy is initiated in a timely manner (Galvin et al. 2010).

In directed pharmacology studies in preclinical species, fedratinib did not inhibit thiamine transporters at clinically relevant concentrations (Harrison et al. 2017), and there was no demonstration of Wernicke's encephalopathy-like symptoms or central nervous system pathology upon administration of fedratinib (Hazell et al. 2017).

Thiamine levels were not routinely collected in previous fedratinib studies. Of the 8 suspected cases of WE, 1 patient had thiamine level tested at the time of symptomatology and the patient's thiamine levels were within normal range (Harrison et al. 2017). Wernicke's encephalopathy can be caused by thiamine deficiency secondary to persistent vomiting, especially in an already malnourished individual (Ogershok et al. 2002; Curto-Garcia et al. 2017).

.

Thiamine levels, results from the FREEDOM trial

Analysis of thiamine levels are measured at screening, on Day 1 of the first 3 cycles, every third cycle and at the EOT during the study (BMS 2021).

At baseline, out of the 34 patients enrolled, 1 patient had a thiamine level below the lower limit of normal (LLN) of 70 nmol/L. The thiamine level was corrected before the patient received fedratinib. During fedratinib treatment, the thiamine levels dropped below the LLN for 4 patients between cycles 2–3 and for 1 patient at end of treatment. The levels returned to normal for these patients with oral thiamine supplementation and did not require fedratinib interruption or dose reduction (Figure 4). Five other patients received thiamine supplementation before (n = 2) or during (n = 3) fedratinib treatment. Thiamine supplementation was prophylactic for 4 patients and empirical for a non-treatment-related AE in 1 patient. As reported above, there were no reported cases of WE (Gupta et al. 2021).

[redacted]

Figure 4. Thiamine levels over time reported in the FREEDOM trial (April 2020)
Individual lines represent thiamine levels over time for patients who experienced thiamine < LLN on-study. Box plots represent the overall median (Q1, Q3) thiamine level at cycles 1, 2, 3, 6, 9, 12, 15, 18, and 21. C, cycle; LLN, lower limit of normal; ULN, upper limit of normal (Gupta et al. 2021).

Management of thiamine levels and Wernicke's encephalopathy in Fredatinib SPC

In the Fedratinib SPC, the following recommendations are provided (Table 5) (EMA 2021a). Thiamine levels and nutritional status in patients should be assessed before starting treatment with fedratinib, periodically during treatment (e.g. monthly for the first 3 months and every 3 months thereafter) and as clinically indicated. Fedratinib treatment should not be started in patients with thiamine deficiency. Before treatment initiation and during treatment, thiamine levels should be replenished if they are low. If encephalopathy is suspected, fedratinib treatment should be discontinued immediately and parenteral thiamine treatment should be initiated while evaluating for all possible causes. Patients should be monitored until symptoms have resolved or improved and thiamine levels have normalized (EMA 2021a).

Table 5. Management of thiamine levels and Wernicke's encephalopathy

Management of thiamine levels and Wernicke's encephalopathy (WE)	Dose reduction
For thiamine levels < normal range (74 to 222 nmol/L)* but ≥ 30 nmol/L without signs or symptoms of WE	Interrupt fedratinib treatment. Dose with daily 100 mg oral thiamine until thiamine levels are restored to normal range*. Consider re-starting fedratinib treatment when thiamine levels are within normal range*.
For thiamine levels < 30 nmol/L without signs or symptoms of WE	Interrupt fedratinib treatment. Initiate treatment with parenteral thiamine at therapeutic dosages until thiamine levels are restored to normal range*. Consider re-starting fedratinib treatment when thiamine levels are within normal range*.

For signs or symptoms of WE regardless of thiamine levels	Discontinue fedratinib treatment and immediately administer parenteral thiamine at therapeutic dosages.

*the normal thiamine range may differ depending on the methods used by the laboratory (EMA 2021a)

Wernicke's encephalopathy can be caused by thiamine deficiency secondary to e.g. persistent vomiting, especially in an already malnourished individual. GI AEs occurred mostly during the first cycle of treatment with fedratinib. Thus, more frequent thiamine level measurement is recommended at the beginning of fedratinib treatment.

