Medicinrådet

Bilag til Medicinrådets anbefaling vedr. momelotinib til behandling af splenomegali eller konstitutionelle symptomer relateret til myelofibrose ved samtidig anæmi

Vers. 1.0

Bilagsoversigt

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

Den 21. marts 2024

Kære Hans Christian

Tak for udkast til vurdering af værdien af momelotinib til behandling af splenomegali eller konstitutionelle symptomer relateret til myelofibrose ved samtidig anæmi.

GSK anerkender i vid udstrækning den kliniske vurdering af momelotinib, der identificerer momelotinibs potentiale som en behandlingsmulighed til en andel af myelofibrosepatienter, der har anæmi. Anæmi er hyppigt forekommende hos patienter med myelofibrose og associeret med dårlig overlevelse. Tilgængelige JAK-hæmmere påvirker ikke anæmi i positiv retning og kan modsat forværre den, hvilket ofte nødvendiggør dosisreduktion eller behandlingsophør. Den kliniske fordel med momelotinib hos anæmiske patienter med myelofibrose afstedkommer mindsket transfusionsbehov og understreger herved behovet for momelotinib for visse myelofibrose patienter.

GSK undrer sig derfor over, at det i vurderingsrapporten er blevet besluttet at indsnævre patientpopulation til udelukkende at omhandle JAK-erfarne patienter. NICE i England har modsat konkluderet, at momelotinib sandsynligvis virker lige så godt som ruxolitinib hos patienter, der ikke tidligere er behandlet med en JAK-hæmmer[1], og samme vurdering blev konkluderet i Norge[2].

I den endelige vurdering af momelotinib, mener GSK, det er vigtigt at have nedenstående for øje:
Tidligt behandlingsophør i momelotinib-armen grundet low-grade hændelser i SIMPLIFY-1:
Der var 15% af de momelotinib-behandlede patienter og 6% af de ruxolitinib-behandlede patienter der tidligt ophørte behandlingen uden en vurdering af TSS ved uge 24 og derfor blev betragtet som nonrespondere. Den protokoldefinerede ruxolitinib startdosis og dosismodifikationsskema bidrog potentielt til den lavere rate af tidlige ruxolitinib behandlingsophør ved at øge andelen af ruxolitinib-behandlede patienter med dosisreduktion eller dosisafbrydelse.Denne andel var mere end dobbelt så stor som andelen for momelotinib.
Inkluderede patienter i SIMPLIFY-1:
Studiet var ikke stratificeret efter TSS ved baseline og patienter med en lav symptombyrde ved baseline (f.eks. TSS <10) blev også inkluderet. Dette kan have påvirket studiet negativt, da TSS-responsraten ved uge 24 var højere hos symptomatiske patienter.

I SIMPLIFY-1 studiet, hvor patienterne var JAK-naive, var momelotinib non-inferior til ruxolitinib i forhold til at mindske miltstørrelsen med 35% efter 24 ugers behandling. Patienter, der fik momelotinib, var i højere grad transfusionsuafhængige, havde bedre hæmoglobinkoncentration og ca. halvt så mange havde transfusionsbehov sammenlignet med dem, der fik ruxolitinib. Det kan formentlig tilskrives den hæmning momelotinib har på ACVR1 receptoren.
GSK håber, at Medicinrådet vil medtage ovenstående med hensyn til den JAK-naive population i deres endelige vurdering af momelotinib.

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[1] 1 (nice.org.uk)
[2] Mom4elotinib (Omjjara) - Nye metoder

Afslutningsvis vil GSK gerne takke for muligheden for at afprøve den nye proces for ansøgning. Det har været en fornøjelse af opleve en smidig arbejdsgang og samtidig med en præcis kommunikation om forventninger og tidslinje for processen.

På vegne af GSK

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08.04.2024
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Forhandlingsnotat

Dato for behandling i Medicinrådet	24.04.2024
Leverandør	GSK
Lægemiddel	Omjjara (momelotinib)
Ansøgt indikation	Momelotinib til behandling af splenomegali eller konstitutionelle symptomer relateret til myelofibrose ved samtidig anæmi.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Omjjara (momelotinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Omjjara	100 mg	30 stk.	39.094	[redacted]	[redacted]
Omjjara	150 mg	30 stk.	39.094	[redacted]	[redacted]
Omjjara	200 mg	30 stk.	39.094	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted]

Konkurrencesituationen

Medicinrådet har tidligere anbefalet Inrebic (fedratinib) til behandling af JAK-naive patienter med myelofibrose. Derudover har Jakavi (ruxolitinib) indikation til behandling af JAK-erfarne patienter.

Tabel 2 viser lægemiddeludgifter pr. patient i relation til Jakavi og Inrebic.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Omjjara (momelotinib)	200 mg	30 stk.	200 mg dagligt	[redacted]	[redacted]
Jakavi (ruxolitinib)	15 mg	56 stk.	15 mg 2 gange dagligt	[redacted]	[redacted]
Inrebic (fedratinib)	100 mg	120 stk.	400 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of momelotinib for treatment of disease-related splenomegaly or symptoms, and anaemia in adult patients with myelofibrosis

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Abbreviations

AE	Adverse event
ASCT	Allogeneic stem cell transplant
BAT	Best available therapy
BIA	Budget impact analysis
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CT	Computed tomography
DIPSS	Dynamic International Prognostic Scoring System
DMC	Danish Medicines Council
DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
EPO	Erythropoietin
ESA	Erythropoietin stimulating agent
ET	Essential thrombocythemia
FDA	Food and drug administration
GP	General practitioner
Hb	Haemoglobin
HR	Hazard ratio
ICC	International Consensus Classification
IPD	Individual patient-level data
IPSS	International Prognostic Scoring System
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
JAKi	JAK inhibitor
MF	Myelofibrosis
MPN	Myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MRI	Magnetic resonance imaging
NMPN	Nordic study group for myeloproliferative neoplasms
NRS	Numeric Rating Scale
ORR	Objective response rate
OS	Overall survival
PGIC	Patient Global Impression of Change
PMF	Primary myelofibrosis
PPP	Pharmacy purchasing price
PV	Polycythaemia vera
RBC	Red blood cells
SAE	Severe adverse event
SLR	Systematic literature review
SPC	Summary of product characteristics

SRR	Splenic response rate
TEAT	Treatment-emergent adverse event
TI	Transfusion independent
TSS	Total symptom score

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Omjjara®
Generic name	Momelotinib
Therapeutic indication as defined by EMA	The indication for momelotinib is treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib (1).
Marketing authorization holder in Denmark	GSK A/S Delta Park 37, 2665 Vallensbæk Strand, Denmark
ATC code	Not yet assigned
Combination therapy and/or co-medication	None required
(Expected) Date of EC approval	January/February 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, granted orphan designation from the European Medicines Agency (EMA) in 2011
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the DMC (yes/no)	None
Dispensing group	BEGR/NBS

Overview of the pharmaceutical	
Packaging – types, sizes/number of units and concentrations	Momelotinib will be available in packages with 100 mg, 150 mg and 200 mg film-coated tablets with 30 film-coated tablets per package

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	The indication for momelotinib is treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are JAK inhibitor naïve or have been treated with ruxolitinib (1).
Dosage regimen and administration	The recommended dose is 200 mg administered as 200 mg tablets taken once daily. Tablets should be swallowed whole, preferably with water, and may be taken with or without food. Treatment should continue until the patient no longer derives benefit or until unacceptable toxicity develops.
Choice of comparator	Ruxolitinib and fedratinib. Momelotinib will introduce a new alternative to currently approved JAK-inhibitors for anaemic patients with symptomatic splenomegaly or constitutional symptoms.
Prognosis with current treatment (comparator)	Currently approved JAK-inhibitors have shown clinical benefit in myelofibrosis (MF); however, one of the most frequently reported serious adverse events (SAEs) is anaemia. Ruxolitinib frequently worsens anaemia and thrombocytopenia, which often leads to dose reductions and treatment interruptions, potentially limiting treatment efficacy. Fedratinib frequently causes gastrointestinal toxicities and can worsen anaemia and thrombocytopenia; it has also been associated with the risk of Wernicke encephalopathy (2). Safe and effective treatment is needed for patients with MF who are anaemic or no longer candidates for receiving currently approved JAK inhibitors.
Type of evidence for the clinical evaluation	Efficacy and safety comparison with ruxolitinib: head-to-head study. Safety comparison with fedratinib: indirect comparison.
Most important efficacy endpoints (difference/ga in compared	**SIMPLIFY-1** Splenic response rate (SRR) at week 24: The non-inferiority proportion difference in response between momelotinib and ruxolitinib was 0.09 (95% CI: 0.02, 0.16 and p=0.011).

Summary	
to comparator)	Total symptom score (TSS) at week 24: The non-inferiority proportion difference was 0.09 (95% CI: -0.08, 0.98 and p=0.98) between momelotinib and ruxolitinib. Overall survival (OS) at week 24: The absolute difference in OS rates [redacted] **SIMPLIFY-2** SRR at week 24: The proportion difference was 0.01 (95% CI: -0.09, 0.10, p=0.90) between momelotinib and best available therapy (BAT). TSS at week 24: The proportion difference [redacted] between momelotinib and BAT. OS at week 24: The absolute difference in OS rates was [redacted] **MOMENTUM** TSS at week 24: The stratified difference was 16% (95% CI: 6, 26, p=0.0095) demonstrating superiority of momelotinib for the primary endpoint. SRR at week 24: The stratified difference was 19% (95% CI: 11, 28, p=0.0006) demonstrating superiority of momelotinib. OS: The absolute difference in OS rates was [redacted], and the HR was 0.73 (95% CI: 0.38, 1.41) and the log-rank test p=0.35.
Most important serious adverse events for the intervention and comparator	**SIMPLIFY-1** In the double-blind phase (24 weeks), 49 subjects (22.9%) in the momelotinib group and 39 subjects (18.1%) in the ruxolitinib group experienced an SAE. The five most frequently reported SAEs by treatment group were pneumonia, atrial fibrillation, anaemia, diarrhoea (1.9% each, 4 subjects) for momelotinib. In the ruxolitinib group, the most frequently reported SAEs were anaemia (3.7%, 8 subjects), pneumonia, pyrexia, and thrombocytopenia (1.4% each, 3 subjects) in the ruxolitinib group. **SIMPLIFY-2** In the randomised-treatment phase (24 weeks), SAEs were reported for 36 (35%) and 12 (23%) subjects in the momelotinib group and best available therapy (BAT) group, respectively. The most reported SAEs (in ≥2 subjects) by treatment group were anaemia (4 subjects, 3.8%); cardiac failure (3 subjects, 2.9%); and acute kidney injury, cellulitis, gastrointestinal haemorrhage, general physical health deterioration, pneumonia, presyncope, pyrexia, respiratory failure, sepsis, supraventricular tachycardia, and upper gastrointestinal haemorrhage (2 subjects each, 1.9%) in the momelotinib group. In the BAT group it was general physical health deterioration, sepsis, and abdominal pain (2 subjects each, 3.8%). SAEs considered related to the study drug by the investigator were reported for 12 (11.5%) momelotinib-treated subjects and 2 (3.8%) BAT-treated subjects. Anaemia was the only preferred term reported as a related SAE in more than 1 subject (2 subjects, 1.9%). **MOMENTUM** During randomised treatment (24 weeks), one or more SAEs for each subject were reported as follows: Any SAE was reported for 45 subjects (34.6%) in the momelotinib group and 26 subjects (40.0%) in the danazol group. The

Summary	
	infections and infestations system organ class had the greatest proportion of subjects with SAEs (20 subjects [15.4%] in the momelotinib group and 11 subjects [16.9%] in the danazol group), followed by blood and lymphatic system disorders (9 subjects [6.9%] in the momelotinib group and 6 subjects [9.2%] in the danazol group). The most reported grade ≥3 SAEs were anaemia (5 subjects, 3.8%) and acute kidney injury (4, 3.1%) in the momelotinib group and pneumonia (6, 9.2%), anaemia (3, 4.6%), and acute kidney injury (3, 4.6%) in the danazol group. The SAEs considered treatment related were thrombocytopenia in 2 subjects (1.5%) and anaemia, atrial fibrillation, and cellulitis in 1 subject each (0.8%) in the momelotinib group, and pneumonia in 2 subjects (3.1%) and acute kidney injury in 1 subject (1.5%) in the danazol group.
Impact on health-related quality of life	Clinical documentation: Not included Health economic model: Not included
Type of economic analysis that is submitted	The analysis is a cost-minimisation analysis based on the clinical claim of at least non-inferior efficacy and safety versus ruxolitinib and on the results of the indirect treatment comparison (ITC) versus fedratinib. The model is a cost-minimisation model.
Data sources used to model the clinical effects	Not applicable (cost-minimisation model)
Data sources used to model the health-related quality of life	Not applicable (cost-minimisation model)
Life years gained	Not applicable (cost-minimisation model)
QALYs gained	Not applicable (cost-minimisation model)
Incremental costs	Vs ruxolitinib: DKK 164,042 Vs fedratinib: DKK 55,995
ICER (DKK/QALY)	Not applicable (cost-minimisation model)
Uncertainty associated with the ICER estimate	Not applicable (cost-minimisation model)

Summary	
Number of eligible patients in Denmark	Incidence of intermediate-2 and high risk: 40 new patients per year. Patients with anaemia at the time of diagnosis: 16 patients. Currently, 160 patients are treated with JAKi treatment.
Budget impact (in year 5)	DKK 6,081,051

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Myelofibrosis

MF is a rare and life-threatening myeloproliferative neoplasm (MPN) characterised by bone marrow fibrosis and chronic inflammation leading to key manifestations of the disease: severe anaemia, enlarged spleen (splenomegaly), and often debilitating constitutional symptoms (3,4). Clinically, these symptoms present as unintended weight loss, night sweats, perhaps slight fever, abdominal discomfort due to growing spleen and liver. Fatigue and loss of physical functions are symptoms that become increasingly manifested as anaemia worsen (3,4).

3.1.2 Anaemia in myelofibrosis

Anaemia is among the cardinal features of MF (5). Around 40% of MF patients have haemoglobin (Hb) levels <10 g/dL (6.21 mmol/L) at diagnosis, and nearly all become anaemic over time whereas many will require red blood cell (RBC) transfusions (5,6). Anaemia and transfusion dependency are consistently associated with poor quality of life and inferior survival prognosis (5,7). Anaemia is a result of a multifactorial process. The bone marrow fibrosis displaces erythropoietic tissue by fibrotic stroma, which for long has been considered one of the main reasons for anaemia (5). However, there are several contributing factors. Because of the fibrosis, the erythropoietic tissue migrates to the spleen where they have suboptimal conditions for erythrogenesis and RBC maturation leading to ineffective erythropoiesis (5). The splenomegaly induced by this migration triggers sequestration and destruction of circulating RBC, which worsen the anaemia. The plasma volume increases with spleen size, which can lead to a component of dilutional anaemia (5). Furthermore, the bone marrow niche in MF is characterised

by abnormal cytokine expression, which enhances both local and systemic inflammation. This results in an inflammatory environment in the rest of the functioning bone marrow disrupting erythrogenesis. In addition, the inflammatory cytokines in the bone marrow of MF patients have been associated with upregulation of circulating hepcidin that interferes with the iron metabolism, which has an effect on the anaemia (5,8). The current JAK inhibitor (JAKi) treatment of MF with either ruxolitinib or fedratinib has also shown to exacerbate anaemia, because it causes therapy-related anaemia via the suppression of residual bone marrow function (3,5).

The pathophysiology of anaemia in MF is presented in Figure 1.

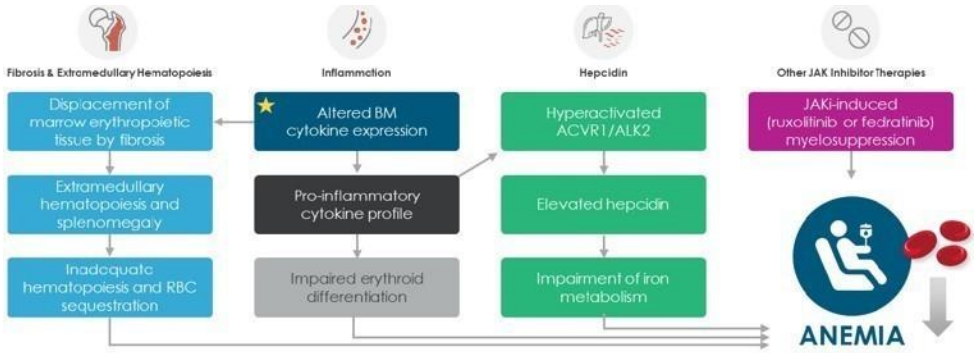


Figure 1 Pathophysiology of anaemia in MF. Source: Neymagon and Mascarenhas 2017 (5).

Figure note: abbreviations: ACRV1 = activin A receptor type 1; ALK2 = activin receptor-like kinase-2; BM = bone marrow; JAK = Janus kinase; JAKi = janus kinase inhibitor; MF = myelofibrosis.

3.1.3 Diagnosis and prognostic tools

Different scoring systems can be used to evaluate the prognosis of patients diagnosed with MF and to guide treatment decisions. The 3 most common prognostic systems are based on clinical and hematologic parameters that categorise patients into 1 of 4 risk groups (low, intermediate-1, intermediate-2, and high risk). Median survival rates decrease as the risk increases. The prognostics systems are the International Prognostic Scoring System (IPSS) recommended for use at diagnosis (9), the Dynamic International Prognostic Scoring System (DIPSS) (10) and DIPSS-plus, both recommended for use during follow-up (11). The prognostic scoring systems including scoring and median survival for each risk group are presented in Figure 2 below.

Scoring System	To be used	Prognostic factors	Risk score	Risk score and median survival (months)			
				Low	Intermediate-1	Intermediate-2	High
IPSS	At diagnosis	Age >65 years Constitutional symptoms Anemia (Hb <10g/dl) Leukocyte count >25 x 10^9/L Circulating blasts ≥1%	1 1 1 1 1	0 points 135 months	1 point 95 months	2 points 48 months	≥3 points 27 months
DIPSS	During follow-up	Age >65 years Constitutional symptoms Anemia (Hb <10g/dl) Leukocyte count >25 x 10^9/L Circulating blasts ≥1%	1 1 2 1 1	0 points Not reached	1-2 points 170 months	3-4 points 48 months	5-6 points 18 months
DIPSS-Plus*	During follow-up	DIPSS low risk DIPSS intermediate-1 DIPSS intermediate-2 DIPSS high risk Unfavorable karyotype^ Platelet count <100 x 10^9/L RBC Transfusion need	0 1 1 1 1 1 1	0 points 185 months	1 point 78 months	2-3 points 35 months	≥4 points 16 months
*First calculate the DIPSS score, and then add the score for transfusion dependency, cytogenetics, and thrombocytopenia to calculate the final DIPSS-plus score ^Prognostic unfavorable 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)							

Figure 2 Prognostic scoring systems IPSS, DIPSS and DIPSS-plus. Source: Nordic MPN study group 2017 (4).

3.2 Patient population

3.2.1 Epidemiology of MF in Denmark and patient population relevant for this application

Because of its low incidence and poor prognosis, there is limited epidemiological data on MF (12). In Europe, MF affects 0.4 per 100,000 people, and most of the people affected by the disease are older people; however, MF can occur at any age (range in DK 2021: 47-92) (13). MF is associated with a shortened survival. Complications of MF are common and contribute to both morbidity and mortality. Causes of mortality include leukemic progression (occurs for 10-30% of MF patients) and comorbid conditions e.g., cardiovascular events (20-50%) and consequences of cytopenia, e.g. infections (20-60%) or bleeding (30%) (3,4). The five-year survival in DK for PMF is estimated to be approximately 55% (13).

According to the Danish Medicines Council (DMC), around 60 patients are annually diagnosed with MF and of these, 40-45 patients are in the intermediate-2 or high-risk groups where treatment with JAK-inhibitors are considered (14). Around 160 patients are currently treated with a JAK inhibitor and with a yearly incidence of 40 newly diagnosed patients, the total population might be around 200 patients. Around 16 new patients per year will have anaemia at the time of diagnosis.

Table 1 Incidence and prevalence in the past 5 years

Year		2018	2019	2020	2021	2022
Incidence in Denmark	**MF**	60	60	60	60	60
	Intermediate-2 or high risk	40	40	40	40	40

Year	2018	2019	2020	2021	2022
Prevalence in Denmark	200 patients				

Table 2 Estimated number of patients eligible for treatment with momelotinib

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years (including both the incident and prevalent population)	16	140	166	168	170

Table 2 shows the number of patients in Denmark who are eligible for treatment with momelotinib the next five years. The numbers in the table are based on the assumptions that 40% of patients have anaemia at diagnosis, 75% of patients have anaemia at year 2 and 95% of patients have anaemia at year 3+.

Table 2 Estimated number of patients eligible for treatment with momelotinib

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years (including both the incident and prevalent population)	16	140	166	168	170

3.3 Current treatment options

3.3.1 Current treatment of myelofibrosis

Treatment of MF is complex and challenging, with limited treatment options. The treatment is based on the prognostic scoring and age (17). Initially, disease-specific treatment is not always indicated for patients in the low or intermediate-1 risk group based on an individual assessment of each patient. Patients in IPSS/DIPPS intermediate-2 and high risk group (or patients below 70 years of age in intermediate-1 risk group with a high transfusion need) might be candidates to an allogeneic stem cell transplant (ASCT), which is the only curative treatment; however, only few patients are eligible due to age and comorbidities. Cytoreductive treatment is indicated for thrombocytosis, symptomatic splenomegaly, or constitutional symptoms. Cytoreductive treatment might include pegylated interferon-α or hydroxyurea. For patients in intermediate-2/high risk groups, JAK-inhibitors are treatment alternatives. Figure 3 provides an overview of the treatment algorithm for MF.

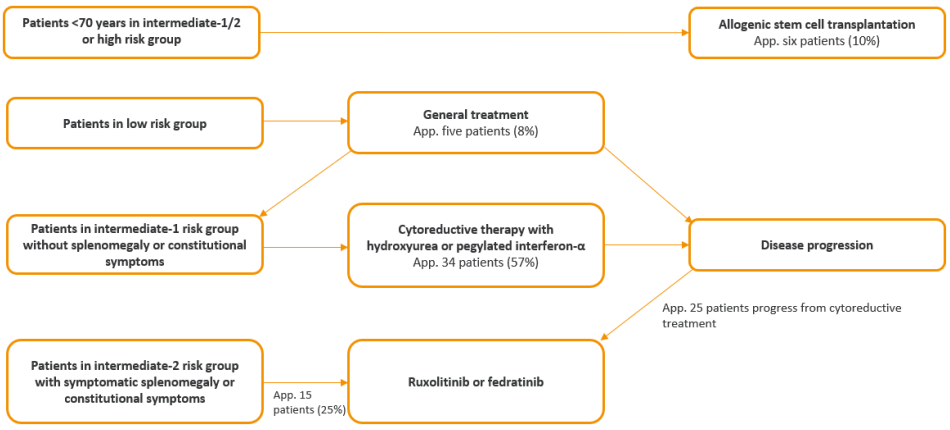


Figure 3 Treatment algorithm for MF. Source: DMC fedratinib evaluation (14).

Figure note: The figure does not include possible treatments when patients experience disease progression after treatment with JAK-inhibitors.

Fedratinib and ruxolitinib are approved JAK-inhibitors, for the treatment of disease-related splenomegaly or symptoms in adults with PMF, post-PV MF, or post-ET MF. Ruxolitinib has been used 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. Ruxolitinib is taken twice daily, and the recommended starting dose (5-20 mg) is based on platelet counts. Fedratinib has been recommended since April 2022 for JAKi-naïve patients. Fedratinib is taken once daily, and the recommended dose is 400 mg (2).

In addition to the disease specific treatment, many patients require additional treatment for anaemia (4–6). The Nordic study group for myeloproliferative neoplasms (NMPN) study group recommend initiating pharmacological treatment of anaemia at Hb levels approximately <110g/L (6.83 mmol/L) in symptomatic patients and to consider it in asymptomatic patients with Hb levels <100 g/L (6.21 mmol/L) (4). Currently, , erythropoiesis stimulating agents (ESA's), blood transfusions and Danazol are used in Denmark as anaemia treatment in MF patients (4,18,19).

3.3.2 Limitations of current treatment alternatives

Although current JAK-inhibitors demonstrate clinical benefit, several limitations exist. For both JAK-inhibitors one of the most reported SAEs are anaemia. Ruxolitinib frequently worsens anaemia and thrombocytopenia, which often leads to dose reductions and treatment interruptions, potentially limiting treatment efficacy. Furthermore, ruxolitinib dosing is based on patient characteristics such as platelet counts, which require close monitoring. Fedratinib frequently causes gastrointestinal toxicities and can worsen anaemia and thrombocytopenia; it has also been associated with the risk of Wernicke encephalopathy (2). Safe and effective treatments are needed for patients with MF who are anaemic or no longer candidates for receiving currently approved JAK inhibitors.

3.4 The intervention: momelotinib

Overview of momelotinib	
Therapeutic indication relevant for the assessment	Momelotinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post-PV MF or post-ET MF and who are JAK inhibitor naïve or have been treated with ruxolitinib (1).
Method of administration	Oral administration and may be taken with or without food.
Dosing	The recommended dose of momelotinib is 200 mg once daily. Dose modifications should be considered for haematologic and nonhematologic toxicities. Dose modifications for adverse reactions are presented in the SPC appendix (1).
Dosing in the health economic model (including relative dose intensity)	200 mg orally once daily was included in the model.
Should the pharmaceutical be administered with other medicines?	None required.
Treatment duration / criteria for end of treatment	Treatment may be continued for as long as the benefit-risk remains positive for patients, as assessed by the treating physician. Patients should discontinue momelotinib if they are unable to tolerate 100 mg once daily.
Necessary monitoring, both during administration and during the treatment period	Complete blood cell count and liver function tests must be performed before initiating treatment, periodically during treatment, and as clinically indicated.
Need for diagnostics or other tests (e.g., companion diagnostics). How are these included in the model?	Complete blood cell count and liver function tests must be performed before initiating treatment, periodically during treatment, and as clinically indicated.
Package size(s)	Momelotinib is available in packages with 200 mg, 150 mg tablets and 100 mg film-coated tablets. Each package comprises 30 film-coated tablets.

3.4.1 The intervention in relation to Danish clinical practice

Momelotinib is the first potent, small-molecule inhibitor of both JAK1/JAK2 and ACVR1, i.e., momelotinib works by inhibiting the JAK signalling pathway and is an alternative treatment to current approved JAK-inhibitors. Furthermore, momelotinib provides a novel approach to treating MF especially for anaemic patients, because of these

combined inhibiting qualities. There remains a significant unmet need for MF patients with anaemia as the JAK inhibitors currently used in Denmark exacerbate anaemia, necessitating dose reductions, discontinuation and/or anaemia supportive therapies, including red blood cell transfusions. The positioning of momelotinib will introduce a new alternative to other JAK-inhibitors for anaemic patients primarily in intermediate-2 & high-risk groups with symptomatic splenomegaly or constitutional symptoms. An overview of the treatment algorithm as presented in the DMC evaluation of fedratinib is presented in Figure 3.

3.5 Choice of comparator(s)

The chosen comparators are ruxolitinib and fedratinib. The rationale for choosing these two comparators is illustrated in Figure 3. As seen, both fedratinib and ruxolitinib are JAK-inhibitors used for the treatment of disease-related splenomegaly or symptoms in adults with PMF, post-PV MF, or post-ET MF. As both JAK-inhibitors are used in Danish clinical practice, both are included as comparators in our application. In the following, the two comparators will be described.

Overview of ruxolitinib	
Generic name	Ruxolitinib
ATC code	L01EJ01
Mechanism of action	Ruxolitinib is a selective inhibitor of JAK1 and JAK2 (IC_{50} values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. MF and PV are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients. Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM. JAK-STAT signalling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GvHD pathogenesis (20).
Method of administration	Ruxolitinib should be taken orally, with or without food. If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose (20).

Overview of ruxolitinib	
Dosing	According to the SPC of ruxolitinib, the recommended starting dose in MF is based on platelet counts (20)
Dosing in the health economic model (including relative dose intensity)	10-20 mg as dosing were included in the model.
Should the pharmaceutical be administered with other medicines?	None required.
Treatment duration/ criteria for end of treatment	Treatment of MF and PV may be continued as long as the benefit-risk remains positive. However, the treatment should be discontinued after six months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy. It is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms (20).
Need for diagnostics or other tests (i.e., companion diagnostics)	A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with ruxolitinib. Complete blood count, including a white blood cell count differential, should be monitored every 2-4 weeks until ruxolitinib doses are stabilised, and then as clinically indicated (20).
Package size(s)	Ruxolitinib is available as 5 mg, 10 mg, 15 mg, and 20 mg tablets. Each package contains 56 tablets (June 2023).

Overview of fedratinib	
Generic name	Fedratinib
ATC code	L01EJ02
Mechanism of action	Fedratinib is a kinase inhibitor with activity against wild type and mutationally activated JAK2 and FLT3. Fedratinib is a JAK2-selective inhibitor with higher inhibitory activity for JAK2 over family members JAK1, JAK3 and TYK2. Fedratinib reduced JAK2-mediated phosphorylation of STAT3/5 proteins, inhibited malignant cell proliferation in vitro and in vivo (21).

Overview of fedratinib	
Method of administration	Fedratinib is for oral use. The capsules should not be opened, broken or chewed. They should be swallowed whole, preferably with water, and may be taken with or without food. Administration with a high fat meal may reduce the incidence of nausea and vomiting, therefore it is recommended to be taken with food (21).
Dosing	The recommended dose is 400 mg once daily. Treatment may be continued for as long as patients derive clinical benefit. Dose modifications should be considered for haematologic and non-haematologic toxicities (21).
Dosing in the health economic model (including relative dose intensity)	Patients in the model received 400 mg fedratinib once daily (21).
Should the pharmaceutical be administered with other medicines?	It is recommended that prophylactic anti-emetics be used according to local practice for the first 8 weeks of treatment and continued thereafter as clinically indicated. Administration of fedratinib with a high fat meal may reduce the incidence of nausea and vomiting (21).
Treatment duration/ criteria for end of treatment	Fedratinib should be discontinued in patients who are unable to tolerate a dose of 200 mg daily. Treatment should also be discontinued in the case of recurrence of a Grade 4 haematologic toxicity, recurrence of ≥ Grade 3 ALT/ AST (> 5.0 to 20.0 x upper limit of normal [ULN]) or bilirubin (> 3.0 to 10.0 ULN), recurrence of ≥Grade 3 amylase/lipase (>2.0 to 5.0 x ULN) and at signs or symptoms of WE regardless of thiamine levels (21).
Need for diagnostics or other tests (i.e., companion diagnostics)	Baseline testing of thiamine (vitamin B1) levels, complete blood count, hepatic panel, amylase/lipase, blood urea nitrogen (BUN) and creatinine should be obtained prior to starting treatment with fedratinib, periodically during treatment and as clinically indicated. Fedratinib treatment should not be started in patients with thiamine deficiency, until thiamine levels have been corrected. Initiating treatment with fedratinib is not recommended in patients with a baseline platelet count below 50 x 10^9 /L and absolute neutrophil count (ANC) <1.0 x 10^9 /L (21).
Package size(s)	Fedratinib is available as 100 mg capsules. A package contains 120 capsules (June 2023).

3.6 Cost-effectiveness of the comparator(s)

Fedratinib was evaluated and recommended by the DMC in April 2022 for the treatment of patients with symptomatic MF who have not previously been treated with a JAK-inhibitor (JAKi-naïve patients). The rationale for the recommendation was that the effect of fedratinib was comparable with ruxolitinib, which was the comparator in the evaluation of fedratinib. Fedratinib was effective in terms of reducing the splenomegaly and relieving symptoms. In addition, the safety of fedratinib and ruxolitinib was comparable despite the two drugs being associated with different types of adverse events (AEs) and reactions. Ruxolitinib has not directly been evaluated or recommended by the DMC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 presents the outcomes included in the present application and the definitions and measurement method for each outcome. The rationale for including each outcome and the validity of the outcomes is also presented in this section.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
SRR24	Week 24	**SIMPLIFY-1** Proportion of participants achieving a ≥35% reduction in spleen volume at week 24 from baseline as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scans. **SIMPLIFY-2** Defined as the proportion of subjects who achieved a spleen volume reduction of ≥35% from baseline at the week 24 assessment as measured by MRI or CT scans. **MOMENTUM** Defined as proportion of subjects who had splenic response based on ≥35% reduction in spleen volume from baseline.	**SIMPLIFY-1** The reduction in splenic volume was measured by MRI and CT scans and evaluated by a blinded central reader. Non-inferiority of momelotinib was determined by whether the lower bound of the two-sided 95% CI for the non-inferiority difference (SRR24 of momelotinib -0.6 x SRR24 of ruxolitinib) was >0 and was calculated based on the stratum-adjusted Cochran-Mantel-Haenszel (CMH) proportion. **SIMPLIFY-2** The spleen volume was obtained through blinded assessment of MRI or CT scans by a central imaging laboratory. The splenic response rate at week 24 was compared between the 2 treatment groups (momelotinib versus BAT) using the CMH approach adjusted for stratification factors based on the intention-to-treat (ITT) population. **MOMENTUM** Binary endpoints such as the proportion of participants achieving a ≥35% reduction in spleen volume at week 24 were analysed using proportions by treatment group and compared with a CMH test stratified by baseline MF-SAF TSS (<22 vs ≥22), baseline palpable spleen length below the left costal margin (LCM) (<12 vs ≥12 cm), and baseline RBC or whole blood units transfused in the 8-week

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			period before randomisation (0, 1-4, ≥5 units) as recorded in the IRT. The exact binomial 95% CI was generated for the per-arm proportion estimate. The magnitude of difference between the 2 proportions was estimated by Cochran-Mantel-Haenszel (CMH) common risk difference.
TSS response rate	Week 24	**SIMPLIFY-1** Defined as the proportion of participants who achieve a ≥50% reduction in TSS from baseline to week 24 as measured by the modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) TSS v2.0 diary. **SIMPLIFY-2** Defined as the proportion of subjects who achieved ≥ 50% reduction in TSS at week 24 as measured by the modified MPN-SAF TSS v2.0 diary. **MOMENTUM** Defined as the proportion of subjects with a ≥50% reduction in mean MF-SAF TSS over the 28 days immediately before the end of week 24 compared with baseline.	**SIMPLIFY-1** Most secondary endpoints were analysed similarly as the primary endpoint (CMH and ITT population). The modified MPN-SAF TSS PRO instrument consists of 8 items assessing the worst daily incidence of tiredness, filling up quickly (early satiety), abdominal discomfort, night sweats, itching (pruritus), bone pain (diffuse not joint pain or arthritis), pain under ribs on the left side, and inactivity. Scoring of the TSS in SIMPLIFY-1 is based on 7 of these items, excluding inactivity. These items assess the impact experienced by the subject in the 24 hours prior to completing the questionnaire. All items are measured using a 0 to 10 Numeric Rating Scale (NRS), with 0 corresponding to “Absent” and 10 corresponding to “Worst Imaginable.” Response rate was calculated using the average of the daily TSS from a consecutive 28-day period prior to week 24. The consecutive 28-day period at week 24 was defined as the latest eligible period of 28 consecutive days which had ≥20 available daily TSS. Response rate in TSS at week 24 was evaluated for subjects in the ITT analysis set who had

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			a baseline TSS >0 or subjects who had a baseline TSS = 0 but nonzero or missing TSS at week 24. **SIMPLIFY-2** The diary was completed at the end of each day with a 24-hour recall period, and the daily TSS was defined as the sum of 7 individual symptom scores (each with a 0 to 10 point scale) collected on the same day (scores for the question of inactivity in the diary were not included in TSS assessments.) The daily TSS was missing if any individual scores were missing. If multiple records were available on the same day, the last record was used as an assessment for that day. **MOMENTUM** The primary analysis of comparison of MF-SAF TSS response between treatments was performed using a stratified CMH test. Baseline MF-SAF TSS was computed as the mean of the TSS values generated on the date of the baseline period triggering per the ePRO device and on the 6 days immediately following that triggering date. If more than 3 daily TSS results were missing from the 7-day baseline assessment period, the score was considered missing.

