Single Technology Appraisal

Momelotinib for treating myelofibrosis-related splenomegaly or symptoms [ID6141]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Momelotinib for treating myelofibrosis-related splenomegaly or symptoms [ID6141]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from GlaxoSmithKline

2. **Company summary of information for patients (SIP)** from GlaxoSmithKline

3. **Clarification questions and company responses**
   a. Clarification response
   b. Clarification response - B4 appendix
   c. Clarification addendum

4. **Patient group, professional group and NHS organisation submissions** from:
   a. MPN Voice-Leukaemia Care

5. **Expert personal perspectives** from:
   a. Professor Tim Somervaille – clinical expert, nominated by GlaxoSmithKline
   b. Dr Donal McLornan – clinical expert, nominated by MPN Voice
   c. Andy Tattersall – patient expert, nominated by MPN Voice

6. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group
   a. EAG report
   b. EAG appendix pre-ACM1

7. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis. ID6141.

Document B

Company evidence submission

August 2023

File name	Version	Contains confidential information	Date
ID6141 Momelotinib in Myelofibrosis NICE STA Document B 9Aug2023	1	Yes	9 August 2023

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Abbreviations

ACVR1	Activin A receptor, type 1	MF-SAF	Myelofibrosis Symptom Assessment Form
AE	Adverse event	MHRA	Medicines and Healthcare Products Regulatory Agency
AIC	Akaike information criterion	MIMS	Monthly index of medical specialties
Allo-SCT	Allogeneic-stem cell transplantation	MMB	Momelotinib
AML	Acute myeloid leukaemia	MMRM	Mixed Models for Repeated Measures
ANC	Absolute neutrophil count	MPN	Myeloproliferative Neoplasm
ANCOVA	Analysis of covariates	MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
BAT	Best available therapy	MRI	Magnetic Resonanse Imaging
BIC	Baysian information criterion	NC	Not computable
BID	Twice daily	NCCN	National Comprehensive Cancer Network
BMT	Bone marrow transplant	NHS	National Health Service
BNF	British National Formulary	NICE	National Institute of Health and Care Excellence
BSH	British Committee for Standards in Haematology	NMB	Net monetary benefit
CCM	Cost-comparison model	NMSC	Nonmelanoma skin cancer
CDF	Cancer Drugs Fund	NR	Not reported
CEAC	Cost-effectiveness acceptability curve	OL	Open label
CEM	Cost-effectiveness model	ORR	Overall response rate
CFB	Change from baseline	OS	Overall survival
CI	Confidence interval	PAS	Patient access scheme
CMH	Cochran-Mantel-Haenszel	PB	Peripheral blood
CTCAE	Common Terminology Criteria for Adverse Events	PET-MF	Post essential thrombocythemia myelofibrosis
DAD	Detailed advice document	PFS	Progression-free survival
DAN	Danazol	PGIC	Patient Global Impression Change
DES	Discrete event simulation	Plt	Platelet
DIPSS	Dynamic International Prognostic Scoring System	PMF	Primary myelofibrosis
eCRF	Electronic case report form	PPV-MF	Post-polycythaemia vera myelofibrosis
EMA	European Medicines Agency	PSS	Personal social services
EMC	Electronic medicines compendium	PSSRU	Personal social services research unit
EPO	Erythropoietin	PV	Polycythaemia vera
EQ-5D	EuroQoL 5-Dimensions	QALY	Quality-adjusted life year
ERG	Evidence review group	QD	Once daily
ESA	Erythropoiesis-stimulating agent	RBC	Red blood cell
ESMO	European Society of Medical Oncology	RCT	Randomised control trial
ET	Essential Thrombocythaemia	RT	Randomised treatment
FED	Fedratinib	RUX	Ruxolitinib
FPE	First patient enrolled	RWE	Real world evidence
Hb	Haemoglobin	SC	Subcutaneous
HMRN	Haematological Malignancy Research Network	SD	Standard Deviation

HR	Hazard ratio	SF-36	Short Form-36
HRG	Health resource group	SHOT	Serious Hazards of Transfusion
HRQoL	Health-Related Quality of life	SLR	Systematic literature review
HSCT	Haematopoietic Stem Cell Transplant	SMC	Scottish medicine consortium
HST	Highly Specialised Technology	SmPC	Summary of Product Characteristics
HSUV	Health state utility values	SRR	Splenic response rate
ICER	Incremental Cost Effectiveness Ratio	STAT	Signal transducers and activators of transcription
ICT	Iron chelation therapy	TD	Transfusion-dependent
IPSS	International Prognostic Scoring System	TEAE	Treatment-emergent adverse event
ITT	Intent-to-treat	TI	Transfusion-independent
JAK	Janus Kinase	TP	Transition probability
JAKi	Janus kinase inhibitor	TR	Transfusion-requiring
KOL	Key opinion leader	TSS	Total symptom score
LFS	Leukaemia-free survival	TTDD	Time to treatment discontinuation or death
LPE	Last patient enrolled	UB	Upper bound
LSM	Least squares mean	WCC	White cell count
LTFU	Long-Term Follow-up	WHO	World Health Organisation
LY	Life year	WTP	Willingness to pay
MACE	Major adverse cardiovascular event	XAP	Extended Access Program
MF	Myelofibrosis	ZINB	Zero Inflated Negative Binomial

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Submission summary

Summary of the decision problem

- [redacted] (momelotinib) is expected to be indicated [redacted] The full expected wording of the indication is given in Section B.1.2.

- This submission describes two distinct subpopulations:
  - Janus kinas inhibitor (JAKi)-naïve patients, who have not received prior treatment with a currently available JAKi (e.g., ruxolitinib) and therefore receive momelotinib as their first JAKi treatment.
  - JAKi-experienced patients, who have previously received a JAKi (e.g., ruxolitinib) and therefore receive momelotinib as a second JAKi treatment.

- 'Moderate to severe' anaemia has no accepted clinical definition in MF, and is therefore defined in this submission as meaning any anaemia severe enough to warrant treatment.

Disease overview and burden

- MF is a rare cancer, which can cause progressive scarring of bone marrow (fibrosis) impairing its normal function.(1) It is expected around 2,080 patients have MF in the UK, of whom around 50% will have the more severe intermediate-2 or high-risk (int-2/HR) presentation that would indicate them for treatment with a JAKi like momelotinib.

- The clinical presentation of MF is highly heterogeneous and often includes constitutional symptoms, splenomegaly and anaemia.(1) Of these, anaemia is a particularly important symptom for the decision problem in this submission as momelotinib has a novel mechanism of action inhibiting the ACVR1 pathway and therefore reducing the symptoms of anaemia, in contrast to existing JAKis which tend to exacerbate the symptoms of anaemia.

- Apart from the small number of patients eligible for allogeneic-stem cell transplant, MF has no curative treatment options. Therefore, disease management is focused on delaying progression and alleviating symptoms. Anaemia and the associated dependence on red blood cell transfusions are important prognostic factors in MF, inversely related to survival.(2-7) This highlights a critical unmet need for a treatment which can address splenomegaly and the other symptoms of MF without itself exacerbating the anaemia symptoms.

Summary of clinical evidence for momelotinib

- Momelotinib was investigated in three large Phase III trials: SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM. In general, SIMPLIFY-1 corresponds to the JAKi-naïve population in this submission SIMPLIFY-2 corresponds to the JAKi-experienced population in this submission and MOMENTUM is a supportive study in a JAKi-experienced, symptomatic and anaemic population.

- The trials together show that momelotinib has meaningful clinical benefits in terms of symptoms and spleen size control in both JAKi-naïve and JAKi-experienced populations. In particular, momelotinib was nominally superior to ruxolitinib and best available therapy (BAT) in terms of transfusion-independence (TI) rates, demonstrating a superior haematologic benefit.

- Results of the trials are described in Table 1, below. Italics indicates a significant or nominally significant result.

Table 1: Summary of Week 24 endpoints

	SIMPLIFY-1		SIMPLIFY-2		MOMENTUM	
	Momelotinib	**Ruxolitinib**	**Momelotinib**	**BAT**	**Momelotinib**	**Danazol**
Spleen response rate	[redacted]	[redacted]	6.7%	5.8%	22.3%	3.1%
Total symptom score response rate	28.4%	42.2%	26.2%	5.9%	24.6%	9.2%
TI rate	66.5%	49.3%	43.3%	21.2%	30.0%	20.0%

Abbreviations: BAT = best available therapy; TI = transfusion-independence

Summary of economic evidence for momelotinib

- Two economic models are presented in this submission, corresponding to the two distinct subpopulations of interest:
    - In the JAKi-naïve population, a cost-comparison model was presented. This was justified as the SIMPLIFY-1 trial used a non-inferiority design, and therefore it could be assumed that momelotinib has at least equivalent clinical outcomes as the comparator, ruxolitinib.
        - The base-case result is that momelotinib results in a saving of [redacted] per patient across a ten-year time horizon, driven by a reduced need for red blood cell transfusions to manage anaemia with momelotinib compared with ruxolitinib.
        - Across all scenario analyses, momelotinib represents a cost-savings to the NHS compared to ruxolitinib. Collectively, the scenario analysis indicates that momelotinib is likely to provide similar health benefits to ruxolitinib at a similar or lower cost.
    - In the JAKi-experienced population, a cost-utility model was presented. This was a three-state discrete time Markov Chain model, designed to specifically track patients through health states relating to their transfusion requirement. This design was selected as impact on transfusion requirements was expected to be the main clinical difference between momelotinib and the comparator, BAT. Therefore, detailed analysis of this pathway was expected to best inform the decision problem.
        - The base-case result is that momelotinib results in an incremental saving of [redacted] and an incremental health gain of 0.341 QALYs. This indicates that momelotinib dominates BAT (i.e., is both cost saving and adding health). Momelotinib dominates BAT even at list price.
        - Scenario analysis indicates that momelotinib continues to offer a net monetary benefit to the NHS in most cases. The magnitude of net monetary benefit is most sensitive to assumptions regarding the survival benefit of being in the TI or transfusion-dependent (TD) state.

B.1.2 Decision problem

The submission covers the technology's full expected marketing authorisation for this indication:

- [redacted] (momelotinib) is expected to be indicated for [redacted]

This submission describes two distinct subpopulations:

- JAKi-naïve patients, who have not received prior treatment with a currently available JAKi (e.g., ruxolitinib) and therefore receive momelotinib as their first JAKi treatment. For these patients, a non-inferiority trial (SIMPLIFY-1) forms the majority of the evidence of effectiveness, and hence a cost-comparison model forms the majority of the economic case.
- JAKi-experienced patients, who have previously received a JAKi (e.g., ruxolitinib) and therefore receive momelotinib as a second JAKi treatment. For these patients, a superiority trial (SIMPLIFY-2) forms the majority of the evidence of effectiveness, and hence a conventional cost-utility analysis comparing momelotinib with best available therapy (BAT) is performed to demonstrate cost-effectiveness.

The decision problem addressed in this submission, compared with that defined in the final scope issued by NICE, is summarised in Table 2.

Table 2. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with disease-related splenomegaly or symptoms of: • PMF (also known as chronic idiopathic MF), • Post-PV MF or, • Post-ET MF.	Adults with **moderate to severe anaemia** and disease-related splenomegaly or symptoms of: • PMF (also known as chronic idiopathic MF), • Post-PV MF or, • Post-ET MF.	The inclusion of moderate to severe anaemia [redacted]. Otherwise as per the NICE final scope.
Intervention	• Momelotinib	• Momelotinib	As per the NICE final scope.
Comparator(s)	For people eligible for treatment with ruxolitinib: • Ruxolitinib. For people whose disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate (including **people with low or int-1 risk disease**): • Established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion).	For people with no previous treatment with JAKi and int-2/HR disease: • Ruxolitinib. For people with prior JAKi exposure, who may be currently receiving JAKi or have discontinued but remain eligible for JAKi treatment: • Established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion and ruxolitinib)	No evidence is presented on people with low or int-1 risk disease due to limitations of the available evidence. Otherwise as per the NICE final scope, noting that the revised wording more closely follows the structure of the evidence and economic modelling (see below)
Outcomes	The outcome measures to be considered include: • Spleen size • Symptom relief (including itch, pain and fatigue) • Overall survival • Leukaemia-free survival • Response rate • Haematologic parameters (including red blood cell transfusion and blood count) • AEs of treatment • HRQoL	The outcome measures to be considered include: • Spleen size (spleen response rate) • Symptom relief (Total symptom score response rate) • Overall survival • Leukaemia-free survival • Response rate • Haematologic parameters (including red blood cell transfusion and blood count) • Treatment-emergent/-related AEs • HRQoL	As per the NICE final scope.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be	<u>JAKi-naïve patients</u> Cost-comparison analysis. The technology is likely to provide similar or greater health benefits at similar or lower cost than technologies	As per the NICE final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account.	recommended in published NICE technology appraisal guidance for the same indication. <u>JAKi-experienced patients</u> Cost-utility analysis to be conducted per NICE guidance. Expressed in terms of incremental cost per QALY. Time horizon for estimating clinical and cost-effectiveness will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products will be taken into account.	
Subgroups to be considered	• People whose disease was previously treated with a JAKi • Prognostic factors such as Hb <10 g/dL, leukocyte count >25 x 10^9/L, circulating blasts (immature blood cells) ≥1%, presence of constitutional symptoms or platelet count	The primary submission will focus on the intent-to-treat population of the pivotal clinical trials of patients (ie, those eligible for JAKi treatment). People whose disease was previously treated with JAKi will be included in the primary analysis, based on SIMPLIFY-2 data. Subgroup analyses in anaemic patients (Hb <10 g/dL and Hb <12 g/dL) will also be included.	As per the NICE final scope.

Abbreviations: AE = adverse event; BSH = British Society for Haematology; DIPSS = Dynamic International Prognostic Scoring System; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = essential thrombocythemia; EQ-5D-5L = EuroQol-5D-5L; Hb = haemoglobin; HR = high-risk; HRQoL = health-related quality of life; int = intermediate; JAKi = Janus kinase inhibitor; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptom Assessment Form; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PGIC = Patients' Global Impression of Change; PGIS = Patient Global Impression scale; PMF = primary myelofibrosis; PRO = patient-reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PV = polycythemia vera; QALY = quality-adjusted life year; SF-36 = Short Form-36

B.1.3 Description of the technology being evaluated

A description of momelotinib, the technology being appraised, has been summarised in Table 3. The summary of product characteristics is included in Appendix C.

Table 3. Technology being appraised

UK approved name and brand name	Momelotinib ([redacted])
Mechanism of action	Momelotinib is an inhibitor of wild type Janus Kinase 1 and 2 (JAK1/JAK2) and mutant JAK2V617F, which contribute to signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK1 and JAK2 recruit and activate STAT (signal transducers and activation of transcription) proteins that control gene transcription impacting inflammation, haematopoiesis, and immune regulation. Momelotinib and its major human circulating metabolite, M21, have higher inhibitory activity for JAK2 compared to JAK3. Momelotinib and M21 additionally inhibit activin A receptor type 1 (ACVR1), which subsequently down regulates liver hepcidin expression resulting in increased iron availability and red blood cell production. Myelofibrosis is a myeloproliferative neoplasm associated with constitutive activation and dysregulated JAK signalling that contributes to elevated inflammation and hyperactivation of ACVR1.
Marketing authorisation/CE mark status	Not currently authorised. MHRA submission expected in [redacted]; MHRA approval expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted]
Method of administration and dosage	The recommended dose is 200 mg orally once daily.
Additional tests or investigations	[redacted]
List price and average cost of a course of treatment	£5,650 per 30-tablet pack (flat pricing across 200 mg, 150 mg and 100 mg)
Patient access scheme (if applicable)	[redacted] per 30-table pack ([redacted])

Abbreviations: MHRA = Medicines and Healthcare products Regulatory Agency; SmPC = Summary of Product Characteristics

B.1.4 Health condition and position of the technology in the treatment pathway

B.1.4.1 Disease overview

B.1.4.1.1 Clinical overview and pathogenesis

Myelofibrosis (MF) is a rare bone marrow cancer, which can cause progressive scarring of bone marrow (fibrosis) impairing its normal function.(1) The clinical presentation of MF is highly heterogeneous and often includes constitutional

symptoms, splenomegaly and cytopenias, the most frequent of which is anaemia.(1) MF is associated with poor health-related quality of life (HRQoL; Section B.1.4.2.3) and very limited survival (Section B.1.4.2.1).(2, 3, 8, 9) MF is not well managed with existing treatment options (JAKis) and there remains an unmet need for an alternative treatment that can address disease symptoms, and not exacerbate haematological toxicities in patients with the most severe disease (int-2/HR), regardless of whether or not they have received prior JAKi treatment (Section B.1.4.3.2).