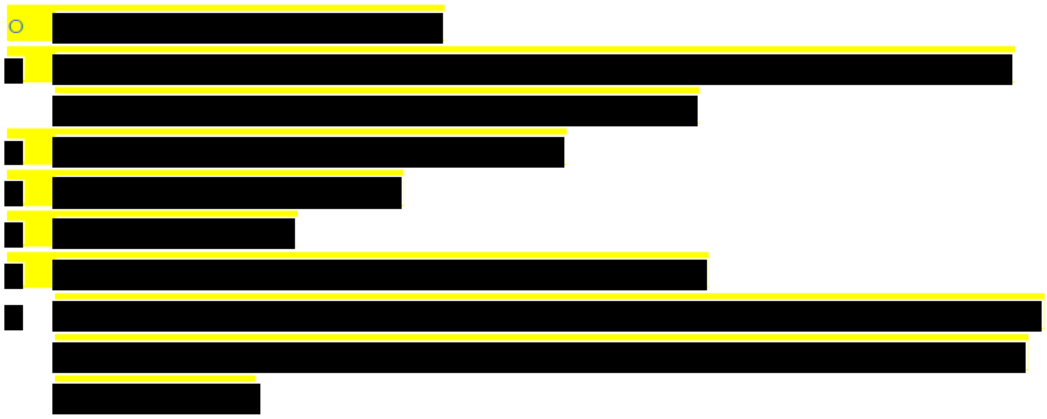
Thiamine Supplementation, Monitoring, and Correction in FREEDOM

The below guidance for the management of thiamine levels and encephalopathy, including Wernicke's is provided in the protocol of the FREEDOM trial. Occurrence of encephalopathy including Wernicke's will be confirmed by brain MRI or autopsy. Analysis of thiamine levels will be at screening, on Day 1 of the first 3 cycles, every third cycle and at the EOT during the study (BMS 2021).

[redacted]

Management of Encephalopathy, including Wernicke's [redacted]

[redacted]



Question 3.

The applicant is requested to go deeper in the argumentation for considering the safety profile of fedratinib comparable to ruxolitinib. The concerns mentioned above do not apply to ruxolitinib. Thus, is there anything else in the AE profiles that counters the lower GI AE reported for ruxolitinib, which would lead to the conclusion of a comparable safety profile?

Safety profile of fedratinib and ruxolitinib

The statement of comparable safety profile of fedratinib and ruxolitinib in the application is not made based on a descriptive comparison of the type and frequency of specific AEs but is based on the overall frequency of any Grade 3/4 events. Grade 3/4 AEs are severe AEs that very often require hospital visit to be managed (including hospitalization), and therefore are expected to be associated with higher health care resources utilization and have a higher budget impact than Grade 1/2 AEs. In addition, descriptive comparison of the type and frequency of specific AEs was found challenging due to the selected number of AEs reported in the relevant trials. Importantly, cross-trial comparison must be made with caution.

In JAKARTA, Grade 3/4 AEs were reported in 52.1% of patients in the 400 mg fedratinib arm at week 24 versus 47.1% in the ruxolitinib arm in the COMFORT-I study (Table 6). At week 48, the frequency of Grade 3/4 AEs was 41.8% in the ruxolitinib arm the COMFORT-II study.

A Serious Adverse Events (SAE) is any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (EMA 1995). Therefore, SAEs are also relevant to consider when assessing safety profile and hospitalization related to management of AEs. In the JAKARTA study, the frequency of SAE at week 24 in the fedratinib arm was lower (20.8%) compared to the ruxolitinib arm in the COMFORT-I study (27.7%).

Another parameter to consider when assessing safety profile is the rate of discontinuation due to AEs. At week 24, the rate of discontinuation was comparable between the 400 mg fedratinib arm in JAKARATA (13.5%) and the ruxolitinib arm in COMFORT-I (11.0%).