OS	**SIMPLIFY-1** Week 24 (randomised-treatment phase), week 24 to week 240 (open-label phase and final analysis) **SIMPLIFY-2** Week 24 (randomised-treatment phase), week 24 to week 228 (extended-treatment phase and final analysis) **MOMENTUM** Week 24 (randomised-treatment phase), week 48 (open-label treatment phase) and entire treatment period (both phases and final analysis)	**SIMPLIFY-1** OS was defined as the interval from the first dose of study drug to death from any cause, i.e. date of death or censoring minus the date of the first dose of study drug in the double-blind phase + 1. Data from surviving subjects were censored at the last date of awareness that a subject was alive. Data including both the double-blind and open label phases were used for both momelotinib and ruxolitinib treatment groups. **SIMPLIFY-2** OS was defined as the interval from the first dose of study drug to death from any cause, i.e. date of death or censoring – date of the first dose of study drug in the randomised-treatment phase + 1. Data from surviving subjects were censored at the last date of awareness that a subject was alive. Data including both the randomised-treatment and extended-treatment phases were used for both BAT and momelotinib treatment groups. **MOMENTUM** OS was defined as the interval from the first study drug dosing date (or randomisation date for subjects who did not receive treatment) to date of death from any cause. Subjects without a documented death at the time of analysis were censored on the last date known to be alive.	**SIMPLIFY-1** OS was summarised using the Kaplan-Meier method. A plot of the Kaplan-Meier curves was provided by treatment group and by treatment group within each stratum. Medians, ranges and corresponding 95% Cis were presented. In addition, stratified log-rank tests were performed, and HRs were calculated to compare treatment group. **SIMPLIFY-2** OS was summarised using the Kaplan-Meier method. A plot of the Kaplan-Meier curves was provided by treatment group and by treatment group within each stratum. Medians, ranges, HRs, and corresponding 95% Cis on the treatment estimates were presented. In addition, stratified log-rank tests were performed. **MOMENTUM** Time-to-event outcomes such as OS were analysed by treatment using Kaplan-Meier methods. Summary statistics were provided by treatment with number of events, median and 95% CI, and survival probabilities at specific time points presented. When comparing the survival curves of the 2 treatment groups, a log-rank test stratified by baseline MF-SAF TSS, baseline spleen length, and baseline RBC or whole blood units transfused as recorded in the IRT was used. A stratified Cox regression model was used to estimate the hazard ratio and its 95% Cl.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

Splenic response rate at week 24

The primary endpoint in the SIMPLIFY studies was SRR rate at week 24 (SRR24). The definition and method of analysis are presented in Table 3. SRR24 was included in the present application as is the primary endpoint in both the SIMPLIFY-1 and SIMPLIFY-2 studies and a secondary endpoint in MOMENTUM and is used as the primary endpoint in other trials assessing other MF therapies (2). SRR24 is also relevant from a clinical perspective, as it is defined as a response criterion for MF by the IWG-MRT/ELN consensus report (22) and can be used as a surrogate measure for survival and symptom reduction (14); thus, it was included in the present application.

Total symptom score response rate at week 24

TSS response rate at week 24 was a secondary endpoint in SIMPLIFY-1 and SIMPLIFY-2. The definition of the outcome is presented in Table 3. TSS response rate at week 24 was included in the present application as reducing the symptom burden is a patient relevant endpoint and the MPN-SAF TSS is a validated instrument developed to assess symptom severity in subjects with MPN hereunder MF (23). The MPN-SAF TSS scores cancer-specific symptoms and is an 8-item version of the MPN-SAF and used in the SIMPLIFY studies. The questionnaire was developed to assess symptom burden and QoL in patients with MPN. Of the 8 questions, 7 were used to calculate TSS. An additional question on tiredness was included. TSS was based on a 70-point scale, with a higher TSS corresponding to more severe symptoms, to ensure that all subjects were evaluable for symptom response in a range considered clinically meaningful. MF-SAF TSS was used in the MOMENTUM trial, and it is regarded as a clinically relevant endpoint as it uses MR-specific symptom scores. It is a 19-item questionnaire specific to the MF population and focuses on specific MF symptoms: abdominal discomfort, pain under left ribs, early satiety, night sweats, itching, bone or muscle pain, and inactivity. Thus, it was included in the present application.

Overall survival

OS is generally considered the gold standard measure of efficacy in oncology clinical trials and is required by regulatory authorities for the approval of new cancer treatments. OS as an endpoint in trials is easily and precisely measured and based on objective and quantitative assessment. Thus, we included it as an efficacy outcome in the present application.

4. Health economic analysis

The health economic analysis was a cost-minimisation analysis of momelotinib compared to ruxolitinib and fedratinib in JAKi-naïve and JAKi-experienced MF patients. A cost-minimisation approach was chosen, as ruxolitinib and fedratinib are clinically equivalent alternatives and momelotinib has been demonstrated to be at least non-inferior to ruxolitinib in the SIMPLIFY-1 trial. Uncertainty in the cost parameters included in the analysis was assessed with deterministic one-way sensitivity analyses (DSAs) and scenario analyses. A budget impact analysis was conducted to assess the budgetary impact of recommending momelotinib for JAKi-naïve and JAKi-experienced MF patients with anaemia.

4.1 Model structure

The applied model was a cost-minimisation model developed in Excel. The model estimated the cost per patient of treating adult JAKi-naïve and JAKi-experienced MF patients with anaemia with momelotinib compared to treatment with ruxolitinib and fedratinib. The cost-minimisation model applied a limited societal perspective in accordance with DMC guidelines, and costs incurred after the first year were discounted by 3.5% per year (24). All relevant costs associated with treating MF patients in a Danish clinical setting were included. Information on the Danish clinical practice for treating these patients came primarily from consultation with three clinical experts. The model applied monthly cycles.

The time horizon of the model was 25 years in the base case. The rationale for the time horizon was based on the median age at diagnosis of MF, which is 70 years in Denmark, and 25 years was regarded as long enough to capture all cost differences between the included alternatives. In addition, the average treatment length of momelotinib, fedratinib, and ruxolitinib was assumed to be 3.5 years in the base case, based on input from the clinical experts, who estimated that the average treatment length was 3-4 years. The clinical experts agreed that the same average treatment length could be applied for all three treatments but noted that the treatment length of momelotinib could be longer, as fewer patients might discontinue treatment due to anaemia. Due to these assumptions, discontinuation was not included in the base case, as this would affect the average treatment length, and the clinical experts expected a similar discontinuation rate between momelotinib, fedratinib, and ruxolitinib. Mortality rates based on the general mortality of the Danish population were applied in the model in accordance with DMC guidelines.

In the summary of product characteristics (SPC) on ruxolitinib, it is stated that treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy. Based on this, a stopping rule was included for all three treatments in the model for patients with no or limited effect, as the clinical expert [redacted] expected that this would also apply to momelotinib and fedratinib. The clinical expert assumed 20%-30% experience limited or no effect after 6 months; thus, 25% were applied in the model.

4.2 Model features

Table 4 presents a summary of the model features.

Table 4 Features of the model

Model features	Description	Justification
Patient population	Adult patients with PMF, post-PV MF, or post-ET MF who are JAKi-naïve or JAKi-experienced and anaemic (for momelotinib)	This patient population is aligned with the momelotinib indication and the ruxolitinib and fedratinib indications.
Perspective	Limited societal perspective	According to DMC guidelines.
Time horizon	Lifetime (25 years)	The median age in the model was 70 years, and the average treatment length 3.5 years.
Cycle length	Monthly cycle length	Based on when it is expected that clinically relevant events occur, e.g., AE assessments, treatment effect assessments, etc.
Half-cycle correction	No	Not applied due to short cycle length.
Discount rate	3.5%	According to DMC guidelines.
Intervention	Momelotinib	NA.
Comparator(s)	Ruxolitinib Fedratinib	Current recommended JAK-inhibitors for treating MF.
Outcomes	No outcomes were included in the model	The model was a cost-minimisation model, i.e., no efficacy parameters were accounted for in the model.

5. Overview of literature

In this section, the literature used in the present application is presented. In JAKi-naïve patients, the efficacy and safety of momelotinib were compared to ruxolitinib in the SIMPLIFY-1 trial (NCT01969838). Safety outcomes of momelotinib and fedratinib in JAKi-naïve patients were also compared in an ITC including the SIMPLIFY-1 trial and the JAKARTA trial (NCT01437787). No comparison of efficacy between momelotinib and fedratinib in either JAKi-naïve or JAKi-experienced patients will be presented in this application due to lack of appropriate evidence to use in an indirect comparative analysis. The COMFORT-I and COMFORT-II study on ruxolitinib was used in the assessment of AEs associated with ruxolitinib treatment in the health economic analysis.

In JAKi-experienced patients, the SIMPLIFY-2 trial (NCT02101268) was used to demonstrate the efficacy of momelotinib compared to best available therapy (BAT) and the MOMENTUM trial (NCT04173494) was used to demonstrate the efficacy of momelotinib compared to danazol in JAKi-experienced patients with anaemia. In terms of safety, The ITC on safety outcomes was also conducted on JAKi-experienced patients and included pooled data from the SIMPLIFY-2 trial, the MOMENTUM trial and the JAKARTA-2 trial (NCT01523171) on fedratinib. In Table 5, we present an overview of the literature used in the present application. The included trials are described in more details in Appendix A.

5.1 Literature used for the clinical assessment

The literature for the ITC was identified through a systematic literature search (SLR), which is presented in Appendix H. To inform the comparison of momelotinib and ruxolitinib, the SIMPLIFY-1 study was used, which is a head-to-head study of momelotinib and ruxolitinib in JAKi-naïve patients. The ITC is attached to the present application; thus, the methodology and statistical analysis applied in the ITC is not described further in the present document.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison
Mesa RA, Kiladjian JJ, Catalano JV, Devos T, Egyed M, Hellmann A, McLornan D, Shimoda K, Winton EF, Deng W, Dubowy RL, Maltzman JD, Cervantes F, Gotlib J. SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naïve Patients With Myelofibrosis. J Clin Oncol. 2017 Dec 1;35(34):3844-3850. Doi: 10.1200/JCO.2017.73.4418. Epub 2017 Sep 20. (25)	SIMPLIFY-1	NCT01969838	First subject screened: 06 December 2013 Last data collection for the primary endpoint (last week 24 MRI): 08 September 2016 Last subject last visit for double-blind phase: 12 September 2016 Data cutoff for interim week 24 interim analysis: 12 September 2016 Data cutoff for interim week 48 interim analysis: 12 September 2017 Last subject last observation for final report: 02 May 2019 Database finalisation for final report: 01 July 2019	Used to demonstrate the efficacy and safety of momelotinib compared to ruxolitinib in JAKi-naïve patients and used in the ITC on safety of momelotinib vs fedratinib in JAKi-naïve patients
Data on file: clinical study report on SIMPLIFY-1: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF) (26)	SIMPLIFY-1	NCT01969838	See above	Momelotinib and ruxolitinib for JAKi-naïve patients with MF and ITC on safety outcomes of momelotinib vs fedratinib in JAKi-naïve patients
Harrison CN, Vannucchi AM, Platzbecker U, Cervantes F, Gupta V, Lavie D, Passamonti F, Winton EF, Dong H, Kawashima J, Maltzman JD, Kiladjian JJ,	SIMPLIFY-2	NCT02101268	First subject screened: 19 June 2014	Used to demonstrate the efficacy of momelotinib in

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison
Verstovsek S. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol. 2018 Feb;5(2):e73-e81. Doi: 10.1016/S2352-3026(17)30237-5. Epub 2017 Dec 20. PMID: 29275119. (27)			Last data collection for the primary endpoint (last Week 24 MRI): 20 July 2016 Last subject last visit for randomised treatment phase: 28 July 2016 Data cutoff for week 24 interim analysis: 28 July 2016 Data cut-off for week 48 interim analysis: 12 September 2017 Database finalisation: 25 June 2019	JAKi-experienced MF patients and used in the ITC on safety outcomes of momelotinib vs fedratinib in JAKi-experienced patients.
Data on file: clinical study report on SIMPLIFY-2: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib (28)	SIMPLIFY-2	NCT02101268	See above	See above
Verstovsek, S., et al., MOMENTUM: momelotinib vs danazol in patients with myelofibrosis previously treated with JAKi who are symptomatic and anemic. Future Oncology, 2021. 17(12): p. 1449-1458 (29) Verstovsek S, Gerds AT, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. The Lancet. 2023 Jan;401(10373):269–80 (30)	MOMENTUM	NCT04173494	First subject screened: 07 February 2020 Last subject last visit for double-blind randomised treatment period: 03 December 2021 Data cutoff for ongoing data for clinical study report: 03 December 2021 Database lock for analysis for this report and treatment unblinding: 13 January 2022	Used in the ITC on safety outcomes of momelotinib vs fedratinib in JAKi-experienced patients

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison
Data on file: clinical study report on MOMENTUM: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy (31).				
Harrison, C., et al., Overall and progression-free survival in patients treated with fedratinib as first-line myelofibrosis (MF) therapy and after prior ruxolitinib (RUX): results from the JAKARTA and JAKARTA2 trials. Hemasphere, 2021. 5: p. S203 (32) Harrison, C.N., et al., Safety and efficacy of fedratinib, a selective oral inhibitor of Janus kinase-2 (JAK2), in patients with myelofibrosis and low pretreatment platelet counts. British Journal of Haematology, 2022 (33) Pardanani, A., et al., Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. JAMA oncology, 2015. 1(5): p. 643-651 (34)	JAKARTA	NCT01437787	From clinicaltrials.gov: Study start: 2011-12 Primary completion (actual): 2014-06 Study completion (actual): 2014-06	Used in the ITC on safety outcomes of momelotinib vs fedratinib in JAKi-naïve patients
Harrison, C.N., et al., Fedratinib improves myelofibrosis-related symptoms and health-related quality of life in patients with myelofibrosis previously treated with ruxolitinib: patient-reported outcomes from the phase II JAKARTA2 trial. HemaSphere, 2021. 5(5). (35) Harrison, C.N., 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. The Lancet Haematology, 2017. 4(7): p. e317-e324. (36)	JAKARTA-2	NCT01523171	From clinical trials: Study start: 2012-04 Primary completion (actual): 2014-04 Study completion (actual): 2014-04	Used in the ITC on safety outcomes of momelotinib vs fedratinib in JAKi-experienced patients and in the comparability of patient characteristics

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison
Harrison, C.N., et al., Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. American journal of hematology, 2020. 95(6): p. 594-60 (37)				
Mesa RA, Gotlib J, Gupta V, Catalano J v, Deininger MW, Shields AL, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patientreported outcomes in COMFORT-I: a randomized, double-blind, placebocontrolled trial. Journal of clinical oncology : official journal of the American Side 49/51 Society of Clinical Oncology 2013;31(10):1285–92 (38) Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A Double Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis. New England Journal of Medicine. 2012;366(9):799–807 (39)	COMFORT-I	NCT00952289	Study start: 2009-08 Study completion: 2015-10	Used for relevant Aes observed with ruxolitinib treatment and comparability of patient characteristics
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;366(9):787–98 (40)	COMFORT-II	NCT00934544	Study start: 2009-07-01 Study completion: 2015-03-04	Used in the assessment of the comparability of patient characteristics

5.2 Literature used for the assessment of health-related quality of life

Not applicable due to cost-minimisation model.

5.3 Literature used for inputs for the health economic model

No literature search was conducted to identify literature or inputs for the health economic model.

6. Efficacy of momelotinib in JAKi-naïve patients

6.1 Efficacy of momelotinib compared to ruxolitinib for JAKi-naïve patients with MF

6.1.1 Relevant studies

In JAKi-naïve patients, the efficacy of momelotinib has been assessed in the SIMPLIFY-1 trial where momelotinib was compared head-to-head with ruxolitinib. The SIMPLIFY-1 study is a non-inferiority head-to-head study of momelotinib versus ruxolitinib in JAKi-naïve MF patients. As the study is a head-to-head study, no additional studies were used in the comparison of momelotinib and ruxolitinib in the JAKi-naïve population. Table 6 presents an overview of the SIMPLIFY-1 and additional information can be found in Appendix A.

Efficacy results in the following are presented for the ITT population that included all randomised subjects: 215 subjects in the momelotinib group and 217 subjects in the ruxolitinib group. In the double-blind treatment phase, 1 subject in each treatment group was randomised but not treated. Thus, a total of 214 subjects in the momelotinib group and 216 subjects in the ruxolitinib group received treatment. Overall, 175 subjects (81.4%) in the momelotinib group and 201 subjects (92.6%) in the ruxolitinib group completed double-blind study treatment, i.e. 40 subjects (18.6%) in the momelotinib group and 16 subjects (7.4%) in the ruxolitinib group prematurely discontinued study drug. The reasons were AEs (19 for momelotinib, 9 for ruxolitinib), death (5 for momelotinib, 0 for ruxolitinib), investigator discretion (4 for momelotinib, 1 for ruxolitinib), insufficient effect (3 for momelotinib, 1 for ruxolitinib), disease progression (3 for momelotinib and 2 for ruxolitinib), subject decision (2 for momelotinib and 2 for ruxolitinib), subject never dosed (1 for momelotinib and 1 for ruxolitinib), non-compliance (1 for momelotinib and 0 for ruxolitinib), protocol deviation (1 for momelotinib and 0 for ruxolitinib) and symptomatic spleen growth (1 for momelotinib and 0 for ruxolitinib).

Table 6 Overview of study design for the SIMPLIFY-1 study

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
SIMPLIFY-1 (NCT01969838)	Phase 3, multicentre, randomised, double-blind trial	24 weeks	Adult patients (≥18 years of age) with palpable splenomegaly ≥5 cm below the left costal margin and a confirmed diagnosis of PMF (WHO criteria) or post–PV or post–ET MF (IWG-MRT criteria). Patients were classified as IPSS high risk, intermediate-2 risk, or intermediate-1 risk with symptomatic splenomegaly or hepatomegaly or anaemia (Hb <10.0 g/dL) and/or unresponsive to available non-JAKi therapy. Patients were JAKi-naïve.	A total of 215 subjects were randomly assigned to receive oral momelotinib. Momelotinib was supplied as tablets for oral administration once daily containing 200 mg of momelotinib. Subjects received momelotinib plus placebo to match ruxolitinib tablets administered orally twice daily.	A total of 217 subjects were randomly assigned to receive ruxolitinib. Ruxolitinib was supplied as tablets for oral administration twice daily. The dose of ruxolitinib was 20 mg twice a day (or modified as per label) and was dependent on platelet count, creatinine clearance, and transaminase levels (AST and ALT).	**Primary endpoint** • SRR rate at week 24 **Secondary endpoints** • TSS response rate at week 24 • RBC transfusion-independence rate at week 24 • RBC transfusion-dependence rate at week 24 • Rate of RBC transfusion through week 24 **Exploratory endpoints** • Splenic response rate over time • Percent change from baseline in spleen volume over time • Palpable spleen size and percent change from baseline over time • Duration of spleen response • TSS response every 4 weeks • Patient Global Impression of Change (PGIC) • MPN-SAF (27-item questionnaire) • EQ-5D-5L • SF-36v2 • New RBC transfusion-independent rate by week 24 • New RBC transfusion-dependent rate by week 24 • RBC transfusion-free response rate over time • Hb, platelets, or ANC, change and percent change from baseline over time

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• Rate of RBC transfusion in the open label phase • Duration of transfusion-independent response for subjects not transfusion-independent at baseline and who achieved transfusion independence at any post-baseline in the double-blind phase • Time to transfusion independence for subjects not transfusion independent at baseline and who achieved transfusion independence at any post-baseline in the double-blind phase • Anaemia response rate at week 24 based on IWG-MRT/ELN criteria • Transfusion independence (TI) by week 48 (post hoc) • Duration of transfusion independence at any time (post hoc) • Proportion of subjects receiving an RBC transfusion (post hoc) • Zero-inflated negative binomial model for total RBC transfusion rate (post hoc) • Recurrent event model for RBC transfusion (post hoc) • Time to first, third, and fifth units of RBC transfusions (post hoc) • Hb increases at week 24 in ITT and TI subgroups (post hoc) • CR and PR based on IWG-MRT/ELN response criteria, or anaemia response at week 24, or MRI/CT spleen response at week 24, or TSS response at week 24 • Overall response rate (ORR) (complete response and partial response) • OS • Leukaemia-free survival

6.1.2 Comparability of studies

Not applicable due to head-to-head study.

6.1.2.1 Comparability of patients across studies

As the comparison of momelotinib and ruxolitinib was based on a direct comparative analysis with data from the head-to-head study SIMPLIFY-1, only baseline characteristics from this trial are presented in Table 7.

Table 7 Baseline characteristics of patients in SIMPLIFY-1 used in the comparative analysis of momelotinib and ruxolitinib in JAKi-naïve patients. Source: Mesa et al. 2017 (25).

	SIMPLIFY-1	
	Momelotinib (N=215)	**Ruxolitinib (N=217)**
Mean age, years (SD)	65.0 (10.67)	64.4 (10.59)
Male	124 (57.7)	120 (55.3)
Mean body mass index, kg/m² (SD)	24.9 (4.02)	25.3 (3.99)
Race		
White	179 (83.3)	178 (82.0)
Black	2 (0.9)	2 (0.9)
Asian	17 (7.9)	20 (9.2)
Hispanic or Latino	6 (2.8)	4 (1.8)
Myelofibrosis subtype		
Primary	128 (59.5)	116 (53.5)
Post-PV	48 (22.3)	50 (23.0)
Post-ET	39 (18.1)	51 (23.5)
IPSS risk category		
Intermediate-1	46 (21.4)	43 (19.8)
Intermediate-2	76 (35.3)	67 (30.9)
High	93 (43.3)	107 (49.3)
JAK2V617F mutation		

	SIMPLIFY-1	
	Momelotinib (N=215)	**Ruxolitinib (N=217)**
Previously tested	187 (87.0)	194 (89.4)
Positive	125 (58.1)	141 (65.0)
Negative	61 (28.4)	53 (24.4)
Not previously tested	28 (13.0)	23 (10.6)
TSS score, mean (SD)	19.4 (13.18)	17.9 (11.47)
ECOG performance status		
0	76 (35.3)	72 (33.2)
1	122 (56.7)	120 (55.3)
2	17 (7.9)	25 (11.5)
Mean Hb, g/dL (SD)	10.6 (2.10)	10.7 (2.38)
Hb ≥8 g/dL	186 (86.5)	195 (89.9)
Transfusion independent	147 (68.4)	152 (70.0)
Transfusion dependent	53 (24.7)	52 (24.0)
Mean platelet count, x 10^3/µL (SD)	301.1 (207.03)	301.5 (255.88)
Mean absolute neutrophil count, x 10^3/µL (SD)	12.0 (13.39)	11.3 (11.04)

Note: Data presented as n (%) unless otherwise noted. No significant between-group differences in any of the listed baseline characteristics. Abbreviations: ECOG = Eastern Cooperative Oncology Group, Hb = haemoglobin, IPSS = International Prognostic Scoring System, TSS = total symptom score.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The patient population relevant for this application corresponds to the population treated with current approved JAK-inhibitors today, i.e., patients in intermediate or high-risk groups with symptomatic splenomegaly or other MF-related symptoms who are not eligible for ASCT. However, patients eligible for treatment with momelotinib must be anaemic, contrasting current approved JAK-inhibitor treatments.

Patients may have received previous disease-specific treatments such as hydroxyurea or pegylated interferon-α but may also have received other JAK-inhibitors as the first disease-specific treatment.

In the previous DMC evaluation of fedratinib (14), the DMC commented that the populations from the included fedratinib and ruxolitinib studies (the JAKARTA (32–34) and COMFORT studies (39,40)) were comparable with the Danish patient population. The patients included in SIMPLIFY-1 have baseline characteristics similar to the patients in JAKARTA and COMFORT-1 (39) and COMFORT-2 (40); therefore, we assume that the population in SIMPLIFY-1 is comparable with the Danish population as well. Most patients in SIMPLIFY-1 were in intermediate-2 and high-risk groups based on IPSS, which correlates well with the eligible Danish patient population. In the table below, key characteristics from JAKARTA and COMFORT-1 and COMFORT-2 are presented, to support the statements above.

The clinical experts were consulted in terms of similarities and important differences between the SIMPLIFY-1 population and the Danish patient population. The clinical experts stated that patients in the study had a high platelet count compared to the Danish population with candidates to JAKi treatment. Also, all patients in Denmark are tested for JAK2 mutations which was only done for 10-13% of patients in SIMPLIFY-1.

As the health economic analysis presented in the present application is a cost-minimisation analysis, no patient characteristics were used in the model and the table in the DMC template comparing patient characteristics from the Danish patient population with the characteristics used in the model was deleted.

Table 8 Baseline characteristics of patients in MF studies to demonstrate comparability of patients

	JAKARTA (34)		JAKARTA-2 (36)	COMFORT-1 (39)		COMFORT-2 (40)		SIMPLIFY-1 (25)	
	Fedratinib 400 mg	Placebo	Fedratinib 400 mg	Ruxolitinib	Placebo	Ruxolitinib	BAT	Momelotinib	Ruxolitinib
Number of patients	96	96	97	155	154	146	73	215	217
Age in years, median (min, max)	63 (39, 86)	66 (27, 85)	67 (62, 72)	66 (43, 91)	70 (40, 86)	67 (35, 83)	66 (35, 85)	67 (28, 85)	66 (25, 86)
Gender (male)	56.3%	57.3%	55.0%	51.0%	57.1%	56.8%	57.5%	57.7%	55.3%
Ethnicity									
Caucasian	90.0%	94.0%	-	89.0%	90.0%	81.0%	91.8%	White: 83.3%	White: 82.0%
Asian	8.0%	5.0%	-	3.0%	3.0%	-	-	7.9%	9.2%
African	1.0%	1.0%	-	4.0%	4.0%	-	-	Black: 0.9%	Black: 0.9%
Other	1.0%	0.0%	-	4.0%	3.0%	-	-	0.9%	0.5%
Unknown	0.0%	0.0%	-	0.0%	0.0%	19.0%	6.8%	-	-
MF subtype									

	JAKARTA (34)		JAKARTA-2 (36)	COMFORT-1 (39)		COMFORT-2 (40)		SIMPLIFY-1 (25)	
	Fedratinib 400 mg	Placebo	Fedratinib 400 mg	Ruxolitinib	Placebo	Ruxolitinib	BAT	Momelotinib	Ruxolitinib
Primary MF	64.6%	60.4%	55.0%	45.2%	54.5%	52.7%	53.4%	59.5%	53.5%
Post-PV	25.0%	28.1%	26.0%	32.3%				22.3%	23.0%
Post-ET	10.4%	11.5%	20.0%	22.6%				18.1%	23.5%
IPSS risk category									
Intermediate-1	-	-	16.0%	-	-	-	-	21.4%	19.8%
Intermediate-2	59.4%	47.9%	48.0%	41.3%	35.1%	50.7%	50.7%	35.3%	30.9%
High	40.6%	52.0%	35.0%	58.1%	64.3%	49.3%	4.3%	43.3%	49.3%
JAK2V617F mutation									
Previously tested	-	-	-	-	-	-	-	87.0%	89.4%
Positive	-	-	-	-	-	-	-	58.1%	65.0%
Negative	-	-	-	-	-	-	-	28.4%	24.4%

	JAKARTA (34)		JAKARTA-2 (36)	COMFORT-1 (39)		COMFORT-2 (40)		SIMPLIFY-1 (25)	
	Fedratinib 400 mg	Placebo	Fedratinib 400 mg	Ruxolitinib	Placebo	Ruxolitinib	BAT	Momelotinib	Ruxolitinib
Not previously tested	-	-	-	-	-	-	-	13.0%	10.6%
JAK2 mutation									
Wild type	31.3%	33.3%	30.0%	25.8%	17.5%	24.0%	27.4%	-	-
Mutant	64.6%	61.5%	63.0%	72.9%	79.9%	75.3%	67.1%	-	-
Unknown	4.2%	5.2%	7.0%	1.3%	2.6%	0.7%	5.5%	-	-
TSS score, mean (SD)	-	-	-	-	-	-	-	19.4 (13.18)	17.9 (11.47)
ECOG performance status									
0	42.7%	32.3%	-	31.1%	25.5%	39.7%	35.6%	35.3%	33.2%
1	49.0%	58.3%	-	57.6%	55.0%	52.7%	50.7%	56.7%	55.3%
2	8.3%	8.3%	-	9.3%	16.8%	6.8%	12.3%	7.9%	11.5%

	JAKARTA (34)		JAKARTA-2 (36)	COMFORT-1 (39)		COMFORT-2 (40)		SIMPLIFY-1 (25)	
	Fedratinib 400 mg	Placebo	Fedratinib 400 mg	Ruxolitinib	Placebo	Ruxolitinib	BAT	Momelotinib	Ruxolitinib
3	0.0%	0.0%	-	2.0%	2.7%	0.7%	1.4%	-	-
Unknown	0.0%	1.0%	-	2.6%	3.2%	0.0%	0.0%	-	-
Mean Hb, g/dL (SD)	-	-	-	-	-	-	-	10.6 (2.10)	10.7 (2.38)
Hb ≥8 g/dL	-	-	-	-	-	-	-	86.5%	89.9%
Hb level, median (min, max)	10.7 g/dL (4.8, 16.8)	10.1 g/dL (4.5, 17.1)	-	10.5 g/dL (6.6, 17.0)	10.5 g/dL (3.5, 17.3)	-	-	-	-
Transfusion independent	-	-	-	-	-	-	-	68.4%	70.0%
Transfusion dependent	-	-	-	-	-	-	-	24.7%	24.0%
Mean platelet count, x 10^3/µL (SD)	-	-	-	-	-	-	-	301.1 (207.03)	301.5 (255.88)

	JAKARTA (34)		JAKARTA-2 (36)	COMFORT-1 (39)		COMFORT-2 (40)		SIMPLIFY-1 (25)	
	Fedratinib 400 mg	Placebo	Fedratinib 400 mg	Ruxolitinib	Placebo	Ruxolitinib	BAT	Momelotinib	Ruxolitinib
Platelet count × 106/mL, median (min, max)	220.5 (31.0, 1155.0)	187.0 (51.6, 1075.0)	-	262 (81, 984)	238 (100, 887)	244 (-)	244 (-)	-	-
Platelet count									
<50 × 10^9/L	-	-	1.0%	-	-	-	-	-	-
50 × 10^9/L to <100 × 10^9/L	-	-	33.0%	-	-	-	-	-	-
≥100 × 10^9/L	-	-	66.0%	-	-	-	-	-	-
Mean absolute neutrophil count, x 10^3/µL (SD)	-	-	-	-	-	-	-	12.0 (13.39)	11.3 (11.04)
Median spleen volume (min, max)	2652 mL (316, 6430)	2660 mL (662, 7911)	-	2597.7 mL (478.1, 7461.8)	2566.3 mL (521, 8880.7)	2407.6 mL (451.3, 7765.6)	2317.9 mL (728.5, 7701.1)	-	-

	JAKARTA (34)		JAKARTA-2 (36)	COMFORT-1 (39)		COMFORT-2 (40)		SIMPLIFY-1 (25)	
	Fedratinib 400 mg	Placebo	Fedratinib 400 mg	Ruxolitinib	Placebo	Ruxolitinib	BAT	Momelotinib	Ruxolitinib
Proportion with 'Palpable spleen' length >10 cm	70.8%	74.0%	-	79.4%	81.8%	67.8%	75.3%	-	-
Total symptom score, mean (SD)	17.56 (13.53)	14.72 (11.954)	-	18.2 (-)	16.9 (-)	-	-	-	-
Previously treated with hydroxyurea	71.9%	56.3%	-	67.1%	56.5%	75.3%	68.5%	-	-

6.1.4 Efficacy – results per SIMPLIFY-1 study

In the following, efficacy results on SRR24, TSS response rate at week 24 and OS are presented.

Splenic response rate at week 24

Fifty-seven subjects (26.5%, 95% CI: 20.7%, 32.9%) in the momelotinib group and 63 subjects (29.0%, 95% CI: 23.5%, 36.0%) in the ruxolitinib group achieved a spleen volume reduction of ≥35% from baseline at week 24. The non-inferiority proportion difference in response was 0.09 (95% CI: 0.02, 0.16 and p<0.011). Momelotinib met the primary endpoint of non-inferiority to ruxolitinib (p=0.011), as the lower bound of the two-sided 95% CI was >0 (25).

Of the 158 non-responders in the momelotinib group and the 153 non-responders in the ruxolitinib group, 31 subjects (14.4%) in the momelotinib group and 13 subjects (6.0%) in the ruxolitinib group did not have spleen volume data available at week 24, primarily due to early study discontinuation (11.2% of subjects in the momelotinib group and 3.2% of subjects in the ruxolitinib group). The 11.2% of subjects in the momelotinib group who did not have spleen data available and participated in the study for <141 days discontinued early for the following reasons: subject decision (3 subjects), death (4 subjects), investigator's discretion (5 subjects), disease progression (2 subjects), and Aes (2 subjects with Grade 4, 5 subjects with Grade 3, 1 subject with Grade 2, and 2 subjects with Grade 1).