MF is classified as a chronic and progressive Philadelphia chromosome negative myeloproliferative neoplasm (MPN).(10, 11) Due to the heterogeneity of MPNs, MF may present as *de novo* (primary MF; PMF), or secondary to essential thrombocythemia (ET; post-ET MF) or polycythemia vera (PV; post-PV MF), with approximately 50% of the patients with MF treated in clinics being post-PV MF and post-ET MF.(12) Once these conditions reach the overtly fibrotic stage, they are indistinguishable clinically and treatment decision making is not differentiated according to primary or secondary MF, therefore in the submission all three aetiologies are simply called ‘MF’.(3, 13)

MF pathogenesis is characterised by dysregulation (constitutive activation) of the JAK-signal transducer and activator of transcription (STAT) pathway. This leads to excessive production of cytokines, which generates an inflammatory environment in the bone marrow. This inflammatory imbalance leads to bone marrow fibrosis and consequently extramedullary haematopoiesis (splenomegaly) to compensate for impaired bone marrow function.(2, 14-16) Aberrant cytokine production and the consequent systemic and local (bone marrow) inflammation contributes to the additional MF symptoms such as anaemia and constitutional symptoms.(15)

Anaemia, splenomegaly, and constitutional symptoms are the three key clinical manifestations in MF and are associated with various medical complications:(17)

- Anaemia is a predictor of poor prognostic outcome and often contributes to fatigue and poor HRQoL

- Organomegaly, including splenomegaly, is often associated with symptoms such as abdominal distension, pain, early satiety, dyspnoea, and diarrhoea

- Constitutional symptoms commonly present as night sweats, low-grade fevers, itching, bone pain, fatigue, unintentional weight loss, and cachexia.

MF is also associated with a number of clinical comorbidities that include portal or pulmonary hypertension, infections, thrombosis, bleeding, and cardiovascular complications.(15, 18, 19)

B.1.4.1.2 Diagnosis and classification

Patients diagnosed with MF are stratified into risk categories using the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS) or Dynamic International Prognostic Scoring System Plus (DIPSS Plus) based on prognostic factors such as, age, presence of constitutional symptoms and haematological parameters (Table 4).(2, 3, 18, 20, 21)

The most commonly used prognostic scoring system used by UK clinicians is DIPSS and/or DIPSS Plus.(22) DIPSS was used to inform patient selection and stratification in SIMPLIFY-2.(23) The DIPSS Plus system builds on the pre-existing DIPSS and considers the incremental mortality risk associated with need for red blood cell transfusion, independent of anaemia status. In the DIPSS scoring system, any patient with anaemia (Hb <10 g/dL) is classified as at least Int-2.(2, 3)

Table 4. Prognosis scoring systems in MF(2, 3)

System	IPSS	DIPSS	DIPSS Plus
Factors (points)	• Age >65 years (1) • Hb <10 g/dL (1) • WCC >25 ×109/L (1) • PB blasts ≥1% (1) • CSx (1)	• Age >65 y (1) • Hb <10 g/dL (2) • WCC >25 ×109/L (1) • PB blasts ≥1% (1) • CSx (1)	• Age >65 y (1) • Hb <10 g/dL (2) • WCC >25 × 109/L (1) • PB blasts ≥1% (1) • CSx (1) • Unfavourable karyotype[a] (1) • Transfusion dependency (1) • Plt <100 × 109/L (1)

System	IPSS	DIPSS	DIPSS Plus
Risk subgroups	**Predictors/points number, n (median OS)**		
Low	0 (11.3 years)	0 (not reached)	0 (15.4 years)
Int-1	1 (7.9 years)	1 to 2 (14.2 years)	1 (6.5 years)
Int-2	2 (4 years)	3 to 4 (4 years)	2 to 3 (2.9 years)
HR	≥3 (2.3 years)	≥5 (1.5 years)	≥4 (1.3 years)

[a]Proposed scoring system not used in standard practice
Hb levels have been converted from g/L to g/dL
Abbreviations: CSx = constitutional symptoms; Hb = haemoglobin; DIPSS = Dynamic International Prognostic Scoring System; HR = high-risk; int = intermediate; IPSS = International Prognostic Scoring System; MF = myelofibrosis; OS = overall survival; PB = peripheral blood; Plt = platelet; WCC = white cell count

The Scope for this submission allows for NICE to make a decision to recommend momelotinib for any patient, regardless of DIPSS status. However, the majority of the evidence is in patients with DIPSS int-2/HR, and this is the point in the treatment pathway where JAKis, like momelotinib, are conventionally used. Therefore, GSK has deviated slightly from the Scope in setting up the decision problem in the submission and presented a case only for approving momelotinib in int-2/HR patients.

B.1.4.1.3 Epidemiology

Prevalence and incidence of MF

MF is a rare condition which primarily affects older adults, with a median age at diagnosis of approximately 67 years.(1, 18) In an analysis of diagnoses between 2010 and 2019 by the Haematological Malignancy Research Network (HMRN), the incidence of any form of MF was 0.60 per 100,000 persons per year in the UK population.(24) Higher incidence rates were reported for males (0.70 per 100,000 persons per year) compared to females (0.40 per 100,000 persons per year).(24) The estimated prevalence of MF is 3.2 per 100,000 persons as of December 2019, corresponding to approximately 2,080 people with MF in the UK.(24-26)

Similar figures were reported in a previous NICE submission (TA386), in which epidemiological estimates of patients with MF in the UK were:(18, 27)

- Incidence: 0.4 per 100,000 persons per year
- Prevalence: 2.2 per 100,000 persons

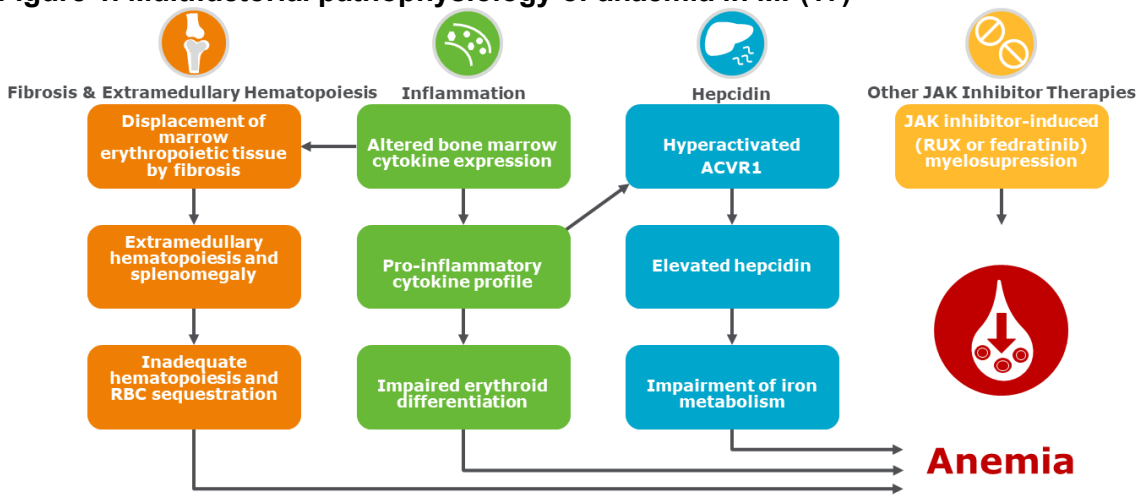
The recently published REALISM study in UK MF patients reported approximately 50% of patients had DIPSS int-2/HR disease at diagnosis.(28) As highlighted in Table 4 (Section B.1.4.1.2), patients classed as int-2/HR have very limited survival expectancy.

B.1.4.1.4 Anaemia in MF

Anaemia is one of the leading negative prognostic factors in MF.(10, 13, 17) It is a condition in which the number of red blood cells (RBCs) is lower than normal.(29) According to the UK REALISM study, 44% of MF patients have anaemia at diagnosis, with 33% of patients presenting with Hb <10 g/dL.(28) As the disease progresses, the proportion of patients with anaemia increases. Within one year of diagnosis up to 58% of patients develop anaemia. Beyond one year of diagnosis, up to 64% of patients develop anaemia.(30)

The pathophysiology of MF-associated anaemia is multifactorial and can be driven by disease and/or commonly used treatments (Figure 1).

Figure 1. Multifactorial pathophysiology of anaemia in MF(17)



Abbreviations: ACVR1 = Activin A receptor type 1; JAK = Janus Kinase; RBC = red blood cell; RUX = ruxolitinib; MF = myelofibrosis

Dysregulation of the JAK-STAT pathway, and the resulting impairment of normal bone marrow function due to fibrosis and inflammation, can lead to low RBC levels and promote anaemia.(1) Compensatory extramedullary haematopoiesis occurs mainly in the spleen, which has limited capacity to produce blood cells and cannot compensate for the impaired bone marrow function in these patients.(15, 17) Furthermore, extramedullary haematopoiesis can lead to an enlargement of the

spleen, which contributes to the sequestration and destruction of circulating RBCs, thus promoting anaemia.(15, 17) In addition to the effects on bone marrow function, JAK-STAT dysregulation leads to chronic activation of activin receptor type 1 (ACVR1), a receptor on the surface of hepatocytes, resulting in elevated hepcidin levels which inhibit iron homeostasis and can cause iron-restricted anaemia.(31)

Disease-related anaemia can be exacerbated in patients with MF by treatment with existing JAKi (ruxolitinib [JAK1/2i] and fedratinib [JAK2i]) owing to myelosuppressive effects through disruption of the JAK-STAT pathway.(5, 15, 18) In contrast, the next generation JAKi momelotinib, inhibits JAK1/2 as well as ACVR1, thus stabilising Hb and improving anaemia associated with MF (Section B.2.7.1.4). The mechanism by which momelotinib mediates an anaemia response is likely due to the additional inhibition of ACVR1 thereby reducing hepcidin levels and elevating serum iron availability for RBC production (Section B.1.3).(15, 21)

The WHO defines normal levels of Hb ≥13 g/dL in men, Hb ≥12 g/dL in women and Hb ≥11 g/dL in pregnant women.(29) However, MF clinicians highlight that defining anaemia in MF is heterogeneous and complex.(32) In a UK advisory board, clinicians stated that solely defining anaemia based on Hb level is crude and many other clinical factors are important such as patient age, fitness, comorbidities (particularly cardiac and respiratory), and prior or existing use of anaemia treatments, when considering whether an individual patient is anaemic and a modification of treatment is required for anaemia management.(32) In a separate advisory board, clinicians advised that the severity and indication to manage anaemia is defined by a patient's ability to tolerate symptoms of anaemia, which can be variable, patient specific and not always correlate with Hb levels.(33)

For the purpose of this submission GSK considers that moderate to severe anaemia means 'treatment-requiring anaemia'. UK clinicians have advised that not all cases of anaemia as defined by WHO require intervention. 'Moderate to severe' anaemia has no accepted clinical definition in MF and is therefore defined in this submission as meaning any clinically relevant anaemia severe enough to warrant treatment; a definition which clinicians advised was more clinically accurate than a strict Hb cut-off.(33) To align with this, the submission assumes in the economic modelling that all

patients who could be candidates for momelotinib require, in addition, some treatment for their anaemia. Where a specific threshold is required for any reason, Hb <12 g/dL is used as the most inclusive threshold that falls under the WHO criteria. While it is likely that in practice not all patients with Hb <12 g/dL would be considered moderately or severely anaemic, clinicians have advised any lower Hb threshold would omit patient groups with clinically relevant treatment-requiring anaemia. Exploratory scenario analysis using different thresholds is undertaken to confirm that this assumption has a limited impact on the overall decision problem.

B.1.4.2 Disease burden

B.1.4.2.1 Impact on survival

MF is associated with a very poor prognosis.(21) Median survival in patients with MF is short, and diminishes in patients classified with higher risk disease:(8)

- All patients with MF: 5.75 years (95% CI: 5.08, 6.3)
- Int-2 patients: 4 years (95% CI: 3.58, 4.92)
- HR patients: 2.25 years (95% CI: 1.92, 2.58)

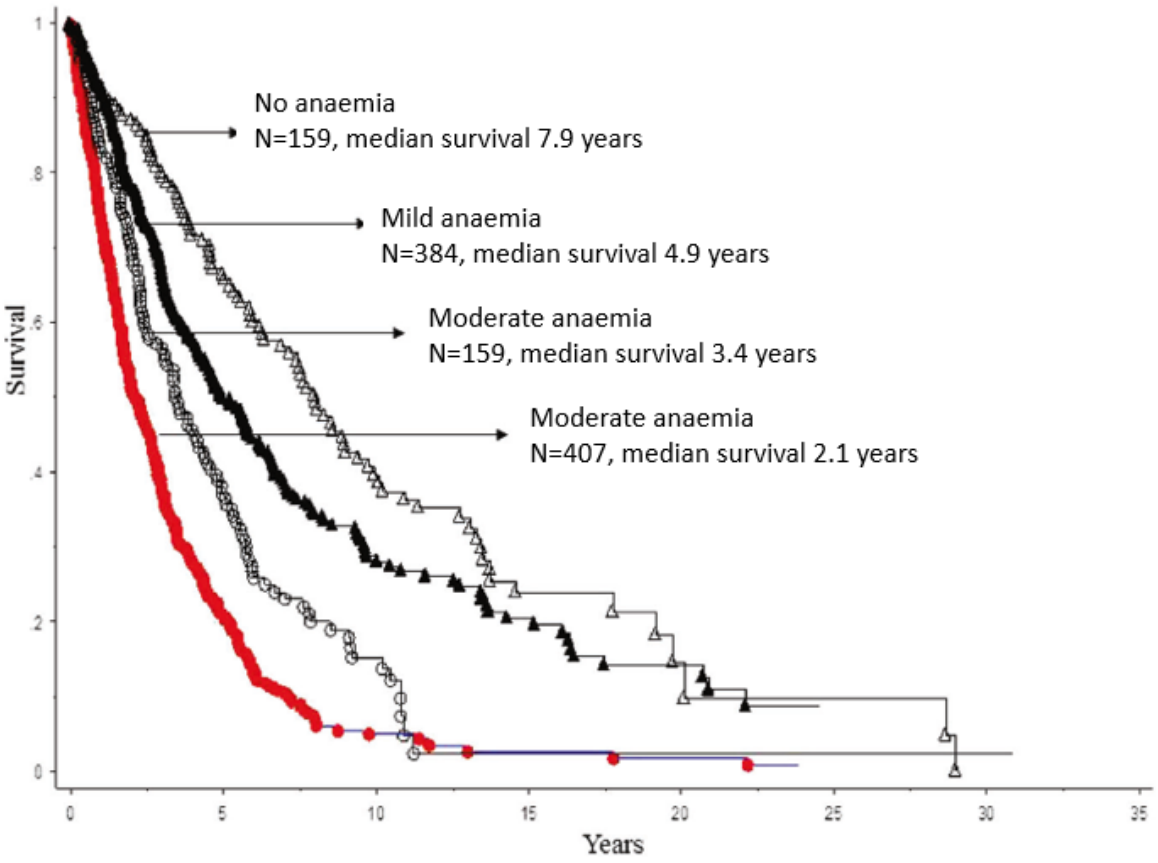
In patients with relapsed, refractory or treatment-intolerant disease, survival outcomes worsen; median OS is approximately 13 to 16 months after ruxolitinib discontinuation (13 months, 95% CI: NR, NR; 14 months, 95% CI: 10, 18; 16 months, 95% CI: 6.3, not estimable).(34-36)

Prognostic risk factors have been leveraged into prognostic scoring systems in MF, which are summarised in Section B.1.4.1.2 .