Table 6. Adverse events reported during JAK-inhibitors treatment in randomized clinical trials investigating fedratinib and ruxolitinib in JAK-inhibitor-naïve MF patients

	JAKARTA: 24 weeks		COMFORT-I: 24 weeks		COMFORT-II: 48 weeks	
Adverse event, %	PBO (n = 95)	400 mg FEDR (n = 96)	PBO (n = 151)	RUX (n = 155)	BAT (n = 73)	RUX (n = 146)
Deaths due to AEs	6.3	1.0	7.3	5.8	5.5	4.1
SAEs	23.2	20.8	35.1	27.7	28.8	30.1
Grade 3 or 4 AEs	30.5	52.1	44.4	47.1	24.7	41.8
Discontinuation due to AEs	8.4	13.5	10.6	11.0	5.5	8.2
Any AEs	93.7	99.0	98.0	97.4	90.4	99.3
Haematological AEs						
Anaemia (grade 3 or 4)	24.2[a]	41.7[a]	19.2[a]	45.2[a]	31	42
Thrombocytopenia (grade 3 or 4)	9.5[a]	11.4[a]	1.3[a]	12.9[a]	7	8
Nonhaematological AEs						
Bruising (any grade)	NR	NR	9.3	18.7	NR	NR
Bruising (grade 3 or 4)	NR	NR	0	0	NR	NR
Dizziness (any grade)	3.2	8.3	6.6	14.8	NR	NR
Dizziness (grade 3 or 4)	0	0	0	0.6	NR	NR
Headache (any grade)	1.1	9.4	5.3	14.8	4	10
Headache (grade 3 or 4)	0	0	0	0	0	1
Diarrhoea (any grade)	15.8	65.6	21.2	23.2	12	23
Diarrhoea (grade 3 or 4)	0	5.2	0	1.9	0	1
Nausea (any grade)	14.7	61.5	19.2	14.8	7	13
Nausea (grade 3 or 4)	0	0	0.7	0	0	1
Vomiting (any grade)	5.3	38.5	9.9	12.3	NR	NR
Vomiting (grade 3 or 4)	0	3.1	0.7	0.6	NR	NR
Bleeding events						
≥ Grade 3 bleeding events	0	2.1	2.0[b]	2.6[b]	NR[b]	NR[b]
Infections						
Urinary tract infection (any grade)	1.1	6.3	5.3	9.0	NR	NR
Herpes zoster (any grade)	1.1	1.0	0.7	1.9	NR	NR

AE = adverse event; BAT = best available therapy; FEDR = fedratinib; NR = not reported; PBO = placebo; RUX = ruxolitinib; SAE = serious adverse event.

[a] Derived based on laboratory values.

While nausea, vomiting and diarrhea were amongst the most frequent all Grade any cause AEs reported during fedratinib treatment, the majority of these AEs were of Grade 1 (ranging from 3[redacted]) and Grade 2 (ranging from[redacted] in JAKARTA (Table 3). The frequency of Grade 3 vomiting was 3.1% and Grade 3 diarrhea was 5.2%, while no Grade 3 nausea were observed (Pardanani et al. 2021).[redacted]

[redacted] Further, GI AEs are not uncommon in clinical trials enrolling MF patients. In the COMFORT study, 23.2% diarrhea, 14.8% nausea, 12.9% constipation and 12.3% vomiting (all Grades) have been reported in the ruxolitinib arm and their frequency were relatively comparable to the placebo arm (Verstovsek et al. 2012). Some Grade 3/4 GI AEs were reported; 1.9% vs 0% diarrhea, 0% vs 0.7% nausea, and 0.6% vs 0.7% vomiting in the ruxolitinib- and placebo-arm, respectively (Verstovsek et al. 2012).

Ruxolitinib has been the standard first-line treatment in Denmark since April 2014 for patients with MF and highly symptomatic splenomegaly and/or constitutional symptoms and in patients with post-ET or post-PV MF and no other therapies have been approved for this patient group since. Thus, clinical experience in regard to management of AEs arising during ruxolitinib therapy has been accumulated during the last 8 years in contrast to fedatinib. Occurance of infections and herpes zoster have been described by Danish hemaotlogists during treatement with ruxolitinib, which are included in Section 4.4 Special warnings and precautions in ruxolitinib SPC but not included in fedratinib SPC (EMA 2021b, 2021a).