The 3.2% of subjects in the ruxolitinib group who discontinued prematurely did so for the following reasons: subject decision (1 subject), death (2 subjects), and Aes (2 subjects with Grade 5, 1 subject with Grade 4, and 1 subject with Grade 3).

Total symptom score at week 24

Sixty subjects (28.4%, 95% CI: 22.5%, 35.0%) in the momelotinib group and 89 subjects (42.2%, 95% CI: 35.4%, 49.2%) in the ruxolitinib group achieved a ≥50% reduction in TSS at week 24 versus baseline. The non-inferiority proportion difference was 0.00 (95% CI: -0.08, 0.08, p=0.98), and non-inferiority of momelotinib to ruxolitinib was not met because the lower bound of the two-sided 95% CI was not >0 (p=0.98). Because non-inferiority of momelotinib to ruxolitinib on response rate in TSS at week 24 was not met, formal sequential testing was stopped and only nominal significance was reported for the remaining α-controlled secondary endpoints (25).

Subjects who discontinued before day 162 were defined as non-responders for this endpoint. Thirty-one (14.7%) subjects in the momelotinib group and 12 (5.7%) subjects in the ruxolitinib group discontinued before day 162. The reason for discontinuation has not been stated in the CSR.

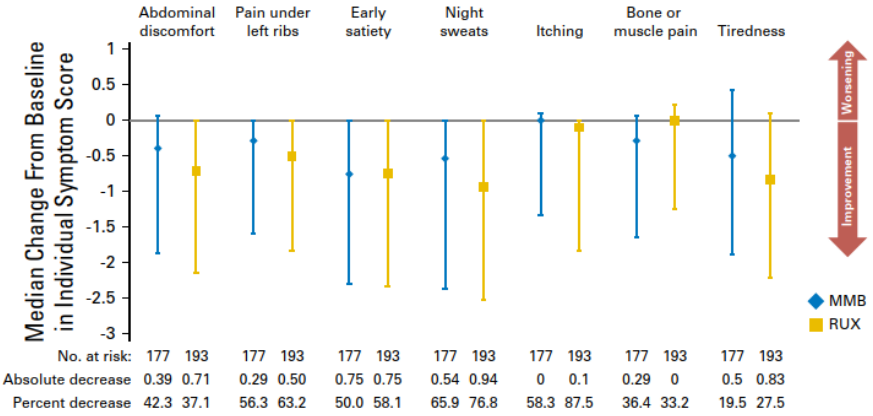


Figure 4 Absolute and percentage changes in individual symptoms of the Myeloproliferative Neoplasm Symptom Assessment Form from baseline to week 24. Source: Mesa et al. 2017 (25).

Overall survival

[redacted] The analysis of overall survival was conducted in the safety analysis set. The Kaplan-Meier plot is presented in Figure 5.

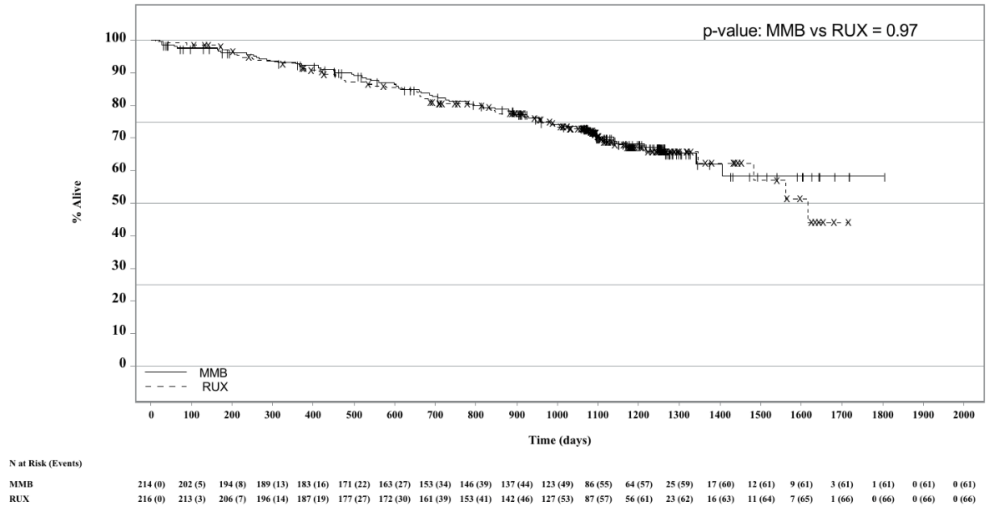


Figure 5 Kaplan-Meier plot of OS (safety analysis set). Source: CSR (data on file).

Table 9 presents an overview of the results from the direct comparative analysis of momelotinib and ruxolitinib from the SIMPLIFY-1 study.

Table 9 Results from the direct comparative analysis of momelotinib vs ruxolitinib for MF patients from the SIMPLIFY-1 study (ITT population, safety population for OS). Source: Mesa et al. 2017 and CSR (25).

Outcome measure	Momelotinib (N=215)	Ruxolitinib (N=217)	Result
SRR at week 24	57 (26.5%, 95% CI: 20.7%, 32.9%)	63 (29.0%, 95% CI: 23.5%, 36.0%)	The non-inferiority proportion difference in response: 0.09 (95% CI: 0.02, 0.16 and p<0.011), stratified CMH method

Outcome measure	Momelotinib (N=211)	Ruxolitinib (N=211)	Result
TSS response rate at week 24	60 (28.4%, 95% CI: 22.5%, 35.0%)	89 (42.2%, 95% CI: 35.4%, 49.2%)	The non-inferiority proportion difference: 0.00 (95% CI: -0.08, 0.08 and p=0.98), stratified CMH method

Outcome measure	Momelotinib (N=214)	Ruxolitinib (N=216)	Result
OS at week 24	[redacted]	[redacted]	[redacted]
OS at week 48	[redacted]	[redacted]	[redacted]
OS final analysis	[redacted]	[redacted]	[redacted]

Notes:
SRR and TSS confidence intervals are calculated with the Clopper Pearsons exact method without stratification. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.

7. Comparative efficacy analyses in JAKi-naïve patients

7.1.1 Differences in definitions of outcomes between studies

Not applicable due to head-to-head study; see section 6.

7.1.2 Method of synthesis

Not applicable due to head-to-head study.

7.1.3 Results from the comparative analysis

Please see Table 9.

7.1.4 Efficacy results

Not applicable due to head-to-head study; see section 6.

8. Modelling of efficacy in the health economic analysis

The health economic analysis in the present application is a cost-minimisation analysis; thus, this section is not relevant and has not been completed, and subheadings have been deleted.

9. Safety outcomes in JAKi-naïve patients

In this section we present safety data on JAKi-naïve patients from SIMPLIFY-1 on momelotinib vs ruxolitinib and data from the ITC on safety outcomes on momelotinib and fedratinib.

9.1 Safety from SIMPLIFY-1: momelotinib vs ruxolitinib

The safety analysis set for the double-blind phase of the SIMPLIFY-1 trial consisted of all subjects in the ITT analysis set, who received at least one dose of momelotinib (214 subjects) or ruxolitinib (216 subjects). Through week 24, the median duration of exposure to study treatment was 23.9 (range: 0.3-26.1) weeks in the momelotinib group and 24.0 (range: 1.3-26.9) weeks in the ruxolitinib group.

An overview of safety events in the double-blind treatment phase (24 weeks) is presented in Table 10. The table shows that during the double-blind treatment phase, a greater proportion of subjects randomised to ruxolitinib experienced a dose reduction or interruption compared with subjects randomised to momelotinib (56.0% versus 26.2%).

A large percentage of subjects in both groups, i.e. 92.5% of subjects in the momelotinib group and 95.4% of subjects in the ruxolitinib group had at least one AE, with treatment-related Aes (adverse reactions) reported for 65.0% and 66.2% of subjects, respectively. Aes leading to discontinuation of the study drug were reported for 13.1% of subjects in the momelotinib group and 5.6% of subjects in the ruxolitinib group. The total number of Aes, number of SAEs, number of CTCAE Grade ≥3 events, and number of adverse reactions reported in the study were not reported in the CSR.

In the double-blind treatment phase of SIMPLIFY-1, the most frequently reported Aes by treatment group were thrombocytopenia (18.7%, 95% CI: 13.5%, 23.9%), diarrhoea (18.2%, 95% CI: 13.1%, 23.4%), and headache (17.8%, 95% CI: 12.6%, 22.9%) for momelotinib. For ruxolitinib, it was anaemia (37.5%, 95% CI: 31.0%, 44.0%), thrombocytopenia (29.2%, 95% CI: 23.1%, 35.2%), diarrhoea (19.9%, 95% CI: 14.6%, 25.2%), and headache (19.9%, 95% CI: 14.6%, 25.2%). The overall safety profile for momelotinib was generally similar to ruxolitinib for non-hematologic Aes; however, there were notable differences in hematologic thrombocytopenia and anaemia Aes for the two groups, as 18.7% and 14.5% of subjects in the momelotinib group experienced thrombocytopenia and anaemia, respectively, compared to 29.2% and 37.5% in the ruxolitinib group.

Overall, during the double-blind phase, SAEs were reported in a similar proportion between the two groups but the rate of SAEs reported was marginally higher in the momelotinib group: 22.9% (95% CI: 17.3%, 28.5%) of subjects compared to 18.1% (95% CI: 12.9%, 23.2%) of subjects in the ruxolitinib group. However, when evaluated on an individual event basis, the difference between the two groups was small and not driven by any single preferred term.

According to the DMC application template, a list of all SAEs with frequency of ≥5% recorded in the study should be presented. However, no SAEs had a frequency of ≥5% in the double-blind treatment phase; thus, this list could not be provided. A full list of SAEs reported in the study is presented in Appendix E.

Table 10 Overview of safety events in the double-blind treatment phase (24 weeks) from the safety analysis set. Source: Mesa et al. 2017 and CSR (data on file).

	Momelotinib (N=214)	Ruxolitinib (N=216)	Difference, % (95% CI)
Number of Aes, n	The total number of Aes observed in the study was not reported		NA
Number and proportion of patients with ≥1 AE, n (%)	198 (92.5%, 95% CI: 89.0%, 96.0%)	206 (95.4%, 95% CI: 92.6%, 98.2%)	Absolute difference: -2.8% (95% CI: -7.3%, 1.7%)

	Momelotinib (N=214)	Ruxolitinib (N=216)	Difference, % (95% CI)
			Relative difference: 0.97 (95% CI: 0.92, 1.02)
Number of SAEs*, n	The total number of SAEs observed in the study was not reported		NA
Number and proportion of patients with ≥1 SAEs, n (%)	49 (22.9%, 95% CI: 17.3%, 28.5%)	39 (18.1%, 95% CI: 12.9%, 23.2%)	Absolute difference: 4.8% (95% CI: -2.8%, 12.5%) Relative difference: 1.27 (95 CI: 0.87, 1.85)
Number of CTCAE Grade ≥3 events, n	Not reported	Not reported	NA
Number and proportion of patients with ≥1 CTCAE Grade 3 events, n (%)*	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	Not reported	Not reported	NA
Number and proportion of patients with ≥1 treatment-emergent adverse events (TEAE) related to study drug, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction or interruption, n (%)	56 (26.2%, 95% CI: 20.3%, 32.1%)	121 (56.0%, 95% CI: 49.4%, 62.6%)	Absolute difference: -29.9% (95% CI: -38.7%, -21.0%) Relative difference: 0.47 (95% CI: 0.36, 0.60)
Number and proportion of patients who discontinued treatment regardless of reason, n (%)	40 (18.6%, 95% CI: 13.5%, 23.9%)	16 (7.4%, 95% CI: 3.9%, 10.9%)	Absolute difference: 11.3% (95% CI: 5.0%, 17.6%) Relative difference: 2.52 (95% CI: 1.46, 4.37)
Number and proportion of patients who discontinued	28 (13.1%, 95% CI: 8.6%, 17.6%)	12 (5.6%, 95% CI: 2.5%, 8.6%)	Absolute difference: 7.5% (95% CI: 2.1%, 13.0%)

	Momelotinib (N=214)	Ruxolitinib (N=216)	Difference, % (95% CI)
treatment due to Aes, n (%)			Relative difference: 2.36 (95% CI: 1.23, 4.51)

*Severity grades were defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

9.2 Safety outcomes from the ITC on JAKi-naïve patients: momelotinib vs fedratinib

The ITC compared safety outcomes between momelotinib and fedratinib. The MAIC approach was used in the ITC with individual patient-level data (IPD) from momelotinib trials, and publicly available aggregate data was retrieved for fedratinib trials reported in available journal articles, conference abstracts, Food and Drug Administration (FDA) regulatory documents, and EMA regulatory documents. The ITC is attached to the application.

The analyses of JAKi-naïve patients were based on the once-daily 200 mg momelotinib group from the SIMPLIFY-1 trial and the once-daily 400 mg fedratinib group from the JAKARTA trial. Outcomes were analysed over the 24-week trial period in the safety population (i.e. patients who received at least one dose of treatment). The safety outcomes included in the analysis were TEAEs that occurred in ≥10% of patients in either the momelotinib or fedratinib groups of the eligible trials. Outcomes meeting this criterion included occurrence of specific Aes (anaemia, thrombocytopenia, diarrhoea, headache, dizziness, abdominal pain, nausea, and fatigue), any Grade 3 or 4 Aes, SAEs, SAEs leading to treatment discontinuation, and SAEs leading to dose reduction. Aes were defined by the National Cancer Institute's (NCI) CTCAE versions v.3.0, v.4.0, and v.5.0.

9.2.1 Description of studies used in the ITC on JAKi-naïve patients

The SIMPLIFY-1 trial was described in section 6. JAKARTA was a phase 3, multicentre, randomised, double-blind, three-armed study, where patients were randomised 1:1:1 either to placebo (N=96), 400 mg fedratinib once daily (N=96), or 500 mg fedratinib once daily (N=97). The study included patients with MF (primary or post-ET/PV-MF), who were in intermediate-2 or high-risk groups and had an enlarged spleen. Patients were allowed to have received prior disease-specific treatments for MF but no other JAK inhibitors. Patients in the placebo arm could cross over to active treatment (randomised 1:1 between 400 and 500 mg fedratinib) when experiencing progressive disease or after having received six treatment cycles (corresponding to 24 weeks). The primary endpoint in the trial was splenic response defined as the proportion of patients who experienced a reduction of ≥35% in spleen volume relative to baseline after 24 weeks of treatment and with the reduction confirmed four weeks later. A key secondary endpoint was reduction of ≥50% in TSS at week 24 measured with MF-SAF relative to baseline. JAKARTA was planned to run for 55 months to ensure adequate follow-up to detect potential differences in overall survival. The study was prematurely stopped by the FDA, as a few patients in the

fedratinib arm developed symptoms of Wernicke's encephalopathy. All patients on fedratinib or placebo treatment were stopped at a median treatment duration of 14 months (400 mg fedratinib). For more information on the JAKARTA study, please see Appendix A.

9.2.2 Safety results from the ITC on JAKi-naïve patients

[redacted]

An overview of safety outcomes from the ITC is presented in Table 11. As seen, momelotinib showed a more favourable safety profile relative to fedratinib in JAKi-naïve patients. Momelotinib was particularly associated with significantly lower risk of key haematological and gastrointestinal Aes over 24 weeks.

Table 11 Comparison of safety outcomes between momelotinib and fedratinib in JAKi-naïve patients. Source: ITC (data on file).

	Percentage of patients with the outcome			Adjusted[1] comparison (momelotinib relative to fedratinib)		
	Fedratinib	Momelotinib (unadj.)	Momelotinib (adjusted)	Risk difference (%)[2]	RR[3]	Odds ratio[3]
[redacted]						

Notes:

1. Adjusted for IPSS (intermediate, high), mean TSS (using MF-SAF v2.0 criteria), platelets (<100 vs ≥100 x 10^9/L), spleen volume (<Median vs ≥Median value reported in JAKARTA), and Hb (<Median vs ≥Median value reported in JAKARTA). ESS for MMB after adjustment is 151.1.
2. Risk differences reflect the difference in percentage points between the absolute risks in each group. Risk differences <0 indicate lower risk of outcome for momelotinib relative to fedratinib; risk differences >0 indicate higher risk of outcome for momelotinib relative to fedratinib.
3. Risk/odds ratios <1 indicate lower risk/odds of outcomes for momelotinib relative to fedratinib; risk/odds ratios >1 indicate higher risk/odds of outcomes for momelotinib relative to fedratinib.

9.3 Safety data from external literature applied in the health economic model

No external literature was used to inform safety data in the health economic model.

10. Efficacy of momelotinib in JAKi-experienced patients

10.1 Efficacy of momelotinib in JAKi-experienced patients

10.1.1 Relevant studies

The efficacy of momelotinib in JAKi-experienced patients has been assessed in the SIMPLIFY-2 study and the MOMENTUM study.

SIMPLIFY-2 was a phase 3, randomised, open-label, multicentre study that assessed the efficacy of momelotinib compared to BAT in patients with PMF, post-PV MF, or post-ET MF whose prior treatment with ruxolitinib was associated with anaemia and/or thrombocytopenia.

Patients were randomly assigned in a 2:1 ratio to either 24 weeks of open-label momelotinib 200 mg once a day or BAT, which included ruxolitinib, chemotherapy, steroids, no treatment, or other standard interventions, after which all patients could receive extended momelotinib treatment. Results were analysed on an ITT basis, and the ITT population comprised 156 patients: 104 received momelotinib and 52 received BAT. Among the 104 subjects randomised to momelotinib, 77 subjects (74.0%) completed the randomised phase and 69 subjects (66.3%) completed 24 weeks of study treatment in the randomised phase, i.e. 35 subjects (33.7%) randomised to momelotinib discontinued

study treatment during the randomised phase. The 27 subjects that discontinued the randomised treatment phase did so due to Aes (6 subjects), death (5 subjects), investigator discretion (4 subjects), subject decision (8 subjects) and disease progression (4 subjects). In the BAT arm, 11 subjects discontinued the randomised treatment phase and did so due to death (4 subjects), investigator discretion (1 subject), subject decision (4 subjects), symptomatic spleen growth (1 subject) and disease progression (1 subject).

MOMENTUM was a phase 3, international, randomised, double-blind, active-controlled study that assessed the differentiated clinical benefit of momelotinib versus danazol in approximately 180 symptomatic, anaemic subjects with MF who previously received JAK inhibitor therapy.

Patients were randomly assigned in a 2:1 ratio to receive either momelotinib plus danazol placebo (i.e. the momelotinib group) or danazol plus momelotinib placebo (i.e. the danazol group). One hundred ninety-five patients were enrolled and received blinded study treatment in the 24-week randomised treatment period (130 in the momelotinib group and 65 in the danazol group). Among the 130 subjects in the momelotinib group and 65 subjects in the danazol group that were randomly assigned to treatment and received blinded study drug in the randomised treatment period, 94 subjects (72.3%) in the momelotinib group and 38 subjects (58.5%) in the danazol group completed randomised treatment. For subjects who discontinued randomised treatment early, Aes were the most common reason overall in both groups (16 subjects, 12.3% for momelotinib and 11 subjects, 16.9% for danazol) followed by subject decision (6, 4.6% momelotinib; 5, 7.7% danazol), insufficient efficacy (6, 4.6% for momelotinib and 3, 4.6% for danazol), death (4, 3.1% for momelotinib and 3, 4.6% for danazol), leukemic transformation (2, 1.5% for momelotinib and 2, 3.1% for danazol), disease progression (1, 0.8% for momelotinib and 2, 3.1% for danazol), lost to follow-up (1, 0.8% for momelotinib and 0 for danazol) and investigator discretion (0 for momelotinib and 1, 1.5% for danazol).

Table 12 Overview of study design of SIMPLIFY-2 and MOMENTUM

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
SIMPLIFY-2 (NCT02101268)	Randomised, phase 3, open-label, multicentre trial	Randomised phase: 24 weeks and extended phase: 168 weeks. The mean duration of exposure to momelotinib was 19.5 weeks (SD 7.7), median 23.9 (IQR 15-9-24.0) and 21.0 weeks (SD 6.9), median 24.1 (IQR 23.7-24.3) for BAT.	Patients with PMF, post-PV MF, or post-ET MF whose prior treatment with ruxolitinib was associated with anaemia and/or thrombocytopenia.	Momelotinib 200 mg tablet once daily	Regimens for BAT could include but were not limited to chemotherapy (e.g. hydroxyurea), anagrelide, a corticosteroid, hematopoietic growth factor, an immunomodulating agent, androgen, or interferon and may include no MF treatment as well as more than 1 treatment.	**Primary endpoint** • Reduction by at least 35% in the spleen volume at 24 weeks compared with baseline, as assessed by MRI or CT scans. **Secondary endpoints** • TSS response at week 24 (proportion of patients who achieved a reduction from baseline to week 24 based on the modified MPN-SAF TSS diary) • RBC transfusion (average number of RBC units per patient-month) • RBC TI at week 24 (proportion of patients who were transfusion-independent at week 24 [absence of RBC transfusions and no Hb <8 g/dL in the previous 12 weeks]) • RBC TD at week 24 (proportion of subjects who were transfusion dependent at week 24, where TD was defined as at least 4 units of RBC transfusion or a Hb level below 8 g/dL in the prior 8 weeks excluding cases associated with clinically overt bleeding. **Exploratory endpoints related to splenic response** • Splenic response rate over time • Percent change from baseline in spleen volume over time • Palpable spleen size and percent change from baseline over time • Duration of spleen response

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						Exploratory endpoints related to symptom response and patient reported outcomes • TSS response every four weeks • PGIC • MPN-SAF • EQ-5D-5L • SF-36v2 **Exploratory endpoints related to anaemia response** • RBC TI rate by week 24 • RBC TD rate by week 24 • New RBC TI rate by week 24 • New RBC TD rate by week 24 • RBC transfusion-free response rate over time • Hb, platelets, or ANC, change and percent change from baseline over time • Rate of RBC transfusion in the ET phase • Duration of TI response for subjects not TI at baseline and who achieved TI at any post-baseline in the RT phase • Time to TI for subjects not TI at baseline and who achieved TI at any post-baseline in the RT phase • Anaemia response rate at week 24 based on IWG-MRT/ELN criteria

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
MOMENTUM (NCT04173494)	International, double-blind, randomised, controlled, phase 3 study	The mean duration of randomised treatment was 20.6 weeks (SD: 6.2) in the momelotinib group and 17.3 weeks (SD: 8.0) in the danazol group. The maximum exposure to momelotinib was 60.7 weeks at the time of data cutoff.	The population comprised symptomatic, anaemic subjects with MF previously treated with an approved JAK inhibitor.	Starting dose of momelotinib 200 mg by mouth once daily, preferably in the morning at a consistent time each day	Starting dose of danazol 600 mg (total daily dose) by mouth administered in the morning and evening in two divided doses	**Primary endpoint** • MF-SAF TSS response rate at week 24 **Key secondary** • TI rate at week 24 • SRR at week 24 based on ≥25% and ≥35% reductions in spleen volume from baseline • Change in MF-SAF TSS from baseline at week 24 • Rate of no transfusion at week 24 **Other secondary** • Duration of MF-SAF TSS response at week 24 • Duration of TI at week 24 • Transfusion and Hb endpoints of transfusion requirements, cumulative transfusion risk at week 24, TD rate at week 24, and Hb responses • Proportion and duration of TI at week 24 in subjects with baseline TD • Safety assessments including the type, frequency, severity, timing of onset, duration, and relationship to study drug of any Aes or abnormalities of laboratory tests, as well as SAEs or Aes leading to discontinuation of study drug • OS and LFS • Changes in disease-related fatigue (assessed by MF-SAF), cancer-related fatigue (assessed by EORTC QLQ-C30), and physical

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						function score (assessed by PROMIS) from baseline at each evaluation time point **Exploratory endpoints** • Changes in EQ-5D index and VAS scores and MF-8D classification from baseline at each evaluation time point • Correlation of plasma concentration of MMB and results of efficacy assessment • MF-SAF TSS response rate at week 24 in baseline TD, TI, and non-TD subsets • Time from first dose to symptomatic splenic progression • Measures of symptom and anaemia response and exploratory analyses including but not limited to mutational analysis • Hospitalisation rates, transfusion rates, and utilisation of other medical care during the 24-week randomised treatment period and study • TI rate at week 24 by baseline ferritin level

10.1.2 Comparability of studies

Both the SIMPLIFY-2 and the MOMENTUM trials were international randomised phase 3 trials, and both trials included MF or post-PV/ET MF patients who were JAKi experienced. Patients in the MOMENTUM trial were also symptomatic (defined as MF-SAF TSS ≥10) and anaemic (defined as Hb <10 g/dL) at screening. The studies are not compared in an indirect comparative analysis but are included to demonstrate the efficacy of momelotinib in JAKi-experienced MF patients with anaemia.

10.1.2.1 Comparability of patients across studies

Table 13 presents the baseline characteristics from the studies used to demonstrate the efficacy and safety of momelotinib in JAKi-experienced patients. In addition to SIMPLIFY-2 and MOMENTUM, the JAKARTA-2 trial was also presented, as this trial on fedratinib was used in the ITC on safety outcomes.

The JAKARTA-2 study was difficult to compare with the momelotinib studies, as Harrison et al. 2017 did not report many of the same baseline characteristics as reported in the momelotinib studies as seen in Table 13. Age, gender, MF subtype, and risk category were reported in all studies. In terms of age, the median age of 67 years in JAKARTA-2 was lower compared to the momelotinib studies, where the median age was 71 and 72 years in MOMENTUM and 67 and 69.5 years in SIMPLIFY-2. The share of male subjects in JAKARTA-2 was 55% and slightly lower than the SIMPLIFY-2 and MOMENTUM studies, where 59.6% and 63.1% of the total population were males, respectively. JAKARTA-2 had a higher proportion of subjects with post-PV than the momelotinib studies and a lower proportion of subjects with PMF. The proportion with post-ET was comparable with the momelotinib studies. JAKARTA-2 had a higher proportion of high-risk subjects than SIMPLIFY-2 but a similar proportion when compared to MOMENTUM. The other baseline characteristics could not be compared.

Table 13 Baseline characteristics of patients in SIMPLIFY-2 and MOMENTUM

	SIMPLIFY-2 (27)		MOMENTUM (30)		JAKARTA-2 (36)
	Momelotinib (N=104)	**BAT (N=52)**	**Momelotinib (N=130)**	**Danazol (N=65)**	**Fedratinib (N=97)**
Age, mean (SD)	Mean (SD): 66.4 (8.1)	Mean (SD): 69.4 (7.4)	Median (IQR): 71 (65-75)	Median (IQR): 72 (67-78)	Median (IQR): 67 (62-72)
Males, n (%)	69 (66%)	24 (46%)	79 (61%)	44 (68%)	53 (55%)
Body-mass index, kg/m², mean (SD)	26.7 (4.8)	26.2 (3.8)	25.2 (3.7)	25.7 (6.0)	-
Ethnic origin, n (%)					

	SIMPLIFY-2 (27)		MOMENTUM (30)		JAKARTA-2 (36)
	Momelotinib (N=104)	BAT (N=52)	Momelotinib (N=130)	Danazol (N=65)	Fedratinib (N=97)
White	83 (80%)	44 (85%)	107 (82%)	50 (77%)	-
Black	6 (6%)	0	2 (2%)	2 (3%)	-
Not reported	15 (14%)	8 (15%)	-	-	-
Hispanic or Latino	5 (5%)	4 (8%)	5 (4%)	6 (9%)	-
Asian	-	-	12 (9%)	6 (9%)	-
MF subtype					
Primary	64 (62%)	30 (58%)	78 (60%)	46 (71%)	53 (55%)
Post-PV	18 (17%)	12 (23%)	27 (21%)	11 (17%)	25 (26%)
Post-ET	22 (21%)	10 (19%)	25 (19%)	8 (12%)	19 (20%)
DIPSS risk category					
Intermediate-1	23 (22%)	16 (31%)	7 (5%)	3 (5%)	16 (16%)
Intermediate-2	62 (60%)	28 (54%)	72 (55%)	40 (62%)	47 (48%)
High	19 (18%)	8 (15%)	50 (38%)	19 (29%)	34 (35%)
Missing	-	-	1 (1%)	3 (5%)	-
Total symptom score	18.5 (13.0)	20.5 (16.0)	-	-	-
ECOG performance status					
0	36 (35%)	19 (37%)	16 (12%)	15 (23%)	-
1	61 (59%)	26 (50%)	83 (64%)	34 (52%)	-
2	7 (7%)	7 (14%)	31 (24%)	16 (25%)	-
Duration of ruxolitinib treatment before randomisation, weeks					
Missing data	13 (13%)	9 (17%)	-	-	-

	SIMPLIFY-2 (27)		MOMENTUM (30)		JAKARTA-2 (36)
	Momelotinib (N=104)	**BAT (N=52)**	**Momelotinib (N=130)**	**Danazol (N=65)**	**Fedratinib (N=97)**
<12 weeks	16 (15%)	10 (19%)	-	-	-
≥12 weeks	75 (72%)	33 (64%)	-	-	-
Mean previous JAK inhibitor duration (weeks)	-	-	138.5 (123.0)	124.8 (120.0)	-
JAK2 Val617Phe mutation					
Previously tested	101 (97%)	49 (94%)	-	-	-
Previously tested positive	69 (66%)	37 (71%)	97 (75%)	51 (78%)	-
Previously tested negative	31 (31%)	12 (23%)	28 (22%)	12 (18%)	-
Not previously tested	3 (3%)	3 (6%)	-	-	-
Unknown or missing	-	-	5 (4%)	2 (3%)	7 (7%)
JAK2 mutational profile					
Wild type	-	-	-	-	29 (30%)
Mutant	-	-	-	-	61 (63%)
Hb g/dL, mean (SD)	9.4 (1.9)	9.5 (1.6)	8.1 (1.1)	7.9 (0.8)	-
Hb, ≥8 g/dL	77 (74%)	46 (89%)	67 (52%)	33 (51%)	-
Transfusion independent					
Yes	32 (31%)	19 (37%)	17 (13%)	10 (15%)	-
No	58 (56%)	27 (52%)	63 (48%)	34 (52%)	-

	SIMPLIFY-2 (27)		MOMENTUM (30)		JAKARTA-2 (36)
	Momelotinib (N=104)	BAT (N=52)	Momelotinib (N=130)	Danazol (N=65)	Fedratinib (N=97)
Platelet count, x 10^2 platelets per µL, mean (SD)	170.8 (148.0)	126.5 (95.9)	-	-	-
Platelet count, <50 × 10^9/L	-	-	-	-	1 (1%)
Platelet count, 50 × 10^9/L to <100 × 10^9/L	-	-	-	-	32 (33%)
≥100 × 10^9/L	-	-	-	-	64 (66%)
Absolute neutrophil count, x 10^2 cells per µL, mean (SD)	10.2 (13.5)	8.0 (9.9)	-	-	-
Platelet count (× 10^9 cells per L)	-	-	Mean (SD): 151.7 (130.9) Median (IQR): 97 (60-196)	Mean (SD): 130.7 (101.0) Median (IQR): 94 (54-175)	-
Neutrophil count (× 10^9 cells per L)	-	-	Mean (SD): 8.6 (11.3) Median (IQR): 4.7 (2.3-8.8)	Mean (SD): 6.9 (8.3) Median (IQR): 3.6 (1.9-7.7)	-
Peripheral blasts (%)	-	-	Mean (SD): 2.1 (2.9) Median (IQR): 1 (0-3)	Mean (SD): 1.9 (2.0) Median (IQR): 1 (1-2)	-
TSS					
Mean	-	-	28.0 (13.8)	25.7 (12.8)	-
Median	-	-	26.4 (16.7-38.0)	23.6 (15.3-36.1)	-

	SIMPLIFY-2 (27)		MOMENTUM (30)		JAKARTA-2 (36)
	Momelotinib (N=104)	BAT (N=52)	Momelotinib (N=130)	Danazol (N=65)	Fedratinib (N=97)
≥22	-	-	77 (59%)	39 (60%)	-
Red blood cell units transfused ≤8 weeks before randomisation					
0	-	-	28 (22%)	13 (20%)	-
1-4	-	-	58 (45%)	27 (42%)	-
≥5	-	-	44 (34%)	25 (38%)	-
Central spleen volume (cm^3)					
Mean (SD)	-	-	2367 (1302)	2288 (1155)	-
Median (IQR)	-	-	2112 (1445–2955)	2059 (1446–2817)	-
Palpable spleen length below the left costal margin ≥12 cm	-	-	55 (42%)	28 (43%)	-

10.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The clinical experts were consulted in terms of the comparability of the study populations and the Danish patient population. The experts commented that the populations in SIMPLIFY-2 and MOMEMNTUM were in general similar to the Danish patient population and did not have any remarks in terms of important differences.

10.1.4 Efficacy – results per SIMPLIFY-2

Splenic response rate at week 24

The primary endpoint of superiority on SRR at week 24 was not met in SIMPLIFY-2. A similar proportion of subjects in the ITT population achieved a splenic response: in the momelotinib group it was achieved by 7 out of 104 subjects (7%, 95% CI: 2.8%, 13.4%) compared with 3 out of 52 subjects in the BAT group (6%, 95% CI: 1.2%, 15.9%), with the proportion difference with the stratified CMH method being 0.01 (95% CI: -0.09, 0.10, p=0.90). Certain unintended study design discrepancies may have contributed to the failure of the primary splenic response endpoint in this study: The study was, de facto, a head-to-head study comparing momelotinib with ruxolitinib, as 88% of subjects in the BAT group were treated with ruxolitinib. Moreover, subjects did not have a wash-out period

for prior ruxolitinib treatment before randomisation. Lack of a wash-out period did not allow for the baseline spleen size to be reset, potentially impacting the assessment of a subsequent splenic response. Additional therapies were not allowed for subjects in the momelotinib group, while subjects who received ruxolitinib in the BAT group were allowed other concurrent or sequential MF therapies.

Total symptom score at week 24

Despite cessation of further formal statistical testing, a substantially higher, and nominally statistically superior, TSS response rate at week 24 was observed in momelotinib-treated subjects in the ITT population compared to those in the BAT control group: 27 out of 103 subjects (26%, 95% CI: 18.0%, 35.8%) and 3 out of 51 subjects (6%, 95% CI: 12.3%, 16.2%) in the momelotinib and BAT group, respectively, indicating a four- to five-fold greater symptomatic response improvement in subjects who received momelotinib compared to BAT. The proportion difference with the stratified CMH method [redacted]. Of the 3 responders in the BAT group, 2 subjects were treated with ruxolitinib, 1 of whom was also treated with hydroxyurea. The third responder had no treatment for MF during the 24-week randomised-treatment phase.