B.1.4.2.2 Impact of anaemia

Anaemia is a common side effect of MF and is an important prognostic factor, inversely related to overall survival (OS).(2, 3, 5) The association between anaemia and poor OS has been demonstrated in a number of studies.(4-7) The severity of anaemia is correlated with worse survival (Figure 2), with TD (TD) patients having the highest risk as evidenced by the DIPSS Plus scoring tool (Table 4).(2-7)

Figure 2. Survival data of patients with MF by the severity of anaemia(4)



Abbreviations: MF = myelofibrosis

Anaemia is commonly treated with red blood cell transfusions (RBC transfusions). At diagnosis nearly one-quarter of patients with MF are dependent on RBC transfusions and nearly half of MF patients with anaemia become dependent on RBC transfusions one year after diagnosis.(15, 30)

RBC transfusions are expensive for the NHS and time-consuming for the patient and the health service, as each unit needs to be transfused over 2 to 3 hours and the infusions carry moderate risks such as infection.(37) Patients receiving regular RBC transfusions can develop an iron overload, a condition associated with cardiomyopathy, iron-mediated cellular injuries, increased risk of infection, arthropathy of large joints, cramps and diabetes.(38, 39) Iron chelating agents can be used to manage iron overload. However, clinicians from the UK clinical advisory board (2023), stated that iron chelating agents have high toxicities and costs.(32) Furthermore, they stated that it is a reasonable expectation that reducing the need

for transfusions and, in particular, achieving TI would reduce the need for iron chelating agents, thus minimising healthcare costs and treatment toxicities.(32)

B.1.4.2.3 Symptom and quality of life burden

Approximately 70% of patients are symptomatic at diagnosis.(8, 40) As the disease progresses all patients will eventually experience symptoms, many of which are debilitating. Symptoms can be due to bone marrow fibrosis and bone marrow failure, systemic inflammation, and/or organomegaly.(41) Both patients and physicians have identified the improvement of symptoms (patients: 70%; physicians: 80%) as the most important treatment goal in MF, followed by better HRQoL (patients: 61%; physician: 52%) and delayed disease progression (patients: 58%; physician: 43%).(9)

The cross-country Landmark health survey (Australia, Canada, Germany, Italy, Japan, UK) found that fatigue was the most common symptom, occurring in 54% of all patients with MF.(9) Other common symptoms in patients with MF were, abdominal discomfort (30%), shortness of breath (29%), night sweats (29%) and difficulty sleeping (27%).(9)

Most patients with MF indicated that their symptoms reduced their HRQoL (83%), with those with the highest risk scores and a high symptom burden most likely to report impaired HRQoL. Furthermore, over half (58%) of patients required assistance from a caregiver.(9)

B.1.4.2.4 Economic burden on patients and the healthcare system

MF also has a substantial impact on patients' ability to work. Overall, 57% of patients with MF in the Landmark Health survey experienced a negative impact on their work. Of the surveyed patients:(9)

- 21% reduced their work hours
- 8% voluntarily left their job
- 11% took early retirement
- 12% started receiving disability living allowance
- 3% moved to a lower-paying job

- 2% experienced involuntary loss of work

Employed patients with MF missed approximately 4.8 hours of work on average over the previous 7 days; 45% stated that they had missed some hours of work in the previous 7 days. A total of 41% of employed patients with MF experienced work impairment overall.(9)

RBC transfusions for managing anaemia constitutes a significant burden on the NHS. The 2023 cost of acquiring one unit of packed red cells is £158, and 1 to 2 units are typically required for each transfusion. In addition to the blood acquisition costs, UK and international studies have demonstrated blood acquisition costs account for less than half of the overall transfusion cost.(42-45) For example, a 2012 literature review, reported the average cost of transfusing two units of blood ranged from £351.04 to £470.00 in 2011 (both ranges from UK studies).(43)

Indirect costs of RBC transfusions to the healthcare system, include, chair time and nurse time due to need to manage adverse events (AEs) of RBC transfusions . According to the 2022 UK SHOT report, the risk of death related to transfusion in the UK is 1 in 63,563 (1.57 per 100,000) components issued and the risk of serious harm is 1 in 15,449 (6.47 per 100,000) components issued.(46) Although, international studies indicate this may be an underestimation.(44)

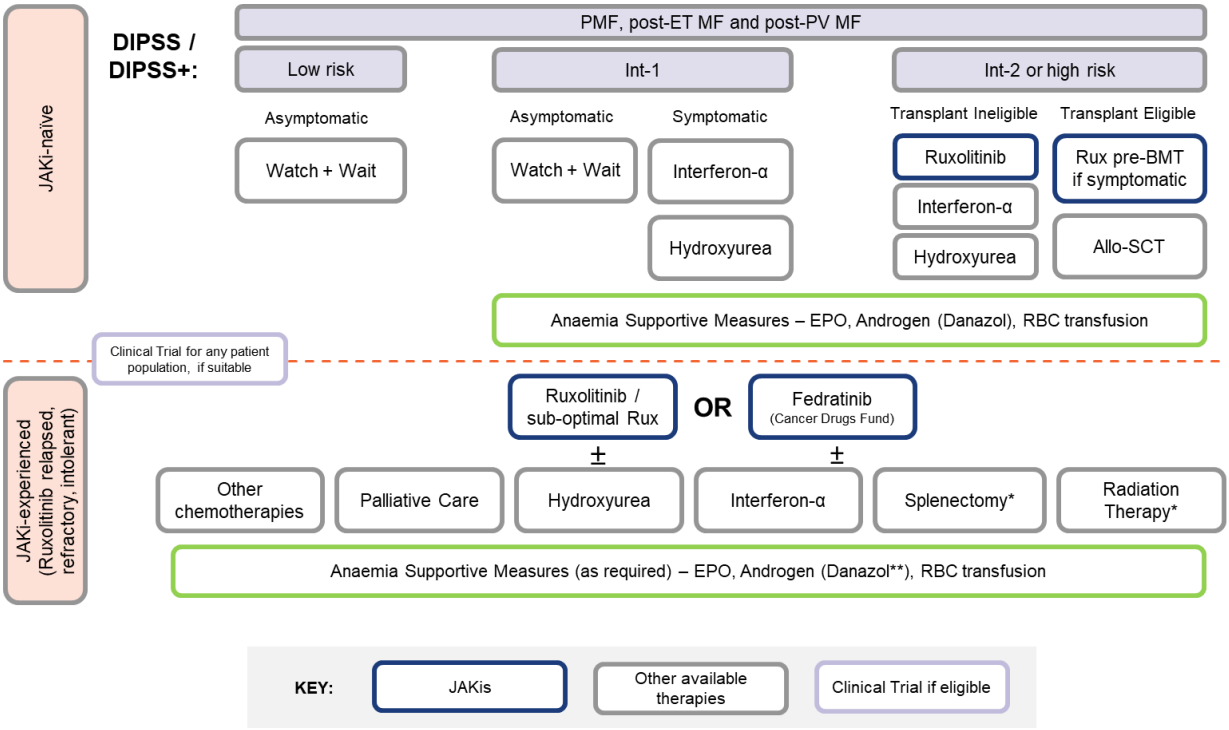
Beyond the healthcare burden of AEs related to blood are the longer-term health impacts of iron overload resulting from repeated RBC transfusions as discussed in Section B.1.4.2.2.

B.1.4.3 Treatment pathway

B.1.4.3.1 Treatment pathway and current treatments

The guidelines most commonly used by UK haematologists are the BSH guidelines for the diagnosis and management of MF, which were first published in 2012 with a subsequent revision in 2014 to include the JAKi, ruxolitinib.(28) Based on the British Society of Haematology (BSH) guidelines, the UK REALISM RWE study and the UK clinical advisory board (2023), the current treatment pathway for patients with MF in the England and Wales is summarised in Figure 3.(3, 32, 47, 48)

Figure 3. Treatment pathway for MF in England and Wales



*Low prominence in treatment pathway
**Danazol is a comparator in the MOMENTUM trial (Section B.2.4.1.3)
Abbreviations: Allo-SCT = allogeneic-stem cell transplant; BMT = Blood and Marrow Transplant; DIPSS = Dynamic International Prognostic Scoring System; EPO = erythropoietin, ET = essential thrombocythemia; Int = intermediate; JAKi = Janus kinase inhibitor; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; RBC = red blood cell

The decision on treatment approach is tailored to the patient based on assessment of their disease severity, presentation of symptoms and prognostic risk categorisation for myelofibrosis (DIPSS and DIPSS Plus).(49) There is one curative approach (allogeneic-stem cell transplant), which will almost always be the first-choice intervention if the patient is eligible, and the management strategy in all other cases will be aimed at delaying progression and managing symptoms.

Allo-SCT is the only potentially curative therapy for MF, with successful transplantation reported to reverse bone marrow fibrosis.(3, 16) However, treatment is only considered for fit patients with int-2/HR MF with prognosis <5 years.(3, 50) Use of allo-SCT is limited due to high treatment-related morbidity and mortality; estimated 1-year treatment-related mortality associated with allo-SCT is approximately 30% and OS is 50%.(50) Therefore, only a small proportion of patients are eligible to undergo treatment. In the UK REALISM RWE study, only 5% patients received allo-SCT therapy.(28) GSK expects it to be rare that a patient who

is eligible for allo-SCT would be offered any alternative treatment, including momelotinib, so allo-SCT is not a comparator in this appraisal.

Examples of treatments which might be included in a regimen for delaying progression and managing symptoms include: hydroxycarbamide, prednisolone, thalidomide, radiotherapy, other chemotherapies, and splenectomy.(3, 28) For patients with DIPSS/DIPSS Plus score of int-2/HR MF (the relevant population for this submission), the JAKis have also emerged as targeted treatment options for patients with MF and splenomegaly and/or MF symptoms.(47) Ruxolitinib is used as initial JAKi therapy for suitable patients and is recommended by NICE (TA386) and clinical guidelines.(27, 32, 47) The REALISM UK real-world study reported the most commonly used first line core management strategies were 'watch and wait' (n=134), ruxolitinib (n=111) and hydroxycarbamide (n=68; Table 5).(28)

Table 5. Initial MF management strategies in the UK REALISM study(28)

Management strategy[a]	n courses (%)	n (persisting ≥6 months)
Watch and wait	134 (67)	81
Ruxolitinib	111 (56)	81
Hydroxycarbamide	68 (34)	44
Allo-HSCT follow up[b]	10 (5)	5
Interferon-α	10 (5)	7
Ruxolitinib + hydroxycarbamide	9 (5)	7
JAKi part of a clinical trial	8 (4)	4

[a]Patients may have had more than one management strategy
[b]Described as such in patients records
Abbreviations: Allo-HSCT = allogeneic-haematopoietic stem cell transplantation; JAKi = Janus kinase inhibitor

For patients who are intolerant or who stop responding to ruxolitinib, fedratinib is available via the Cancer Drugs Fund (TA756, CDF).(51) Fedratinib is outside the Scope of the appraisal (as it is not established clinical practice) so is not discussed further. Regardless, both ruxolitinib and fedratinib demonstrate clinical benefit through spleen volume reduction and symptom reduction when compared with placebo and BAT, reinforcing the relevance the JAK-STAT pathway as a clinically important molecular target in MF.

However, both JAKis can exacerbate disease-related anaemia which can lead to treatment failure and further toxicities.(5, 49, 52, 53) UK clinicians stated in an advisory board that many patients who experience haematological or other toxicities will remain on ruxolitinib or dose-adjusted ruxolitinib despite being 'sub-optimally

treated'.(33) In addition, for patients who substantially reduce or stop ruxolitinib there are concerns of the proinflammatory state and deterioration which can occur following JAKi withdrawal.(54)

Management of MF-related anaemia

Available therapies for the treatment of anaemia of MF include erythropoiesis-stimulating agents (ESAs), androgens, corticosteroids, and immunomodulating drugs (Table 6).(3, 19) Furthermore, patients with anaemia might require RBC transfusions, which have notable system costs and side effects for patients. The UK REALISM RWE study documented anaemia in nearly half of patients at diagnosis, with 33% of patients requiring transfusions during the study period.(28) However it is known that nearly half of MF patients with anaemia become TD within one year of diagnosis.(15, 30)

According to the UK clinical advisory board (2022), supportive measures for patients on ruxolitinib therapy mirror those used in the overall MF population and include ESAs (20% to 60% of patients), RBC transfusions (10% to 25% of patients) and other treatments such as corticosteroids, danazol and thalidomide (<10% of patients).(33)

Table 6. Current therapies for the treatment of MF-related anaemia(3, 12, 19, 33, 55-57)

Treatment	Characteristics
RBC transfusions	• Recommended in PMF patients with symptomatic anaemia • Regular transfusions lead to iron overload, resulting in complications such as liver damage, liver cirrhosis, pancreatic islet cell damage, diabetes, hypothyroidism and hypogonadism
ESAs (e.g., erythropoietin)	• Limited to patients with low erythropoietin levels (125 u/l) • Response rates are variable, and frequently responses are not maintained over time • Limited efficacy in TD population • Risk of vascular complications • May exacerbate splenomegaly • Patients eventually become refractory (median duration of response 19.3 months) • Requires intravenous administration
Androgens (e.g., danazol)	• For patients who have anaemia and are TD • Contraindicated in patients with androgen-dependent tumours, thrombosis/history of thrombosis, severely impaired cardiac/hepatic/renal function and pregnancy/breastfeeding • Lack of proven benefit in anaemia (evidence derived from 50 case reports) • Higher toxicity and lower success rate than erythropoietin • Difficult to source in the UK

Treatment	Characteristics
Steroids	• Similar response rates to danazol with higher side effect burden
Immunomodulating drugs (e.g., thalidomide)	• Improvement of erythropoiesis with beneficial effects on anaemia • Associated with multiple AEs

Abbreviations: AE = adverse events; ESA = erythropoiesis-stimulating agents; MF = myelofibrosis; PMF = primary myelofibrosis; RBC = red blood cell; TD = transfusion-dependent; UK = United Kingdom

B.1.4.3.2 Unmet need

In recent years, the JAKi ruxolitinib has emerged as the primary targeted treatment for those patients with int-2/HR MF who are not eligible for allo-SCT.(47) While ruxolitinib can improve MF symptoms and manifestations, it is less suitable for patients with anaemia due to haematological toxicities and it is associated with treatment-related anaemia.(5, 47, 49, 52, 58, 59)

Unfortunately, there are few suitable alternatives to ruxolitinib. Given the prognostic importance of anaemia and the absence of an effective treatment for the population of patients with anaemia and MF, JAKi-naïve patients have a significant, definable unmet medical need. This unmet need is highlighted by current BSH guidance which recommends that patients with MF-associated anaemia should be enrolled in JAKi clinical trials.(3, 47)

There is an additional unmet need in JAKi-experienced patients. UK clinicians stated in an advisory board that when ruxolitinib toxicities progress, or when symptom and spleen response starts to wane, patients typically remain on treatment with an adjusted dose (and potentially other supportive therapies).(32) In a further advisory board, clinicians confirmed many patients who experience haematological or other toxicities will remain on ruxolitinib or dose-adjusted ruxolitinib despite being ‘sub-optimally treated’.(33)

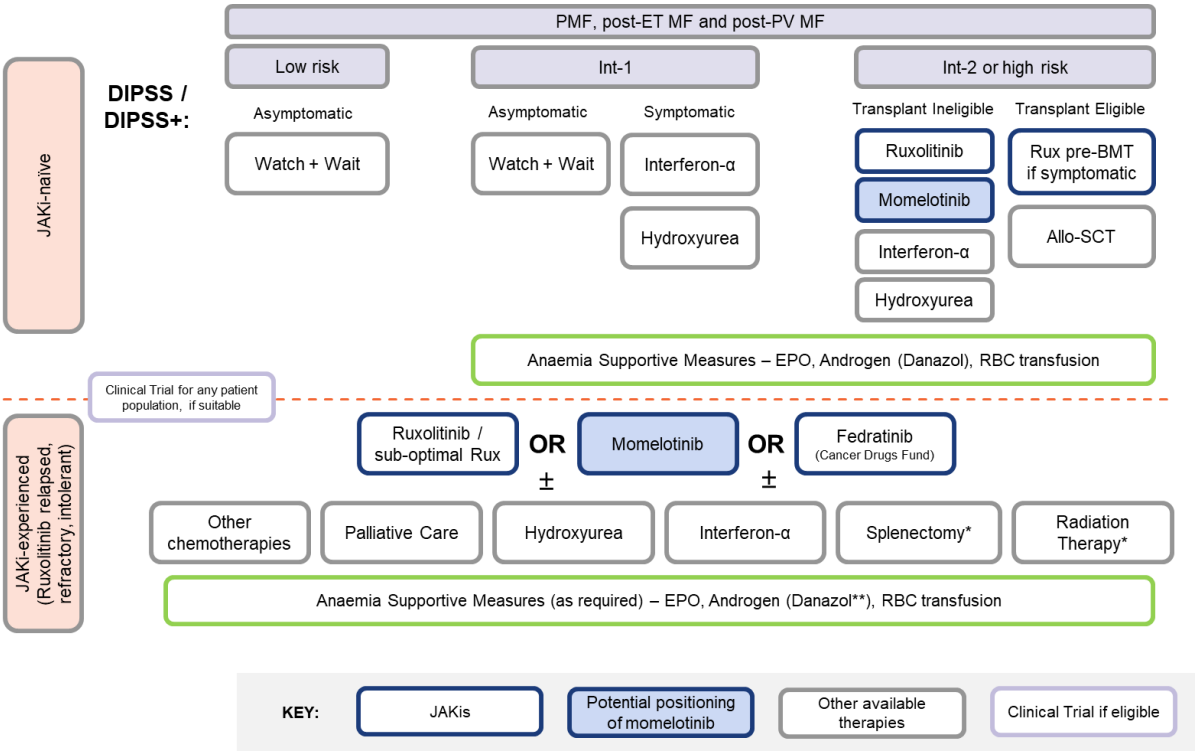
Although strictly out of Scope for this appraisal, it should be noted that even if fedratinib was to leave the CDF and enter routine commissioning the unmet need would still remain. Like ruxolitinib, fedratinib is associated with haematological toxicity.(32, 54) Furthermore, clinicians may be reluctant to take patients off ruxolitinib to transition to fedratinib due to the mandated washout prior to use which risks disease flare-up and AEs of ruxolitinib discontinuation syndrome.(32, 54)

In summary, there remains an unmet need for MF patients for an alternative JAKi which can treat manifestations of the disease while stabilising or improving haemoglobin/anaemia outcomes.