The JAKARTA trials showed that fedratinib was generally safe and well tolerated, and provided meaningful reductions in splenomegaly and symptoms in patients with MF, which led to the approval by the European Commission on 8 February 2021. Based on the available data, fedratinib is an effective oral selective JAK2 inhibitor with a manageable safety profile that will provide clinicians with an additional treatment option for patients with MF and disease-related splenomegaly or symptoms.

Overall, the safety analysis suggested a similar frequency for Grade 3/4 AEs, SAEs, and discontinuation rate for fedratinib and ruxolitinib. Descriptive comparison of the frequency of specific AEs was challenging due to availability of safety data. In addition, because most efficacy outcomes in the ITC were numerically in favour of fedratinib, cost-minimisation may be considered to be an appropriate modelling approach.

Network meta-analysis of the efficacy and tolerability of JAK inhibitors in MF

Sureau et al. have recently published the results of a systematic review and network meta-analysis of the efficacy and tolerability of JAK inhibitors in MF (Sureau et al. 2021). Seven studies were included in the network meta-analysis including 1953 patients randomly assigned to 4 JAK inhibitors, ruxolitinib, fedratinib, pacritinib, momelotinib, or control. The studies included for ruxolitinib and fedratinib are similar to the application, i.e. COMFORT-I, COMFORT-II and JAKARTA. The primary endpoint was a spleen volume reduction (SVR) higher than 35% after 24 weeks of treatment. Secondary endpoints included the total symptom score reduction (TSSR) evaluated using the Myelofibrosis Symptom Assessment Form (MF SAF) 2.0, and two main AEs due to Grade 3/4 anemia and grade 3/4 thrombocytopenia over the 24 weeks of treatment. Grade 3 anemia was defined as a hemoglobin rate < 8 g/dL and a platelets count < 50.10^9/L.
The analysis on grade 3/4 anemia and thrombocytopenia AEs during JAK inhibitor therapy was conducted with data from the 7 studies and a total of 1953 patients, with a moderate heterogeneity across trials (I^2=54% [0.0%; 86.8%]) and (I^2 = 32.8% [0.0%; 93.0%]), respectively. Bayesian network meta-

analysis showed significantly less grade 3/4 anemia with momelotinib than with ruxolitinib, fedratinib, or pacritinib. The analysis did not show any statistically significant difference between ruxolitinib and fedratinib, and pacritinib (OR [Crl 95%] for fedratinib versus ruxolitinib, 0.85 [0.51-1.47]). For thrombocytopenia, Bayesian network meta-analysis demonstrated fewer occurrence of grade 3/4 events with fedratinib compared to ruxolitinib, momelotinib, and pacritinib (OR [Crl 95%] for fedratinib versus ruxolitinib, 0.21 [0.03-0.92]). The results of the analyses using the frequentist method were consistent with those obtained with the Bayesian method. As expected, the review of the nonhematological toxicity profile suggested differences between the four JAK inhibitors with more gastrointestinal events for fedratinib and pacritinb and occurrence of potential cases of WE and relation to thiamine level were described.

The authors acknowledged the main bias of this systematic review and meta-analysis, being the low number of trials included mainly due to the small number of comparative studies conducted in myelofibrosis but highlighted that all outcomes included in these analyses were objectively assessed in the original trials. In regard to fedratinib, the results of the meta-analysis suggested that this selective JAK2 inhibitor was less toxic on platelets than ruxolitinib, while no statistically significant difference were found for anemia. Further, the results of the efficacy analysis on splenomegaly and disease-related symptoms were not significantly different for fedratinib and ruxolitinib. Based on those results, the authors concluded that fedratinib is a valuable alternative to ruxolitinib in first line therapy in ruxolitinib-naïve patients (Sureau et al. 2021).

Question 4.

With the above comments in mind, the Danish Medicines Council request that the cost minimization model allow to handle different adverse reaction profiles for the two medicines, i.e. differentiated costs for each treatment should be attributable depending on the respective adverse reaction rates and the related standard costs.

The model has been updated to handle your request and you can differentiate the cost between the different AE for your report.

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