Overall survival

[redacted] These analyses suggest that the survival rate was similar in the momelotinib group and the BAT group, in which approximately 88% of subjects were treated with ruxolitinib, followed by a switch to momelotinib after week 24 in 40 of the 52 subjects in the control group. The Kaplan-Meier plot is shown in [redacted]

Mesa et al. 2022 (41) presents mature analyses of OS observed with extended momelotinib treatment in the SIMPLIFY-1 and SIMPLIFY-2 studies. In addition, patients whose disease did not progress and who tolerated momelotinib treatment while enrolled in SIMPLIFY-1 or SIMPLIFY-2 were eligible to enrol in an ongoing open-label, extended access protocol (NCT03441113) at the completion of these phase 3 studies. Survival data captured during this extension protocol were also included in the analyses presented in

Mesa et al. 2022 (41). OS was analysed using Kaplan-Meier analyses and compared between groups with stratified log-rank tests and proportional hazard Cox regression models stratified by randomisation stratification factors. OS was calculated as time from first dose of study drug to death of any cause.

At a median follow-up of 3.43 years in the momelotinib arm and 3.47 years in the ruxolitinib arm of SIMPLIFY-1, 66 (30.8%) patients in the momelotinib arm and 73 (33.8%) patients in the ruxolitinib arm who crossed over to momelotinib had died. The OS HR between ruxolitinib to momelotinib crossover patients and patients originally randomised to momelotinib was 1.02 (95% CI: 0.73, 1.43). The OS rates at 2, 4 and 6 years were 81.6%, 62.9% and 56.5% in the momelotinib arm and 80.6%, 64.4%, and 52.7% in the ruxolitinib to momelotinib crossover arm. At a median follow-up of 3.22 years in SIMPLIFY-2 in the BAT/ruxolitinib arm and 3.07 years in the momelotinib arm of SIMPLIFY-2, 47 (45.2%) momelotinib-randomised patients and 23 (44.2%) BAT/ruxolitinib to momelotinib crossover patients had died. Median OS from baseline was 3.1 (95% CI: 1.8, NE) years in BAT/ruxolitinib to momelotinib crossover patients and 2.9 (95% CI: 2.3, NE) years in originally momelotinib-randomised patients with a HR=0.98 (95% CI: 0.59, 1.62). The OS rate at 2 years was 65.8% in the momelotinib arm and 61.2% in the BAT/ruxolitinib to momelotinib crossover arm.

Mesa et al. 2022 (41) presents mature survival data from the two phase 3 SIMPLIFY trials, which demonstrate that extended treatment with momelotinib is associated with excellent OS, regardless of whether a JAKi-naïve patient was initially randomised to momelotinib or to ruxolitinib followed by momelotinib in SIMPLIFY-1, or whether a previously ruxolitinib-treated patient was initially randomised to momelotinib or to BAT/ruxolitinib followed by momelotinib in SIMPLIFY-2. In the SIMPLIFY-1 non-inferiority study, the two treatment arms produced nearly identical OS outcomes, providing confidence that survival is similar for patients whose initial frontline JAKi is momelotinib or ruxolitinib.

Results on SRR, TSS, and OS are summarised in Table 14.

Table 14 Results from SIMPLIFY-2 (ITT population, safety population for OS. Randomised treatment phase). Source: CSR and Harrison et al. 2017 (25, 34).

Outcome measure	Momelotinib (N=104)	BAT (N=52)	Result
SRR at week 24	7 (7%, 95% CI: 2.8%, 13.4%)	3 (6%, 95% CI: 1.2%, 15.9%)	Proportion difference, stratified CMH method: 0.01 (95% CI: -0.09, 0.10, p=0.90)
Outcome measure	**Momelotinib (N=103)**	**BAT (N=51)**	**Result**
TSS response rate at week 24	27 (26%, 95% CI: 18.0%, 35.8%)	3 (6%, 95% CI: 12.3%, 16.2%)	The proportion difference with the stratified CMH: [redacted]

Outcome measure	Momelotinib (N=104)	BAT (N=52)	Result
Outcome measure	Momelotinib (N=104)	BAT (N=52)	Result*
OS at week 24	[redacted]	[redacted]	[redacted]
OS at week 48	[redacted]	[redacted]	[redacted]
OS, final analysis	[redacted]	[redacted]	[redacted]

Notes:
SRR and TSS confidence intervals were estimated with the Clopper Pearson exact method without stratification. Death in randomised-treatment phase is death occurring on or after the first randomised-treatment dose up to the earliest of the last randomised-treatment dose plus 30 days, or the first extended-treatment dose minus one day. Death in the extended-treatment phase is death occurring on or after the first extended-treatment dose up to the last extended-treatment momelotinib dose plus 30 days. Death in the follow-up phase is death occurring after 30 days of the last dose in the randomised-treatment or extended-treatment phase, whichever was latest. Overall survival (months) = (date of death or censoring – date of first dose in the RT phase + 1) / 30.4375.
*Absolute differences were calculated based on the HR and rate in the comparator arm.

10.1.5 Efficacy – results per MOMENTUM

Splenic response rate at week 24

The SRR at week 24 outcome (proportion with a ≥35% reduction in spleen volume from baseline at week 24) was met and demonstrated momelotinib to be statistically significantly superior to danazol. Thirty subjects out of 130 in the momelotinib group (23%, 95% CI: 16%, 31%) and 2 out of 65 subjects in the danazol group (3%, 95% CI: 0%, 11%) achieved the reduction, with a difference in proportions of 19% (95% CI: 11%, 28%, p=0.0006)(30).

Total symptom score at week 24

The MOMENTUM trial met the primary efficacy endpoint of statistically significant superiority of momelotinib over danazol in the proportion of subjects with ≥50% reduction from baseline at week 24 in MF-SAF TSS: The MF-SAF TSS response rate was 25% (95% CI: 17%, 33%) for the momelotinib group and 9% (95% CI: 4%, 19%) for the danazol group, with a difference in proportions of 16% (95% CI: 6%, 26%, p=0.0095) (30).

Overall survival

During the entire treatment period including both the randomised-treatment phase (24 weeks) and the open-label treatment phase (48 weeks), a total of 41 deaths occurred, in 25 of 130 subjects (19%) from the former randomised momelotinib group and 16 of 65 subjects (25%) from the former randomised danazol group. The HR was estimated to 0.73 (95% CI: 0.38, 1.41, log-rank test p=0.3510), a trend favouring momelotinib. The median OS was not reached in either group. The median follow-up time for OS was 275 days (95%

CI: 238, 314; range 41-476), with 105 (81%) of 130 patients censored in the momelotinib group, and 295 days (95% CI: 233, 333; range 26-523) with 49 (75%) of 65 censored in the danazol group (30) (see Figure 6).

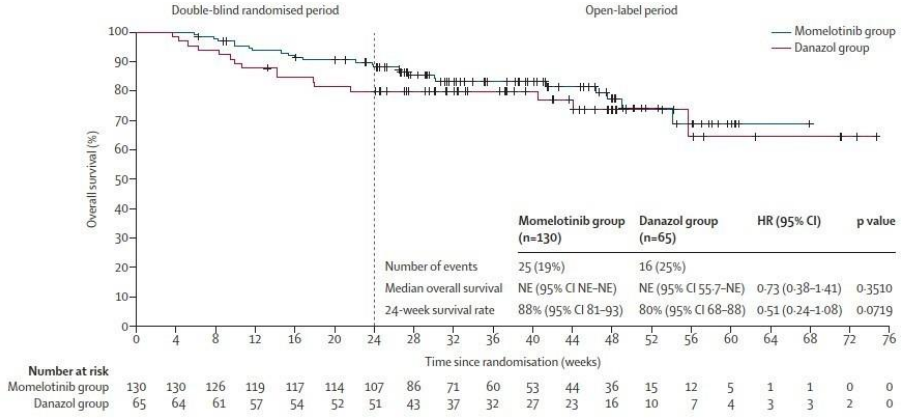


Figure 6 Overall survival in the ITT population. Source: Verstovsek et al. 2023 (30).

Table 15 Results from MOMENTUM (ITT population). Source: CSR and Verstovsek et al. 2023 (37, 38).

Outcome measure	Momelotinib (N=130)	Danazol (N=65)	Result
SRR at week 24	30 (23%, 95% CI: 16%, 31%)	2 (3%, 95% CI: 0%, 11%)	Stratified CMH difference: 19% (95% CI: 11, 28, p=0.0006)
Outcome measure	**Momelotinib (N=130)**	**Danazol (N=65)**	**Result**
TSS response rate at week 24	32 (25%, 95% CI: 17%, 33%)	6 (9%, 95% CI: 3%, 19%)	Stratified CMH difference: 16% (95% CI: 6, 26, p=0.0095)
Outcome measure	**Momelotinib (N=130)**	**Danazol (N=65)**	**Result**
OS (entire treatment period)	25 (19%, 95% CI: 12%, 26%)	16 (25%, 95% CI: 14%, 35%)	Absolute differences in OS rates: 13% (95% CI: -10%, 32%) HR: 0.7 (95% CI: 0.4, 1.4), log-rank test p=0.3510

Notes:

TSS and SRR confidence intervals are exact binomial intervals. Two-sided p-value from CMH test using baseline MF-SAF TSS (<22 vs ≥22), baseline palpable spleen length below the left costal margin (<12 vs ≥12 cm), and baseline RBC or whole blood units transfused in the eight-week period before randomisation (0, 1-4, ≥5 units) as strata.

11. Comparative analyses of efficacy

No comparative analysis of efficacy in JAKi-experienced patients will be presented in the present application due to lack of appropriate evidence to use in an indirect comparative analysis of efficacy of momelotinib and fedratinib.

11.1.1 Differences in definitions of outcomes between studies

Not applicable.

11.1.2 Method of synthesis

Not applicable.

11.1.3 Results from the comparative analysis

Not applicable.

11.1.4 Efficacy – results per [outcome measure]

Not applicable.

12. Modelling of efficacy in the health economic analysis

The health economic analysis in the present application is a cost-minimisation analysis; thus, this section is not relevant and has not been completed, and subheadings have been deleted.

13. Safety outcomes of JAKi-experienced patients

13.1 Safety data from the ITC on JAKi-experienced patients: momelotinib vs fedratinib

The ITC compared safety outcomes between momelotinib and fedratinib. The method used in the ITC was described in section 9.

The analyses of JAKi-experienced patients were based on pooled data from the once-daily 200 mg momelotinib group of the SIMPLIFY-2 and MOMENTUM trials and the once-daily

400 mg fedratinib group from the JAKARTA-2 trial. Outcomes were analysed over the 24-week trial period in the safety population (i.e. patients who received at least one dose of treatment). The safety outcomes included in the analysis were TEAEs that occurred in ≥10% of patients in either the momelotinib or fedratinib arm of the eligible trials. Outcomes meeting this criterion included occurrence of specific Aes (anaemia, thrombocytopenia, diarrhoea, headache, dizziness, abdominal pain, nausea, and fatigue), any Grade 3 or 4 Aes, SAEs, SAEs leading to treatment discontinuation, and SAEs leading to dose reduction. Aes were defined by the NCI CTCAE versions v.3.0, v.4.0, and v.5.0.

13.1.1 Description of the studies used in the ITC on JAKi-experienced patients

The SIMPLIFY-2 and MOMENTUM trials were described in section 10; thus, only JAKARTA-2 will be described here. For more information on all studies, please see Appendix A.

JAKARTA-2 was a single-arm, open-label, non-randomised, phase 2, multicentre study done at 31 sites in nine countries; it enrolled adult patients with a current diagnosis of intermediate or high-risk PMF, post-PV MF, or post-ET MF who were found to be ruxolitinib resistant or intolerant after at least 14 days of treatment. Patients received oral fedratinib at a starting dose of 400 mg once per day, for six consecutive 28-day cycles. The primary endpoint was spleen response (the proportion of patients with a ≥35% reduction in spleen volume from baseline) at end of cycle 6 (24 weeks), assessed centrally (36). Secondary endpoints included symptom response (the proportion of patients with a 50% or more reduction in TSS from baseline to end of cycle 6), proportion of patients with a 50% or more reduction in palpable spleen length from baseline to end of cycle 6, spleen response at end of cycle 3 (12 weeks), percentage change in spleen volume from baseline to end of cycle 3 and end of cycle 6, and safety.

13.1.2 Safety results from the ITC in JAKi-experienced patients

[redacted]

Table 16 Comparison of safety outcomes between momelotinib vs fedratinib in JAKi-experienced patients

	Percentage of patients with the outcome			Adjusted[1] comparison (momelotinib relative to fedratinib)		
	Fedratinib	Momelotinib (unadj.)	Momelotinib (adjusted)	Risk difference (%)[2]	Risk ratio[3]	Odds ratio[3]
Anaemia (Grade 3 or 4)	[redacted]					
Anaemia (Any Grade)	[redacted]					
Thrombocytopenia (Grade 3 or 4)	[redacted]					

Thrombocytopenia (Any Grade)	[redacted]					
Diarrhoea (Any Grade)	[redacted]					
Headache (Any Grade)	[redacted]					
Dizziness (Any Grade)	[redacted]					
Abdominal Pain (Any Grade)	[redacted]					
Nausea (Any Grade)	[redacted]					
Fatigue (Any Grade)	[redacted]					
≥1 AE (Grade 3 or 4)	[redacted]					
SAE	[redacted]					
SAE leading to treatment discontinuation	[redacted]					
SAE leading to dose reduction	[redacted]					

Notes:

1. Adjusted for DIPSS (intermediate-1, intermediate-2, high), mean TSS (using MF-SAF v2.0 criteria), platelets (<100 vs ≥100 x 10^9/L), spleen volume (<Median vs ≥Median value reported in JAKARTA-2), Hb (<10 vs ≥10 g/dL), and spleen length (<Median vs ≥Median value reported in JAKARTA-2). ESS for momelotinib after adjustment was 79.4.
2. Risk differences reflect the difference in percentage points between the absolute risks in each group. Risk differences <0 indicate lower risk of outcome for momelotinib relative to fedratinib; risk differences >0 indicate higher risk of outcome for momelotinib relative to fedratinib.
3. Risk/odds ratios <1 indicate lower risk/odds of outcome for momelotinib relative to fedratinib; risk/odds ratios >1 indicate higher risk/odds of outcomes for momelotinib relative to fedratinib.

13.2 Safety data from external literature applied in the health economic model

No external literature was used to inform safety data in the health economic model.

14. Documentation of health-related quality of life (HRQoL)

This section has not been completed as the health economic model was a cost-minimisation model, i.e. no health-related quality of life data was included.

14.1 Health state utility values (HSUVs) used in the health economic model

Not applicable as the model is a cost-minimisation model. Thus, related subheadings have been deleted.

14.2 Presentation of the health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable as the model is a cost-minimisation model. Thus, related subheadings have been deleted.

15. Resource use and associated costs

All costs related to treating MF patients with the three alternatives were included in the cost model. To estimate the resource use and identify unit costs, the SPCs on momelotinib, fedratinib, and ruxolitinib; data from the trials; input from the Danish clinical experts; and assumptions were applied. In the following, descriptions of each cost element and how the element was valued in the health economic analysis are presented.

15.1 Pharmaceutical costs (intervention and comparator)

All drug costs included in the model were based on the pharmacy purchasing price (PPP) obtained in November 2023. The PPP of the available packages of each treatment is presented in Table 17.

Momelotinib

Patients on momelotinib received an initial dose of 200 mg orally once daily, based on the momelotinib SPC (1). The dose could be reduced to 150 mg or 100 mg once daily due to Aes. In SIMPLIFY-1, 16.3% had their dose reduced mainly due to Aes or per protocol. It was not reported whether the dose was reduced to 150 mg or 100 mg, and based on this, we assumed that 8.2% had their dose reduced to 150 mg and the remaining 8.1% were

reduced to 100 mg. The clinical experts informed that dose reductions are typically introduced after 1-3 months of treatment, and 2 months were applied in the model.

Ruxolitinib

The starting dose of ruxolitinib depends on the patient's platelet count. Based on the DMC evaluation of fedratinib where ruxolitinib was included as the comparator, starting doses of 10 mg, 15 mg and 20 mg orally twice daily were included in the model. The 5 mg starting dose is used when the patient has a low platelet count but was not included in the model as it was regarded as a suboptimal treatment due to no other alternative treatment options. In the base case, it was assumed that 100% of patients on ruxolitinib received the 15 mg orally twice daily starting dose.

Fedratinib

The fedratinib dose in the model was 400 mg orally once daily, based on the SPC (21). Based on the DMC evaluation of fedratinib, it was assumed that 25% of patients initiating treatment with fedratinib will switch to ruxolitinib due to Aes, which was implemented in the model. According to the clinical experts, treatment switch from fedratinib to ruxolitinib usually occurs 3 months after treatment initiation.

Table 17 Pharmaceutical costs used in the model. Source: Medicinpriser.dk (November 2023).

Pharmaceutical	Strength	Package size	PPP, DKK
Momelotinib	100 mg	30 tablets	39,094
	150 mg	30 tablets	39,094
	200 mg	30 tablets	39,094
Ruxolitinib	10 mg	56 tablets	23,606
	15 mg	56 tablets	24,379
	20 mg	56 tablets	24,379
Fedratinib	100 mg	120 tablets	31,550

15.2 Pharmaceutical costs – co-administration

In the previous DMC evaluation of fedratinib, the DMC included costs for loperamide and ondansetron for patients in the fedratinib arm (14). Loperamide is administered to prevent diarrhoea, while ondansetron is administered to prevent nausea and vomiting. The DMC concluded that 2/3 of patients would receive ondansetron and that around half of these patients would receive 4 mg daily, while the other half would receive 8 mg daily. Thus, 33% of the patients on fedratinib treatment received ondansetron 4 mg, and 33% received ondansetron 8 mg in the model. For loperamide, it was assumed that all patients

receive a package of 6 tablets per month when on fedratinib treatment, based on a clinical assessment (14).

Treatment with fedratinib can lead to lack-of-thiamine (b1-vitamin) levels; therefore, patients on fedratinib should receive supplementary thiamine in the model. It was assumed that all patients on fedratinib receive 100 mg thiamine daily. No co-administrations costs were included for momelotinib and ruxolitinib.

Table 18 Pharmaceutical costs for co-administrations

Pharmaceutical	Strength	Package size	PPP, DKK	Source
Loperamide "Mashal"	2 mg	60 blisters	119.95	Medicinpriser.dk (November 2023)
Ondansetron "Bluefish"	4 mg	100 blisters	106.00	Medicinpriser.dk (November 2023)
Ondansetron "Bluefish"	8 mg	100 blisters	160.00	Medicinpriser.dk (November 2023)
Thiamine B1-vitamin "Solgar"	100 mg	100 tablets	131.00	Med24.dk (November 2023)*

*Based on the pharmacy selling price (PSP) from Med24.dk

15.3 Treatment of anaemia

Over 40% of MF patients are anaemic at diagnosis, and almost all become anaemic over time; thus, anaemia treatment was included in the model. Anaemia treatment in the model comprised of blood transfusions and ESA treatment. The RADS treatment guideline was used for ESA treatment in the model and darbepoetin alfa (Aranesp®) was included and the dosing was based on the RADS guideline (42); patients received a low dose 150 µg per week for 8 weeks followed by a high dose of 300 µg per week for at least 8 additional weeks. The switch was assumed to occur after 1.8 months in the model. Based on our consultation of the clinical experts it was assumed that patients start receiving darbepoetin alfa after 2 months (2 cycles in the model). Patients receive darbepoetin alfa for 6 months in the model based on the assumption that most patients will no longer have effect of darbepoetin alfa after 6 months of treatment. Patients would not receive additional ESA treatment in the remaining treatment length. To estimate the proportion of patients receiving ESA treatment in the model, the proportions of patients with grade 3 and 4 anaemia from SIMPLIFY-1 were applied for momelotinib and ruxolitinib, i.e. 5.6% for momelotinib and 23.1% for ruxolitinib (25). Fedratinib was not included in the SIMPLIFY-1 study and therefore assumed to be the same as ruxolitinib, which was regarded as an acceptable assumption due to the similar rates of grade 3 and 4 anaemia observed in JAKARTA and COMFORT-1 of 41.7% and 45.2%, respectively.

The rate of RBC transfusions per month adjusted for strata from the ITT population in SIMPLIFY-1 was applied to quantify blood transfusions in the model; a rate of [redacted] transfusions per month was applied for momelotinib and a rate of [redacted] transfusions per month was applied for ruxolitinib (26). Transfusion rate data is presented and further described in Appendix B. Since fedratinib was not part of SIMPLIFY-1, the ruxolitinib rate of monthly RBC transfusions was applied for fedratinib based on the similar proportion of patients developing grade 3 and 4 anaemia and the general equality of these two JAKi treatments. The rates were ascribed to 100% of the population in all three treatment arms and it was assumed that patients received blood transfusions from day one in the model. Applying the same blood transfusion rate of [redacted] per month for momelotinib throughout the treatment length was regarded as a conservative approach since the need for blood transfusions for patients treated with momelotinib may be reduced over time due to the favourable impact on anaemia of momelotinib, which is not an attribute of ruxolitinib or fedratinib.

Table 19 Pharmaceutical costs related to anaemia treatment

Pharmaceutical	Strength	Package size	PPP, DKK	Source
Darbepoetin alfa (Aranesp®)	150 µg	4 x 0.3 mL vials	8,456	Medicinpriser.dk (December 2023)
Darbepoetin alfa (Aranesp®)	300 µg	0.6 mL pen	4,228	Medicinpriser.dk (December 2023)

Table 20 Unit cost of a blood transfusion used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Blood transfusion	Momelotinib: [redacted] per month Ruxolitinib: [redacted] per month Fedratinib: [redacted] per month	3,969	16PR02	The DRG 2023 tariff was derived by combining the procedure code DD474A and the diagnosis code BOQA0

15.4 Administration costs

All treatments included in the model were administered orally; thus, no administration costs for momelotinib, fedratinib, and ruxolitinib were included in the model. ESAs are administered subcutaneously, and it was assumed that all patients administer ESAs at home.

15.5 Disease management costs

In the previous DMC evaluation of fedratinib (14), the DMC stated that it is clinical practice in Denmark for patients on ruxolitinib to have one monthly monitoring visit during the first four months of treatment and every three months thereafter. Furthermore, the DMC stated that they expect patients on fedratinib to be followed the same way; however, patients on fedratinib will have an additional visit in the initial phase to assess how the patient tolerates the treatment. Thus, patients on fedratinib will have 7 monitoring visits in the first year, while patients on ruxolitinib will have 6 monitoring visits in the first year. It is expected that patients on momelotinib will be followed the same way as ruxolitinib, and 6 monitoring visits in the first year were included for momelotinib.

The unit cost of a monitoring visit was based on the DRG 2023 tariff "01MA98" of DKK 2,321, which was chosen based on the unit cost applied for monitoring visits in the DMC evaluation of fedratinib.

The DMC stated in the previous fedratinib evaluation that the thiamine levels would be regularly tested in patients on fedratinib. They expected that patients would be tested every fourth week of the first 12 weeks of treatment and thereafter every 12th week. Moreover, it is Danish clinical practice to measure the thiamine levels weekly for three weeks if the levels drop below 70 nM/L. This happened for around 15% of patients in the JAKARTA trial; therefore, the DMC added costs for three additional thiamine measurements for 15% of patients on fedratinib in their evaluation. Based on this, these costs were also included in the fedratinib arm in the present health economic analysis, and the tests were assumed to occur in month 2 in the model. No general practitioner (GP) visits were included in the model.

Table 21 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Monitoring visit	Momelotinib: First year: 6 Following years: 4 Fedratinib: First year: 7 Following years: 4 Ruxolitinib: First year: 6 Following years: 4	2,321	01MA98	DRG 2023
Thiamine measurement	Momelotinib: 0 Fedratinib: First year: 6 Following years: 4 Ruxolitinib: 0	1,379	-	Rigshospitalets Labportal (43), 2023

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Blood samples	Momelotinib: First year: 6 Following years: 4 Fedratinib: First year: 7 Following years: 4 Ruxolitinib: First year: 6 Following years: 4	50	-	Clinical expert estimate and assumption

15.6 Costs associated with management of adverse events

Costs for managing Aes were included in the model. The Aes included in the model were based on the Aes included in the DMC evaluation of fedratinib and presented in Table 22. The DRG tariffs from the fedratinib evaluation were also applied in the present analysis and updated to 2023 costs. Please note the anaemia is not included in this section as management of anaemia was described in section 15.3.

Table 22 Treatment requiring Aes observed at week 24 for momelotinib, ruxolitinib, and fedratinib and rates applied in the model. Source: SIMPLIFY-2 (27) and SIMPLIFY-1 (25), COMFORT-1 (38), and JAKARTA (32).

	Momelotinib	Ruxolitinib	Fedratinib	Unit cost, DKK	DRG 2023 tariff
Thrombocytopenia (grade 3-4)	6.7	12.9 %	11.4%	2,321	01MA98
Subcutaneous haematoma (grade 1-2)	7.5%	18.7%	18.7%	2,321	01MA98
Dizziness (grade 3-4)	0%	0.6%	0.0%	2,321	01MA98
Diarrhea (grade 3-4)	2%	1.9%	5.2%	26,929	06MA14
Nausea (grade 1-2)	17%	14.8%	61.5%	2,321	01MA98
Nausea (grade 3-4)	2.0%	0.0%	0.0%	2,321	01MA98
Vomiting (grade 1-2)	6.7%	12.3%	38.5%	2,321	01MA98
Vomiting (grade 3-4)	0%	0.6%	3.1%	26,929	06MA14

	Momelotinib	Ruxolitinib	Fedratinib	Unit cost, DKK	DRG 2023 tariff
Bleeding (grade 3-4)	1%	2.6%	2.1%	37,779	06MA05
Urinary tract infection (grade 1-4)	10.6%	9.0%	6.3%	2,321	01MA98
Herpes zoster (grade 1-4)	1.9%	1.9%	1.0%	2,321	01MA98

15.7 Subsequent treatment costs

In the DMC evaluation of fedratinib, the DMC stated that some patients on fedratinib will switch to ruxolitinib due to gastrointestinal AEs. The DMC estimated that 25% of patients on fedratinib would switch to ruxolitinib. However, the switch should not be regarded as a second-line treatment choice, as these patients will still benefit from fedratinib and the switch is only to avoid gastrointestinal AEs and maintain the treatment effect. This assumption was also applied in the present health economic analysis. It should be noted that this assumption only impacts the cost side due to differences in the treatment-related costs of fedratinib and ruxolitinib. No subsequent treatment costs were assumed for momelotinib or ruxolitinib. Based on input from the clinical experts, it was assumed that the 25% of patients who switch treatment do so after 3 months of treatment if they experience gastrointestinal AEs.

15.8 Patient costs

In accordance with DMC guidelines, patient-related time use and costs and transportation costs were included in the model. No caregiver time or costs were included in the model. The patient time associated with momelotinib, fedratinib, and ruxolitinib was based on the time spent on treatment-related activities and traveling back and forth from, e.g. visits to the hospital. Based on the DMC guidelines (44), a cost of DKK 203 per patient hour was applied. Transportation costs were also included. A distance of 20 km to and from the hospital (40 km in total per visit) was assumed, and a unit cost per km of DKK 3.73 was applied in accordance with DMC guidelines (44). Thus, a transportation cost of DKK 149 was applied for each hospital visit. It was assumed that patients spend 30 minutes on transportation to and from the hospital, i.e. 60 minutes per visit. The activities for which patient time use was ascribed and the time spent by the patient on each activity are presented in Table 23. Each activity was ascribed a transportation cost.

Table 23 Patient time use used in the model (transportation time not included)

Activity	Time spent (minutes)	Source
Monitoring visit	20 minutes per visit	Time use based on clinical expert input
Visit for managing Aes	20 minutes per visit	Time use based on clinical expert input
Thiamine measurements (fedratinib arm)	20 minutes per measurement	Assumption due to lack of estimate from clinical experts
Blood sample	20 minutes per visit	Time use based on clinical expert input
Blood transfusion	240 minutes per transfusion	Time use based on clinical expert input: patients receive 2 blood bags during one transfusion and one bag takes 1 hour to be administered. The clinical expert estimated two hours for preparation

15.9 Other costs (e.g. costs for home care nurses, out-patient rehabilitation, and palliative care costs)

No other costs were identified as relevant for the health economic analysis.

16. Results

16.1 Base case overview

Table 24 provides an overview of the settings applied in the base case of the health economic analysis.

Table 24 Base case overview

Feature	Description
Comparator	Fedratinib and ruxolitinib
Type of model	Cost-minimisation model
Type of analysis	Cost-minimisation analysis
Time horizon	25 years

Feature	Description
Treatment line	First-line
Measurement and valuation of health effects	Not applicable
Costs included	Pharmaceutical costs Co-administration costs Costs of anaemia treatment Disease management costs Costs of managing adverse events Patient costs and transportation costs
Dosage of pharmaceutical	Momelotinib: 200-100 mg once daily Fedratinib: 400 mg once daily Ruxolitinib: 15-20 mg twice daily
Average time on treatment	3.5 years
Inclusion of waste	Not included

16.1.1 Base case results

In the base case, the incremental cost per patient for momelotinib compared to ruxolitinib was DKK 164,042 over a time horizon of 25 years.

In the base case, the incremental cost per patient for momelotinib compared to fedratinib was DKK 55,995 over a time horizon of 25 years.

Table 25 Base case results of momelotinib versus ruxolitinib, discounted estimates (DKK)

	Momelotinib	Ruxolitinib	Difference
Pharmaceutical costs	1,220,314	849,828	370,485
Pharmaceutical costs – co-administration	0	0	0
Treatment of anaemia	57,909	206,669	-148,760
Administration costs	0	0	0

	Momelotinib	Ruxolitinib	Difference
Disease management costs (monitoring)	28,346	28,346	0
Costs associated with management of adverse events	2,131	3,282	-1,151
Subsequent treatment costs	0	0	0
Patient costs	25,511	82,043	-56,532
Total costs	**1,334,210**	**1,170,168**	**164,042**
Total life years	**Not applicable**		
Total QALYs	**Not applicable**		
Incremental cost per patient		**164,042**	
Incremental costs per life year gained		**Not applicable**	
Incremental cost per QALY gained (ICER)		**Not applicable**	

Table 26 Base case results of momelotinib versus fedratinib, discounted estimates (DKK)

	Momelotinib	Fedratinib	Difference
Pharmaceutical costs	1,220,314	950,151	270,163
Pharmaceutical costs – co-administration	0	1,853	-1,853
Treatment of anaemia	57,909	208,295	-150,385
Administration	0	0	0
Disease management costs (monitoring)	28,346	43,234	-14,888

	Momelotinib	Fedratinib	Difference
Costs associated with management of adverse events	2,131	7,030	-4,899
Subsequent treatment costs	0	0	0
Patient costs	25,511	67,653	-42,143
Total costs	**1,334,210**	**1,278,215**	**55,995**
Total life years	**Not applicable**		
Total QALYs	**Not applicable**		
Incremental cost per patient		**55,995**	
Incremental costs per life year gained		**Not applicable**	
Incremental cost per QALY gained (ICER)		**Not applicable**	

16.2 Sensitivity analyses

Uncertainty in the input parameters in the cost-minimisation model has been explored through various sensitivity analyses, which are presented here.

16.2.1 Deterministic sensitivity analyses

The DSAs included in the application are presented in Table 27 (momelotinib vs fedratinib) and Table 28 (momelotinib vs ruxolitinib). In the present application, we present the DSAs with the largest impact on the base case result, as numerous DSAs were performed to assess the parameter uncertainty. In the DSAs, the point estimate applied in the model was varied by -/+20%. + 20% was marked as high and – 20% was marked as low. Figure 7 and Figure 8 show tornado diagrams from the DSAs. As seen, the parameters with the biggest impact on the base case result in the comparison between momelotinib and fedratinib were the drug prices on momelotinib 200 mg and fedratinib, the share of patients on momelotinib and fedratinib with no or limited effect after 6 months, the drug price of ruxolitinib 15 mg (as some patients on fedratinib switch to ruxolitinib) and the procedure cost for blood transfusions.

In the comparison of momelotinib and ruxolitinib, the parameters with the biggest impact on the base case result were the drug prices of momelotinib 200 mg and ruxolitinib 15 mg, the share of population on ruxolitinib with platelet count 100,000 to <200,000/mm^3, the shares with limited or no effect after 6 months in both arms, the share with anaemia grade 3-4 in the ruxolitinib arm and the procedure cost for blood transfusions.

The conducted scenario analyses did not affect the result of the base case much expect for reducing the time horizon to 1 year.