B.1.4.3.3 Place in therapy

The proposed positioning of momelotinib is for patients classed as int-2/HR and anaemic regardless of previous use of other approved JAKis (Figure 4).

Figure 4. Proposed positioning of momelotinib



*Low prominence in treatment pathway
**Danazol is a comparator in the MOMENTUM trial (Section B.2.4.1.3)
Abbreviations: Allo-SCT = allogeneic-stem cell transplant; BMT = Blood and Marrow Transplant; DIPSS = Dynamic International Prognostic Scoring System; EPO = erythropoietin; ET = essential thrombocythemia; Int = intermediate; JAKi = Janus kinase inhibitor; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; RBC = red blood cell

For JAKi-naïve patients who are eligible for ruxolitinib with evidence of anaemia, momelotinib offers an alternative treatment which is less likely to exacerbate anaemia symptoms. In the UK clinical advisory board (2023), clinicians stated that for JAKi-naïve patients, several patient factors would be important when considering momelotinib treatment, such as anaemia, presence of other MF symptoms, presence of spleen symptoms, patient fitness/age, and comorbidities.(32)

For JAKi-experienced patients who experience anaemia or haematological toxicity on ruxolitinib, momelotinib offers an alternative treatment. Clinicians have advised that the presence of haematological toxicity, including anaemia, is the most relevant factor which would be considered whether to switch a patient from an existing JAKi to momelotinib.(32) The clinicians confirmed momelotinib would be considered for use in these patients in accordance with the BSH 2014 guidance on continuing or stopping ruxolitinib therapy.(32)

B.1.5 Equality considerations

Fatigue is a prevalent symptom for patients with MF, which impacts patient HRQoL and causes implications for patients with care responsibilities and those still in work.(2, 3) Severe and chronic fatigue is recognised as a disability under the Equalities Act 2010, and therefore is a protected characteristic. As the submission presents evidence that momelotinib leads to fewer clinical or biochemical markers for fatigue-inducing anaemia, the impact of a negative recommendation would be to differentially burden patients with a disability over those who are not disabled in this way.

Further, GSK notes that anaemia disproportionately affects certain protected groups. For example, women who menstruate are especially affected due to loss of iron in the blood. Those who cannot receive a blood transfusion due to strong philosophical or religious commitments, such as Jehovah's Witnesses, are also disproportionately affected due to lacking access to an important treatment option for anaemia. Although the most typical MF patient will not be a pre-menopausal woman or Jehovah's Witness, the differing impact of recommendations on this group should not be overlooked just because the incidence is uncommon.

MF, particularly MF with anaemia, is an ultra-orphan condition. It is both chronic and severely disabling, and has the potential for lifelong management. Therefore, there is a case that momelotinib could have been routed through the highly specialised technology (HST) assessment process. Unlike many other HSTs, the side effect profile of momelotinib is such that it could plausibly be administered in any secondary NHS setting (e.g., treatment would not be "concentrated in very few centres"). Also, momelotinib does not have a high acquisition cost, likely saving the

NHS money overall compared to alternative treatments. This raises a major equalities issue if momelotinib is not approved for use in the NHS, since typical approval ICER thresholds for the HST route are in the £100,000 / QALY range, while typical approval ICER thresholds for the STA route are in the £20,000 - £30,000 per QALY range.(60) Patients with identically burdensome rare diseases from the perspective of social value judgements made about treating rare diseases may have unequal access to treatment because positive aspects of momelotinib (the ease of administration and low acquisition costs) prevent the drug from being routed to these patients through the more permissive appraisal process.

B.2 Clinical effectiveness

B.2.1 Summary of clinical effectiveness evidence

- The pivotal clinical studies (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM) collectively show that momelotinib has substantial clinical benefits for patients with MF. These benefits were also observed in patients with anaemia and thrombocytopenia, regardless of prior JAKi treatment.
- Momelotinib has a comparable treatment effect to existing JAKi in treating established signs and symptoms of MF, such as splenomegaly and constitutional symptoms, with additional benefits relating to TI reflected across all trials, which is a key prognostic factor in MF.(23, 61-64)
- Furthermore, the results demonstrated that patients can safely transition immediately from ruxolitinib/BAT while maintaining spleen volume response and symptom control. (65) Momelotinib demonstrated a favourable safety profile, which was consistent across subgroups of patients with anaemia and thrombocytopenia.(66)
- Overall, across the three pivotal studies, momelotinib has shown a favourable benefit-risk profile in patients with MF.

JAKi-naïve patients

- Evidence supporting the clinical effectiveness of momelotinib in JAKi-naïve MF patients is provided by the SIMPLIFY-1 trial. This was a multicentre, randomised, double-blind Phase III non-inferiority trial comparing momelotinib (n=215) and ruxolitinib (n=217).(61)
- SIMPLIFY-1 demonstrated the non-inferiority of momelotinib to ruxolitinib for the primary endpoint (proportion of patients with spleen volume reduction ≥35% from baseline to Week 24; [redacted] versus [redacted], respectively; proportion difference: [redacted].(61)
- Momelotinib showed benefits in most key secondary endpoints, particularly those concerning haematological parameters.(61, 62)
    - A nominally significantly higher proportion of patients were TI at Week 24 in the momelotinib group (66.5%) vs the ruxolitinib group (49.3%). A lower proportion of patients in the momelotinib arm lost TI status compared with patients in the ruxolitinib arm (2% and 20% reduction, respectively).
    - Over the 24-week randomised treatment phase, momelotinib increased mean haemoglobin (Hb) levels whereas ruxolitinib decreased them. Following transition to momelotinib at Week 24, patients originally randomised to ruxolitinib had a rapid increase in mean Hb levels. Hb levels were maintained at a similar level to those of patients originally randomised to momelotinib for the duration of the open-label phase.
    - Platelet counts were maintained in the momelotinib group but dropped in the ruxolitinib group.
- Non-inferiority was not met for the secondary endpoint of ≥50% reduction in MF symptoms (TSS) from baseline to Week 24.(61) Several aspects of the study design may have confounded the assessment of symptom response. Clinicians from a UK advisory board acknowledged the similarity in improvements across individual symptom domains and considered the demonstration of non-inferior spleen response by momelotinib to be a positive result that was not undermined by not meeting the symptom response endpoint.(32)

JAKi-experienced patients

- Evidence supporting the clinical effectiveness of momelotinib in JAKi-experienced patients is primarily derived from SIMPLIFY-2. This was a multicentre, randomised, open-label Phase III superiority trial comparing momelotinib (n=104) versus best available therapy (BAT) (n=52) in MF patients who had suboptimal response or haematological toxicity after receiving

ruxolitinib.(23) BAT was administered according to standard of care and investigator's discretion with 88.5% of patients continuing to receive ruxolitinib.(23)

- For all primary and secondary endpoints, a higher point estimate was observed in the momelotinib arm compared to BAT arm. Statistical significance was not met in the primary endpoint of splenic response rate.(26) This may have been influenced by study design features, including the high proportion of patients in the BAT arm treated with ruxolitinib which was not expected in the statistical analysis plan and lack of a washout period which led to lack of additional spleen volume response. This view was supported by UK clinicians.(32)
- Again, benefit of momelotinib on haematological parameters was demonstrated.(23, 63)
    - A nominally significantly higher proportion of patients treated with momelotinib (43.3%) versus the BAT group (21.2%) were TI at Week 24. The proportion of patients who were TI increased by 12.5% in the momelotinib group and decreased by 15.3% in the BAT group from baseline to Week 24.
    - Mean Hb levels increased from baseline to Week 24 by [redacted] in the momelotinib group and decreased by [redacted] in the BAT group. Mean platelet levels improved over time from baseline with momelotinib and were higher than BAT throughout the randomised treatment phase.
- More patients had a reduction of ≥50% in MF symptoms (measured by TSS) from baseline at Week 24 in the momelotinib group (26.2%) than the BAT group (5.9%; nominal p<0.001).(23, 63).
- Additional data supporting the clinical effectiveness of momelotinib in a JAKi-experienced, symptomatic, and anaemic MF population is provided by the MOMENTUM trial. This was a multicentre, randomised, double-blind Phase III trial evaluating the non-inferiority and superiority of momelotinib (n=130) compared with danazol (an anaemia treatment, n=65) in JAKi-experienced, symptomatic and anaemic MF patients aged ≥18 years.(64)
    - Momelotinib demonstrated a significantly improved splenic treatment effect compared with danazol. The ≥35% response rate in the momelotinib arm was 22.3% and 3.1% in the danazol group (p=0.0011).
    - A higher proportion of patients in the momelotinib group (30.0%) versus the danazol group (20.0%) were TI at Week 24, demonstrating non-inferiority to danazol (non-inferiority difference of [redacted]; one-sided p=0.0116).
    - Both momelotinib and danazol increased mean Hb concentration, with patients in the momelotinib group exhibiting a greater increase in Hb that was sustained over time compared with patients who received danazol. For patients who switched from danazol to momelotinib in the open-label phase, Hb levels further increased.
    - The proportion of patients who had improvement of MF symptoms (measured by TSS response at Week 24) was significantly higher in the momelotinib group (24.6%) than the proportion of patients in the danazol group (9.2%; p=0.0095).
    - Safety and tolerability associated with momelotinib
- In JAKi-naïve patients in SIMPLIFY-1, momelotinib was well-tolerated, and a similar AE profile was observed across subgroups of patients with anaemia and thrombocytopenia:(61, 62)
    - In the double-blind treatment phase, fewer patients treated with momelotinib experienced anaemia (13.6% vs 38.0%) and thrombocytopenia (18.7% vs 29.2%) events than those treated with ruxolitinib.
    - No evidence of new or progressive toxicity was observed in patients who switched from ruxolitinib to momelotinib in the open-label phase, without a washout period.
- Similarly, in JAKi-experienced patients in SIMPLIFY-2, momelotinib had a manageable safety and tolerability profile with no evidence of new or progressive toxicity in patients who switched from BAT to momelotinib during the extension phase.(23, 63) MOMENTUM also demonstrated

a favourable safety profile which was consistent with that observed in SIMPLIFY-1 and SIMPLIFY-2, with no new safety signals observed.(64)

- The long-term safety of momelotinib was evaluated in a pooled analysis of the extended access study of patients included in the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM studies:(66)
    - Median duration of momelotinib exposure was 11.3 months (range: 0.1 to 90.4 months), and patients were able to maintain a high momelotinib dose intensity throughout treatment.
    - Grade ≥3 nonhaematologic treatment-emergent AE (TEAEs) were infrequent, and grade ≥3 haematologic TEAEs such as thrombocytopenia and anaemia were experienced by 16.4% and 14.8% of patients, respectively.

B.2.2 Identification and selection of relevant studies

An SLR was conducted with a cut-off date of 9 February 2023 to identify published clinical trials of treatment options for adult patients with int-2/HR MF. GSK consulted with UK clinicians in May 2023, and they confirmed that no additional relevant data for MF treatments (excluding momelotinib) was published. The included population scope for the SLR was broader than the population of interest for the submission as it was conducted from a global perspective, including adult patients (≥18 years old) with int-2/HR MF (PMF and post-PV/ET MF), with int-2/HR MF defined as any of the following:

- Any mention of an int-2/HR MF population
- Using criteria similar to SIMPLIFY-1 (Section B.2.4): Int-2/HR risk per the IPSS for PMF, or int-1 risk IPSS with associated symptomatic splenomegaly, hepatomegaly, anaemia (defined as Hb <10.0 g/dL) and/or unresponsive to available therapy
- Using criteria similar to SIMPLIFY-2 (Section B.2.4): Int-2/HR risk as defined by DIPSS, or int-1 risk as defined by DIPSS and associated with symptomatic splenomegaly, and/or hepatomegaly

A total of 1,388 records were identified through database searches and 49 conference proceedings were identified from the grey literature search for a total of 1,473 publications, with no duplicates found during the initial search. From these publications, 24 articles were included reporting on 14 unique trials. For each treatment of interest, Phase II trials were excluded from data extraction if Phase III trial(s) for the same treatment were available. Full details of the SLR, including the search strategy, study selection process and detailed results, are presented in Appendix D.

Of the 14 trials, three investigated momelotinib (SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM) and are described in detail below.

B.2.3 List of relevant clinical effectiveness evidence

Three Phase III RCTs support the use of momelotinib in adults with MF:

- SIMPLIFY-1 (NCT01969838), comparing momelotinib versus ruxolitinib in JAKi-naïve patients(61)
- SIMPLIFY-2 (NCT02101268), comparing momelotinib versus BAT in prior ruxolitinib-treated patients(23)
- MOMENTUM (NCT04173494), comparing momelotinib versus danazol in JAKi-experienced patients(64)

A summary of SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM is provided in Table 7.

Table 7. Clinical effectiveness evidence

Study	SIMPLIFY-1 (NCT01969838)(61)	SIMPLIFY-2 (NCT02101268)(23)	MOMENTUM (NCT04173494)(64)
Study design	Multicentre, randomised, double-blind, Phase III, non-inferiority trial	Multicentre, randomised, open-label, Phase III, superiority trial	Multicentre, randomised, double-blind, Phase III trial Primary and secondary endpoints: either superiority or non-inferiority
Population	JAKi-naïve patients aged ≥18 years with PMF or post-PV/-ET MF	Currently or previously ruxolitinib-treated patients aged ≥18 years with PMF or post-PV/-ET MF, who had suboptimal response[a] or haematological toxicity[b] after receiving ruxolitinib	JAKi-experienced, symptomatic and anaemic patients aged ≥18 years with PMF or post-PV/-ET MF
Intervention(s)	Momelotinib 200mg once daily	Momelotinib 200mg once daily	Momelotinib 200mg once daily
Comparator(s)	Ruxolitinib 20mg twice daily	BAT	Danazol 300mg twice daily
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	No
Rationale if study not used in model	N/A	N/A	The SIMPLIFY-2 trial provides all necessary head-to-head data (against BAT) to reflect UK clinical practice of MF treatment, as well as the decision problem. Danazol is used to treat anaemia, rather than MF in anaemic patients.

Study	SIMPLIFY-1 (NCT01969838)(61)	SIMPLIFY-2 (NCT02101268)(23)	MOMENTUM (NCT04173494)(64)
			The trial provides valuable clinical context of momelotinib's efficacy in an MF population with anaemia (Hb <10 g/dL) compared with an anaemia treatment. However, it is not required for the economic analysis.
Reported outcomes specified in the decision problem	• Spleen size • Symptom relief (including itch, pain and fatigue) • Overall survival • Leukaemia-free survival • Response rate • Haematologic parameters (including RBC transfusions and blood count) • AEs of treatment • HRQoL	• Spleen size • Symptom relief (including itch, pain and fatigue) • Overall survival • Leukaemia-free survival • Response rate • Haematologic parameters (including RBC transfusions and blood count) • AEs of treatment • HRQoL	• Spleen size • Symptom relief (including itch, pain and fatigue) • Overall survival • Leukaemia-free survival • Response rate • Haematologic parameters (including RBC transfusions and blood count) • AEs of treatment • HRQoL
All other reported outcomes	N/A	N/A	N/A

[a]Requirement for RBC transfusions while on ruxolitinib treatment, or
[b]Required a dose adjustment of ruxolitinib to <20 mg twice daily and also had grade ≥3 anaemia, thrombocytopenia, or haematoma (bleed) when receiving ruxolitinib treatment
Abbreviations: AEs = adverse events; BAT = best available therapy; ET = essential thrombocythemia; HRQoL = health-related quality of life; Hb = haemoglobin; JAKi = Janus kinase inhibitor; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; RBC = red blood cell; UK = United Kingdom.

B.2.4 Summary of methodology of the relevant clinical effectiveness evidence

B.2.4.1 Study methodology

A summary of the study designs and methodology of the SIMPLIFY-1 (NCT01969838), SIMPLIFY-2 (NCT02101268) and MOMENTUM (NCT04173494) studies is presented in Table 8.