Table 27 One-way sensitivity analyses results, momelotinib compared to fedratinib

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	55,995	NA	NA
Momelotinib, price (DKK), 200 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: -149,578 High: 261,569	NA	NA
Fedratinib, price (DKK)	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 206,919 High: -94,928	NA	NA
Treatment stopping rules, momelotinib, share of population with no/limited effect at month 6	-/+ 20%	Included to assess the impact of this parameter	Low: 130,122 High: -18,132	NA	NA
Treatment stopping rules, fedratinib, share of population with no/limited effect at month 6	-/+ 20%	Included to assess the impact of this parameter	Low: 1,713 High: 110,278	NA	NA
Ruxolitinib, price (DKK), 15 mg	-/+ 20%	Included as the DMC requests that drug prices are	Low: 95,102 High: 16,889	NA	NA

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		included in the DSA			
Procedure costs, unit costs (DKK), blood transfusions	-/+ 20%	Included to assess the impact of this parameter	Low: 82,595 High: 29,396	NA	NA
Ruxolitinib, share of population with this platelet count, platelet count 100,000 to <200,000/mm^3	-/+ 20%	Included to assess the impact of this parameter	Low: 95,102 High: 55,995	NA	NA
Momelotinib, price (DKK), 150 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 36,633 High: 75,358	NA	NA
Momelotinib, price (DKK), 100 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 36,869 High: 75,122	NA	NA
Treatment length (years)	-/+ 20%	Included to assess the impact of this parameter	Low: 40,100 High: 73,343	NA	NA
Treatment stopping rules, ruxolitinib, share of population with no/limited effect at month 6	-/+ 20%	Included to assess the impact of this parameter	Low: 42,044 High: 69,947	NA	NA
Fedratinib, share of population who switch treatment	-/+ 20%	Included to assess the impact of	Low: 48,111 High: 63,880	NA	NA

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		this parameter			
Share of population on momelotinib treated for anaemia, blood transfusions	-/+ 20%	Included to assess the impact of this parameter	Low: 42,414 High: 55,995	NA	NA
Drug acquisition costs, price (DKK), erythropoietin high dose	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 58,782 High: 53,209	NA	NA
Share of population on momelotinib treated for anaemia, erythropoietin	-/+ 20%	Included to assess the impact of this parameter	Low: 54,915 High: 57,076	NA	NA
Drug acquisition costs, price (DKK), erythropoietin low dose	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 56,686 High: 55,305	NA	NA
B1-vitamin, price (DKK)	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 56,183 High: 55,807	NA	NA
Share of patients with B1-vitamin levels <70 nm/L	-/+ 20%	Included to assess the impact of this parameter	Low: 56,086 High: 55,905	NA	NA
Ondansetron, price (DKK)	-/+ 20%	Included as the DMC requests	Low: 56,071 High: 55,920	NA	NA

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		that drug prices are included in the DSA			
Loperamide, price (DKK)	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 56,052 High: 55,939	NA	NA
Ondansetron, price (DKK)	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 56,046 High: 55,945	NA	NA

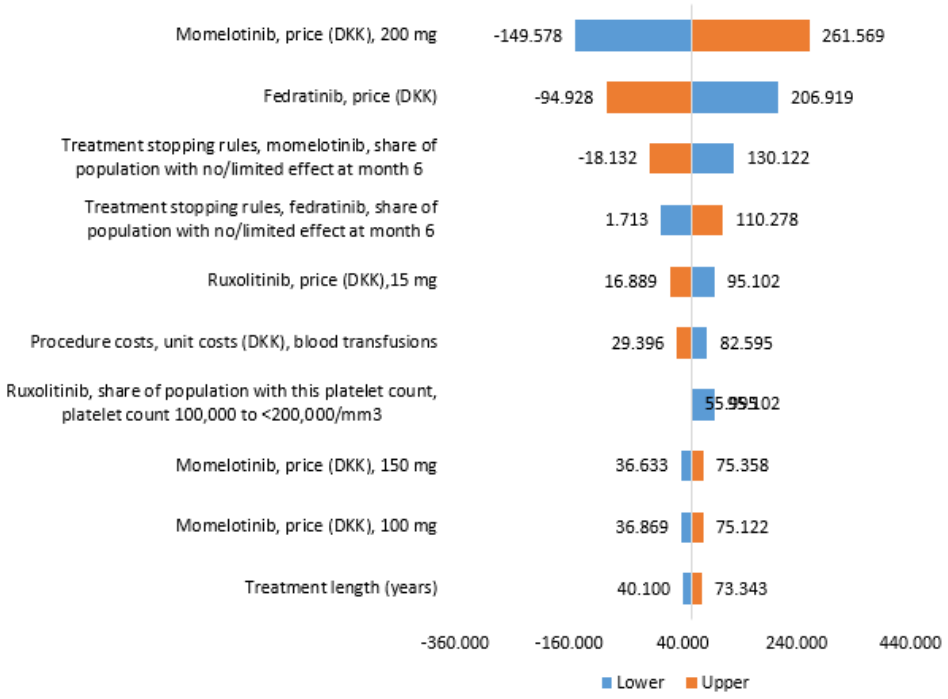


Figure 7 Tornado diagram from DSA of momelotinib vs fedratinib

Table 28 One-way sensitivity analyses results, momelotinib vs ruxolitinib

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	164,042	NA	NA
Momelotinib, price (DKK), 200 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: -41,531 High: 369,616	NA	NA
Ruxolitinib, price (DKK),15 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 334,008 High: -5,923	NA	NA
Ruxolitinib, share of population with this platelet count, platelet count 100,000 to <200,000/mm^3	-/+ 20%	Included to assess the impact of this parameter	Low: 334,008 High: 164,042	NA	NA
Treatment stopping rules, momelotinib, share of population with no/limited effect at month 6	-/+ 20%	Included to assess the impact of this parameter	Low: 238,169 High: 89,916	NA	NA
Treatment stopping rules, ruxolitinib, share of population with no/limited effect at month 6	-/+ 20%	Included to assess the impact of this parameter	Low: 99,295 High: 228,790	NA	NA
Procedure costs, unit costs (DKK), blood transfusions	-/+ 20%	Included to assess the impact of this parameter	Low: 190,418 High: 137,666	NA	NA
Treatment length (years)	-/+ 20%	Included to assess the impact of this parameter	Low: 140,492 High: 186,376	NA	NA

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Momelotinib, price (DKK), 150 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 144,680 High: 183,405	NA	NA
Momelotinib, price (DKK), 100 mg	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 144,916 High: 183,169	NA	NA
Share of population on momelotinib treated for anaemia, blood transfusions	-/+ 20%	Included to assess the impact of this parameter	Low: 150,461 High: 164,042	NA	NA
Drug acquisition costs, price (DKK), erythropoietin high dose	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 166,832 High: 161,253	NA	NA
Share of population on momelotinib treated for anaemia, erythropoietin	-/+ 20%	Included to assess the impact of this parameter	Low: 162,962 High: 165,123	NA	NA
Drug acquisition costs, price (DKK), erythropoietin low dose	-/+ 20%	Included as the DMC requests that drug prices are included in the DSA	Low: 164,629 High: 163,456	NA	NA

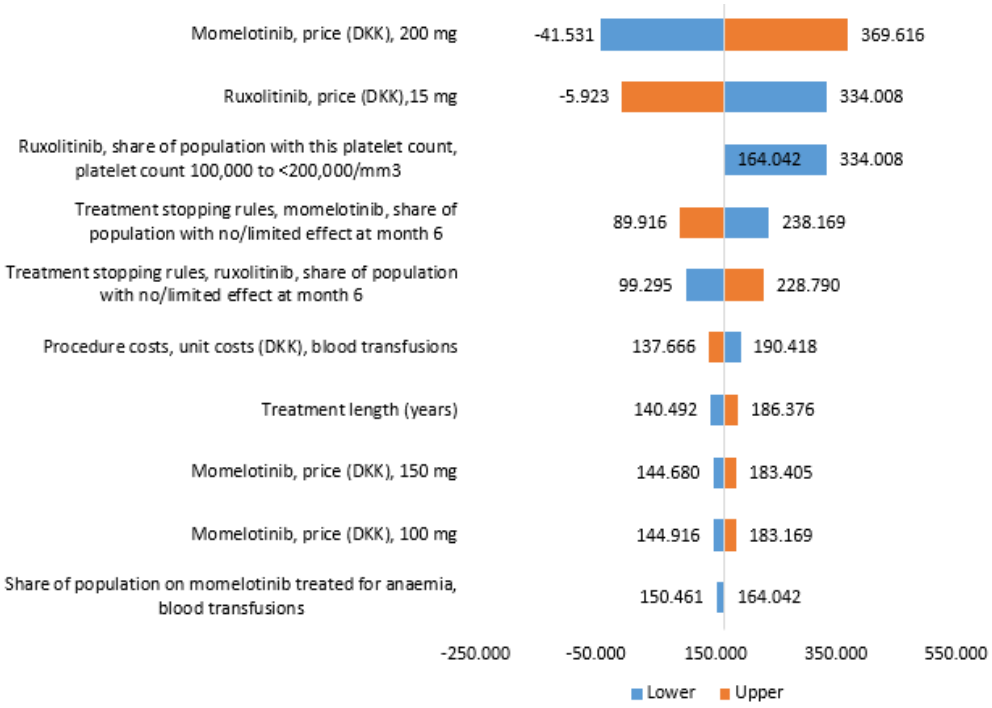


Figure 8 Tornado diagram from DSA of momelotinib vs ruxolitinib

Table 29: Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	Ruxolitinib: 164,042 Fedratinib: 55,995	NA	NA
Time horizon of 1 year	Reducing the time horizon from 25 years to 1 year	According to the DMC guideline, scenario analyses on the time horizon should be presented.	Ruxolitinib: 52,043 Fedratinib: -6,432	NA	NA
Time horizon of 3 years	Reducing the time	According to the DMC guideline,	Ruxolitinib:		

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	horizon from 25 years to 3 years	scenario analyses on the time horizon should be presented.	147,549 Fedratinib: 44,192		
Reduction of the rate of RBC transfusions for momelotinib	[redacted]	The transfusion need for patients on momelotinib may decrease over time, which is not accounted for in the base case.	Ruxolitinib: [redacted] Fedratinib: [redacted]	NA	NA
Assessing the impact of a percentage of the population of momelotinib not having anaemia costs	10% based on input from the clinical expert [redacted]	Requested by the DMC at the dialogue meeting	Ruxolitinib: 157,059 Fedratinib: 49,012	NA	NA

16.2.2 Probabilistic sensitivity analyses

Not applicable since the analysis and model is a cost-minimisation analysis and model.

17. Budget impact analysis

The purpose of the budget impact analysis (BIA) was to estimate the budgetary impact of recommending momelotinib as standard treatment for MF patients who are JAKi-naïve or JAKi-experienced. The budget impact was estimated per year in the first 5 years after the recommendation of momelotinib. The BIA compares the expenditures in the scenario where momelotinib is recommended as a possible standard treatment and the scenario where momelotinib is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The expenditure per patient is equivalent to the cost per patient without patient and transportation costs. A treatment length of 3.5 years was applied in the budget impact analysis, and as in the base case, no discontinuation was applied.

Number of patients (including assumptions of market share)

As stated in the DMC fedratinib evaluation, 40-45 patients are annually diagnosed with MF in the intermediate-2 or high-risk groups and an incidence of 40 patients was applied (14). As mentioned, 40% of MF patients will have anaemia at the time of diagnosis, i.e. the annual incidence of momelotinib candidates will be 16. The remaining24 incident patients will be candidates to ruxolitinib and fedratinib as these will not be anaemic at the time of diagnosis. For the incidence, it was assumed that 75% of the 24 patients on ruxolitinib and fedratinib will develop anaemia app. one year after the diagnosis, i.e. 6 patients will continue treatment with ruxolitinib/fedratinib in year 2 and 18 patients will switch to momelotinib in year 2. In year 3, almost all (assumed 95%) of the remaining 6 patients will become anaemic and switch to momelotinib, i.e. 0 of the patients initiating treatment in year 1 will receive ruxolitinib/fedratinib in year 3 and all 24 patients will have switched to momelotinib. A 50/50 split between ruxolitinib and fedratinib was assumed for the patients without anaemia.

In addition, some of the patients who are currently being treated with ruxolitinib or fedratinib will become anaemic and switch to momelotinib. Currently, 160 patients are treated with a JAKi and these patients will gradually develop anaemia and switch to momelotinib. In addition, it was assumed that some of the prevalent patients would finalise treatment with the JAK inhibitors each year and therefore, the prevalence was assumed to drop with 40 patients each year resulting in 0 prevalent patients in year 5. The proportion of patients developing anaemia was also assumed to be 75% in year 2 and 95% in year 3 for the prevalent population. In year 1 of the BIA, the 160 patients currently treated with JAKi are included along with 40 newly diagnosed patients each year, i.e. 200 patients in total.

The number of patients expected to receive momelotinib, fedratinib, and ruxolitinib, respectively, in the first five years after the recommendation is presented in Table 30.

Table 30 Number of new patients expected to be treated over the next five-year period if momelotinib is recommended (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Momelotinib	16	140	166	168	170
Fedratinib	92	30	17	16	15
Ruxolitinib	92	30	17	16	15
			Non-recommendation		
Momelotinib	0	0	0	0	0
Fedratinib	100	100	100	100	100
Ruxolitinib	100	100	100	100	100

Budget impact

An overview of the results of the budget impact analysis is presented in Table 31. Over all 5 years in the budget impact analysis, the budget impact is DKK 31,109,739. A graphic presentation of the results is presented in Figure 9.

Table 3132 Expected budget impact (in DKK) of recommending momelotinib for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Momelotinib is recommended	80,834,129	74,213,755	75,114,222	60,429,756	53,215,599
Momelotinib is NOT recommended	80,183,209	66,319,100	65,794,911	53,265,955	47,134,548
Budget impact of the recommendation	**650,921**	**7,894,655**	**9,319,311**	**7,163,801**	**6,081,051**

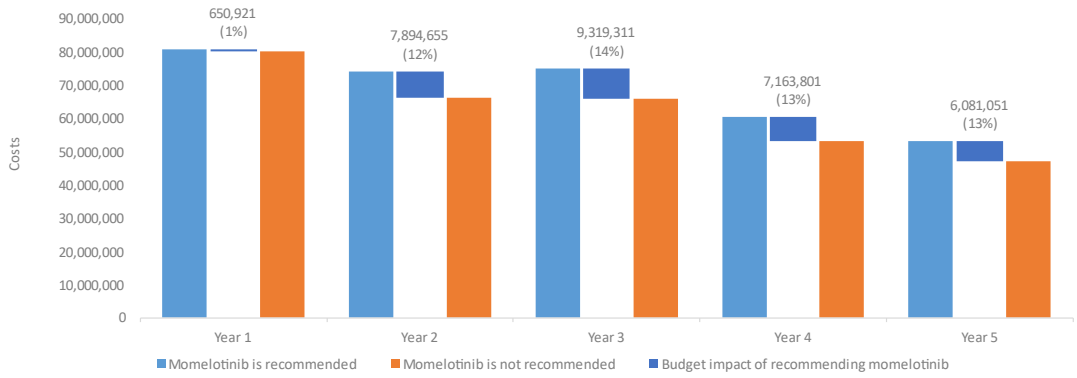


Figure 9 Budget impact of recommending momelotinib

18. List of experts

Three clinical experts were consulted for input to the present application. Two clinical experts did not agree to appear by name in the application. The last consulted clinical expert was [redacted].

References

1. European Medicines Agency. Summary of product characteristics: Omjjara.

2. Medicinrådet. Bilag til Medicinrådets anbefaling vedrørende fedratinib til behandling af myelofibrose [Internet]. 2022. Available from: https://medicinraadet.dk/media/cjejkzqa/bilag-til-medicinr%C3%A5derts-anbefaling-vedr-fedratinib-til-myelofibrose-vers-1-0_adlegacy.pdf

3. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 May;98(5):801–21.

4. The Nordic MPN Study Group. Nordic care program for patients with Essential Thrombocythemia, Polycythemia Vera and Primary Myelofibrosis (4th version) [Internet]. 2017 Mar [cited 2023 Jun 26]. Available from: https://nmpn.org/index.php/guidelines/17-nmpn-care-program-2017/file

5. Naymagon L, Mascarenhas J. Myelofibrosis-Related Anemia: Current and Emerging Therapeutic Strategies. HemaSphere. 2017 Dec;1(1):e1.

6. Chifotides HT, Bose P, Verstovsek S. Momelotinib: an emerging treatment for myelofibrosis patients with anemia. J Hematol OncolJ Hematol Oncol. 2022 Dec;15(1):7.

7. Elena C, Passamonti F, Rumi E, Malcovati L, Arcaini L, Boveri E, et al. Red blood cell transfusion-dependency implies a poor survival in primary myelofibrosis irrespective of IPSS and DIPSS. Haematologica. 2011 Jan 1;96(1):167–70.

8. Pardanani A, Finke C, Abdelrahman RA, Lasho TL, Tefferi A. Associations and prognostic interactions between circulating levels of hepcidin, ferritin and inflammatory cytokines in primary myelofibrosis. Am J Hematol. 2013 Apr;88(4):312–6.

9. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009 Mar 26;113(13):2895–901.

10. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010 Mar 4;115(9):1703–8.

11. Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, et al. DIPSS Plus: A Refined Dynamic International Prognostic Scoring System for Primary Myelofibrosis That Incorporates Prognostic Information From Karyotype, Platelet Count, and Transfusion Status. J Clin Oncol. 2011 Feb 1;29(4):392–7.

12. Shallis RM, Wang R, Davidoff A, Ma X, Podoltsev NA, Zeidan AM. Epidemiology of the classical myeloproliferative neoplasms: The four corners of an expansive and complex map. Blood Rev. 2020 Jul;42:100706.

13. D. H. Society. Danish database for chronic myeloma proliferative neoplasms: annual report 2021. 2022 Dec.

14. Medicinrådet. Medicinrådets anbefaling vedr. fedratinib til behandling af myelofibrose [Internet]. 2022. Available from: https://medicinraadet.dk/media/dbmbaak5/medicinr%C3%A5dets-anbefaling-vedr-fedratinib-til-myelofibrose-vers-1-0-x_adlegacy.pdf

15. Moulard O, Mehta J, Olivares R, Iqbal U, Mesa RA. Epidemiology of Myelofibrosis (MF), Polycythemia Vera (PV) and Essential Thrombocythemia (ET) in the European Union (EU). Blood. 2012 Nov 16;120(21):1744–1744.

16. Orphanet. Primary myelofibrosis. [Internet]. 2019 [cited 2023 Jun 26]. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=824

17. Dansk Studiegruppe for Kroniske Myeloide Sygdomme (DSKMS). Primær Myelofibrose (PMF) Vejledning for diagnostik, monitorering og behandling [Internet]. myeloid.dk; 2013 [cited 2023 Aug 12]. Available from: http://www.myeloid.dk/filearchive/3a2b7ab4ea015ec017792ea36fe3edac.pdf

18. Vannucchi AM, Barbui T, Cervantes F, Harrison C, Kiladjian JJ, Kröger N, et al. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26:v85–99.

19. Medicinrådet. Behandlingsvejledning inklusiv lægemiddelrekommandation for brug af Erythropoietin Stimulerende Lægemidler (ESA) ved kroniske hæmatologiske lidelser karakteriserende ved knoglemarvssvigt [Internet]. 2020. Available from: https://medicinraadet.dk/media/fizd4vex/behandlingsvejl-inkl-laegemiddelrek-for-brug-af-esa-ved-knoglemarvssvigt-vers-12_adlegacy.pdf

20. The European Medicines Agency. Summary of product characteristics: Jakavi [Internet]. [cited 2023 Jun 26]. Available from: https://www.ema.europa.eu/en/documents/product-information/jakavi-epar-product-information_en.pdf

21. The European Medicines Agency. Summary of product characteristics: Inrebic [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/inrebic-epar-product-information_en.pdf

22. Tefferi A, Cervantes F, Mesa R, Passamonti F, Verstovsek S, Vannucchi AM, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood. 2013 Aug 22;122(8):1395–8.

23. Emanuel RM, Dueck AC, Geyer HL, Kiladjian JJ, Slot S, Zweegman S, et al. Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score: Prospective International Assessment of an Abbreviated Symptom Burden Scoring System Among Patients With MPNs. J Clin Oncol. 2012 Nov 20;30(33):4098–103.

24. Finansministeriet. Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente [Internet]. 2021. Available from: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf

25. Mesa RA, Kiladjian JJ, Catalano JV, Devos T, Egyed M, Hellmann A, et al. SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis. J Clin Oncol. 2017 Dec 1;35(34):3844–50.

26. GSK. CLINICAL STUDY REPORT: A phase 3, Randomized Study to Evaluate: the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib_data on file. 2021.

27. Harrison CN, Vannucchi AM, Platzbecker U, Cervantes F, Gupta V, Lavie D, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol. 2018 Feb;5(2):e73–81.

28. GSK. CLINICAL STUDY REPORT: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF).

29. Verstovsek S, Chen CC, Egyed M, Ellis M, Fox L, Goh YT, et al. MOMENTUM: momelotinib vs danazol in patients with myelofibrosis previously treated with JAKi who are symptomatic and anemic. Future Oncol. 2021 Apr;17(12):1449–58.

30. Verstovsek S, Gerds AT, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. The Lancet. 2023 Jan;401(10373):269–80.

31. GSK. CLINICAL STUDY REPORT: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy (data on file). 2022 Apr.

32. Harrison C, Kiladjian JJ, Verstovsek S, Vannucchi A, Mesa R, Reiter A, et al. MPN-164: Overall Survival (OS) and Progression-Free Survival (PFS) in Patients Treated with Fedratinib as First-Line Myelofibrosis (MF) Therapy and after Prior Ruxolitinib (RUX): Results from the JAKARTA and JAKARTA2 Trials. Clin Lymphoma Myeloma Leuk. 2021 Sep;21:S356.

33. Harrison CN, Schaap N, Vannucchi AM, Kiladjian J, Passamonti F, Zweegman S, et al. Safety and efficacy of fedratinib, a selective oral inhibitor of Janus kinase-2 (JAK2), in

patients with myelofibrosis and low pretreatment platelet counts. Br J Haematol. 2022 Jul;198(2):317–27.

34. 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;1(5):643.

35. Harrison CN, Schaap N, Vannucchi AM, Kiladjian JJ, Jourdan E, Silver RT, et al. Fedratinib Improves Myelofibrosis-related Symptoms and Health-related Quality of Life in Patients with Myelofibrosis Previously Treated with Ruxolitinib: Patient-reported Outcomes from the Phase II JAKARTA2 Trial. HemaSphere. 2021 May;5(5):e562.

36. Harrison CN, Schaap N, Vannucchi AM, Kiladjian JJ, 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):e317–24.

37. Harrison CN, Schaap N, Vannucchi AM, Kiladjian 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.

38. Mesa RA, Gotlib J, Gupta V, Catalano JV, Deininger MW, Shields AL, et al. Effect of Ruxolitinib Therapy on Myelofibrosis-Related Symptoms and Other Patient-Reported Outcomes in COMFORT-I: A Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Oncol. 2013 Apr 1;31(10):1285–92.

39. 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 Mar;366(9):799–807.

40. 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;366(9):787–98.

41. Mesa R, Harrison C, Oh ST, Gerds AT, Gupta V, Catalano J, et al. Overall survival in the SIMPLIFY-1 and SIMPLIFY-2 phase 3 trials of momelotinib in patients with myelofibrosis. Leukemia. 2022 Sep;36(9):2261–8.

42. Rådet for anvendelse af dyr sygehusmedicin. Behandlingsvejledning inklusiv lægemiddelrekommandation for brug af Erythropoietin Stimulerende Lægemidler (ESA) ved kroniske hæmatologiske lidelser karakteriserede ved knoglemarvssvigt [Internet]. [cited 2023 Dec 13]. Available from: https://rads.dk/media/2537/anaemi-behandlingsvejl-inkl-laegemiddelrekom-april-2015.pdf

43. Rigshospitalet. Rigshospitalets Labportal [Internet]. [cited 2023 Aug 29]. Available from: https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6815

44. Medicinrådet [Danish Medicines Council]. Medicinrådets metodevejledning for vurdering af nye lægemidler (Version 1.2) [The Danish Medicines Council's process guide for assessing new pharmaceuticals] [Internet]. 2021 Feb [cited 2022 Apr 24]. Available from: https://medicinraadet.dk/media/hciai0yz/medicinr%C3%A5dets_metodevejledning_for_vurdering_af_nye_l%C3%A6gemidler-vers-_1-2_adlegacy.pdf

45. GSK. A systematic literature review of efficacy and safety outcomes in phase 2 and later clinical trials of myelofibrosis (data on file). 2022 Sep.

46. Higgins J.P., et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.

47. Akers J., Aguiar-Ibáñez R., Baba-Akbari A. Systematic reviews: CRD's guidance for undertaking reviews in health care. York, UK: Centre for Reviews and Dissemination. University of York; 2009.

48. National Institute for Health Care and Excellence. The guidelines manual: process and methods (PMG6). 2012.

49. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339(jul21 1):b2535–b2535.

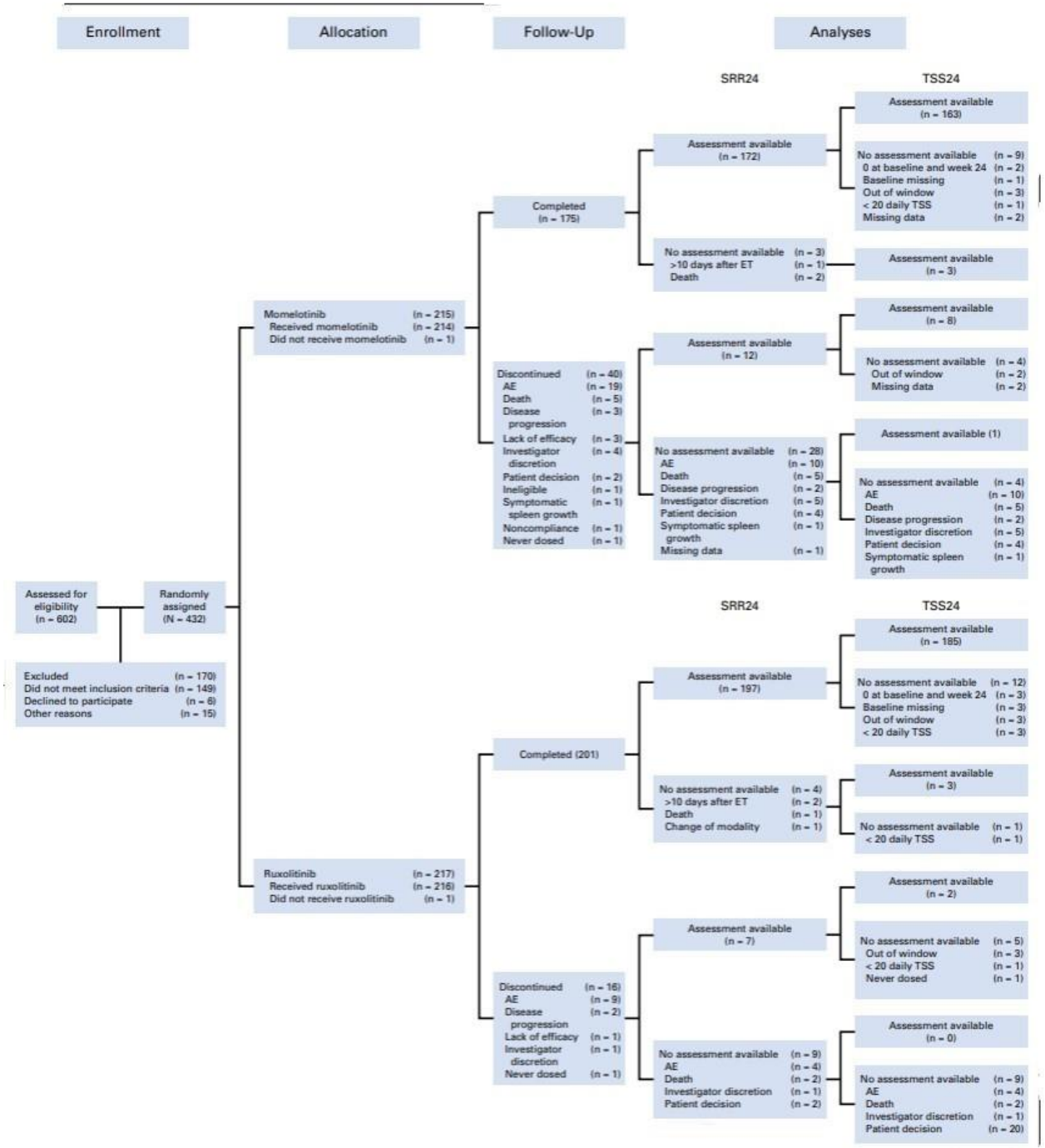
50. 12. NI for HC and E. PMG10 Appendix C: Methodology checklist: randomised controlled trials [Internet]. [cited 2022 Aug 8]. Available from: https://www.nice.org.uk/process/pmg10/chapter/appendix-c-methodology-checklist-randomised-controlled-trials#notes-on-use-of-methodology-checklist-randomised-controlled-trials

51. Gerds AT, Verstovsek S, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis previously treated with a JAK inhibitor (MOMENTUM): an updated analysis of an international, double-blind, randomised phase 3 study. Lancet Haematol. 2023 Sep;10(9):e735–46.

Appendix A. Main characteristics of studies included

Table 33 Main characteristic of SIMPLIFY-1

Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	**NCT number: NCT01969838**
Objective	The objective of the trial was to evaluate the non-inferiority of momelotinib compared with ruxolitinib in JAK inhibitor-naïve patients with MF.
Publications – title, author, journal, year	Mesa RA, Kiladjian JJ, Catalano JV, Devos T, Egyed M, Hellmann A, McLornan D, Shimoda K, Winton EF, Deng W, Dubowy RL, Maltzman JD, Cervantes F, Gotlib J. SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naïve Patients With Myelofibrosis. J Clin Oncol. 2017 Dec 1;35(34):3844-3850. doi: 10.1200/JCO.2017.73.4418. Epub 2017 Sep 20.
Study type and design	SIMPLIFY-1 was a randomised, parallel-assigned, multi-center study in participants with PMF or post-PV/ET MF who have not yet received treatment with a JAK-inhibitor. An overview of the study design of SIMPLIFY-1 is presented below. 
Sample size (n)	A total of 432 patients underwent random assignment, of whom 215 were assigned to receive momelotinib and 217 were assigned to receive ruxolitinib. 214 in the momelotinib group and 216 in the ruxolitinib group received one or more doses of study drug. The 24-week double-blind phase was completed by 376 patients (momelotinib (n = 175), ruxolitinib (n = 201); 368 patients continued in the open-label phase of the study (171 from the momelotinib group and 197 from the ruxolitinib group switched to momelotinib). The disposition of patients is presented below (intention-to-treat analysis set).


Enrollment
Allocation
Follow-Up
Analyses
SRR24
TSS24
Assessed for eligibility (n = 602)
Randomly assigned (N = 432)
Excluded (n = 170)
Did not meet inclusion criteria (n = 149)
Declined to participate (n = 6)
Other reasons (n = 15)
Momelotinib (n = 215)
Received momelotinib (n = 214)
Did not receive momelotinib (n = 1)
Completed (n = 175)
Assessment available (n = 172)
Assessment available (n = 163)
No assessment available (n = 9)
0 at baseline and week 24 (n = 2)
Baseline missing (n = 1)
Out of window (n = 3)
< 20 daily TSS (n = 1)
Missing data (n = 2)
No assessment available (n = 3)
>10 days after ET (n = 1)
Death (n = 2)
Assessment available (n = 3)
Discontinued (n = 40)
AE (n = 19)
Death (n = 5)
Disease progression (n = 3)
Lack of efficacy (n = 3)
Investigator discretion (n = 4)
Patient decision (n = 2)
Ineligible (n = 1)
Symptomatic spleen growth (n = 1)
Noncompliance (n = 1)
Never dosed (n = 1)
Assessment available (n = 12)
Assessment available (n = 8)
No assessment available (n = 4)
Out of window (n = 2)
Missing data (n = 2)
No assessment available (n = 28)
AE (n = 10)
Death (n = 5)
Disease progression (n = 2)
Investigator discretion (n = 5)
Patient decision (n = 4)
Symptomatic spleen growth (n = 1)
Missing data (n = 1)
Assessment available (1)
No assessment available (n = 4)
AE (n = 10)
Death (n = 5)
Disease progression (n = 2)
Investigator discretion (n = 5)
Patient decision (n = 4)
Symptomatic spleen growth (n = 1)
Ruxolitinib (n = 217)
Received ruxolitinib (n = 216)
Did not receive ruxolitinib (n = 1)
Completed (201)
Assessment available (n = 197)
Assessment available (n = 185)
No assessment available (n = 12)
0 at baseline and week 24 (n = 3)
Baseline missing (n = 3)
Out of window (n = 3)
< 20 daily TSS (n = 3)
No assessment available (n = 4)
>10 days after ET (n = 2)
Death (n = 1)
Change of modality (n = 1)
Assessment available (n = 3)
No assessment available (n = 1)
< 20 daily TSS (n = 1)
Discontinued (n = 16)
AE (n = 9)
Disease progression (n = 2)
Lack of efficacy (n = 1)
Investigator discretion (n = 1)
Never dosed (n = 1)
Assessment available (n = 7)
Assessment available (n = 2)
No assessment available (n = 5)
Out of window (n = 3)
< 20 daily TSS (n = 1)
Never dosed (n = 1)
No assessment available (n = 9)
AE (n = 4)
Death (n = 2)
Investigator discretion (n = 1)
Patient decision (n = 2)
Assessment available (n = 0)
No assessment available (n = 9)
AE (n = 4)
Death (n = 2)
Investigator discretion (n = 1)
Patient decision (n = 20)

Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	NCT number: NCT01969838

Main inclusion criteria

Key inclusion criteria (from clinicaltrials.gov):

- Palpable splenomegaly at least 5 cm below the left costal margin
- Confirmed diagnosis of PMF or post-PV/ET MF
- Requires MF therapy, in the opinion of the investigator
- Classified as high risk OR intermediate-2 risk as defined by the IPSS for PMF, or intermediate-1 risk (IPSS) associated with symptomatic splenomegaly, hepatomegaly, anaemia (haemoglobin < 10.0 g/dL), and/or unresponsive to available therapy
- Acceptable laboratory assessment obtained within 14 days prior to the first dose of study drug:
  - Absolute neutrophil count ≥0.75 x 10^9/L in the absence of growth factor in the prior 7 days
  - Platelet Count ≥ 50 x 10^9/L (≥100 x 10^9/L if aspartate aminotransferase or alanine aminotransferase is ≥ 2 x the upper limit of the normal range (ULN) in the absence of platelet transfusion(s) or thrombopoietin mimetics in the prior 7 days
  - Peripheral blood blast count <10%
  - AST and ALT ≤3 x ULN (≤5 x ULN if liver is involved by extramedullary haematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days)
  - Calculated creatinine clearance (CrCL) of ≥ 45 mL/min
  - Direct bilirubin ≤ 2.0 x ULN
- Life expectancy of >24 weeks
- Males and females of childbearing potential must agree to use protocol-specified method(s) of contraception
- Females who are nursing must agree to discontinue nursing before the first dose of study drug

Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	NCT number: NCT01969838
	• Able to understand and willing to sign the informed consent form
Main exclusion criteria	Key exclusion criteria (from clinicaltrials.gov): • Prior splenectomy • Splenic irradiation within three months prior to the first dose of study drug • Eligible for allogeneic bone marrow or stem cell transplantation • Uncontrolled inter-current illness, per protocol. • Known positive status for human immunodeficiency virus (HIV) • Chronic active or acute viral hepatitis A, B, or C infection, or a hepatitis B or C carrier • Prior use of a JAK1 or JAK2 inhibitor • Use of chemotherapy, immunomodulating therapy, biologic therapy, radiation therapy, or investigational therapy within 4 weeks of the first dose of study drug • Presence of peripheral neuropathy ≥CTCAE Grade 2 • Unwilling or unable to undergo an MRI or CT scan
Intervention	A total of 215 participants were randomly assigned to receive oral momelotinib. Momelotinib was supplied as tablets for oral administration once daily containing 200 mg of momelotinib. Participants received momelotinib plus placebo to match ruxolitinib tablets administered orally twice daily.

Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	NCT number: NCT01969838
Comparator(s)	A total of 217 participants were randomly assigned to receive ruxolitinib. Ruxolitinib was supplied as tablets for oral administration twice daily. The dose of ruxolitinib ranged from 5 to 20 mg twice daily and was dependent on platelet count, creatinine clearance and transaminase levels (AST and ALT).
Follow-up time	Participants were randomised (1:1) to receive either momelotinib or ruxolitinib for 24 weeks during a double-blind treatment phase, after which they were eligible to receive open-label momelotinib for up to an additional 216 weeks. Clinic visits were at screening (initial visit and ensuing assessments to determine eligibility), baseline (visit <10 days before random assignment), random assignment (visit for administration of first dose of study drug), and every 2 weeks during the double-blind phase. After discontinuation of study medication, assessments continued for 12 additional weeks, after which participants were contacted for survival follow-up approximately every 6 months for up to 5 years from the date of enrolment or until study termination. For those participants planning to continue treatment with momelotinib following the end of the study, the Early Study Drug Discontinuation (ESDD), 30-day, 12-week, and survival follow-up visits were not required.
Is the study used in the health economic model?	No.
Primary, secondary and exploratory endpoints	**Primary Endpoint** • SRR rate at week 24 (SRR24) ○ Defined as the proportion of participants achieving a ≥35% reduction in spleen volume at week 24 from baseline as measured by MRI or CT. **Secondary Endpoints** • TSS response rate at week 24

- Defined as the proportion of participants who achieve a ≥50% reduction in TSS from baseline to week 24 as measured by the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPNSAF TSS) v2.0 diary.

- RBC transfusion-independence rate at week 24
  - Defined as the proportion of participants who are transfusion-independent at week 24 (absence of RBC transfusions and no Hb <8 g/dL in the prior 12 weeks)
- RBC transfusion-dependence rate at week 24
  - Defined as the proportion of participants who are transfusion dependent at week 24 (at least 4 units of RBC transfusions, or a Hb level <8 g/dL in the prior 8 weeks)
- Rate of RBC transfusion through week 24
  - Defined as the average number of RBC units per participant per month.

Exploratory Endpoint

- Splenic response rate over time
- Percent change from baseline in spleen volume over time
- Palpable spleen size and % change from baseline over time
- Duration of spleen response
- TSS Response by every 4 weeks
- PGIC
- MPN-SAF (27-item questionnaire)
- EQ-5D-5L
- SF-36v2

Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	NCT number: NCT01969838

- New RBC transfusion-independent rate by week 24
- New RBC transfusion-dependent rate by week 24
- RBC transfusion-free response rate over time
- Hb, platelets, or ANC, change and percent change from baseline over time
- Rate of RBC transfusion in the open label phase
- Duration of transfusion-independent response for subjects not transfusion-independent at baseline and who achieved transfusion-independent at any post-baseline in the double-blind phase
- Time to transfusion-independent for subjects not transfusion-independent at baseline and who achieved transfusion-independent at any post-baseline in the double-blind phase
- Anaemia response rate at week 24 based on IWG-MRT/ELN criteria
- Transfusion independence by week 48 (post hoc)
- Duration of transfusion-independent at any time (post hoc)
- Proportion of subjects receiving an RBC transfusion (post hoc)
- Zero-inflated negative binomial model for total RBC transfusion rate (post hoc)
- Recurrent event model for RBC transfusion (post hoc)
- Time to first, third, and fifth units of RBC transfusions (post hoc)
- Hb increases at Week 24 in ITT and TI subgroups (post hoc)
- CR and PR based on IWG-MRT/ELN response criteria, or anaemia response at Week 24, or MRI/CT spleen response at Week 24, or TSS response at Week 24
- ORR (CR or PR)
- Overall survival
- Leukaemia-free Survival

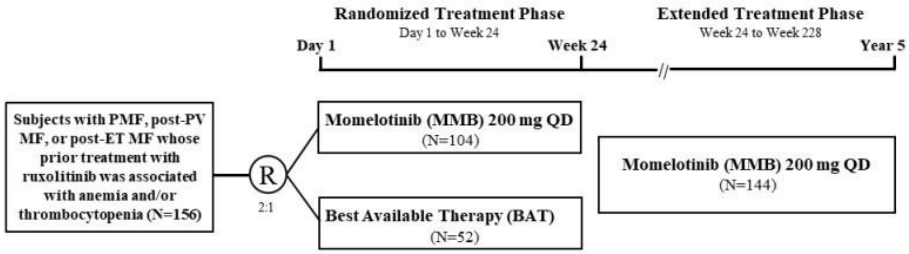
Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	NCT number: NCT01969838

Method of analysis	The primary endpoint was a reduction of ≥35% in spleen volume from baseline at week 24 (spleen response rate, SRR24), as assessed by MRI or CT scan and evaluated by a blinded central reader. The primary hypothesis was that momelotinib is non-inferior to ruxolitinib. On the basis of the assumption of the common treatment effect on SRR being 34% (lower bound of the 95% CI on the ruxolitinib effect on SRR) that was observed in the COMFORT-1, a total sample size of 420 provides >90% power for testing the non-inferiority hypothesis on SRR24. Non-inferiority of momelotinib was determined by whether the lower bound of the two-sided 95% CI for the non-inferiority difference (SRR24 of momelotinib -0.6 x SRR24 of ruxolitinib) was >0 and was calculated based on the stratum-adjusted CMH proportion. Four endpoints at week 24 were designated as secondary endpoints for which sequential testing was performed in the order listed to control the type 1 error rate: TSS response rate (proportion of patients who achieved a ≥50% reduction from baseline to week 24 on the basis of the modified Myeloproliferative Neoplasm Symptom Assessment Form TSS diary); RBC transfusion-independence rate (proportion of patients who were transfusion-independent at week 24 [absence of RBC transfusions and no Hb <8 g/dL in the prior 12 weeks]); RBC transfusion-dependence rate (proportion of patients who were transfusion-dependent [≥4 units of RBC transfusions, or Hb <8 g/dL in the prior 8 weeks]); and rate of RBC transfusion (average number of RBC units per subject-month during treatment). Most secondary endpoints were evaluated similarly to the primary endpoint (CMH approach), with the exception of the RBC transfusion rate, which was analysed using a negative binomial regression method adjusted for stratification factors with an offset parameter to account for follow-up time. The primary endpoint analysis served as the gatekeeper for the secondary endpoint analyses, such that only if the primary efficacy hypothesis was rejected could the formal, statistical testing be undertaken for the four secondary efficacy endpoints sequentially in the order listed above. If a null hypothesis was not rejected, formal sequential testing was stopped and only nominal significance would be cited for the remaining secondary endpoints. Exploratory endpoints included ORR, which was defined as the proportion of patients who achieve a CR or PR according to the IWG-MRT and/or ELN criteria. The composite clinical improvement rate was defined as the proportion of patients who achieved CR and PR on the basis of IWG-MRT and/or ELN response criteria or who achieved anaemia response, MRI/CT spleen response, or TSS response at week 24. Efficacy end points were analysed in the intent-to-treat population consisting of all patients randomly assigned, except TSS response rate, which was analysed in all randomly assigned patients with baseline TSS >0 or with baseline TSS of 0, but week 24 TSS missing or >0. Patients without baseline and/or week 24 visit assessments for the corresponding endpoint were regarded as splenic non-responders, TSS

Trial name: A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib versus Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	NCT number: NCT01969838
	non-responders, not transfusion independent, or transfusion dependent at week 24. Differences between treatment arms for continuous endpoints were assessed using analysis of covariance, with treatment and stratification factors as factors and baseline values as covariates. Differences between treatment arms were compared using CMH approach after adjusting for stratification factors. Sensitivity analyses for the primary endpoint included analysis on per-protocol analysis set, using last observation carried forward for missing data, unstratified method, and fixed margin method. TEAEs were monitored continuously, graded for severity and relationship to treatment, and summarised by treatment group.
Subgroup analyses	Analyses were conducted in the overall population of SIMPLIFY-1 and in a symptomatic subset (patients with baseline TSS ≥10) to remove the distribution of asymptomatic patients (Mesa et al. 2021). The objective of this analysis was to explore TI response rates at week 24 for momelotinib and ruxolitinib in randomized patients in SIMPLIFY-1 by baseline Hb and platelet levels and transfusion status (Kiladijan et al. 2021).
Other relevant information	None.

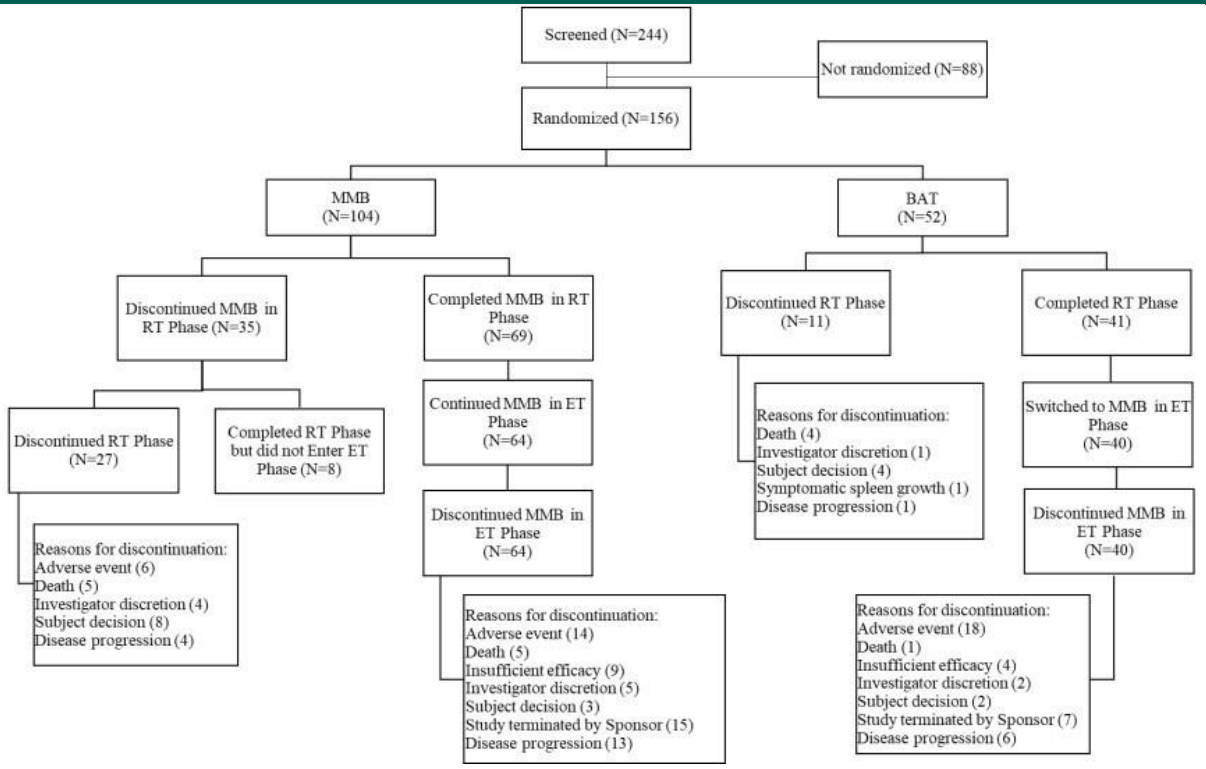
Table 34 Main characteristic of SIMPLIFY-2. Sources: Harrison et al. 2018 and CSR data on file (26,27).

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
Objective	The objective of the trial was evaluating the superiority of momelotinib compared with best available therapy (BAT) in JAK inhibitor-experienced patients with MF.

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
Publications – title, author, journal, year	Harrison CN, Vannucchi AM, Platzbecker U, Cervantes F, Gupta V, Lavie D, Passamonti F, Winton EF, Dong H, Kawashima J, Maltzman JD, Kiladjian JJ, Verstovsek S. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol. 2018 Feb;5(2):e73-e81. doi: 10.1016/S2352-3026(17)30237-5. Epub 2017 Dec 20.
Study type and design	SIMPLIFY-2 is a randomised, open-label, multi-centre phase 3 study in anaemic or thrombocytopenic participants with PMF or post-PV/ET MF who had received treatment with a JAK inhibitor. No washout period for previous MF treatment was required before randomisation. The randomisation was stratified by transfusion dependence and by baseline TSS. An overview of the study design of SIMPLIFY-2 is presented below. 
Sample size (n)	A total of 244 subjects were screened for eligibility, and of these, 156 patients were randomly assigned to treatment, of whom 104 received momelotinib and 52 received BAT. All patients randomly assigned to treatment received at least one dose of the study drug. Among the 104 subjects randomised to momelotinib, 77 subjects (74.0%) completed the randomised treatment phase and 69 subjects (66.3%) completed 24 weeks of study treatment in the randomised treatment phase. Thirty-five subjects (33.7%) randomised to momelotinib discontinued study treatment during the randomised treatment phase.

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib

NCT number: NCT02101268



Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
	Abbreviations: MMB = momelotinib, RT = randomised treatment, BAT = best available therapy, ET = extended treatment, ITT = intention-to-treat. Source: CSR data on file (26).

Main inclusion criteria	Key inclusion criteria (from clinicaltrials.gov):
	• Palpable splenomegaly at least 5 cm below left costal margin
	• Confirmed diagnosis of PMF in accordance, or Post-PV/ET MF
	• Currently or previously treated with ruxolitinib for PMF or Post-PV/ET MF for at least 28 days, and characterised by
	  ○ Requirement for RBC transfusion while on ruxolitinib treatment, OR
	  ○ Dose adjustment of ruxolitinib to <20 mg twice daily at start of or during ruxolitinib treatment AND at least one of the following while on ruxolitinib treatment:
	  ▪ ≥ CTCAE Grade 3 thrombocytopenia, OR
	  ▪ ≥ CTCAE Grade 3 anaemia, OR
	  ▪ ≥ CTCAE Grade 3 hematoma (bleed)
	• High risk OR intermediate-2 risk as defined by DIPSS, OR intermediate-1 risk as defined by DIPSS and associated with symptomatic splenomegaly, and/or hepatomegaly
	• If receiving myelofibrosis therapy, must be on a stable dose of the same regimen for at least 2 weeks prior to screen date and through the screening period
	• If not receiving myelofibrosis therapy, must remain off therapy for at least 2 weeks prior to screen date and through the screening period
	• Acceptable laboratory assessments obtained within 14 days prior to Randomization
	  ○ Absolute neutrophil count > 0.75 x 10^9/L in the absence of growth factor in the prior 7 days
	  ○ Peripheral blood blast count <10%

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
	○ Aspartate transaminase and alanine transaminase ≤ 3 x the ULN (≤5 x ULN if liver is involved by extramedullary haematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days) ○ Calculated creatinine clearance of ≥ 45 mL/min ○ Direct bilirubin ≤ 2.0 x ULN • Life expectancy >24 weeks • Negative serum pregnancy test for female subjects (unless surgically sterile or greater than two years post-menopausal) • Males and females of childbearing potential must agree to use protocol-specified method(s) of contraception • Females who are nursing must agree to discontinue nursing before the first dose of momelotinib • Able to understand and willing to sign informed consent form
Main exclusion criteria	Key exclusion criteria (from clinicaltrials.gov): • Prior splenectomy • Splenic irradiation within 3 months prior to randomisation • Use of investigational agent within 28 days prior to randomisation • Prior treatment with momelotinib • Hematopoietic growth factor (granulocyte growth factor, erythropoiesis stimulating agent, thrombopoietin mimetic) within 28 days prior to randomisation • Uncontrolled inter-current illness, per protocol • Known positive status for HIV • Chronic active or acute viral hepatitis A, B, or C infection, or hepatitis B or C carrier • Presence of peripheral neuropathy ≥CTCAE Grade 2 • Unwilling or unable to undergo an MRI or CT scan per study protocol requirements

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
Intervention	A total of 104 participants were randomly assigned to receive oral momelotinib. Momelotinib was supplied as tablets for oral administration once daily containing 200 mg of momelotinib. Participants received momelotinib plus placebo to match ruxolitinib tablets administered orally twice daily.
Comparator(s)	A total of 52 participants were randomly assigned to BAT. In the BAT treatment arm, patients received treatment at doses and schedules determined by the investigator in accordance with standard of care. Regimens for BAT could include but were not limited to chemotherapy (e.g. hydroxyurea), anagrelide, corticosteroid, hematopoietic growth factor, immunomodulating agent, androgen, interferon, and may include no MF treatment. Therapy could be changed at any time during the study except during the screening period. The most commonly administered treatments in the BAT group were ruxolitinib (89%), hydroxyurea (23%), and corticosteroids (12%). In 14 patients (27%), ruxolitinib was administered in combination with other therapies, most commonly hydroxyurea (17%), followed by corticosteroids (12%). After completion of the randomised treatment phase, participants were eligible to receive momelotinib for the duration of the study during the extended treatment phase for up to 204 weeks.
Follow-up time	Participants were randomised (2:1) to receive either momelotinib or BAT for 24 weeks during the randomised treatment phase, after which they will be eligible to receive momelotinib in an extended treatment phase for up to an additional 204 weeks. After discontinuation of study medication, assessments continued for 12 additional weeks, after which participants were contacted for survival follow-up approximately every 6 months for up to 5 years from the date of enrolment or until study termination. For those subjects continuing treatment with momelotinib following the end of the study, the End of Treatment, 30-day, 12-week, and survival follow-up visits were not required.
Is the study used in the health economic model?	No, due to cost-minimisation model

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268

Primary, secondary and exploratory endpoints	**Primary Endpoint**
	• SRR at week 24
	  ○ SRR at week 24 is defined as the proportion of participants achieving a ≥35% reduction in spleen volume at week 24 from baseline as measured by MRI or CT.
	Secondary Endpoints
	• Response rate in total symptom score at week 24
	  ○ TSS is defined as the proportion of participants who achieve a ≥50% reduction in TSS from baseline to week 24 as measured by the MPNSAF TSS v2.0 diary.
	• Rate of RBC transfusion through week 24
	  ○ Rate of RBC transfusion is defined as the average number of RBC units per participant per month.
	• RBC transfusion independence rate at week 24
	  ○ RBC transfusion independence is the proportion of participants who are transfusion independent at week 24, defined as absence of RBC transfusions and no haemoglobin level below 8 g/dL in the prior 12 weeks.
	• RBC transfusion dependence rate at week 24
	  ○ RBC transfusion dependence is the proportion of participants who are transfusion dependent at week 24, defined as at least 4 units of RBC transfusions, or a haemoglobin level below 8 g/dL in the prior 8 weeks.
	Exploratory endpoints
	• ORR
	  ○ Defined as the proportion of patients who achieve a CR or PR according to the IWG-MRT and/or ELN criteria.
	• Composite clinical improvement rate

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
	○ Defined as the proportion of patients who achieved CR and PR, or achieved anaemia response, MRI/CT spleen response, or TSS response at week 24.
Method of analysis	Efficacy analyses were performed on an intent-to-treat basis for all patients randomly assigned to treatment. The exception was for TSS response at week 24, which excluded patients who had missing baseline scores or whose baseline and week 24 scores were both 0, which led to an incalculable percentage change from baseline at week 24 and, therefore, an undetermined TSS response at week 24. On the basis of assumptions of BAT treatment effect on spleen response at week 24 of 1% (0 of73 patients had a spleen response in and of 20% with momelotinib (previously observed at a total sample size of 150 provided more than 95% power at a two-sided level of 0-05 using Fisher's exact test. The between-treatment comparison used the Cochran-Mantel-Haenszel approach adjusted for stratification factors. Given the novelty of the study patient population, there was no historical reference to inform assumptions for the control group. It was anticipated that statistical power for the secondary endpoint analyses could be over 80%, should the differences between groups reach 25%. Sequential testing was done for the four secondary endpoints in the order listed above to control the type 1 error (controlled at a two-sided 0-05 significance level). The analysis of secondary endpoints was done similarly to that of the 24-week spleen response primary endpoint, except for rate of RBC transfusion, which was analysed through the negative binomial regression method. The primary endpoint analysis served as the gatekeeper for the secondary endpoint analyses, such that only if the primary efficacy hypothesis was rejected could the formal, sequential statistical testing be done for the four secondary efficacy endpoints. The CMH approach, after adjusting for stratification factors, was used to compare differences between treatment groups for categorical endpoints (27).
Subgroup analyses	Subgroup analyses were performed as pre-specified by age, gender, race, transfusion dependence at baseline, spleen volume at baseline, TSS at baseline, haemoglobin level at baseline, DIPSS, JAK2V617F mutation status, MF disease status, duration of ruxolitinib treatment received prior to randomisation (<12 weeks, ≥12 weeks), and highest dose of ruxolitinib received since randomisation. Post hoc subgroup analyses were also performed for the following subgroups: transfusion independent at baseline; non-transfusion independent at baseline; TSS ≥ 10 at baseline; haemoglobin < 10 g/dL at baseline; TSS ≥ 10 g/dL and haemoglobin <10 g/dL at baseline; and platelet count at baseline (26).

Trial name: A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib	NCT number: NCT02101268
Other relevant information	None.

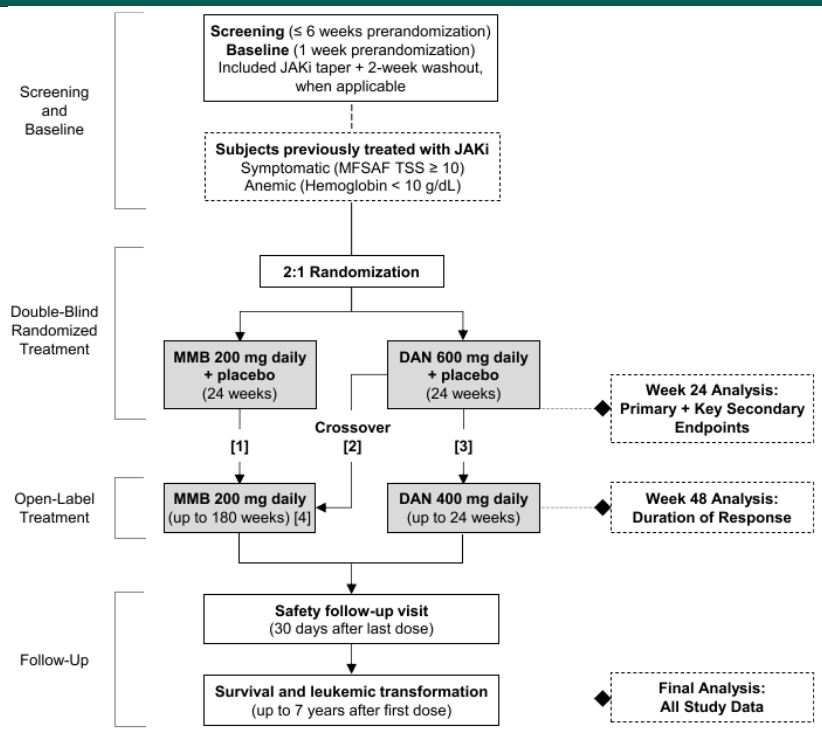
Table 35 Main characteristic of MOMENTUM. Sources: Verstovsek et al. 2023 and CSR data on file (30,31).

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494
Objective	The purpose of the clinical study is to compare the effectiveness and safety of momelotinib to danazol in treating and reducing: 1) disease related symptoms, 2) the need for blood transfusions and 3) splenomegaly, in adults with primary MF, post-PV MF or post-ET MF.
Publications – title, author, journal, year	• Verstovsek S, Gerds A, Vannucchi A, Al-Ali HK, Lavie D, Kuykendall A, Grosicki S, Iurlo A, Goh YT, Lazaroiu M, Egyed M, Fox ML, McLornan D, Perkins A, Yoon SS, Gupta V, Kiladjian JJ, Donahue R, Kawashima J, Mesa R. MPN-483 Thrombocytopenic Myelofibrosis (MF) Patients Previously Treated With a JAK Inhibitor in a Phase 3 Randomized Study of Momelotinib (MMB) versus Danazol (DAN) [MOMENTUM]. Clin Lymphoma Myeloma Leuk. 2022 Oct;22 Suppl 2:S340. doi: 10.1016/S2152-2650(22)01464-1. • Verstovsek, S., et al., Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. The Lancet, 401. 2023. 401(10373):269-280 • Gerds A, Verstovsek S, Vannucchi A, Al-Ali HK, Lavie D, Kuykendall A, Grosicki S, Iurlo A, Goh YT, Lazaroiu M, Egyed M, Fox ML, McLornan D, Perkins A, Yoon SS, Gupta V, Kiladjian JJ, Donahue R, Kawashima J, Mesa R. MPN-483 Thrombocytopenic

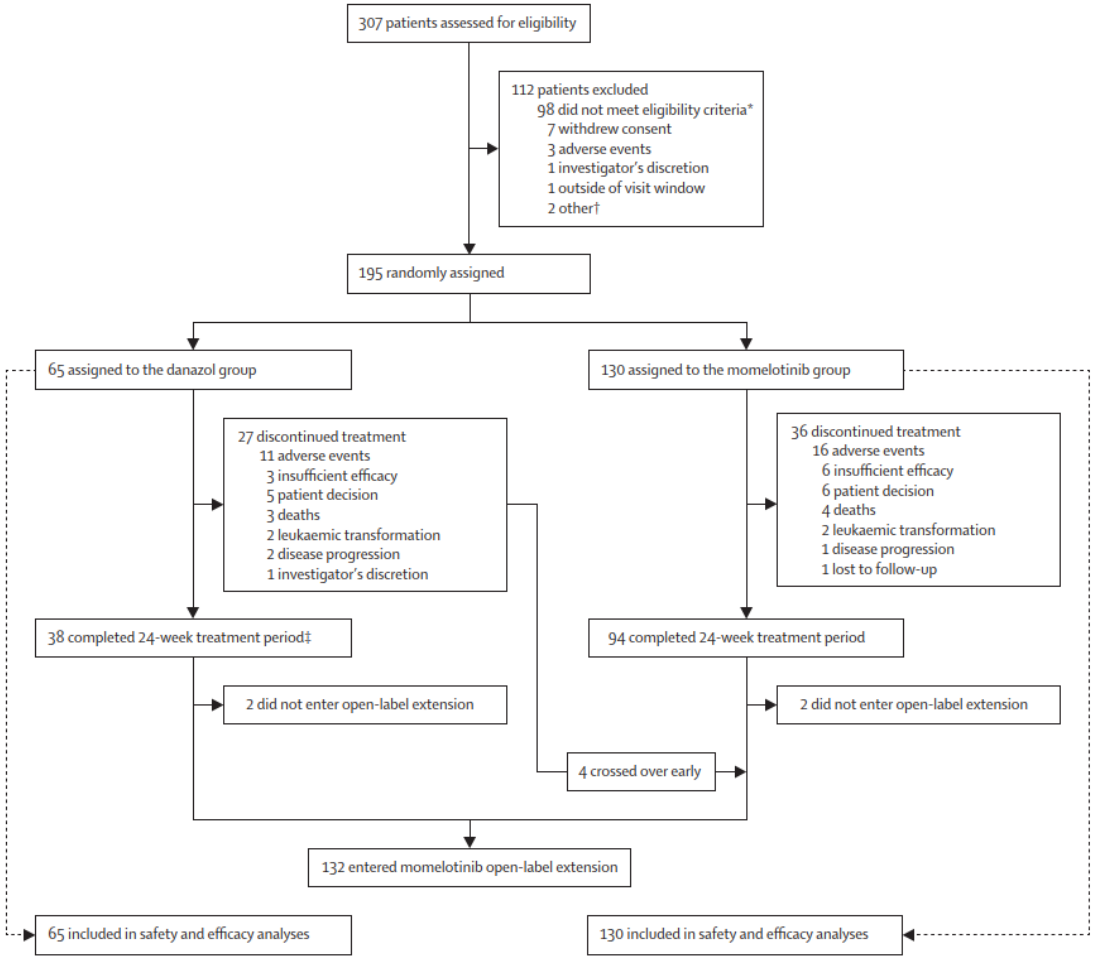
Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494
	Myelofibrosis (MF) Patients Previously Treated With a JAK Inhibitor in a Phase 3 Randomized Study of Momelotinib (MMB) versus Danazol (DAN) [MOMENTUM]. Clin Lymphoma Myeloma Leuk. 2022 Oct;22 Suppl 2:S340. doi: 10.1016/S2152-2650(22)01464-1. • Gerds AT, Verstovsek S, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, Grosicki S, Iurlo A, Goh YT, Lazaroiu MC, Egyed M, Fox ML, McLornan D, Perkins A, Yoon SS, Gupta V, Kiladjian JJ, Granacher N, Lee SE, Ocroteala L, Passamonti F, Harrison CN, Oh S, Klencke BJ, Yu J, Donahue R, Kawashima J, Mesa R. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis previously treated with a JAK inhibitor (MOMENTUM): an updated analysis of an international, double-blind, randomised phase 3 study. Lancet Haematol. 2023 Sep;10(9):e735-e746. doi: 10.1016/S2352-3026(23)00174-6. Epub 2023 Jul 27. PMID: 37517413.
Study type and design	MOMENTUM is a randomised, double-blind, multi-centre phase 3 study in symptomatic and anaemic myelofibrosis patients, who have previously received JAKi treatment. Subjects must be symptomatic with a MF-SAF v4.0 TSS of ≥10 at screening and be anaemic with Hb <10 g/dL. For subjects with ongoing JAKi therapy at screening, JAKi therapy must be tapered over a period of at least 1 week, followed by a 2-week non-treatment washout interval prior to randomisation. An overview of the study design of MOMENTUM is presented below.

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy

NCT number: NCT04173494



Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494
Sample size (n)	195 patients were enrolled and received blinded study treatment in the 24-week randomised treatment period (130 [67%] in the momelotinib group and 65 [33%] in the Danazol group. 94 (72%) of 130 patients in the momelotinib group and 38 (58%) of 65 in the danazol group completed randomised treatment. An overview is provided below.


307 patients assessed for eligibility
112 patients excluded
98 did not meet eligibility criteria*
7 withdrew consent
3 adverse events
1 investigator's discretion
1 outside of visit window
2 other†
195 randomly assigned
65 assigned to the danazol group
130 assigned to the momelotinib group
27 discontinued treatment
11 adverse events
3 insufficient efficacy
5 patient decision
3 deaths
2 leukaemic transformation
2 disease progression
1 investigator's discretion
36 discontinued treatment
16 adverse events
6 insufficient efficacy
6 patient decision
4 deaths
2 leukaemic transformation
1 disease progression
1 lost to follow-up
38 completed 24-week treatment period‡
94 completed 24-week treatment period
2 did not enter open-label extension
2 did not enter open-label extension
4 crossed over early
132 entered momelotinib open-label extension
65 included in safety and efficacy analyses
130 included in safety and efficacy analyses

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494

	Figure note: *Most common reasons for not meeting eligibility criteria were having laboratory values outside of the required parameters (n=37) or having a total symptom score of less than 10 (n=15). †Other reasons for exclusion included improved Hb concentrations (n=1) and death (n=1). ‡Of the 38 patients who were randomised to the danazol group (masked treatment) and completed therapy during the 24-week randomised treatment period, none chose to continue to open-label Danazol treatment. Source: Verstovsek et al. 2023 (30).

Main inclusion criteria	Key inclusion criteria (from clinicaltrials.gov):
	• Age ≥18 years
	• Confirmed diagnosis of PMF in accordance with the World Health Organization (WHO) 2016 criteria, or Post-PV/ET MF in accordance with the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT criteria).
	• Symptomatic, defined as a TSS of ≥10 units assessed by a single MF-SAF v4.0 assessment during Screening prior to Day BL1.
	• Anaemic, defined as a Hb <10 g/dL in screening/baseline period.
	• Previously treated with an approved JAK inhibitor for PMF or Post-PV/ET MF for ≥90 days, or ≥28 days if JAK inhibitor therapy is complicated by RBC transfusion requirement of ≥4 units in 8 weeks, or Grade 3/4 AEs of thrombocytopenia, anaemia, or hematoma.
	• Baseline splenomegaly, defined as having a palpable spleen at ≥5 cm, below the left costal margin, or with volume ≥450 cm^3 on imaging (ultrasound, MRI or CT are acceptable), assessed during screening at any point prior to randomisation.
	• High risk, intermediate-2, or intermediate-1 risk MF as defined by DIPSS, or DIPSS-plus.
	• No allogeneic stem cell transplant planned.
	• Acceptable laboratory assessments:
	  ○ ANC ≥ 0.75 × 10E9/L.
	  ○ Platelet count (PLT) ≥ 25 × 10E9/L (without requirement for platelet transfusion).
	  ○ Peripheral blast count < 10%.

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494

	○ Alanine aminotransferase/ glutamic-oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/ serum glutamic-pyruvic transaminase (ALT/SGPT) ≤ 3 × ULN (≤ 5 × ULN if liver is involved by extramedullary haematopoiesis as judged by the investigator or if related to iron chelator therapy that was started within the prior 60 days). ○ Calculated creatinine clearance (CCr) ≥ 30 mL/min according to Cockcroft-Gault. ○ Direct bilirubin ≤ 2.0 × ULN.
Main exclusion criteria	Key exclusion criteria (from clinicaltrials.gov): • Use of the following treatments within the time periods noted: ○ Prior momelotinib treatment at any time. ○ Approved JAK inhibitor therapy (e.g. fedratinib or ruxolitinib) within 1 week prior to the first day of baseline. ○ Active anti-MF therapy within 1 week prior to the first day of baseline. ○ Potent Cytochrome P450 3A4 (CYP3A4) inducers within 1 week prior to randomisation. ○ Investigational agent (including investigational JAK inhibitors) within 4 weeks prior to randomisation. ○ ESA within 4 weeks prior to randomisation. ○ Danazol within 3 months prior to randomisation. ○ Splenic irradiation within 3 months prior to randomisation. ○ Current treatment with simvastatin, atorvastatin, lovastatin or rosuvastatin. • History of prostate cancer, with the exception of localised prostate cancer that has been treated surgically or by radiotherapy with curative intent and presumed cured. • Prostate specific antigen (PSA) >4 ng/mL. • Unsuitable for spleen volume measurements due to prior splenectomy or unwilling or unable to undergo an MRI or CT scan for spleen volume measurement per protocol requirements. • Any of the following (criteria a - k):

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494

- Uncontrolled intercurrent illness including, but not limited to: active uncontrolled infection (subjects receiving outpatient antibacterial and/or antiviral treatments for infection that is under control or as infection prophylaxis may be included in the trial).
- Significant active or chronic bleeding event ≥Grade 2 per CTCAE v5.0, within 4 weeks prior to randomisation.
- Unstable angina pectoris within 6 months prior to Randomization.
- Symptomatic congestive heart failure within 6 months prior to randomisation.
- Uncontrolled cardiac arrhythmia within 6 months prior to Randomization.
- QTcF interval >500 msec, unless attributed to bundle branch block.
- Current progressive thrombosis despite treatment.
- History of porphyria.
- Child-Pugh score ≥10.
- Psychiatric illness, social situation, or any other condition that would limit compliance with trial requirements or may interfere with the interpretation of study results, as judged by investigator or sponsor.
- Inability or unwillingness to comply with the protocol restrictions on MF therapy and other medications prior to and during study treatment.