Table 8. Comparative summary of trial methodology

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)	SIMPLIFY-2 (NCT02101268)(23, 63)	MOMENTUM (NCT04173494)(64, 67)
Location	Europe, North America, Asia and Australia	Europe and North America	Europe, North America, Asia and Australia
Trial design	Multicentre, randomised, double-blind Phase III trial	Multicentre, randomised, open-label Phase III trial	Multicentre, randomised, double-blind Phase III trial
Eligibility criteria for participants	JAKi-naïve patients aged ≥18 years with PMF or post-PV/-ET MF **Key inclusion criteria:** • Palpable splenomegaly at least 5cm below left costal margin • Confirmed diagnosis of PMF in accordance with WHO criteria, post-PV MF, or post-ET MF in accordance with IWG-MRT criteria • Required MF therapy in the opinion of the investigator • Int-2/HR risk as defined by the IPSS for PMF or int-1 risk as defined by IPSS and associated with symptomatic splenomegaly, hepatomegaly, anaemia (Hb <10.0 g/dL), and/or unresponsiveness to available therapy • Acceptable laboratory assessments obtained within 14 days prior to the first dose of study drug • ECOG PS 0, 1, or 2 • Life expectancy >24 weeks **Key exclusion criteria:** • 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 intercurrent illness including but not limited to active uncontrolled infection (subjects receiving outpatient antibacterial and/or antiviral treatments for infection that was under control or as infection prophylaxis could be included in the study), active or chronic bleeding event within 4 weeks prior to the first dose of	Currently or previously ruxolitinib-treated patients aged ≥18 years with PMF or post-PV/-ET MF, who had suboptimal response[a] or haematological toxicity[b] after receiving ruxolitinib **Key inclusion criteria:** • Palpable splenomegaly at least 5cm below left costal margin • Confirmed diagnosis of PMF in accordance with WHO criteria, post-PV MF, or post-ET MF in accordance with IWG-MRT criteria • Current or previous treatment with ruxolitinib for PMF, post-PV MF, or post-ET MF for ≥28 days and characterised by the following: ○ Requirement for RBC transfusions while on ruxolitinib treatment, or ○ Dose adjustment of ruxolitinib to <20mg twice daily at the start of, or during, ruxolitinib treatment and at least one of the following while on ruxolitinib treatment: CTCAE Grade ≥3 thrombocytopenia, anaemia, haematoma (bleed) • Int-2/HR risk as defined by the DIPSS or int-1 risk as defined by DIPSS and associated with symptomatic splenomegaly and/or hepatomegaly • If receiving MF therapy, must have been on a stable dose of the same regimen for ≥2 weeks prior to the screen date and through the screening period • If not receiving MF therapy, must have remained off therapy for ≥2 weeks prior to the screen date and through the screening period • Acceptable laboratory assessments obtained within 14 days prior to the first dose of study drug	Symptomatic and anaemic JAKi-experienced patients aged ≥18 years with PMF or post-PV/-ET MF **Key inclusion criteria:** • Palpable splenomegaly at least 5cm below left costal margin, or with volume ≥450cm^3 on MRI/CT • Confirmed diagnosis of PMF in accordance with WHO 2016 criteria, post-PV MF, or post-ET MF in accordance with IWG-MRT criteria • Symptomatic, defined as an MF-SAF TSS of ≥10 units assessed by a single assessment at screening (MF-SAF v4.0) • Anaemia, defined as having Hb <10 g/dL • Previous treatment with JAKi for PMF, post-PV MF, or post-ET MF for ≥90 days, or for ≥28 days if ≥4 units RBC transfusions in 8 weeks, or grade 3/4 AEs of thrombocytopenia, anaemia, or haematoma: • HR, int-2 risk, or int-1 risk as defined by DIPSS or DIPSS plus • No allogeneic-stem cell transplant planned • Acceptable laboratory assessments • ECOG PS 0, 1, or 2 • Life expectancy >24 weeks **Key exclusion criteria:** • Prior treatment with momelotinib • Approved JAKi treatment within one Week before baseline assessment • Active anti-MF therapy within one Week before baseline assessment • Strong CYP3A4 inducer within one Week prior to randomisation • Use of investigational agent within four weeks prior to randomisation

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)	SIMPLIFY-2 (NCT02101268)(23, 63)	MOMENTUM (NCT04173494)(64, 67)
	study drug, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by the treating physician • QTc interval >450 msec, unless attributed to bundle branch block • History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to randomisation, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥5 years • Known positive status for HIV • Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier • Prior use of a JAK1 or JAK2 inhibitor • Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers or dual inhibitors of CYP3A4 and CYP2C9 within one Week prior to the first dose of study drug • Use of chemotherapy, immunomodulating therapy, biologic therapy, radiation therapy, or investigational therapy within four weeks of the first dose of study drug	• ECOG PS 0, 1, or 2 • Life expectancy >24 weeks **Key exclusion criteria:** • Prior splenectomy • Splenic irradiation within three months prior to the first dose of study drug • Use of investigational agent within 28 days prior to randomisation • Prior treatment with momelotinib • Haematopoietic growth factor (granulocyte growth factor, erythropoiesis-stimulating agent, thrombopoietin mimetic) within 28 days prior to randomisation • Uncontrolled intercurrent illness including but not limited to active uncontrolled infection (subjects receiving outpatient antibacterial and/or antiviral treatments for infection that was under control or as infection prophylaxis could be included in the study), active or chronic bleeding event within 4 weeks prior to the first dose of study drug, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by the treating physician • QTc interval >450 msec, unless attributed to bundle branch block • History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to randomisation, adequately treated Stage 1 or 2 cancer currently in complete remission, or	• Erythropoiesis-stimulating agent within four weeks prior to randomisation • Danazol within three months prior to randomisation • Splenic irradiation within three months prior to randomisation • Current treatment with simvastatin, atorvastatin, lovastatin or rosuvastatin • History of prostate cancer, except localised prostate cancer treated surgically or by radiotherapy with curative intent and presumed cured • PSA >4ng/mL • Unsuitable for spleen volume measurements due to prior splenectomy or unwilling/unable to undergo an MRI or CT scan for spleen volume measurement • Uncontrolled intercurrent illness including but not limited to active uncontrolled infection (subjects receiving outpatient antibacterial and/or antiviral treatments for infection that was under control or as infection prophylaxis could be included in the study), active or chronic bleeding event within 4 weeks prior to the first dose of study drug, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by the treating physician • QTc interval >500 msec, unless attributed to bundle branch block • Current progressive thrombosis despite treatment • History of porphyria • Child-Pugh score ≥10 • Prior or concurrent malignancy whose natural history or treatment had a significant potential to interfere with efficacy/safety assessment of investigational treatment

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)	SIMPLIFY-2 (NCT02101268)(23, 63)	MOMENTUM (NCT04173494)(64, 67)
	• Changes to dose of iron chelator therapy within 14 days of the first dose of study drug • Unresolved nonhaematologic toxicities from prior therapies that were CTCAE Grade ≥1 • Presence of peripheral neuropathy CTCAE Grade ≥2 • Unwilling or unable to undergo an MRI or CT scan • Known hypersensitivity to the study drugs, the metabolites, or formulation excipients	any other cancer that has been in complete remission for ≥5 years • Known positive status for HIV • Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier • Unresolved nonhaematologic toxicities from prior therapies that were CTCAE Grade >1 • Use of strong CYP3A4 inducers within 1 Week prior to randomisation • Changes to dose of iron chelator therapy within 14 days prior to randomisation • Presence of peripheral neuropathy CTCAE Grade ≥2 • Unwilling or unable to undergo an MRI or CT scan as specified in the protocol • Known hypersensitivity to momelotinib, its metabolites, or formulation excipients	• Known clinically significant anaemia due to iron vitamin B12, or folate deficiencies, or autoimmune or hereditary haemolytic anaemia, or gastrointestinal bleeding, or thalassaemia • Known positive status for HIV • Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier • Unresolved nonhaematologic toxicities CTCAE Grade >1 • Presence of peripheral neuropathy CTCAE Grade ≥2 • Known hypersensitivity to momelotinib or danazol, their metabolites, or formulation excipients
Settings and locations where the data were collected	131 clinical centres in Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Japan, the Netherlands, Poland, Republic of Korea, Romania, Singapore, Spain, Sweden, Taiwan, the UK, and the US	52 clinical centres in Canada, Germany, Israel, Italy, Spain, the UK and the US	107 clinical centres across 21 countries worldwide (including UK sites)
Trial drugs	Subjects were randomly assigned (1:1) to receive: • Momelotinib 200mg once daily AND ruxolitinib placebo twice daily (n=214)[c] • Ruxolitinib 20mg twice daily AND momelotinib placebo once daily (n=216)[a]	Subjects were randomly assigned (2:1) to receive: • Momelotinib 200mg once daily (n=104) • BAT administered according to standard of care and investigators' discretion (n=52)	Subjects were randomly assigned (2:1) to receive: • Momelotinib 200mg once daily AND danazol placebo twice daily (n=130) • Danazol 300mg twice daily AND momelotinib placebo once daily (n=65)
Permitted and disallowed concomitant medication	Antihypertensive therapy was disallowed on the day of the first momelotinib (or momelotinib placebo) dose until 4 hours after administration. Strong CYP3A4 inhibitors, or dual CYP3A4 and CYP2C9 inhibitors, could only be coadministered with prior sponsor approval Other disallowed concomitant medications were:	Antihypertensive therapy was disallowed on the day of the first momelotinib dose until 4 hours after administration. Strong CYP3A4 inhibitors could only be coadministered with prior sponsor approval Other disallowed concomitant medications were: • Experimental therapy • MF treatment other than momelotinib, including haematopoietic growth factor	Antihypertensive therapy was disallowed on the day of the first momelotinib dose until 4 hours after administration. Strong CYP3A4 inhibitors could only be coadministered with prior sponsor approval Other disallowed concomitant medications were: • JAKi • Alkylating agents • Hypomethylating agents

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)	SIMPLIFY-2 (NCT02101268)(23, 63)	MOMENTUM (NCT04173494)(64, 67)
	• Experimental therapy/procedure • MF treatment other than momelotinib • Chemotherapy • Immunomodulator • Systemic corticosteroids • Erythropoiesis-stimulating agent • Interferon • JAKi • Granulocyte colony stimulating factor[d]		• Interferons • Immunomodulator • Systemic corticosteroids • Erythropoiesis-stimulating agent • Androgens • Growth factors • Splenic irradiation • Splenectomy • Investigational agents
Primary outcomes (including scoring methods and timings of assessments)	Spleen response rate, defined as proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks, as assessed by MRI/CT scan	Spleen response rate, defined as proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks, as assessed by MRI/CT scan	MF-SAF TSS response rate[f], defined as proportion of patients with a ≥50% reduction in mean MF-SAF TSS over the 28 days immediately before the end of Week 24 compared with baseline. TI rate, defined as the proportion of patients with no RBC transfusions or whole blood transfusion plus all Hb value ≥8 g/dL at Week 24
Other outcomes used in the economic model/specified in the scope	MPN-SAF TSS response rate[e], RBC TI rate, RBC TD rate, rate of RBC transfusions, ORR, OS, LFS	MPN-SAF TSS response rate[e], RBC TI rate, RBC TD rate, rate of RBC transfusions, ORR, OS, LFS	Spleen response rate (≥25%; ≥35%), change in MF-SAF from baseline, rate of zero transfusions, OS, LFS
Pre-planned subgroups	• Age (<65 years or ≥65 years) • Gender (male or female) • Race (white or all other races) • Baseline spleen volume (< median or ≥ median) • Baseline TSS (quartiles: <Q1, ≥Q1 and < median, ≥ median and <Q3, ≥Q3) • Baseline TD (defined as requiring ≥4 units of transfusion or a Hb <8 g/dL in the 8 weeks prior to randomisation) • Baseline Hb (<8 g/dL or ≥8 g/dL) • Baseline platelet count (<100, ≥100 and ≤200, >200 [10^9/L]) • IPSS prognostic category (int or HR) • MF disease status (PMF, post-PV MF, or post-ET MF) • JAK2V617F mutation (positive or negative, based on medical history)	• Age (<65 years or ≥65 years) • Gender (male or female) • Race (white or all other races) • Baseline spleen volume (< median or ≥ median) • Baseline Hb (<8 g/dL or ≥8 g/dL) • DIPSS prognostic category (int or HR) • MF disease status (PMF, post-PV MF, or post-ET MF) • JAK2V617F mutation (positive or negative, based on medical history) • Duration of ruxolitinib received prior to randomisation (≥12 weeks or <12 weeks) • Highest dose of ruxolitinib received since randomisation (≥20mg twice daily or <20mg twice daily [BAT arm only])	• Transfusion status (TI/TR/TD) at baseline • Transfusion status (TI/non-TI) at baseline • Age (<65 years or ≥65 years) • Sex (male or female) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other) • Baseline platelet count (<50, ≥50 but ≤150, >150 but ≤300, >300; ≤150, >150; ≤200, >200 [10^9/L]) • Baseline MF-SAF TSS (<22, ≥22) • Baseline spleen volume (< median or ≥ median) • RBC transfusions or whole blood units transfused in the 8-week period prior to randomisation (0, 1 to 4, ≥5 units) • Baseline Hb (<8 or ≥8 g/dL) • Baseline glomerular filtration rate (30 to 60; ≥60mL/min) • DIPSS prognostic category (int or HR)

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)	SIMPLIFY-2 (NCT02101268)(23, 63)	MOMENTUM (NCT04173494)(64, 67)
	• Graphical region (Western Europe, Eastern Europe, or Asia)		• MF disease status (PMF, post-PV MF, or post-ET MF) • JAK2 mutation (positive, negative, unknown) • Prior JAKi total daily dose received immediately before enrolment (0, <20mg ruxolitinib twice daily or 200mg fedratinib, ≥20mg ruxolitinib twice daily or >200mg fedratinib) • Geographic region (Asia, Australasia, Europe, North America) • Duration of JAKi treatment received before randomisation (<12 weeks, ≥12 weeks) • Receiving ongoing JAKi at screening (yes, no)
Post-hoc subgroups	• Baseline TI • Baseline non-TI • Baseline TSS (≥10) • Baseline Hb (<10 g/dL, <12 g/dL and ≥12 g/dL) • Baseline TSS ≥10 AND Hb <10 g/dL • Baseline platelet count (≤150, >150; ≤300, >300 [10^9/L])	• Baseline TI • Baseline non-TI • Baseline TSS (<10 or ≥10) • Baseline Hb (<10 g/dL or ≥10 g/dL) • Baseline TSS ≥10 AND Hb <10 g/dL • Baseline platelet count (<100, <150, ≥100; ≤200, >200 [10^9/L])	N/A

[a]Required RBC transfusions on ruxolitinib
[b]Required a dose adjustment of ruxolitinib to <20mg twice daily and also had grade ≥3 anaemia, thrombocytopenia, or haematoma (bleed) when receiving ruxolitinib treatment
[c]Refers to patients receiving ≥1 dose of study drug; 215 and 217 patients were randomly assigned to the momelotinib and ruxolitinib arms, respectively
[d]Unless for treatment of neutropenic fever
[e] In the SIMPLIFY studies, the modified MPN-SAF v2.0 consisted of 8 items: tiredness, early satiety, abdominal discomfort, night sweats, itching, bone pain, pain under ribs on left side, and inactivity, with scoring based on 7 of these items (excluding inactivity) on a scale from 1 to 10, for a maximum (worst) TSS of 70; the full, 27-item MPN-SAF questionnaire was also administered.
[f] In MOMENTUM, the MF-SAF v4.0 consisted of 7 items: tiredness, early satiety, abdominal discomfort, night sweats, itching, bone pain, and pain under ribs on left side, with scoring on a scale from 1 to 10, for a maximum (worst) TSS of 70. The MF-SAF v4.0 was selected for use in this study to replace other versions of the instrument used in earlier MF studies.
Abbreviations: AE = adverse event; BAT = best available therapy; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DIPSS = Dynamic International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; ET = essential thrombocythemia; Hb = haemoglobin; HIV = human immunodeficiency virus; IPSS = International Prognostic Scoring System; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; JAKi = Janus kinase inhibitor; LFS = leukaemia-free survival; OS = overall survival; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptoms Assessment Form; MRI = magnetic resonance imaging; PMF = primary myelofibrosis; PSA = prostate-specific antigen; PV = polycythemia vera; QTc = corrected QT interval; RBC = red blood cell; TD = transfusion-dependence; TI = transfusion-independence; TR = transfusion-requiring; TSS = total symptom score; WHO = World Health Organisation

B.2.4.1.1 SIMPLIFY-1 (NCT01969838)

SIMPLIFY-1 included MF patients who were JAKi-naïve (no prior treatment with a JAKi; N=432).(61) The SIMPLIFY-1 population was representative of patients with relatively less advanced disease compared with SIMPLIFY-2 and MOMENTUM. The trial included subpopulations of patients with anaemia and thrombocytopenia. SIMPLIFY-1 was designed to assess non-inferiority between momelotinib and ruxolitinib. In the double-blind treatment phase, patients were randomised 1:1 to receive either:(61)

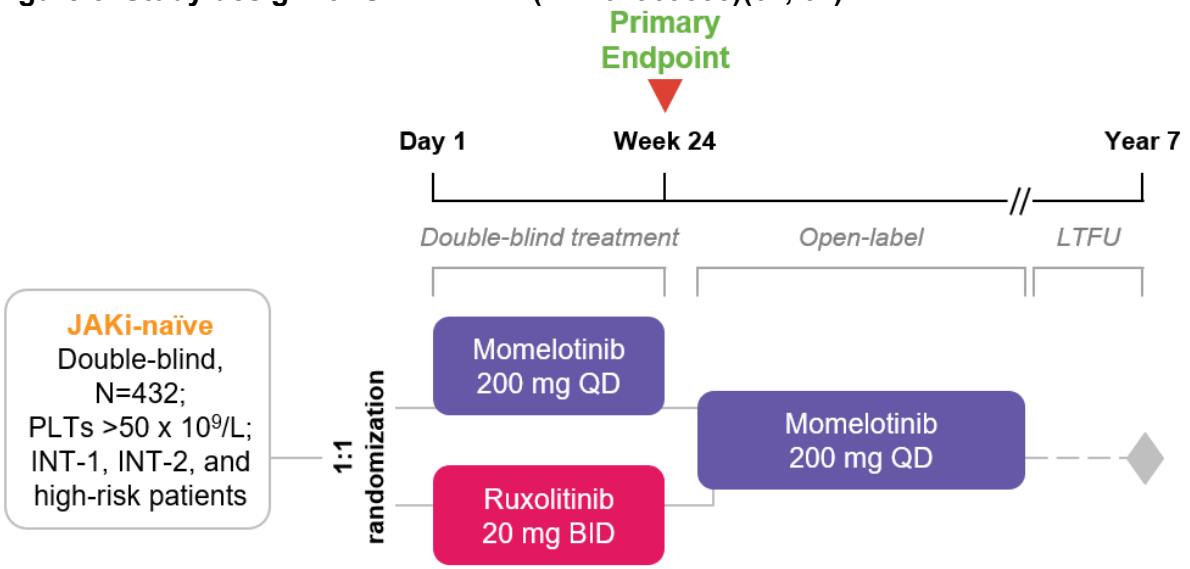
- Momelotinib once daily and ruxolitinib placebo twice daily
- Ruxolitinib twice daily and momelotinib placebo once daily

The primary endpoint for SIMPLIFY-1 was spleen response rate at Week -24, defined as the proportion of patients who had a ≥35% reduction in spleen volume at Week 24 from baseline, as measured by MRI or CT.(61)

Following the conclusion of the 24-week double-blind treatment period, patients were able to participate in an open-label treatment phase where they could receive momelotinib for up to an additional 216 weeks. Patients who were originally assigned to the momelotinib group during the study continued treatment at their existing dosage during the open-label phase. Those who were originally assigned to the ruxolitinib group and wished to remain in the study began momelotinib at a dose equivalent to their previous momelotinib placebo dose, without tapering or washout.(61, 62)

The study design is illustrated in Figure 5.

Figure 5. Study design for SIMPLIFY-1 (NCT01969838)(61, 62)



Note: Treatment assignment was stratified by TI (yes or no; defined as ≥4 units of RBC transfusions or haemoglobin level <8 g/dL in the 8 weeks before random assignment, excluding patients associated with clinically overt bleeding) and platelet count (<100 x 10^9/L, ≥100 x 10^9/L and ≤200 x 10^9/L, or >200 x 10^9/L)
Abbreviations: BID = twice daily; INT = intermediate; JAKi = Janus kinase inhibitor; LTFU = long-term follow-up; PLT = platelet; QD = once daily; RBC = red blood cell; TI = transfusion-independence

B.2.4.1.2 SIMPLIFY-2 (NCT02101268)

SIMPLIFY-2 included MF patients who were JAKi-experienced (prior treatment with ruxolitinib) and had suboptimal responses or haematological toxic effects (N=156).(23) The SIMPLIFY-2 population represented patients with more severe disease than those included in SIMPLIFY-1. The trial included subpopulations of patients with anaemia and thrombocytopenia. SIMPLIFY-2 was designed to assess the superiority of momelotinib over BAT. In the open-label treatment phase, patients were randomised 2:1 to receive either:(23)

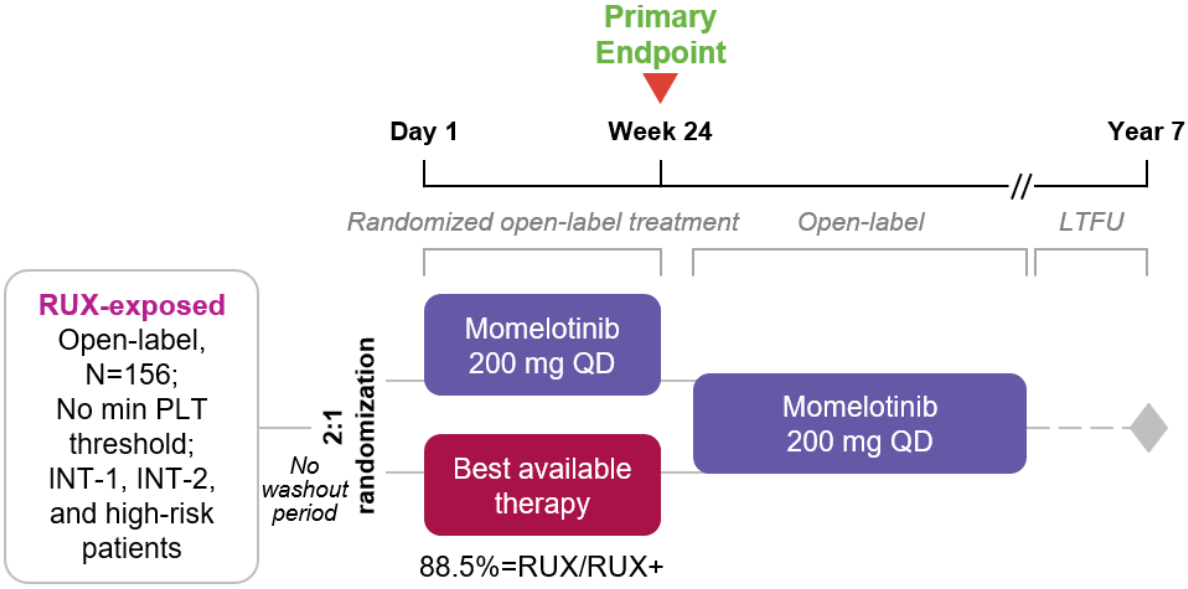
- Momelotinib once daily
- BAT

The primary endpoint for SIMPLIFY-2 was spleen response rate at Week -24, defined as the proportion of patients who had a ≥35% reduction in spleen volume at Week 24 from baseline, as measured by MRI or CT.(23)

Because BAT could not be blinded, the SIMPLIFY-2 trial had an open-label design. After completion of the initial 24-week open-label treatment phase, patients had the option to receive momelotinib in an open-label treatment phase for up to an additional 204 weeks.(63)

The study design is illustrated in Figure 6, with additional detail provided in Appendix D.

Figure 6. Study design for SIMPLIFY-2 (NCT02101268)(23, 63)



Note: Treatment assignment was stratified by TI (yes or no; defined as ≥4 units of RBC transfusions or haemoglobin level <8 g/dL in the 8 weeks before random assignment, excluding patients associated with clinically overt bleeding) and baseline TSS (<18 or ≥18).
Abbreviations: INT = intermediate; QD = once daily; LTFU = long-term follow-up; PLT = platelet; RBC = red blood cell; RUX = ruxolitinib; TI = transfusion-independence; TSS = total symptom score

B.2.4.1.3 MOMENTUM (NCT04173494)

The MOMENTUM trial provided the pivotal safety and efficacy data for symptomatic (TSS ≥ 10) and anaemic (Hb <10 g/dL) MF patients who were JAKi-experienced. The MOMENTUM population represented patients with the most severe disease of the three trials in the Phase III program. MOMENTUM was designed to assess the superiority of momelotinib over danazol, other than for the coprimary endpoint of TI rate at Week 24, which was assessed for non-inferiority.(68) In the double-blind treatment phase, patients were randomised 2:1 to receive either:(64)

- Momelotinib once daily and danazol placebo twice daily
- Danazol twice daily and momelotinib placebo once daily

The other coprimary endpoint in MOMENTUM was MF-SAF TSS response rate, defined as proportion of patients with a ≥50% reduction in mean MF-SAF TSS over the 28 days immediately before the end of Week 24 compared with baseline.(64)

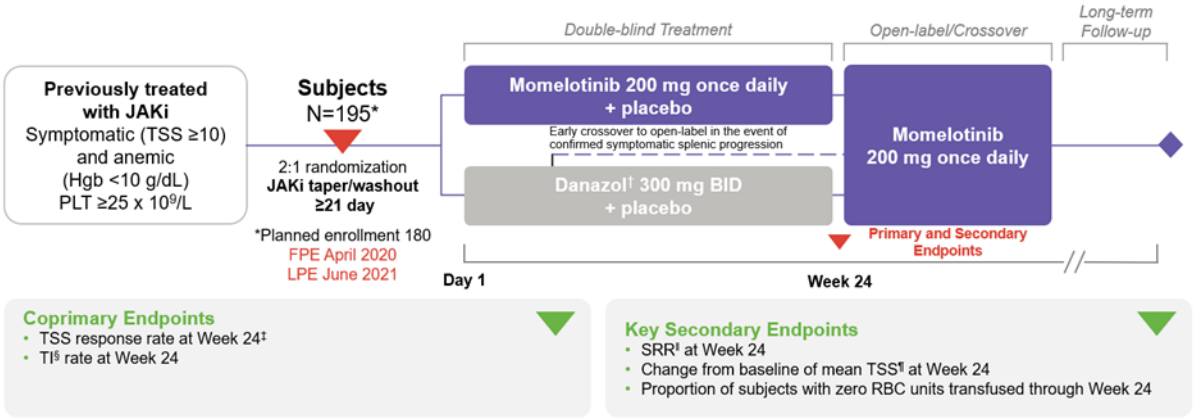
After completion of the 24-week double-blind treatment phase, patients were eligible for open-label momelotinib for up to 180 weeks. Crossover from danazol to open-label momelotinib was allowed:(67)

- At the end of Week 24 if the patient completed the randomised treatment period
- At the end of Week 24 if the patient discontinued danazol early but continued study assessments and did not receive prohibited medications (unless approved by the sponsor)
- Before the end of Week 24 if the patient met criteria for confirmed splenic progression.

Danazol-treated patients who experienced a clinical benefit after Week 24 were eligible for open-label danazol treatment through to Week 48 (400 mg total daily dose).(64)

The study design is illustrated in Figure 7, with additional detail provided in Appendix D.

Figure 7. Study design for MOMENTUM (NCT04173494)(64, 67)



†Danazol was selected as an appropriate comparator given its use to ameliorate anaemia in patients with MF, as recommended by NCCN and ESMO guidelines; ‡TSS response rate defined as the proportion of subjects who achieve ≥50% reduction in MF-SAF TSS over the 28 days immediately prior to the end of Week 24 compared with baseline; §TI defined as not requiring RBC transfusions for ≥12 weeks, with all haemoglobin levels during the ≥12-week interval of ≥8 g/dL; ‖SRR defined as the proportion of subjects who have a reduction in spleen volume of ≥25% from baseline; ¶Mean change from baseline in TSS at Week 24 will analysed using an MMRM for the momelotinib and danazol groups.
Abbreviations: BID = twice daily; DAN = danazol; ESMO = European Society for Medical Oncology; FPE = first patient enrolled; Hgb: haemaglobin; LPE = last patient enrolled; Janus Kinase inhibitor; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptom Assessment Form; MMB = momelotinib; MMRM = mixed models for repeated measures; NCCN = National Comprehensive Cancer Network; PLT = platelet; RBC = red blood cell; SRR = spleen response rate; TI = transfusion-independence; TSS = total symptom score

B.2.4.2 Baseline characteristics

B.2.4.2.1 SIMPLIFY-1 (NCT01969838)

The baseline characteristics for SIMPLIFY-1 are presented in Table 9. Further detail and information on patient disposition is provided in Appendix D.

Table 9. Baseline characteristics for SIMPLIFY-1(61)

Characteristic	Momelotinib (n=215)	Ruxolitinib (n=217)
Mean age, years (SD)	65.0 (10.67)	64.4 (10.49)
Male sex, n (%)	124 (57.7%)	120 (55.3%)
MF subtype, n (%)		
PMF	128 (59.5%)	116 (53.5%)
Post-PV	48 (22.3%)	50 (23.0%)
Post-ET	39 (18.1%)	51 (23.5%)
Risk category, n (%)		
Intermediate-1	46 (21.4%)	43 (19.8%)
Intermediate-2	76 (35.3%)	67 (30.9%)
High	93 (43.3%)	107 (49.3%)
TSS, mean (SD)	19.4 (13.18)	17.9 (11.47)
Mean Hb, g/dL (SD)	10.6 (2.10)	10.7 (2.38)
Hb ≥8 g/dL, n (%)	186 (86.5%)	195 (89.9%)
Mean platelet count, $x10^3/\mu L$	301.1 (207.03)	301.5 (255.88)
TI, n (%)	147 (68.4%)	150 (70.0%)
TD, n (%)	53 (24.7%)	52 (24.0%)

Abbreviations: ET = essential thrombocythemia; Hb = haemoglobin; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation; TD = transfusion-dependent; TI = transfusion-independent; TSS = total symptom score

B.2.4.2.2 SIMPLIFY-2 (NCT02101268)

The baseline characteristics for SIMPLIFY-2 are presented in Table 10. Further detail and information on patient disposition is provided in Appendix D.

Table 10. Baseline characteristics for SIMPLIFY-2(23)

Characteristic	Momelotinib (n=104)	BAT (n=52)
Mean age, years (SD)	66.4 (8.1)	69.4 (7.4)
Male sex, n (%)	69 (66%)	24 (46%)
MF subtype, n (%)		
PMF	64 (62%)	30 (58%)
Post-PV	18 (17%)	12 (23%)
Post-ET	22 (21%)	10 (19%)
Risk category, n (%)		
Intermediate-1	23 (22%)	16 (31%)
Intermediate-2	62 (60%)	28 (54%)
High	19 (18%)	8 (15%)
TSS, mean (SD)	18.5 (13.0)	20.5 (16.0)
Duration of prior ruxolitinib, n (%)		

Characteristic	Momelotinib (n=104)	BAT (n=52)
Missing	13 (13%)	9 (17%)
<12 weeks	16 (15%)	10 (19%)
≥12 weeks	75 (72%)	33 (64%)
Mean Hb, g/dL (SD)	9.4 (1.9)	9.5 (1.6)
Hb ≥8 g/dL, n (%)	77 (74%)	46 (89%)
Mean platelet count, $x10^3/\mu L$	170.8 (148)	126.5 (95.9)
TI, n (%)	32 (31%)	19 (37%)
TD, n (%)	58 (56%)	27 (52%)

Abbreviations: ET = essential thrombocythemia; Hb = haemoglobin; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation; TD = transfusion-dependent; TI = transfusion-independent; TSS = total symptom score

B.2.4.2.3 MOMENTUM (NCT04173494)

The baseline characteristics for MOMENTUM are presented in Table 11. Further detail and information on patient disposition is provided in Appendix D.

Table 11. Baseline characteristics for MOMENTUM(64)

Characteristic	Momelotinib (n=130)	Danazol (n=65)
Mean age, years (IQR)	71 (65 to 75)	72 (67 to 78)
Male sex, n (%)	79 (61%)	44 (68%)
MF subtype, n (%)		
PMF	78 (60%)	46 (71%)
Post-PV	27 (21%)	11 (17%)
Post-ET	25 (19%)	8 (12%)
Risk category, n (%)		
Intermediate-1	7 (5%)	3 (5%)
Intermediate-2	72 (55%)	40 (62%)
High	50 (38%)	19 (29%)
Missing	1 (1%)	3 (5%)
Duration of previous JAKi treatment, mean weeks (SD)	138.5 (123.0)	124.8 (120.0)
TSS, mean (SD)	28.0 (13.8)	25.7 (12.8)
Mean Hb, g/dL (SD)	8.1 (1.1)	7.9 (0.8)
Hb ≥8 g/dL, n (%)	67 (52%)	33 (51%)
Mean platelet count, $x10^9/L$	151.7 (130.9)	130.7 (101.0)
TI, n (%)	17 (13%)	10 (15%)
TD, n (%)	63 (48%)	34 (52%)

Abbreviations: ET = essential thrombocythemia; Hb = haemoglobin; IQR = interquartile range; JAKi = Janus kinase inhibitor; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation; TD = transfusion-dependent; TI = transfusion-independent; TSS = total symptom score

B.2.4.3 Expert elicitation

Expert opinion was gathered in an advisory board held in November 2022 with six experienced clinical experts (consultant haematologists from England, Scotland and Northern Ireland).(33) Key objectives were to understand the current UK MF patient pathway, identify the unmet needs in the current treatment landscape, understand

how patients with anaemia are managed and the impact of anaemia on HRQoL, understand the perception of where momelotinib should be positioned in the treatment landscape, and to identify evidence gaps that could limit the positioning of momelotinib in the treatment pathway.