- Subjects with a prior or concurrent malignancy, whose natural history or treatment has a significant potential to interfere with the safety or efficacy assessment of the investigational regimen.
- Known clinically significant anaemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary haemolytic anaemia, or gastrointestinal bleeding or thalassemia.
- Known positive status for HIV.
- Chronic active or acute viral hepatitis A, B, or C infection, or hepatitis B or C carrier (testing required for hepatitis B and C).
- Unresolved non-hematologic toxicities from prior therapies that are >Grade 1 per CTCAE v5.0.
- Presence of peripheral neuropathy ≥Grade 2 per CTCAE v5.0.
- Women who are already pregnant or lactating.

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494
Intervention	A total of 130 participants were randomly assigned to receive oral momelotinib. Momelotinib was supplied as tablets for oral administration once daily containing 200 mg of momelotinib. Participants received momelotinib plus placebo to match danazol capsules administered orally twice daily
Comparator(s)	A total of 65 participants were randomly assigned to danazol. Danazol was supplied as capsules for oral administration twice daily containing 300 mg of danazol. Participants received danazol plus placebo to match momelotinib plus placebo in the intervention arm.
Follow-up time	Subjects randomised (2:1) to receive momelotinib who completed the randomised treatment period to the end of week 24 could continue to receive momelotinib in the open-label extended treatment period to the end of week 204 (a total period of treatment of approximately 4 years) if the subject tolerates and continues to benefit from momelotinib. Subjects randomised to receive danazol may cross-over to momelotinib open-label treatment in the following circumstances: • at the end of week 24 if they complete the randomised treatment period; or • at the end of week 24 if they discontinue treatment with danazol but continue study assessments and do not receive prohibited medications including alternative active anti-MF therapy; or • at any time during the randomised treatment period if they meet the protocol-defined criteria for radiographically-confirmed symptomatic splenic progression. Subjects randomised to receive danazol who are receiving clinical benefit at the end of week 24 may choose to continue danazol therapy up to week 48. The comparator treatment, danazol, is an approved medication in the US and in some other countries and is recommended by national guidelines as a treatment for anaemia in MF.

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494
Is the study used in the health economic model?	No.

Primary, secondary and exploratory endpoints	**Primary endpoint**
	• Response rate in total symptom score at week 24
	  ○ TSS is defined as the proportion of participants who achieve a ≥50% reduction in TSS from baseline to week 24 as measured by the MPNSAF TSS v2.0 diary.
	Secondary endpoints
	• Number of Participants with TI at week 24
	  ○ TI status was defined as not requiring red blood cell or whole blood transfusion (except in the case of clinically overt bleeding) for ≥12 weeks, with all haemoglobin levels during the terminal ≥12-week interval of ≥ 8 g/dL (except in the case of clinically overt bleeding).
	• SRR of ≥25% at week 24
	  ○ Measured as the percentage of participants who had splenic response at week 24. A splenic response was defined as a reduction in spleen volume of ≥ 25% from baseline.
	• SRR of ≥35% at week 24
	  ○ Measured as the percentage of participants who had splenic response at week 24. A splenic response was defined as a reduction in spleen volume of ≥35% from baseline.
	• Change in MF-SAF TSS from baseline at week 24
	  ○ Defined as the change from baseline in mean MF-SAF TSS over the 28 days immediately before the end of week 24. TSS was measured using the MF-SAF v4.0. The MF-SAF v4.0 comprises 7 domains representing the 7 most

relevant symptoms of MF identified through existing patient- and clinician-based evidence: fatigue, night sweats, pruritus, abdominal discomfort, pain under the left ribs, early satiety, and bone pain. Participants scored each symptom domain using an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). The MF-SAF TSS was calculated as the sum of scores of the 7 domains for a possible range of scores of 0 to 70, with a higher TSS corresponding to more severe symptoms. A reduction from baseline corresponded to a lessening of MF symptoms.

Exploratory endpoints

- Rate of No Transfusion at week 24
  - Defined as the percentage of participants with zero red blood cell or whole blood units transfused during the 24-week randomized treatment period.
- Duration of the End of Week 24 MF-SAF TSS Response
  - For participants who achieved a Week 24 TSS response, the duration of response was defined as the number of days from the start of the initial 28-day period (during the 24-Week Randomized Treatment Period), in which the participant had a ≥ 50% reduction from baseline TSS to the first day of the 7-day assessment that determines the mean TSS for the 28-day period during which the participant's TSS equalled or exceeded their baseline value. TSS will be assessed during the last 7 days (± 7 days) of each month during the open label extended treatment period until Week 48.
- Average Duration of TI at Week 24
  - Measured in participants who achieved TI status at Week 24. TI status was defined as the number of days from the first day of a period of at least 12 weeks, during which a participant received no transfusions and had no haemoglobin <8 g/dL (except in the case of clinically overt bleeding), to the first red blood cell or whole blood transfusion or haemoglobin level < 8 g/dL (again, except in the case of clinically overt bleeding) (assessed until the end of week 48).

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494

- Cumulative Transfusion Risk at Week 24
  - Cumulative transfusion risk was calculated as the estimated mean cumulative number of red blood cell or whole blood units transfused during the randomized treatment period.
- TD Rate at Week 24
  - Defined as the percentage of participants with TD. Participants were defined as having TD if they met both of the following requirements in the 8 weeks immediately before the end of Week 24: ≥4 red blood cell or whole blood units were transfused (except in the case of clinically overt bleeding), each in response to a haemoglobin assessment of ≤9.5 g/dL; and there were ≥2 haemoglobin assessments with ≥28 days between the earliest and latest haemoglobin assessments.
- Number of Participants With a Haemoglobin Response
  - Hb response was defined as increases of ≥1, ≥1.5, or ≥2 g/dL from baseline in Hb over the 24-week randomised treatment period and the last 12 weeks of the period with any Hb values within 4 weeks after a transfusion excluded. Assessed in all participants and in the subset of participants who were TI at baseline.
- Percentage of Baseline TD Participants With TI Status at Week 24
  - Participants were defined as having TD if they met both of the following requirements in the 8 weeks immediately before the end of Week 24: ≥4 red blood cell or whole blood units were transfused (except in the case of clinically overt bleeding), each in response to a Hb assessment of ≤9.5 g/dL; and there were ≥2 haemoglobin assessments with ≥28 days between the earliest and latest Hb assessments. TI status was defined as not requiring red blood cell transfusion (except in the case of clinically overt bleeding) for ≥ 12 weeks immediately prior to the end of Week 24, with Hb levels ≥ 8 g/dL.
- Average Duration of TI at Week 24 in Baseline TD Participants
  - Measured in participants who achieved TI status at Week 24 who were TD at baseline. TI status was defined as the number of days from the first day of a period of at least 12 weeks, during which a participant received no transfusions and had no haemoglobin <8 g/dL (except in the case of clinically overt bleeding), to the first red

blood cell or whole blood transfusion or haemoglobin level <8 g/dL (again, except in the case of clinically overt bleeding) (assessed until the end of week 48).

- Number of Participants Who Experienced an AE
  - An AE was defined as any untoward medical occurrence in a trial participant administered an investigational product(s), a comparator product, or an approved drug regardless of the causal relationship with treatment. A SAE was defined as an AE that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, resulted in in a congenital anomaly/ birth defect in the offspring of an exposed female participant or offspring of a female partner of a male participant, or required medical or surgical intervention. AEs at Grade 3 (severe) or above based on CTCAE Version 5.0, relationship of AEs to study drug, serious AEs and AEs leading to discontinuation of study drug were reported. Any clinically significant changes in laboratory tests and spleen measurements were also recorded as AEs.
- Overall Survival
  - Defined as the interval from the first study drug dosing date to death from any cause.
- Leukaemia-free Survival
  - Defined as the interval from the first study drug dosing date to any evidence of leukemic transformation and/or death.
- Change From Baseline in Disease-related Fatigue as Assessed by MF-SAF v4.0
  - The MF-SAF v4.0 comprises 7 domains representing the 7 most relevant symptoms of MF identified through existing patient- and clinician-based evidence: fatigue, night sweats, pruritus, abdominal discomfort, pain under the left ribs, early satiety, and bone pain. Participants scored each symptom domain using an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). The total possible range of scores was 0 to 70, with higher scores corresponding to more severe MF symptoms. An increase in score from baseline indicated a worsening of MF symptoms, and a decrease in score from baseline indicated an improvement in MF symptoms.

- Change From Baseline in Cancer-related Fatigue as Assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
    - The EORTC QLQ-C30 is comprised of 5 functional scales (physical, role, emotional, social, cognitive), eight single item symptom scales (fatigue, pain, nausea/vomiting, appetite loss, constipation, diarrhoea, insomnia, dyspnoea), as well as sub-scales assessing global health/quality of life and financial impact. Most items use a 4-point Likert scale from "not at all" to "very much" and a one-week recall period with the exception of the final two items which use a 7-point scale response from "very poor" to "excellent". Raw scores were transformed to a 0-100 scale, with higher scores representing better functioning/quality of life. An increase in scores from baseline indicated an improved functioning/quality of life, and a decrease in scores from baseline indicated a worsened functioning/quality of life.
- Change From Baseline in Physical Function Score as Assessed by Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Short Form 10b

The PROMIS Physical Function Short Form 10b consists of 14 questions; each with a 5-point response. The PROMIS short form assesses the self-reported capability of a participant rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands. Participants scored each response on a scale from 1 (unable to do) to 5 (without any difficulty, or not at all). The total possible range of scores was 14 to 70, with higher scores corresponding to a greater physical function ability. An increase in score from baseline indicated an improvement in physical function ability, and a decrease in score from baseline indicated a reduction in physical function ability.

Method of analysis	MOMENTUM was designed to enrol at least 180 patients, including approximately 120 in the momelotinib group and 60 in the danazol group, providing 90% power to detect a true difference of 15% (17% vs 2%) in the primary endpoint of TSS response rate and 14% (15% vs 1%) in the proportion of patients with splenic response for superiority with a two-sided alpha of 0.05. Under the assumption of a true difference of 20% (41% vs 21%), the power to show non-inferiority in transfusion independence at the

Trial name: A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic, Anemic Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post-Essential Thrombocythemia (ET) Myelofibrosis Who Were Previously Treated With JAK Inhibitor Therapy	NCT number: NCT04173494

	non-inferiority margin of 0.8 in response ratio scale exceeds 90%. Efficacy analyses were done according to the ITT principle, with data from all randomly assigned patients, although the ITT and safety populations were identical. To control study-wide type I error, the five key secondary endpoints were to be evaluated in hierarchical order only if the primary endpoint showed significance (two-sided p≤0.05) in favour of momelotinib. For the endpoint of transfusion independence rate at week 24, non-inferiority was the hypothesis test included within the hierarchy, whereas superiority was tested within the hierarchy for all other endpoints. A one-sided p-value was generated for the non-inferiority test. Evaluating a treatment effect with non-inferiority with an acceptable prespecified margin when superiority over the active control group is actually expected, but with its magnitude of benefit uncertain, has been recommended as a practical approach in comparison to designing a much larger study to assure enough power for superiority (i.e. hybrid design). If a stratum-adjusted difference between the proportion of transfusion-independent patients in the momelotinib group and 80% of the proportion of transfusion-independent patients in the danazol group was significantly larger than 0, non-inferiority was to be declared. Superiority was to be evaluated descriptively outside the hierarchy if non-inferiority was demonstrated. Overall survival and leukaemia-free survival were analysed using the Kaplan-Meier method and compared between groups with stratified log-rank tests and proportional hazard Cox regression models stratified by randomisation stratification factors. Analysis of overall survival up to week 24 was post hoc. Additionally, a post-hoc analysis of cumulative incidence of non-COVID-19 deaths, in which Gray's test for non-parametric cumulative incidence comparison by competing risk analysis was used and the Fine and Gray method stratified by randomisation stratification factors was used to estimate the hazard ratio (HR) for non-COVID-19 deaths in which COVID-19 deaths were considered as competing events. The follow-up for time-to-event endpoint was summarised by the reverse Kaplan-Meier method.
Subgroup analyses	A subgroup analysis examined the efficacy and safety of momelotinib and danazol in thrombocytopenic patients with baseline platelet counts of ≤150, <100, and <50 x 10^9/L.
Other relevant information	None.

Table 36 Main characteristic of JAKARTA

Trial name: Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis (JAKARTA)	NCT number: NCT01437787)
Objective	The primary objective was to evaluate the efficacy of 400 mg or 500 mg fedratinib once daily compared with placebo in the reduction of spleen volume determined by MRI (or CT scan in patients with contraindications for MRI) and confirmed 4 weeks later.
Publications – title, author, journal, year	Harrison, C., et al., Overall and progression-free survival in patients treated with fedratinib as first-line myelofibrosis (MF) therapy and after prior ruxolitinib (RUX): results from the JAKARTA and JAKARTA2 trials. Hemasphere, 2021. 5: p. S203 (32) Harrison, C.N., et al., Safety and efficacy of fedratinib, a selective oral inhibitor of Janus kinase-2 (JAK2), in patients with myelofibrosis and low pretreatment platelet counts. British Journal of Haematology, 2022 (33) Pardanani, A., et al., Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. JAMA oncology, 2015. 1(5): p. 643-651 (34)
Study type and design	A phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study
Sample size (n)	289
Main inclusion criteria	From clinicaltrials.gov: • Diagnosis of PMF or Post-PV MF or Post-ET MF, according to the 2008 World Health Organization and International Working Group of Myelofibrosis Research and Treatment (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 (ANC) ≥1.0 x 10exp9/L

Trial name: Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis (JAKARTA)	NCT number: NCT01437787)
	○ Platelet count ≥50 x 10exp9/L ○ Serum creatinine ≤1.5 x ULN ○ Serum amylase and lipase ≤1.5 x ULN
Main exclusion criteria	From clinicaltrials.gov: • 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 into 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 JAK2 inhibitor. • Known active (acute or chronic) Hepatitis A, B, or C; and hepatitis B and C carriers • AST or ALT ≥2.5 x ULN • Total Bilirubin: ○ Exclude if ≥3.0 x ULN ○ Patients with total bilirubin between 1.5-3.0 x 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, non-alcoholic steatohepatitis [NASH])

Trial name: Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis (JAKARTA)	NCT number: NCT01437787)
Intervention	Patients in the intervention arm received either 400 mg (N=96) or 500 mg (N=97) fedratinib once daily for at least 6 consecutive 28-day cycles and until disease progression, relapse, or excess toxicity
Comparator(s)	Patients in the comparator arm received placebo for at least 6 consecutive 28-day cycles and until disease progression, relapse, or excess toxicity
Follow-up time	The follow-up time for the duration of response was subjected 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
Primary, secondary and exploratory endpoints	Primary endpoint (from clinicaltrials.gov): Response rate defined as the proportion of patients who have a ≥35% reduction in volume of spleen size at the end of cycle 6, and confirmed 4 weeks thereafter Secondary endpoint (from clinicaltrials.gov): • SRR: Proportion of patients with ≥50% reduction from baseline to the end of cycle 6 in the total symptom score. • OS of either 400 mg/day or 500 mg/day of IMP as compared to placebo. • PFS of either 400 mg/day or 500 mg/day of IMP as compared to placebo. • Proportion of patients who have ≥25% reduction in volume of spleen size at end of cycle 6, and confirmed 4 weeks thereafter • Duration of spleen response, measured by MRI (or CT scan in patients with contraindications for MRI).

Trial name: Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis (JAKARTA)	NCT number: NCT01437787)
	• Clinical and laboratory events graded by the NCI CTCAE v4.03.
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	Subgroup analyses were conducted on baseline characteristics for RR, OS and PFS
Other relevant information	None

Table 37 Main characteristic of JAKARTA-2

Trial name: Phase II, Open Label, Single Arm Study of SAR302503 In Myelofibrosis Patients Previously Treated With Ruxolitinib (JAKARTA2)	NCT number: NCT01523171
Objective	The primary objective was to evaluate the efficacy of once daily dose of fedratinib in subjects 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
Publications – title, author, journal, year	Harrison, C.N., et al., Fedratinib improves myelofibrosis-related symptoms and health-related quality of life in patients with myelofibrosis previously treated with ruxolitinib: patient-reported outcomes from the phase II JAKARTA2 trial. HemaSphere, 2021. 5(5). (35) Harrison, C.N., 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. The Lancet Haematology, 2017. 4(7): p. e317-e324. (36) Harrison, C.N., et al., Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. American journal of hematology, 2020. 95(6): p. 594-60 (37)

Trial name: Phase II, Open Label, Single Arm Study of SAR302503 In Myelofibrosis Patients Previously Treated With Ruxolitinib (JAKARTA2)	NCT number: NCT01523171
Study type and design	A phase 2, multicentre, open-label, single-arm study
Sample size (n)	97
Main inclusion criteria	Inclusion criteria (from clinicaltrials.gov) • Diagnosis of PMF or Post-PV MF or Post-ET MF, according to the 2008 World Health Organization and IWG-MRT response criteria • Subjects 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 subjects who discontinued ruxolitinib due to intolerability or allergy) and discontinued the treatment for at least 14 days prior to the first dose of fedratinib • MF classified as Intermediate-1 with symptoms, Intermediate-2 or high-risk by Dynamic International Prognostic Scoring System • Spleen ≥5 cm below costal margin as measured by palpation • Male and female subjects ≥18 years of age • Signed written informed consent

Main exclusion criteria	Exclusion criteria (from clinicaltrials.gov)
	• Splenectomy
	• ECOG performance status of >2 before the first dose of fedratinib at cycle 1 day1
	• The following laboratory values within 14 days prior to the initiation of fedratinib:
	  ○ Absolute Neutrophil Count (ANC) <1.0 x 10exp9/L
	  ○ Platelet count <50 x 10exp9/L
	  ○ Serum creatinine >1.5 x ULN
	  ○ Serum amylase and lipase >1.5 x ULN
	• AST or ALT ≥2.5 x ULN
	• Total bilirubin ≥3.0 x ULN
	• Subjects with total bilirubin between 1.5-3.0 x ULN must be excluded if the direct bilirubin fraction is ≥25% of the total

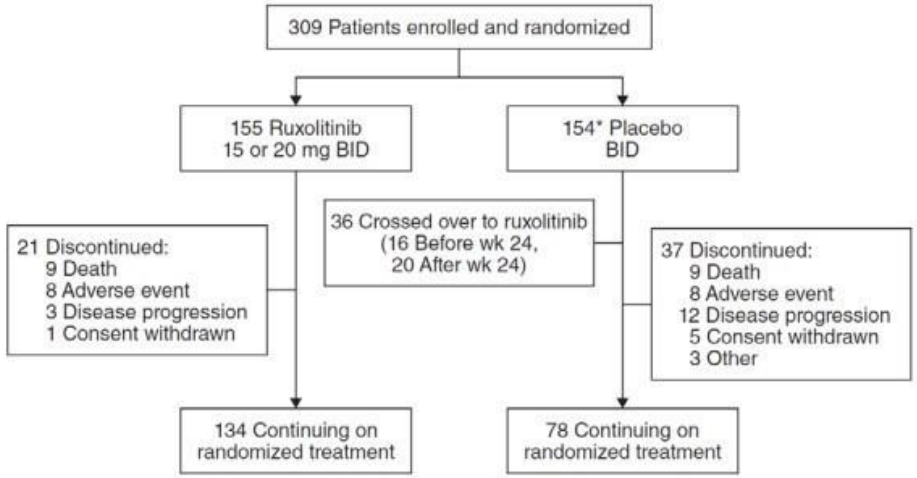
Trial name: Phase II, Open Label, Single Arm Study of SAR302503 In Myelofibrosis Patients Previously Treated With Ruxolitinib (JAKARTA2)	NCT number: NCT01523171
	• Subjects with known active (acute or chronic) Hepatitis A, B, or C; and Hepatitis B and C carriers • Prior history of chronic liver disease (e.g., chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, non-alcoholic steatohepatitis [NASH]) • Subjects 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 subject 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 fedratinib; darbepoetin use within 28 days prior to initiation of fedratinib. The only chemotherapy allowed will be hydroxyurea within 1 day prior to initiation of fedratinib • Uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4), angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery bypass graft surgery, transient ischemic attack, or pulmonary embolism within 3 months prior to initiation of fedratinib
Intervention	400 mg fedratinib
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
Primary, secondary and exploratory endpoints	Primary endpoint: • Response rate, defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen at the end of Cycle 6 as measured by MRI (or CT scan in subjects with contraindications for MRI)

Trial name: Phase II, Open Label, Single Arm Study of SAR302503 In Myelofibrosis Patients Previously Treated With Ruxolitinib (JAKARTA2)	NCT number: NCT01523171
	Secondary endpoint: • SRR: Proportion of subjects with a ≥50% reduction from baseline to the end of Cycle 6 in the total symptom score using the modified MF-SAF • Duration of spleen response, measured by MRI (or CT scan in subjects with contraindications for MRI) • Proportion of subjects with a ≥50% reduction in length of spleen by palpation from baseline at the end of cycle 6 • Response rate at the end of cycle 3, defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen at the end of cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI) • Percent change of spleen volume at the end of cycles 3 and 6 from baseline as measured by MRI (or CT scan in subjects with contraindications for MRI) • Safety, as assessed by clinical, laboratory, ECG, and vital sign events; graded by the NCI CTCAE v4.03 • Plasma concentrations of fedratinib • The effect of fedratinib on the JAK2V617F allele burden
Method of analysis	Spleen response was measured using MRI/CT and continuous variables were summarized using descriptive statistics. A 1-sided significance level of $\alpha = 2.5\%$ was used for hypothesis testing. Chi-squared testing was not performed due to the early termination study
Subgroup analyses	Subgroup analyses were conducted on baseline characteristics and disease characteristics, platelet count and patients resistant versus intolerant to ruxolitinib
Other relevant information	None

Table 38 Main characteristic of COMFORT-I. Source: Verstovsek et al. 2012 (39).

Trial name: Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment: The COMFORT-I Trial	NCT number: NCT00952289
Objective	To compare the efficacy and safety of ruxolitinib tablets to matching placebo tablets in patients diagnosed with PMF or post-PV MF or Post-ET MF
Publications – title, author, journal, year	Mesa RA, Gotlib J, Gupta V, Catalano J v, Deininger MW, Shields AL, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patientreported outcomes in COMFORT-I: a randomized, double-blind, placebocontrolled trial. Journal of clinical oncology : official journal of the American Side 49/51 Society of Clinical Oncology 2013;31(10):1285–92 (38) Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A Double Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis. New England Journal of Medicine. 2012;366(9):799–807 (39)
Study type and design	Randomised, double-blind, placebo-controlled phase 3 trial was conducted at 89 sites in the United States, Australia, and Canada
Sample size (n)	309 patients were enrolled: 155 randomized to ruxolitinib, and 154 to placebo.

Trial name: Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment: The COMFORT-I Trial	NCT number: NCT00952289



Main inclusion criteria	From clinicaltrials.gov: • Subjects must be diagnosed with PM), post-PV MF or post-ET MF according to the 2008 World Health Organization criteria • Subjects with myelofibrosis requiring therapy must be classified as high risk OR intermediate risk level 2 according to the prognostic factors defined by the International Working Group • Subjects with an ECOG performance status of 0, 1, 2 or 3 • Subjects who have not previously received treatment with a JAK inhibitor

Trial name: Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment: The COMFORT-I Trial	NCT number: NCT00952289
Main exclusion criteria	From clinicaltrials.gov: • Subjects with a life expectancy of less than 6 months • Subjects with inadequate bone marrow reserve as demonstrated by specific clinical laboratory counts • Subjects with inadequate liver or renal function • Subjects with clinically significant bacterial, fungal, parasitic or viral infection which require therapy • Subjects with an active malignancy over the previous 5 years except specific skin cancers. • Subjects with severe cardiac conditions • Subjects who have had splenic irradiation within 12 months
Intervention	The starting dose of ruxolitinib was 15 mg or 20 mg twice daily, depending on baseline platelet count (100 to 200×109/l or >200×109/l, respectively). The dose was adjusted for lack of efficacy or excess toxicity per protocol.
Comparator(s)	Placebo tablets
Follow-up time	The prospectively defined data cutoff occurred when half the patients remaining in the study completed the week 36 visit, and all completed the week 24 evaluation or discontinued treatment.
Is the study used in the health economic model?	No

Trial name: Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment: The COMFORT-I Trial	NCT number: NCT00952289
Primary, secondary and exploratory endpoints	Primary from clinicaltrials.gov: • Number of Participants Achieving ≥ 35% Reduction in Spleen Volume From Baseline to Week 24 measured at Baseline and Week 24 Secondary from clinicaltrials.gov: • Maintenance of a ≥ 35% Reduction From Baseline in Spleen Volume Among Patients Initially Randomized to Receive Ruxolitinib measured at Baseline Visit and every 12 weeks until the data cut-off date (up to 14 months). • Duration of Maintenance of a ≥ 35% Reduction From Baseline in Spleen Volume Among Patients Initially Randomized to Receive Ruxolitinib measured at Baseline Visit and every 12 weeks until the data cut-off date (up to 14 months). • Number of Participants With a ≥ 50% Reduction in Total Symptom Score From Baseline to Week 24 measured at Baseline and Week 24. Baseline total score was the average of the daily total scores for the last 7 days prior to randomization. The Week 24 total score was the average of daily total scores from the 28 days prior to the Week 24 visit. • Change From Baseline to Week 24 in Total Symptom Score measured at Baseline and Week 24. Baseline total score was the average of the daily total scores for the last 7 days prior to randomization. The Week 24 total score was the average of daily total scores from the 28 days prior to the Week 24 visit. • Overall Survival measured from randomization to the data cut-off date (up to 14 months). • Overall Survival time measured from randomization to the data cut-off date (up to 14 months). • Overall Survival - Extended Data measured from randomization to 4 months after the data cut-off date (up to 18 months). • Overall Survival time - Extended Data measured from randomization to 4 months after the data cut-off date (up to 18 months). • Overall Survival at Week 144 • Overall Survival time at Week 144
Method of analysis	The overall survival analysis was updated at the time of a planned data cutoff 4 months after the primary analysis. Patients completed the MFSAF every night; this electronic diary evaluated, on a scale of 0 (absent) to 10 (worst imaginable), night sweats, itching, abdominal discomfort, pain under the ribs on the left side, feeling of fullness (early satiety), muscle/bone pain, and inactivity. TSS was the sum of individual symptom scores, excluding inactivity. The study was designed to enroll 240 patients, providing 97% power to detect a treatment difference in spleen volume response at a 2-sided alpha level of 0.05 assuming ≥30% response rate for ruxolitinib and ≤10% response rate for placebo. Analyses were conducted in accordance with ITT principles. For all applicable variables, however, patients with missing

Trial name: Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment: The COMFORT-I Trial	NCT number: NCT00952289
	baseline values were excluded from analyses of change and percent change from baseline. In analyses of change from baseline to week 24, patients who discontinued or crossed over before week 24 were counted as non-responders (for response measures of spleen volume reduction and symptom improvement). Comparative secondary efficacy variables were tested in a fixed-sequence-testing procedure at an alpha level of 0.05. Durability of spleen response and survival were analysed using the Kaplan-Meier method (39).
Subgroup analyses	Post hoc analyses of subgroups were conducted.
Other relevant information	None

Table 39 Main characteristic of COMFORT-II. Source: Harrison et al. 2012 (40).

Trial name: Controlled Myelofibrosis Study With Oral Janus-associated Kinase (JAK) Inhibitor Treatment-II: The COMFORT-II Trial	NCT number: NCT00934544
Objective	The purpose was to compare the efficacy, safety and tolerability of ruxolitinib given twice daily to the best-available therapy, in subjects with MF
Publications – title, author, journal, year	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;366(9):787–98 (40)
Study type and design	Open-label, randomised phase 3 study
Sample size (n)	219 patients underwent randomisation, of whom 146 were assigned to receive ruxolitinib and 73 were assigned to receive the best available therapy

Trial name: Controlled Myelofibrosis Study With Oral Janus-associated Kinase (JAK) Inhibitor Treatment-II: The COMFORT-II Trial	NCT number: NCT00934544
Main inclusion criteria	From clinicaltrials.gov: • Subjects must be diagnosed with PMF, PPV-MF or PET-MF according to the 2008 World Health Organization criteria • Subjects with MF requiring therapy must be classified as high risk OR intermediate risk level 2 according to the prognostic factors defined by the International Working Group • Subjects with an ECOG performance status of 0, 1, 2 or 3 • Subjects with peripheral blood blast count of < 10% • Subjects who have not previously received treatment with a JAK inhibitor
Main exclusion criteria	From clinicaltrials.gov: • Subjects with a life expectancy of less than 6 months • Subjects with inadequate bone marrow reserve as demonstrated by specific clinical laboratory counts • Subjects with any history of platelet counts < 50,000/µL or ANC < 500/µL except during treatment for a myeloproliferative disorder or treatment with cytotoxic therapy for any other reason • Subjects with inadequate liver or renal function • Subjects with clinically significant bacterial, fungal, parasitic or viral infection which require therapy • Subjects with an active malignancy over the previous 5 years except specific skin cancers • Subjects with severe cardiac conditions • Subjects who have had splenic irradiation within 12 months

Trial name: Controlled Myelofibrosis Study With Oral Janus-associated Kinase (JAK) Inhibitor Treatment-II: The COMFORT-II Trial	NCT number: NCT00934544
Intervention	Treatment with ruxolitinib was initiated at a dose of 15 mg twice daily in 38% of the patients and at a dose of 20 mg twice daily in 62%. The median dose intensity of ruxolitinib was 30 mg per day (range, 10 to 49)
Comparator(s)	Among patients receiving the best available therapy, the most common therapies were antineoplastic agents (in 51%) — most frequently hydroxyurea (47%) — and glucocorticoids (16%); a total of 33% of patients received no therapy
Follow-up time	48 weeks
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary endpoint from clinicaltrials.gov: • Percentage of Participants With at Least 35% Reduction in Spleen Volume From Baseline at Week 48 measured at baseline and week 48 Secondary endpoints from clinicaltrials.gov: • Duration of Maintenance of Spleen Volume Reduction (Median) • Duration of Maintenance of Spleen Volume Reduction (Kaplan-Meier Estimates) • Percentage of Participants With at Least 35% Reduction in Spleen Volume From Baseline at Week 24 • Time to First at Least 35% Reduction in Spleen Volume From Baseline by Treatment (Primary Analysis) • Progression-free Survival (PFS)

Trial name: Controlled Myelofibrosis Study With Oral Janus-associated Kinase (JAK) Inhibitor Treatment-II: The COMFORT-II Trial	NCT number: NCT00934544
	• Leukemia-free Survival (LFS) • Overall Survival (OS) • Percentage of Participants With Bone Marrow Histomorphology at Week 48 (Primary Analysis) • Bone Marrow Histomorphology • Duration of Follow-up by Treatment
Method of analysis	The efficacy analysis was performed according to the intention-to-treat principle, with data from all patients who underwent randomisation. The database cutoff date was January 4, 2011, the date on which the last patient completed the week 48 study visit. Patients who did not undergo an assessment of spleen volume at week 48 were considered not to have had a response. The two groups were compared with the use of the exact Cochran–Mantel–Haenszel test, stratified according to prognostic category (intermediate-2 risk or high risk). The family-wise alpha level was controlled at 0.05 overall for two prespecified comparisons (the primary and key secondary end points). The key secondary end point was to be tested only if the primary end point showed significance at a two-sided alpha level of 0.05. No formal adjustment for multiple comparisons has been made. Survival curves for leukemia-free survival, overall survival, and progression-free survival were estimated with the use of the Kaplan–Meier method. Hazard ratios and the corresponding 95% confidence intervals were estimated with the use of the Cox proportional-hazards model, stratified according to baseline prognostic category; the between-group treatment difference was tested with the use of a stratified two-sided log-rank test
Subgroup analyses	Included subgroups defined according to sex, myelofibrosis subtype, and prognostic category (all prespecified analyses) and JAK2 V617F mutation status (a post hoc analysis)
Other relevant information	None

Appendix B. Efficacy results per study

Results per study

Results of SIMPLIFY-1 (NCT01969838)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
SRR at week 24	Momelotinib	215	26.5% (95% CI: 20.7%, 32.9%)	-2.5%	-11.0%, 5.9%	Not reported	0.09	0.02, 0.16	p<0.011	Non-inferiority proportion difference in response, stratified CMH method	Mesa et al. 2017
	Ruxolitinib	217	29.0% (95% CI: 23.5%, 36.0%)								
TSS response rate at week 24	Momelotinib	211	28.4% (95% CI: 22.5%, 35.0%)	-13.7%	-22.8%, -4.7%	Not reported	0.00	-0.08, 0.08	0.98	Non-inferiority proportion difference in response, stratified CMH method	Mesa et al. 2017
	Ruxolitinib	211	42.2% (95% CI: 35.4%, 49.2%)								
OS at week 24	Momelotinib	214	[redacted])	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	HR presented. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	CSR
	Ruxolitinib	216	[redacted]								
	Momelotinib	215	[redacted])	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]		CSR

Results of SIMPLIFY-1 (NCT01969838)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS at week 48	Ruxolitinib	217	[redacted])							HR presented. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	
OS final analysis	Momelotinib	215	[redacted])	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	HR presented. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	CSR
	Ruxolitinib	217	[redacted])			Not reported					

Results of SIMPLIFY-2 (NCT02101268)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SRR at week 24	Momelotinib	104	7% (95% CI: 2.8%, 13.4%)	1.0%	-7.0%, 8.9%	Not reported	0.01	-0.09, 0.10	0.90	Proportion difference in response, stratified CMH method	Harrison et al. 2017
	BAT	52	6% (95% CI: 1.2%, 15.9%)								
TSS response rate at week 24	Momelotinib	103	26% (95% CI: 18.0%, 35.8%)	20.3%	9.7%, 31.0%	Not reported	[redacted]	[redacted]	[redacted]	Proportion difference in response, stratified CMH method	Harrison et al. 2017
	BAT	51	6% (95% CI: 12.3%, 16.2%)								
OS at week 24	Momelotinib	104	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	HR presented. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	CSR
	BAT	52	[redacted]								
OS at week 48	Momelotinib	104	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	HR presented. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	CSR
	BAT	52	[redacted]								

Results of SIMPLIFY-2 (NCT02101268)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS final analysis	Momelotinib	104	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	[redacted]	HR presented. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	CSR
	BAT	52	[redacted]								

Results of MOMENTUM (NCT04173494)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SRR at week 24	Momelotinib	130	23% (95% CI: 16, 31)	19%	11%, 28%	0.0006	19%	11%, 28%	0.0006	Proportion difference in response, stratified CMH method	Verstovsek et al. 2023
	Danazol	65	3% (95% CI: 0, 11)								
TSS response	Momelotinib	130	25% (95% CI: 17%, 33%)	16%	6%, 26%	0.0095	16%	6%, 26%	0.0095		Verstovsek et al. 2023

Results of MOMENTUM (NCT04173494)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
rate at week 24	Danazol	65	9% (95% CI: 3%, 19%)							Proportion difference in response, stratified CMH method	
OS (entire treatment period)	Momelotinib	130	19% (12%, 26%)	13%	-10%, 32%	Not reported	0.7	0.4, 1.4	0.3510	HR presented from a stratified Cox proportional hazards model with a single factor of treatment group and baseline MFSAF TSS score (< 22 vs ≥ 22), baseline palpable spleen length below the left costal margin (<12 cm vs ≥12 cm), and baseline RBC or whole blood units transfused in the 8-week period before randomisation (0, 1-4, ≥ 5 units) as strata and p-value from log-rank test. Absolute differences in OS rates are calculated based on the HR and the rate in the comparator arm.	Verstovsek et al. 2023
	Danazol	65	25% (14%, 35%)								

RBC transfusions

Table 40 [redacted]

[redacted]

Table 41 [redacted]

The RBC transfusion rate in the subpopulation was calculated using the same approach as described above.