Experts were selected based on their experience in the therapy area, and to represent a range of treatment centres. Ahead of the meeting, the advisors completed a pre-meeting exercise, based on the NICE/SMC MF treatment pathways, and a questionnaire about anaemia management.(33)

A second advisory board was held in May 2023 with five of the clinical experts from the first advisory board, one additional clinical expert and two UK health economists.(32) The key objectives of this advisory board were to receive feedback on UK health technology assessment strategy, discuss the approach to the economic analysis and receive feedback on the clinical plausibility of the model assumptions.(32) Alongside the meeting, clinical advisors completed a questionnaire on resource use in the management of MF patients.

B.2.4.4 Real-world evidence

No real-world studies of momelotinib effectiveness have been completed to date.

B.2.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses performed in the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials is provided in Table 12, with further information presented in the following sections. Details of participant flow in each trial are provided in Appendix D.

Table 12. Summary of statistical analyses

Trial number (acronym)	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SIMPLIFY-1 (NCT01969838)(61, 62)	The primary efficacy endpoint was the proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks. The primary hypothesis was that momelotinib is non-inferior to ruxolitinib	Difference in spleen response rate calculated based on stratum-adjusted Cochran-Mantel-Haenszel proportions. The primary analysis was conducted using the ITT population, consisting of all patients randomly assigned. The primary and following secondary endpoints were tested for significance in a hierarchical sequence at a 2-sided significance level of 0.05: • TSS response rate • RBC TI rate • RBC TD rate • Rate of RBC transfusions Secondary endpoints were also evaluated using a Cochran-Mantel-Haenszel approach, other than rate of RBC transfusions which was evaluated using negative binomial regression	The sample size was calculated based on the primary efficacy endpoint. A common treatment effect of 34% (lower bound of the 95% CI in ruxolitinib arm) was assumed based on the COMFORT-1 study.(52) Based on this assumption, a total sample size of 420 would provide >90% power for testing the non-inferiority hypothesis.	eCRFs were used in to capture data from protocol-defined assessments and were reviewed by study monitors to verify data against source documentation and verify protocol adherence. Sponsor clinical data management teams reviewed the data for completeness, consistency and accuracy. Patient disposition, including reasons for discontinuation or withdrawal was documented according to treatment group.
SIMPLIFY-2 (NCT02101268)(23, 63)	The primary efficacy endpoint was the proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks.	Difference in spleen response rate calculated based on stratum-adjusted Cochran-Mantel-Haenszel proportions. The primary analysis was conducted using the ITT population, consisting of	The sample size was calculated based on the primary efficacy endpoint. A BAT treatment effect of 1% (based on COMFORT-2,(49) where no patients had a spleen response) and a momelotinib treatment effect of 20% (28% to 31% previously observed)(69) was assumed. Based on these assumptions, a total sample size of 150 would provide >95%	eCRFs were used in to capture data from protocol-defined assessments and were reviewed by study monitors to verify data against source documentation and verify protocol adherence. Sponsor clinical data management teams reviewed the data for

Trial number (acronym)	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	The primary hypothesis was that momelotinib is superior to BAT	all patients randomly assigned. The primary and following secondary endpoints were tested for significance in a hierarchical sequence at a 2-sided significance level of 0.05: • TSS response rate • Rate of RBC transfusions • RBC TI rate • RBC TD rate Secondary endpoints were also evaluated using a Cochran-Mantel-Haenszel approach, other than rate of RBC transfusions which was evaluated using negative binomial regression	power for testing the superiority hypothesis.	completeness, consistency and accuracy. Patient disposition, including reasons for discontinuation or withdrawal was documented according to treatment group.
MOMENTUM (NCT04173494)(64, 67)	The coprimary endpoints were the: • Proportion of patients with a ≥50% reduction in mean MF-SAF TSS over the 28 days immediately before the end of Week 24 compared with baseline • Proportion of patients with RBC transfusion - independence status at the end of Week 24 The primary hypothesis was that momelotinib is superior to danazol (note the coprimary endpoint on RBC transfusion -	Difference in MF-SAF TSS response rate calculated based on stratum-adjusted Cochran-Mantel-Haenszel proportions. The primary analysis was conducted using the ITT population, consisting of all patients randomly assigned. Coprimary and secondary endpoints were tested for significance in a hierarchical sequence at a 2-sided significance level of 0.05:	The sample size was calculated based on the primary efficacy endpoint. A treatment difference of 15% in the primary endpoint and 14% in spleen response rate was assumed. Based on these assumptions, a total sample size of 180 would provide >90% power for testing the superiority hypothesis.	eCRFs were used in to capture data from protocol-defined assessments and were reviewed by study monitors to verify data against source documentation and verify protocol adherence. Sponsor clinical data management teams reviewed the data for completeness, consistency and accuracy. Patient disposition, including reasons for discontinuation or withdrawal was documented according to treatment group.

Trial number (acronym)	Hypothesis	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	independent status was tested for non-inferiority)	• RBC TI rate (tested for non-inferiority in the hierarchy) • Spleen response rate (≥25%) • Change from baseline in mean MF-SAF TSS • Spleen response rate (≥35%) • Rate of zero transfusions Secondary endpoints were also evaluated using a Cochran-Mantel-Haenszel approach, other than change from baseline in MF-SAF TSS which evaluated using an MMRM		

Abbreviations: BAT = best available therapy; eCRF = electronic case report form; ITT = intent-to-treat; MF-SAF = Myelofibrosis Symptoms Assessment Form; MMRM = mixed model repeated measures; RBC = red blood cell; TSS = total symptom score

B.2.5.1 SIMPLIFY-1 (NCT01969838)

B.2.5.1.1 Study population and sample size

SIMPLIFY-1 enrolled JAKi-naïve patients aged ≥18 years with PMF or post-PV/-ET MF. The sample size was based on the primary efficacy endpoint of spleen response rate, and considered the following:(61)

- The primary efficacy objective was to demonstrate that momelotinib is non-inferior to ruxolitinib
- A common treatment effect of 34%, which was a conservative assumption based on the lower bound of the 95% CI of spleen response rate for ruxolitinib in the COMFORT-1 trial(52, 62)

Based on the above, a total sample size of 420 (210 in each treatment group) would provide >90% power to detect the non-inferiority of momelotinib to ruxolitinib at a 2-sided significance level of 0.05.

B.2.5.1.2 Patient populations analysed

The efficacy analysis was conducted using the intent-to-treat (ITT) population, which included all randomised patients. The exception was for the endpoint of TSS response rate, which was assessed in all randomised patients with baseline TSS >0, or baseline TSS of 0 but with TSS missing or >0 at Week 24. The safety population included all patients who were randomised and received ≥1 dose of study drug.(61)

B.2.5.1.3 Statistical analyses

For the primary endpoint of spleen response rate, non-inferiority was shown if the lower bound of the two-sided 95% CI for the difference between the momelotinib and ruxolitinib groups was >0, using stratum-adjusted Cochran-Mantel-Haenszel proportions. Sequential testing was conducted for the following four secondary endpoints to control the type 1 error rate:(61)

- TSS response rate
- RBC TI rate
- RBC TD rate
- Rate of RBC transfusions

The primary and four secondary endpoints, in the order above, were tested for significance in a hierarchical sequence at a 2-sided significance level of 0.05. If statistical significance was not achieved for any of the endpoints in the hierarchical sequence, formal statistical testing was stopped, and only nominal significance could be achieved for subsequent endpoints. Secondary endpoints were also evaluated using a Cochran-Mantel-Haenszel approach, except for the rate of RBC transfusions which was evaluated using negative binomial regression.(61) A summary of the statistics provided, without multiplicity adjustment, for exploratory endpoints is presented in Table 13. The primary analysis for all exploratory efficacy endpoints was on the ITT analysis set, unless otherwise specified.

Table 13. Statistics for exploratory efficacy endpoints (SIMPLIFY-1)(61)

Endpoint	Endpoint type	Statistics provided
Spleen response rate over time	Categorical	• n, % for each category • Proportion difference between treatment groups and corresponding 95% CIs provided and analysed using Cochran-Mantel-Haenszel approach to adjust for stratification factors
ORR		
Derived rate of clinical improvement at Week 24		
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		
Anaemia response rate at Week 24		
RBC transfusion-free response rate over time		
TSS response by every 4 weeks		
TSS response based on moving Weekly average		
ECOG performance status		
PGIC		
MPN-SAF		
EQ-5D-5L		
SF-36 v2		
Percent change from baseline in spleen volume over time	Continuous	• Change from baseline, best/worst/minimal/maximal change or % change from baseline • Best/minimal/maximal change or % change from baseline, as well as change and % change from baseline at each visit analysed using ANCOVA with treatment and stratification factors as factors and baseline values as covariates • Stratified Wilcoxon Rank Sum (van Elteren) test • % change from baseline at Week 24 for spleen volume and TSS also analysed using MMRM
Hb, platelets or ANC, change and % change from baseline over time		
Palpable spleen size and % change from baseline over time		
Rate of RBC transfusions in the OL phase		
Modified MPN-SAF 2.0 individual scores		
Duration of spleen response	Time to event	• Kaplan-Meier plots
Duration of TI response[a]		

Endpoint	Endpoint type	Statistics provided
Time to TI response[a]		• Descriptive statistics only for 'time to TI response' (n, mean, SD, median, Q1, Q3, minimum, and maximum) • Stratified log-rank tests performed
Duration of transfusion-free response[b]		
Leukaemia-free survival		

[a]In patients not TI at baseline, who had TI post-baseline in the double-blind phase
[b]In patients not transfusion-free at baseline
Abbreviations: ANC = absolute neutrophil count; ANCOVA = analysis of covariates; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQoL 5-dimensions 5-level; Hb = haemoglobin; MMRM = mixed model repeated measures; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; OL = open-label; ORR = overall response rate; PGIC = Patient Global Impression of Change; RBC = red blood cell; SF-36 = short form 36; TI = transfusion-independent; SD = standard deviation; TSS = total symptom score;

B.2.5.1.4 Planned analyses

The primary analysis was planned for when all patients had reached the Week 24 time point (data cut-off 12 September 2016). An additional follow-up analysis was conducted using data collected in the open-label phase (data cut-off 12 September 2017).(62, 70)

No formal interim efficacy analysis was conducted.(62, 70)

B.2.5.1.5 Patient flow

Detailed information on patient flow in SIMPLIFY-1 is provided in Appendix D, including the CONSORT diagram.

B.2.5.2 SIMPLIFY-2 (NCT02101268)

B.2.5.2.1 Study population and sample size

SIMPLIFY-2 enrolled current or prior ruxolitinib-treated patients aged ≥18 years with PMF or post-PV/-ET MF. The sample size was based on the primary efficacy endpoint of spleen response rate, and considered the following:(23)

- The primary efficacy objective was to demonstrate that momelotinib is superior to BAT
- An assumed BAT treatment effect of 1%, based on COMFORT-2, where no patients had a spleen response(49, 69)
- An assumed momelotinib treatment effect of 20%, based on spleen response rates of 28% to 31% previously observed with momelotinib

Based on the above, a total sample size of 150 (100 in the momelotinib group and 50 in the BAT group) would provide >95% power to detect the superiority of momelotinib to BAT at a 2-sided significance level of 0.05.(63)

The study was designed to demonstrate the superiority of momelotinib versus BAT other than ruxolitinib, based on an assumption that the majority of patients in the BAT arm would be treated with hydroxyurea, immunomodulatory drugs, ESAs, corticosteroids, or ruxolitinib at a subtherapeutic dose.(63) However, after enrolment, ruxolitinib dosing was established in guidelines and clinical practice, and thus most patients in the BAT arm continued receiving ruxolitinib alone or in combination (46 [88.5%] of 52; Table 14). Other treatments used included hydroxyurea alone (12 [23%]), and corticosteroids alone (6 [12%]).(23)(63)

Table 14. Composition of BAT arm in SIMPLIFY-2(63)

BAT (n=52)	n (%)
Ruxolitinib	46 (88.5)
Hydroxyurea	12 (23.1)
Prednisone/prednisolone	6 (11.5)
Danazol	3 (5.8)
ESA	2 (3.8)
No therapy	2 (3.8)
Anagrelide	1 (1.9)
Aranesp	1 (1.9)
Aspegic	1 (1.9)
Thalidomide	1 (1.9)

Abbreviations: BAT = best available therapy; ESA = erythropoietin stimulating agent

A total of 14 patients (27%) were treated with ruxolitinib plus additional therapies, most commonly ruxolitinib plus hydroxyurea (9 [17%]), followed by ruxolitinib plus corticosteroids (6 [12%]; Table 15).(23)

Table 15. Therapies used in combination in the SIMPLIFY-2 BAT arm(63)

Combination BAT	n (%)
Patients ≥2 therapies since randomisation	16 (30.8)
Other drugs received with ruxolitinib	14 (26.9)
Ruxolitinib	14 (26.9)
Hydroxyurea	9 (17.3)
Prednisone/prednisolone	6 (11.5)
Danazol	2 (3.8)
Anagrelide	1 (1.9)
Aspirinegic	1 (1.9)
ESA	1 (1.9)
Thalidomide	1 (1.9)
Other drugs but not in combination with ruxolitinib	2 (3.8)
Aranesp	1 (1.9)
Danazol	1 (1.9)
ESA	1 (1.9)
Hydroxyurea	1 (1.9)

B.2.5.2.2 Patient populations analysed

The efficacy analysis was conducted using the ITT population, which included all randomised patients. The exception was for the endpoint of TSS response rate, which was assessed in all randomised patients with baseline TSS >0, or baseline TSS of 0 but with TSS missing or >0 at Week 24. The safety population included all patients who were randomised and received ≥1 dose of study drug.(23, 63)

B.2.5.2.3 Statistical analyses

For the primary endpoint of spleen response rate, superiority was shown if the lower bound of the 2-sided 95% CI for the difference between the momelotinib and BAT groups was >0, using stratum-adjusted Cochran-Mantel-Haenszel proportions.(23, 63) Sequential testing was conducted for the following four secondary endpoints to control the type 1 error rate:

- TSS response rate
- Rate of RBC transfusions
- RBC TI rate
- RBC TD rate

The primary and four secondary endpoints, in the order above, were tested for significance in a hierarchical sequence at a 2-sided significance level of 0.05. If statistical significance was not achieved for any of the endpoints in the hierarchical sequence, formal statistical testing was stopped, and only nominal significance could be achieved for subsequent endpoints. Secondary endpoints were also evaluated using a Cochran-Mantel-Haenszel approach, except for the rate of RBC transfusions which was evaluated using negative binomial regression. A summary of the statistics provided, without multiplicity adjustment, for exploratory endpoints is presented in Table 16. The primary analysis for all exploratory efficacy endpoints was on the ITT analysis set, unless otherwise specified.(23)

Table 16. Statistics for exploratory efficacy endpoints (SIMPLIFY-2)(71)

Endpoint	Endpoint type	Statistics provided
Spleen response rate over time	Categorical	• n, % for each category • Proportion difference between treatment groups and corresponding 95% CIs provided and analysed using Cochran-Mantel-Haenszel approach to adjust for stratification factors
ORR		
Derived rate of clinical improvement at Week 24		
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		
Anaemia response rate at Week 24		
RBC transfusion-free response rate over time		
TSS response by every 4 weeks		
TSS response based on moving weekly average		
ECOG performance status		
PGIC		
MPN-SAF		
EQ-5D-5L		
SF-36 v2		
Percent change from baseline in spleen volume over time	Continuous	• Change from baseline, best/worst/minimal/maximal change or % change from baseline • Best/minimal/maximal change or % change from baseline, as well as change and % change from baseline at each visit analysed using ANCOVA with treatment and stratification factors as factors and baseline values as covariates • Stratified Wilcoxon Rank Sum (van Elteren) test • % change from baseline at Week 24 for spleen volume and TSS also analysed using MMRM
Hb, platelets or ANC, change and % change from baseline over time		
Palpable spleen size and % change from baseline over time		
Rate of RBC transfusion in the OL phase		
Modified MPN-SAF 2.0 individual scores		
Duration of spleen response	Time to event	• Kaplan-Meier plots • Descriptive statistics only for 'time to TI response' (n, mean, SD, median, Q1, Q3, minimum, and maximum) • Stratified log-rank tests performed
Duration of TI response[a]		
Time to TI response[a]		
Duration of transfusion-free response[b]		
Leukaemia-free survival		

[a]In patients not TI at baseline, who achieved TI post-baseline in the double-blind phase
[b]In patients not transfusion-free at baseline
Abbreviations: ANC = absolute neutrophil count; ANCOVA = analysis of covariates; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQoL 5-dimensions 5-level; Hb = haemoglobin; MMRM = mixed model repeated measures; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; OL = open-label; ORR = overall response rate; PGIC = Patient Global Impression of Change; RBC = red blood cell; SD = standard deviation; SF-36 = short form 36; TI = transfusion-indpendent; TSS = total symptom score

B.2.5.2.4 Planned analyses

The primary analysis was planned for when all patients had reached the Week 24 time point (data cut-off 28 July 2016). An additional follow-up analysis was conducted using data collected in the extension phase (data cut-off 12 September 2017).(63, 71)

No formal interim efficacy analysis was conducted.(63, 71)

B.2.5.2.5 Patient flow

Detailed information on patient flow in SIMPLIFY-2 is provided in Appendix D, including the CONSORT diagram.