Table 42 [redacted]

Table 43 [redacted]

Appendix C. Comparative analysis of efficacy

Not applicable.

Appendix D. Extrapolation

Not applicable due to cost-minimisation model where only costs are accounted for.

Appendix E. Serious adverse events

SIMPLIFY-1

In the table below, we present SAEs reported by ≥2 subjects with a frequency of ≥5% in the safety analysis set of the SIMPLIFY-1 study.

Table 44 SAEs reported by ≥2 subjects with a frequency of ≥5% in the safety analysis set. Source: CSR data on file.

	Double-blind Phase		Open-label Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	**Momelotinib (N=214)**	**Ruxolitinib (N=216)**	**Continuing momelotinib (N=171)**	**Switch (ruxolitinib to momelotinib) (N=197)**	**Overall exposed to momelotinib (N=411)**
Number of subjects with any serious TEAE	49 (22.9%)	39 (18.1%)	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Double-blind Phase		Open-label Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	Momelotinib (N=214)	Ruxolitinib (N=216)	Continuing momelotinib (N=171)	Switch (ruxolitinib to momelotinib) (N=197)	Overall exposed to momelotinib (N=411)
Clostridium difficile colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Escherichia urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia viral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angina unstable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure acute	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inguinal hernia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Double-blind Phase		Open-label Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	Momelotinib (N=214)	Ruxolitinib (N=216)	Continuing momelotinib (N=171)	Switch (ruxolitinib to momelotinib) (N=197)	Overall exposed to momelotinib (N=411)
Oesophageal varices haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varices oesophageal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic haematoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Double-blind Phase		Open-label Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	**Momelotinib (N=214)**	**Ruxolitinib (N=216)**	**Continuing momelotinib (N=171)**	**Switch (ruxolitinib to momelotinib) (N=197)**	**Overall exposed to momelotinib (N=411)**
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignant melanoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uterine cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Double-blind Phase		Open-label Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	Momelotinib (N=214)	Ruxolitinib (N=216)	Continuing momelotinib (N=171)	Switch (ruxolitinib to momelotinib) (N=197)	Overall exposed to momelotinib (N=411)
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gouty arthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table note: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = Treatment-Emergent Adverse Event; SOC = System Organ Class Adverse events were mapped according to MedDRA Version 22.0 Multiple events were counted only once per subject for each SOC and PT. SOCs and then PTs within an SOC were presented by descending order of the frequencies under the last column. The most severe event within a PT was counted for each subject.

SIMPLIFY-2

In the table below, we present SAEs reported by ≥2 subjects with a frequency of ≥5% in the safety analysis set of the SIMPLIFY-2 study.

Table 45 SAEs reported by ≥2 subjects with a frequency of ≥5% in the safety analysis set. Source: CSR data on file.

	RT Phase		ET Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	Momelotinib (N=104)	BAT (N=52)	Continuing (momelotinib to momelotinib) (N=64)	Switch (BAT to momelotinib) (N=40)	Overall exposed to momelotinib
Any SAE	37 (35.6%)	12 (23.1%)	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Left ventricular failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supraventricular tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	RT Phase		ET Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	Momelotinib (N=104)	BAT (N=52)	Continuing (momelotinib to momelotinib) (N=64)	Switch (BAT to momelotinib) (N=40)	Overall exposed to momelotinib
Pneumonia aspiration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haematemesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	RT Phase		ET Phase (Weeks 24 to 48)		Total
System Organ Class Preferred Term	Momelotinib (N=104)	BAT (N=52)	Continuing (momelotinib to momelotinib) (N=64)	Switch (BAT to momelotinib) (N=40)	Overall exposed to momelotinib
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subarachnoid haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table note: Abbreviations: BAT = best available therapy; ET = Extended Treatment; MMB = momelotinib; PT = Preferred Term; RT = Randomised Treatment; SOC = System Organ Class; Adverse events were mapped according to MedDRA Version 22.0. Multiple AEs were counted only once per subject for each SOC and PT. The most severe AE within a PT was counted for each subject.

MOMENTUM

In the table below, we present SAEs reported by ≥2 subjects with a frequency of ≥5% in the safety analysis set of the MOMENTUM study.

Table 46 SAEs reported by ≥2 subjects in any group in the safety analysis set. Source: CSR data on file.

	Randomised treatment		Entire momelotinib treatment period			
System Organ Class Preferred Term	**Momelotinib (N=130)**	**Danazol (N=65)**	**Momelotinib (N=38)**	**Momelotinib → Momelotinib (N=92)**	**Danazol → Momelotinib (N=40)**	**Momelotinib overall (N=170)**
Subjects with ≥1 event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders						
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders						
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions						
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations						
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Randomised treatment		Entire momelotinib treatment period			
System Organ Class Preferred Term	Momelotinib (N=130)	Danazol (N=65)	Momelotinib (N=38)	Momelotinib → Momelotinib (N=92)	Danazol → Momelotinib (N=40)	Momelotinib overall (N=170)
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders						
Fluid overload	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Acute myeloid leukaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transformation to acute myeloid leukaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders						
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders						
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table note: Shaded cells indicate AEs ≥5 percentage points higher over the comparator group. Bold numbers in parentheses (1) and (2) indicate the number of subjects with events considered treatment related. Subjects randomised to danazol without crossover to momelotinib were summarised in the randomised treatment period analysis only.

Table 47 Grade ≥3 SAEs in ≥2 subjects in any group in the safety analysis set. Source: CSR (data on file).

	Randomised treatment		Entire momelotinib treatment period			
System Organ Class Preferred Term	**Momelotinib (N=130)**	**Danazol (N=65)**	**Momelotinib (N=38)**	**Momelotinib → momelotinib (N=92)**	**Danazol → Momelotinib (N=40)**	**Momelotinib overall (N=170)**
Subjects with ≥1 event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders						
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions						
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations						
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders						
Fluid overload	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Acute myeloid leukaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Randomised treatment		Entire momelotinib treatment period			
System Organ Class Preferred Term	Momelotinib (N=130)	Danazol (N=65)	Momelotinib (N=38)	Momelotinib → momelotinib (N=92)	Danazol → Momelotinib (N=40)	Momelotinib overall (N=170)
Transformation to acute myeloid leukaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders						
Syncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders						
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table note: Shaded cells indicate adverse events ≥ 5 percentage points higher over the comparator group. Subjects randomised to danazol without crossover to momelotinib were summarised in the randomised treatment period analysis only.

Appendix F. Health-related quality of life

Not applicable since HRQoL not included in the model

Appendix G. Probabilistic sensitivity analyses

Not applicable

Appendix H. Literature searches for the clinical assessment
Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A global systematic literature review (SLR) was adapted to the present application. The primary objective of the global SLR was to conduct an SLR of published phase 2, phase 3, and phase 4 clinical trials of available therapies for MF. Identified studies were screened at two levels (level 1 on title/abstract and level 2 on full text) by two researchers independently and in parallel based on pre-defined inclusion and exclusion criteria (see Table 52). Any disagreements were resolved by discussion with and/or independent arbitration by a third reviewer. An overview of how studies were identified and selected for the SLR is presented in **Error! Reference source not found.**.

The literature search was conducted across databases, conference proceedings, and websites on February 9, 2023. The following databases were searched to identify relevant studies published since 2010 via the Ovid platform:

- MEDLINE and MEDLINE In-Process (via Ovid)
- Embase (via Ovid)
- Cochrane Library (via Ovid)
    - Central Register of Controlled Trials (CENTRAL)
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Review of Effects (DARE)

Additionally, the following conference proceedings were searched for abstracts published in the most recent two years available for each conference (2021 and 2022):

- American Society of Hematology (ASH)
- American Society of Clinical Oncology (ASCO)
- European Hematology Association (EHA)
- European Society of Medical Oncology (ESMO)
- The British Society for Haematology (BSH)
- Society of Hematologic Oncology (SOHO)

The conference abstracts were searched in 2 ways: 1) Using Ovid and 2) Manual search using conference websites. For the Ovid search, we employed the same search strategy for both full-text articles and conference abstracts. In our manual search on conference websites keywords such as 'myelofibrosis,' 'momelotinib,' 'fedratinib,' and 'ruxolitinib' were used (see Table 50).

Supplementary websites, including the National Institute for Health and Care Excellence (NICE) website, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) website, the International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov, were searched to identify recent health technology assessments and ongoing clinical trials, respectively.

Table 48 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Via Ovid	2010 to 2023	9 February 2023
Medline	Via Ovid	2010 to 2023	9 February 2023
Cochrane library	Via Ovid	2010 to 2023	9 February 2023

Table 49 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Searched to identify recent health technology assessments	9 February 2023
EudraCT	https://eudract.ema.europa.eu/	Searched to identify ongoing clinical trials	9 February 2023
ICTRP	https://trialsearch.who.int/	Searched to identify ongoing clinical trials	9 February 2023

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	Searched to identify ongoing clinical trials	9 February 2023

Table 50 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASH	http://www.hematology.org	Skimming through abstract collection	Myelofibrosis, momelotinib, fedratinib and ruxolitinib	9 February 2023
ASCO	www.asco.org/	Skimming through abstract collection	Myelofibrosis, momelotinib, fedratinib and ruxolitinib	9 February 2023
EHA	https://ehaweb.org/	Skimming through abstract collection	Myelofibrosis, momelotinib, fedratinib and ruxolitinib	9 February 2023
ESMO	www.esmo.org/	Skimming through abstract collection	Myelofibrosis, momelotinib, fedratinib and ruxolitinib	9 February 2023
BSH	https://b-s-h.org.uk/	Skimming through abstract collection	Myelofibrosis, momelotinib, fedratinib and ruxolitinib	9 February 2023
SOHO	http://www.sohoonline.org	Skimming through abstract collection	Myelofibrosis, momelotinib, fedratinib and ruxolitinib	9 February 2023

H.1.1 Search strategies

The search strategy was based on the PICOS-T elements with reference to systematic searching best practice recommendations of the Cochrane Handbook for Systematic Reviews of Intervention Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Health Care (46,47) and NICE guidance for literature searching and evidence submission (48).

Search results were merged using reference management software (i.e., EndNote) to remove duplicate records. All titles and abstracts were reviewed for information that clearly met the inclusion and exclusion criteria stated in Table 52. The full texts of studies that passed the first level of screening were retrieved and reviewed using the same inclusion/exclusion criteria. Multiple publications from the same study were identified and linked. The search terms constituted the following two topics:

- Terms to capture the study population.
- Terms to capture relevant study designs.

Search terms included key words (free text), subject headings (e.g., medical subject headings [MeSH]) and the relationship between the search terms (e.g., Boolean). Additional criteria were added (where appropriate/possible depending on the search interface used) to restrict the search results to English publications describing studies in humans after 2010. Table 51 presents the search strategy applied in the databases and results obtained on 9 February 2023.

Table 51 Search strategy

No.	Query	Results
#1	exp Primary Myelofibrosis/ or Myelofibrosis.ab,ti,kw.	24,712
#2	(myelofibrosis or post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis or primary myelofibrosis or chronic idiopathic myelofibrosis or agnogenic myeloid metaplasia or idiopathic myelofibrosis or myelosclerosis with myeloid metaplasia).ab,ti,kw.	21,838
#3	((polycythaemia vera adj4 myelofibrosis) or (polycythemia vera adj4 myelofibrosis) or (polycythemia rubra vera adj4 myelofibrosis) or (polycythaemia rubra vera adj4 myelofibrosis) or (Vaquez-Osler disease adj4 myelofibrosis) or (Osler-Vaquez disease adj4 myelofibrosis) or (polycythemia adj4 myelofibrosis) or (polycythaemia adj4 myelofibrosis) or (erythremia adj4 myelofibrosis) or (erythraemia adj4 myelofibrosis)).ab,ti,kw.	2,449
#4	((thrombocythemia adj4 myelofibrosis) or (thrombocythaemia adj4 myelofibrosis)).ab,ti,kw.	2,820
#5	1 or 2 or 3 or 4	24,887
Intervention and comparators		
#6	(ruxolitinib or INCB018424 or INC424 or (jakafi or jakavi or opzelura)).ab,ti,kw.	7,853
#7	(fedratinib or SAR302503 or TG101348 or Inrebic).ab,ti,kw	642
#8	(pacritinib or SB1518 or Vonjo).ab,ti,kw	407

#9	(momelotinib or CYT-387 or CYT-11387 or GS-0387).ab,ti,kw	326
#10	((best adj available adj treatment$) or (best adj available adj therap$) or BAT).ab,ti,kw	40,814
#11	exp Hydroxyurea/ or (Hydroxyurea or Hydrea or Droxia).ab,ti,kw	44,833
#12	exp corticosteroid/ or (corticosteroid or prednisone or deltasone or sterapred or "liquid pred" or prednisolone or omnipred or "pred mild" or "pred forte" or "orapred ODT" or veripred or "millipred DP" or pediapred or methylprednisolone or depo-medrol or medrol or methacort or depopred or predacorten).ab,ti,kw.	1,565,319
#13	exp Interferon-alpha/ or ("Interferon alfa" or HuIFN-alpha-Le or Multiferon or peginterferon alfa-2a or pegasys).ab,ti,kw.	121,894
#14	exp Immunomodulator/ or (thalidomide or thalomid or lenalidomide or revlimid).ab,ti,kw.	3611035
#15	exp Androgens/ or (androgen or danazol).ab,ti,kw.	396,577
#16	(decitabine or dacogen).ab,ti,kw.	7,531
#17	(Cytarabine or Cytosar or Depocyt or "cytosine arabinoside").ab,ti,kw.	33,145
#18	exp Platelet Aggregation Inhibitors/ or (anagrelide or agrylin).ab,ti,kw	527,231
#19	("epoetin alfa" or "epoetin alfa-epbx" or epogen or retacrit).ab,ti,kw.	2,943
#20	("purine analog" or "purine analogue" or mercaptopurine or purixan or tioguanine or tabloid).ab,ti,kw.	13,843
#21	(melphalan or evomela).ab,ti,kw.	24,612
#22	(busulfan or busulfex or myleran).ab,ti,kw.	14,859
#23	(pomalidomide or pomalyst or imnovid).ab,ti,kw.	4,146
#24	(azacytidine or 5-Azacytidine or U-18496 or CC-486 or Ladakamycin or Azacytidine or "4-Amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one" or Vidaza or Azadine or Onureg).ab,ti,kw.	10,046
#25	(cladribine or Leustatin or Mavenclad).ab,ti,kw.	5,080
#26	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	5,293,711
#27	5 and 26	8,802

Study design

#28	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	3,418,647
#29	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$)).tw.	1,828,170
#30	(phase ii$ or phase iii$ or phase iv$ or phase 2$ or phase 3$ or phase 4$).tw.	421,734
#31	Non Randomized Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or "Quasi Experimental".tw.	73,597
#32	(single arm or open label).tw.	183,560
#33	case report.tw. or letter/ or historical article/ or Case Study/ or Editorial.pt. or Letter.pt. or Note.pt. or review.pt. or metaanalysis.pt. or exp review/ or exp "meta analysis"/ or exp "Systematic Review"/ or (literature adj3 review$).ti. or (systematic$ adj2 (review$ or overview)).ti. or (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti. or ((hand adj2 search$) or (manual$ adj2 search$)).ti,sh.	14,390,766
#34	28 or 29 or 30 or 31 or 32	4,384,744
#35	34 not 33	3,322,448
#36	Exp Animal/ or ”non human”	Not reported
#37	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).tw.	9,768,498
#38	36 or 37	52,552,040
#39	exp Human/ or "Human Experiment".tw.	45,838,309
#40	38 not (38 and 39)	12,713,753
#41	(27 and 35) not 40	1,870
Filters		
#42	limit 41 to yr="2010 -Current"	1,681
#43	limit 42 to english language	1,659
#44	remove duplicates from 43	1,388

Table note:'*' and '$' stand for any character; '?' stands for one or no character; 'exp:' exploded MeSH term; 'ti,ab' title abstract; '.ti' title; '.pt' publication type.

H.1.2 Systematic selection of studies

Study selection was undertaken in three steps, including two levels of article screening and data extraction as presented in **Error! Reference source not found.**. The detailed inclusion/exclusion criteria provided in Table 52 were used as a guideline for the study selection to ensure that all decisions regarding the inclusion and exclusion of studies were consistent.

Level 1 screening based on titles and abstracts

Citations from multiple database searches were imported to an Endnote Library. Duplicates were removed using the "Find Duplicates" function, and unique studies to be screened were exported to an Excel spreadsheet. In Excel, titles and abstracts supplied by each citation were reviewed manually by two experienced reviewers independently. Any discrepancies between the two reviewers were resolved through consensus by the two reviewers or reconciled by a third reviewer. Citations that did not match the criteria in Table 52 were excluded at level 1. For the excluded studies, a reason for exclusion was selected hierarchically from the following list and noted in the screening workbook by each individual screener:

- E1 – Duplicate
- E2 – Non-English
- E3 – Non-human
- E4 – Incorrect population
- E5 – Incorrect study design
- E6 – Incorrect intervention/comparator
- E7 – Incorrect outcomes
- E8 – Other (specify in notes)

Finalised level 1 screening results included screening decisions from the screener (e.g. include/exclude/maybe) and reasons for exclusion for each study excluded (e.g. E1 - Duplicate, from list above). For instances where the screener assigned exclusion reason E8 - other, the specified rationale for exclusion was noted. For all studies meeting the inclusion criteria after screening titles and abstracts, full texts were obtained. If a determination to include or exclude could not be made based solely on the title and abstract, the full text was obtained for level 2 screening.

Level 2 screening based on full text publication

The full text of the publications selected for inclusion at level 1 were again screened by two reviewers independently and in parallel in level 2. Any discrepancies in the inclusion/exclusion decisions between reviewers were reconciled by a third reviewer. Full-text articles were reviewed to determine relevance based on the same inclusion and exclusion criteria used for level 1 screening. Studies that met any exclusion criteria were removed, and the reason for exclusion were recorded. The same hierarchy of reasons for

exclusion as described above for level 1 screening was followed. Publications reporting the same study were linked, and one publication was selected as the primary data source and the remaining ones for the same study were classified as secondary data sources. Studies that satisfied the inclusion criteria after level 2 screening were selected for data extraction.

Finalised level 2 screening results included screening decisions from each screener, reasons for exclusion from each screener for each study excluded, and the adjudicated final decision in an Excel workbook. A full list of included and excluded articles during Level II screening were compiled in a table in Excel detailing title, abstract, and reason for exclusion (for excluded studies).

Data extraction screening based on full text publication

The full text of the publications selected for inclusion at level 2 were again screened by two reviewers independently and in parallel to determine eligibility for data extraction. Any discrepancies in the inclusion/exclusion decisions between reviewers were reconciled by a third reviewer. Full-text articles were reviewed to determine eligibility for data extraction based on additional exclusion criteria below:

- Studies conducted at a single centre were not included for data extraction.
- Studies conducted or analysed in a subgroup were not included for data extraction.
- For each treatment of interest, phase 2 trials were excluded from data extraction if phase 3 trial(s) for the same treatment were available.

Finalised screening results included the adjudicated final decision in an Excel workbook. A full list of included and excluded articles during data extraction screening were compiled in a table in Excel. The study selection process was reported in a PRISMA diagram describing the study selection process, reason for exclusion per level of screening, and the list of articles selected for data extraction (49).

Table 52 from the global SLR has been adjusted to reflect the scope of the present application.

Table 52 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult (age ≥18 years) patients with intermediate to high-risk MF	• Patients < 18 years old • Patients with conditions other than those specified in the inclusion criteria • Not in human (laboratory studies)
Intervention/comparators	Any JAK inhibitors and non-JAK inhibitor treatments. The list of treatments is summarised here: • Momelotinib (CYT-387, CYT-11387, GS-0387)	Any study not including a cancer-directed treatment or studies including interventions not relevant for this application.

	• Fedratinib (SAR302503, TG101348, Inrebic) • Ruxolitinib (INCB018424, INC424, Jakafi, jakavi, opzelura) Interventions from the global SLR not relevant for the present application was removed.	
Outcomes	Studies reporting at least one of the outcomes regarded as relevant for the present application: • SRR • OS • TSS reduction • Safety outcomes such as anaemia (any grade, grades 3 or 4) or thrombocytopenia (any grade, grades 3 or 4) Outcomes from the global SLR that was not regarded as relevant for the present application were removed.	Studies that do not report any of the outcomes in the inclusion criteria.
Study design/publication type	• Phase 2 trials • Phase 3 trials • Phase 4 trials	• Observational or retrospective studies • Phase I trials • Literature review articles
Language restrictions	Only English literature was included	Literature in different languages than English was excluded
Time period	2010 to present	Studies published before 2010

A total of 1,473 records were identified, with no duplicates found during the initial search. Therefore, a total of 1,473 records were assessed for eligibility based on title and abstract. In the figure below, the PRISMA diagram for study selection is presented. Of the 1,473 records assessed for eligibility based on title and abstract (level 1), 280 studies were further assessed for inclusion based on full-text review. At the end of the full-text review (level 2), 150 articles met the inclusion criteria based on their full-text publication(s), but 126 were excluded from data extraction. Only phase 3 trials (or phase 2 if phase III trials were not available) and trials conducted in multiple centres were extracted. This resulted in a total of 24 articles for data extraction in the global SLR.

In the adaptation for the present application, only trials and related publications with interventions of interest (momelotinib, fedratinib and ruxolitinib) were included. This resulted in a total of 12 articles being included for data extraction in the present application.

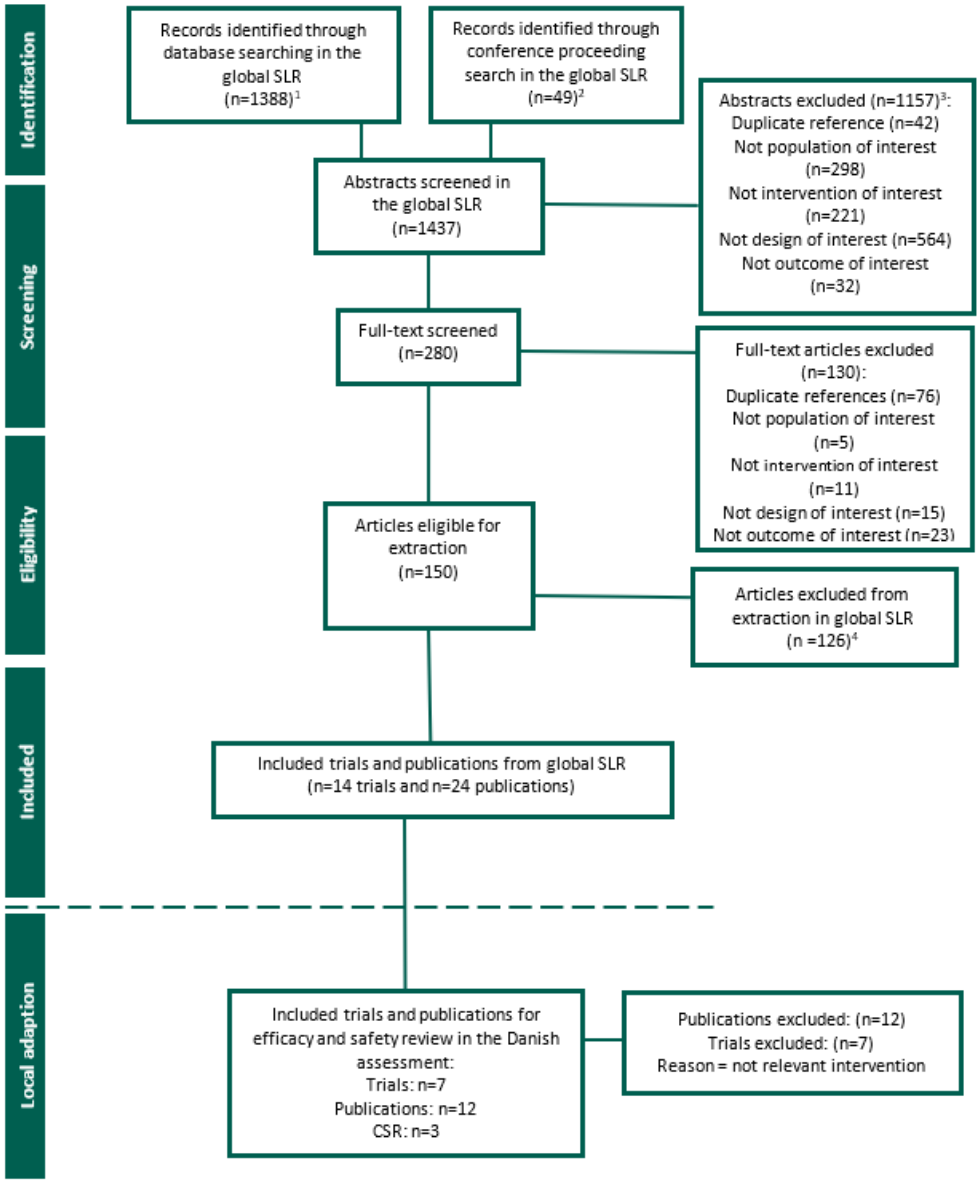


Figure 10 The PRISMA flow diagram showing study selection

Note: Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses 1. Ovid search of relevant publications between 1 January 2010 and 9 February 2023 was conducted by database for this SLR. 2. Conference proceedings in the past 2 years were searched. ASH 2020-2022, ASCO 2020-2021, EHA 2020-2021, ESMO 2020-2021, BSH 2020-2022 were included in the Ovid search. ASCO 2022, EHA 2022, ESMO 2022, BSH 2022, SOHO 2020-2021 were searched by hand. 3. Detailed inclusion and exclusion criteria are displayed in Table 52. 4. Phase II trials were excluded from data extraction if phase III trials for the same intervention is available. Single center trials were excluded.

Table 53 Overview of study design for studies included in the application

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
SIMPLIFY-1	The primary objective was to determine the efficacy of momelotinib compared with ruxolitinib as measured by SRR at week 24.	Phase 3, multi-centre, randomised, double-blind trial.	Adult patients with PMF or post-PV or post-ET MF. Patients were JAKi-naïve.	Total: 432 Momelotinib: 215 Ruxolitinib: 217	SRR rate at week 24 (SRR24)	TSS response rate at week 24 RBC transfusion-independence rate at week 24 RBC transfusion-dependence rate at week 24 Rate of RBC transfusion through week 24.
SIMPLIFY-2	The primary objective was to determine the efficacy of momelotinib versus BAT in subjects with PMF, post-PV MF, or post-ET MF whose prior treatment with ruxolitinib was associated with anaemia and/or thrombocytopenia.	Randomised, phase 3, open-label, multi-centre trial.	Patients with PMF, post-PV MF, or post-ET MF whose prior treatment with ruxolitinib was associated with anaemia and/or thrombocytopenia.	Total: 156 Momelotinib: 104 Best available therapy: 52	SRR rate at week 24 (SRR24)	TSS response at week 24 RBC transfusion (average number of RBC units per patient-month) RBC transfusion independence at week 24 RBC transfusion dependence at week 24.
MOMENTUM	To determine the efficacy of momelotinib versus Danazol assessed by improvement in MF-SAF TSS in subjects with PMF, post-PV MF, or post-ET MF	International, double-blind, randomised, controlled, phase 3 study.	Symptomatic, anaemic patients with MF previously treated with an approved JAK inhibitor.	Total: 195 Momelotinib: 130 Danazol: 65	MF-SAF TSS response rate at week 24	Transfusion independence rate at week 24 SRR at week 24 Change in MF-SAF TSS from baseline at week 24

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	who were previously treated with approved JAK inhibitor therapy.					Rate of no transfusion at week 24.
JAKARTA	To evaluate the efficacy and safety of fedratinib therapy in patients with primary or secondary (post-PV or post-ET) MF.	Phase 3, multicentre, randomised, double-blinded, three-armed study.	Patients with MF (primary or post-ET/PV-MF), who were in intermediate-2 or high-risk groups and had an enlarged spleen. Patients were allowed to have received prior disease-specific treatment for MF but no other JAK-inhibitors.	Total: 289 Fedratinib: 400 mg: 96 Fedratinib 500 mg: 97 Placebo: 96	SRR at week 24	MF-SAF TSS at week 24
JAKARTA-2	To assess the efficacy and safety of fedratinib, a JAK2-selective inhibitor, in patients with ruxolitinib-resistant or ruxolitinib-intolerant MF.	Single-arm, open-label, non-randomised, phase 2, multicentre study, done at 31 sites in 9 countries.	Adult patients with a current diagnosis of intermediate or high-risk PMF, post-PV, or post-ET MF, found to be ruxolitinib resistant or intolerant after at least 14 days of treatment.	Fedratinib: 97	SRR at week 24	TSS reduction from baseline to cycle 6 (24 weeks) Proportion of patients with a 50% or more reduction in palpable spleen length from baseline to end of cycle 6 (week 24) Spleen response at end of cycle 3 (12 weeks)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						Percentage change in spleen volume from baseline to end of cycle 3 and end of cycle 6.
COMFORT-I	Assess the efficacy and safety of ruxolitinib to matching placebo in MF patients.	Randomised, phase 3, double-blind placebo-controlled study.	Adult MF patients who had not previously received treatment with a JAKi.	309 (ruxolitinib:155 ; placebo: 154)	Proportion of patients achieving a ≥35% reduction in spleen volume from baseline to week 24, measured by MRI or computed tomography	Duration of maintenance of spleen volume reduction, proportion of patients with ≥50% reduction in TSS from baseline to week 24 using the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, change in TSS from baseline to week 24, and overall survival
COMFORT-II	To compare the efficacy, safety and tolerability of ruxolitinib given twice daily to the best-available therapy, in subjects with MF	Randomised, open-label, phase 3 study	Adult MF patients who had not previously received treatment with a JAKi.	219 (ruxolitinib:146 ; best-available-therapy: 73)	Reduction of 35% or more in spleen volume from baseline at week 48	Reduction of 35% or more in spleen volume from baseline at week 24, the length of time that a reduction in spleen volume of at least 35% was maintained, the time to a reduction in spleen volume of 35% or

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						more from baseline, progression-free survival, leukemia-free survival, overall survival, and change in marrow histomorphology features

H.1.3 Quality assessment

Each of the 14 trials included in the data extraction of the global SLR was critically appraised for risk of bias using the criteria outlined by NICE (Process and Methods Guidance) for RCTs (50). For the purposes of quality assessment, the primary publication for each trial was reviewed by a single reviewer, who evaluated individual dimensions of potential bias (selection, performance, attrition, detection) and provided overall assessments of internal and external validity. A second reviewer reviewed the quality assessment for each trial. The assessments of internal and external validity for each trial are provided in Table 54. In the following, we present the assessment of the trials included in the adaptation for the present application, i.e. the 7 included trials.

Overall, SIMPLIFY-1, MOMENTUM, JAKARTA and COMFORT-I) were considered to be the highest quality (++) in both respects. These trials were all double-blind, randomised, controlled, included >150 patients per trial across >50 sites from multiple countries, and included comparable baseline groups. Outcomes were deemed to be precisely defined and reliably assessed, and attrition appeared reasonably balanced across study groups.

SIMPLIFY-2 and COMFORT-II were considered to have high quality (++) external validity and middle quality (+) internal validity. These trials were both randomised, controlled, included >150 patients across >50 sites from multiple countries. Outcomes were also deemed to be precisely defined and reliably assessed, and attrition appeared reasonably balanced across study groups. However, the studies were open-label trials which contributed to the middle internal validity rating.

JAKARTA-2 received a middle- or high-quality rating for external validity (either + or ++) and a low-quality rating for internal validity. The trial was large (>90 patients), multicounty and a multicentre (≥40 sites) trial but a single-arm trial which contributed to the +/++ rating for external validity and the – rating for internal validity.

Table 54 Risk of bias assessment (adapted from global SLR). Source: global SLR (data on file).

Trial	Primary publication	Overall assessment of internal validity	Overall assessment of external validity
SIMPLIFY-1	Mesa 2017	++	++
SIMPLIFY-2	Harrison 2017	+	++
MOMENTUM	Verstovsek 2023	++	++
JAKARTA	Pardanani 2015	++	++
JAKARTA-2	Harrison 2017	-	+
COMFORT-I	Verstovsek 2012	++	++
COMFORT-II	Harrison 2012	+	++

Limitations of this literature review include the precision of search terms used. Although efforts were made to use broad and effective search terms, it is still possible that some relevant trials were still missed. Furthermore, there is inherent variability and potential for human error in decision making associated with literature reviews. The use of two screeners and a third independent adjudicator were intended to alleviate this concern to the extent possible. Additionally, the search was restricted to the English language, which raises the possibility that relevant trials published in other languages will be missed, but this possibility is expected to be small given the search topic.

H.1.4 Unpublished data

[redacted]

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Not applicable since HRQoL not included in the model.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

Not applicable.

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