B.2.5.3 MOMENTUM (NCT04173494)

B.2.5.3.1 Study population and sample size

MOMENTUM enrolled symptomatic (TSS ≥ 10) and anaemic (Hb <10 g/dL) JAKi-experienced patients aged ≥18 years with PMF or post-PV/-ET MF. The sample size was based on the coprimary efficacy endpoints of TSS response rate and TI rate, and key secondary endpoint of spleen response rate.(64, 67) The trial was designed to enroll a sample size of ≥180 (randomised 2:1; 120 in the momelotinib group and 60 in the danazol group), which would provide 90% power at a 2-sided significance level of 0.05 to detect a true difference in treatment effect of:(64, 67)

- 15% in TSS response rate (17% versus 2%)
- 24% in TI rate (45% versus 21%)
- 14% in spleen response rate (15% versus 1%)

B.2.5.3.2 Patient populations analysed

The efficacy analysis was conducted using the ITT population, which included all randomised patients. The safety population included all patients who were randomised and received ≥1 dose of study drug. The ITT and safety populations were identical in MOMENTUM.(64, 67)

B.2.5.3.3 Statistical analyses

For the coprimary endpoint of MF-SAF TSS response rate, superiority was shown if the lower bound of the 2-sided 95% CI for the difference between the momelotinib and danazol groups was >0, using stratum-adjusted Cochran-Mantel-Haenszel proportions. Sequential testing was conducted for the following coprimary and secondary endpoints to control the type 1 error rate:(64, 67)

- RBC TI rate (coprimary endpoint)

    - A stratum-adjusted 2-sided 95% CI was calculated for the difference between the proportion of TI patients in the momelotinib arm and 80% of the proportion of TI patients in the danazol arm. If the lower bound of the CI was >0, non-inferiority was declared.
    - If non-inferiority was declared, superiority was then tested using a stratified Cochran-Mantel-Haenszel test and results were considered descriptive.
- Spleen response rate (≥25%)
- Change from baseline in mean MF-SAF TSS
- Spleen response rate (≥35%)
- Rate of zero transfusions

The coprimary and four secondary endpoints, in the order above, were tested for significance in a hierarchical sequence at a 2-sided significance level of 0.05. If statistical significance was not achieved for any of the endpoints in the hierarchical sequence, formal statistical testing was stopped, and only nominal significance could be achieved for subsequent endpoints. Secondary endpoints were also evaluated using a Cochran-Mantel-Haenszel approach, except for the rate of RBC transfusions which was evaluated using negative binomial regression.

A summary of the statistics provided, without multiplicity adjustment, for other secondary efficacy endpoints is presented in Table 17. The primary analysis for all other secondary efficacy endpoints used the ITT analysis set.(64, 67)

Table 17. Statistics for other efficacy endpoints (MOMENTUM)(67)

Endpoint	Endpoint type	Statistics provided
TI rate at Week 24[a]	Categorical	• n, % for each category • Proportion difference between treatment groups and corresponding 95% CIs provided and analysed using Cochran-Mantel-Haenszel approach to adjust for stratification factors
TD rate at Week 24		
Hb response rate by Week 24		
Change from baseline in disease-related fatigue (MF-SAF v4.0)	Continuous	• Descriptive statistics for symptom scores, and their change and % change from baseline • Change from baseline analysed using MMRM
Change from baseline in cancer-related fatigue (EORTC QLQ-C30)		
Change from baseline in PROMIS Physical Function Score		
Duration of Week 24 MF-SAF TSS response	Time to event	• Kaplan-Meier methods used • Descriptive statistics (n, median, 95% CI, survival probabilities) • Stratified log-rank tests performed for comparison of time to each event between treatment groups • Stratified Cox regression model to estimate HRs and 95% CI • Cumulative transfusion risk evaluated using ZINB model
Duration of TI at Week 24		
Time to first (third, fifth) RBC transfusions or whole blood unit transfused		
Cumulative transfusion risk at Week 24		
Duration of TI response[a]		
Overall survival		
Leukaemia-free survival		

[a]In patients with baseline TD

Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; Hb = haemoglobin; HR = hazard ratio; MMRM = mixed model repeated measures; MF-SAF = Myelofibrosis Symptom Assessment Form; PROMIS = Patient-Reported Outcomes Measurement Information System; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TSS = total symptom score; ZINB = zero-inflated negative binomial

B.2.5.3.4 Planned analyses

The primary analysis was planned for when all patients had reached the Week 24 time point (data cut-off 03 December 2021).(67)

No formal interim efficacy analysis was conducted.(67)

B.2.5.3.5 Patient flow

Detailed information on patient flow in MOMENTUM is provided in Appendix D, including the CONSORT diagram.

B.2.6 Critical appraisal of the relevant clinical effectiveness evidence

B.2.6.1 Quality assessment

The NICE checklist for the quality assessment of the risk of bias for RCTs was used to appraise the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials. A detailed overview of these quality assessments for each of these trials identified by the

clinical SLR is provided in Appendix D. A high level summary of the quality assessment is presented in Table 18; the overall risk of bias was found to be low in all three trials.

The SIMPLIFY-2 trial, per the statistical analysis plan, was designed without consideration for the usage of ruxolitinib within BAT; the design was based on the treatment effect of the BAT arm of the COMFORT trial, which excluded the use of ruxolitinib or any JAKi. The change in standard of care for ruxolitinib-experienced patients was reflected in the treatment composition of the comparator arm of SIMPLIFY-2, but not in the trial design and statistical analysis. At the time of SIMPLIFY-2 protocol development, BAT treatments were anticipated to comprise hydroxyurea, steroids or ESA.(23) Subsequently, however, ruxolitinib dosing guidelines became widely available.(23) Along with increased clinical experience, this led to a large majority of patients in the BAT group receiving ruxolitinib (88.5%), in contrast to expectations when the study was designed to show superiority.(23) As described below, this treatment composition is reflective of English clinical practice.

Further, there was no washout period in SIMPLIFY-2, which may explain the low splenic response rates observed in both arms of this study, effectively confounding primary endpoint analysis.(23) Patients entering the study had either suboptimal responses or haematological toxicity with ruxolitinib, but were not necessarily ruxolitinib-refractory (characterised by lack or loss of initial splenic response to ruxolitinib).(23) Patients who were receiving ruxolitinib at enrolment were required to maintain their existing dose throughout the screening period up until baseline.(23) Thus, in effect, most patients either maintained therapeutic ruxolitinib doses or switched to momelotinib at baseline, effectively maintaining their active treatment rather than adding additional therapy. As a de-facto crossover trial, SIMPLIFY-2 was not suited to assess the superiority of momelotinib over BAT. Nevertheless, it provides valuable data supporting the use of momelotinib in JAKi-experienced patients and is highly relevant for decision making.

Table 18. Quality assessment results

Study name	SIMPLIFY-1 (NCT01969838)(61, 62)	SIMPLIFY-2 (NCT02101268)(23, 63)	MOMENTUM (NCT04173494)(64, 67)
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes
Have the authors identified all important confounding factors?	Yes	Yes	Yes
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	No[a]	Yes
Was the follow-up of patients complete?	Yes	Yes	No
Are the results precise (for example, in terms of confidence interval and p values)?	Yes	No	Yes

[a]Unforeseen confounding factors may have impacted results of this study (see discussion in Section B.2.6.1)

B.2.6.2 Applicability of the study results to clinical practice in England

The results of these trials are expected to be applicable to patients in routine clinical practice in England. SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM all included patients recruited from sites in the UK.(62, 63, 67) Specifically, UK patients were recruited from [redacted]) in SIMPLIFY-1, [redacted]) in SIMPLIFY-2 and [redacted]) in MOMENTUM.(62, 63, 67) No by-country analyses were conducted but enrolled patients were considered to be similar across countries in terms of disease characteristics, treatment history etc. Furthermore, no significant differences were observed by geographical region (e.g., Europe, North America, Asia, Australia) in subgroup analyses of the primary endpoint in each study.(62, 63, 67)

Feedback from clinical experts in the November 2022 advisory board indicated that the patient populations (JAKi-naïve/JAKi-experienced and range of risk categories), study designs and endpoints of SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM were relevant to clinical practice in the UK.(32)

- In SIMPLIFY-1, the control arm was treated with ruxolitinib which is the standard of care in England for treating splenomegaly and symptoms associated with MF in JAKi-naïve patients.(32)
- Despite the unintended high usage of ruxolitinib in the comparator BAT arm of SIMPLIFY-2 (88.5%)(63), contributing to the failure of momelotinib to demonstrate superiority over BAT in terms of spleen response rate, it nevertheless resulted in a comparator which accurately reflects established clinical practice for JAKi-experienced patients in England.(32) UK clinicians consulted during an advisory board have confirmed that patients rarely, if ever, cease ruxolitinib treatment despite suboptimal response due to a lack of alternatives and the risk of ruxolitinib discontinuation syndrome.(32) Therefore, SIMPLIFY-2 is well placed to inform the comparative effectiveness of momelotinib versus established clinical practice in JAKi-experienced patients in England.
- In MOMENTUM, patients in the control arm received danazol, which experts at the advisory board confirmed is used in clinical practice in England as an anaemia treatment.(32)

In SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM, patients could receive concomitant treatment with RBC transfusions to manage anaemia, which reflects NHS management standard practice.(3) Furthermore, patients could receive iron chelation therapy (ICT) where indicated and clinically appropriate to mitigate the toxicity associated with repeated RBC transfusions.(62, 63, 67) Clinical experts at the advisory board again confirmed this is how anaemia is managed in English clinical practice.(32)

B.2.7 Clinical effectiveness results of the relevant trials

A summary of prespecified outcomes assessed in SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM is presented in Table 19.

Table 19. Summary of prespecified efficacy endpoints

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)			SIMPLIFY-2 (NCT02101268)(23, 63)**			MOMENTUM (NCT04173494)(64, 67, 72)		
	Momelotinib	**Ruxolitinib**	**Proportion difference (95% CI)**	**Momelotinib**	**BAT**	**Proportion difference (95% CI)**	**Momelotinib**	**Danazol**	**Treatment difference (95% CI)**
Primary efficacy endpoints									
Spleen response rate, i.e., the proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks	[redacted]	[redacted]	[redacted]	6.7%	5.8%	0.01 (-0.09, 0.10); p=0.90	-	-	-
MF-SAF TSS response rate, i.e., the proportion of patients with a ≥50% reduction in mean MF-SAF TSS over the 28 days immediately before the end of Week 24 compared with baseline	-	-	-	-	-	-	**Coprimary endpoint:** 24.6%	**Coprimary endpoint:** 9.2%	**Coprimary endpoint:** [redacted] p=0.0095
Secondary efficacy endpoints									
MPN-SAF TSS response rate, i.e., the proportion of patients with a ≥50% reduction in mean MPN-SAF TSS at Week 24 compared with baseline	28.4%	42.4%	0.09 (95% CI: -0.08, 0.08); p=0.98	26.2%	5.9%	[redacted] p<0.001	-	-	-
TI rate i.e., the proportion of patients who had no RBC transfusions or no Hb levels <8 g/dL in the previous 12 weeks at Week 24*	66.5%	49.3%	[redacted] nominal p<0.001	43.3%	21.2%	[redacted] nominal p=0.0012	**Coprimary endpoint:** 30.0%	**Coprimary endpoint:** 20.0%	**Coprimary endpoint:** [redacted] one-sided p=0.0116

Trial	SIMPLIFY-1 (NCT01969838)(61, 62)			SIMPLIFY-2 (NCT02101268)(23, 63)**			MOMENTUM (NCT04173494)(64, 67, 72)		
	Momelotinib	Ruxolitinib	Proportion difference (95% CI)	Momelotinib	BAT	Proportion difference (95% CI)	Momelotinib	Danazol	Treatment difference (95% CI)
TD rate i.e., the proportion of patients who had 4 units of RBC transfusions or Hb levels <8 g/dL in the previous 12 weeks at Week 24	30.2%	40.1%	[redacted] nominal p=0.019	50.0%	63.5%	[redacted] nominal p=0.10	-	-	-
Spleen response rate i.e., the proportion of patients with a ≥25% reduction in spleen volume at Week 24*	-	-	-	-	-	-	39.2%	6.2%	[redacted] p<0.0001
Spleen response rate i.e., the proportion of patients with a ≥35% reduction in spleen volume at Week 24*	-	-	-	-	-	-	22.3%	3.1%	[redacted] p=0.0011
Mean TSS change from baseline at Week 24	-	-	-	-	-	-	-11.5	-3.9	LSM difference -6.2 (-10.0, -2.4); p=0.0014

* The data in MOMENTUM CSR were updated on three endpoints due to a previous data error. ** No washout period.
Abbreviations: CI = confidence interval; LSM = least squares mean; Hb = haemoglobin; MF-SAF = Myelofibrosis Symptoms Assessment Form; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment; RBC = red blood cell; TSS = total symptom score;

B.2.7.1 SIMPLIFY-1 (NCT01969838)

B.2.7.1.1 Primary endpoint: spleen response rate

The primary endpoint in SIMPLIFY-1, spleen response rate, was defined as the percentage of patients with a ≥35% reduction in spleen volume from baseline at Week 24, as assessed by magnetic resonance imaging or computed tomography scans.(61)

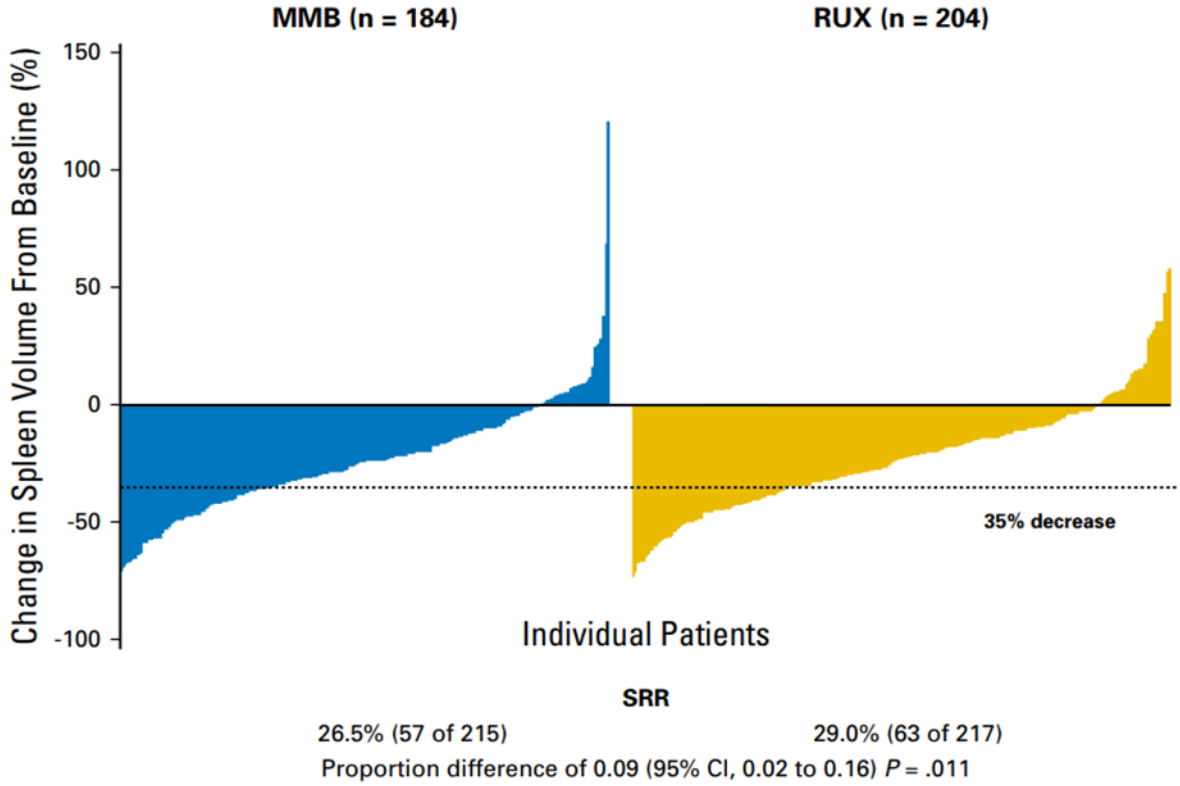
The proportion of patients who achieved a response at Week 24 in the momelotinib group ([redacted]) was similar to the proportion of patients in the ruxolitinib group ([redacted]).(61) The proportion difference between treatment groups was [redacted]; Figure 8).(61) Thus, the primary endpoint was met, demonstrating the non-inferiority of momelotinib to ruxolitinib [redacted]; Table 20).(62)

Table 20. Analysis of spleen response rate (≥35% reduction in spleen volume) at Week 24 (SIMPLIFY-1; ITT)(62)

	Momelotinib (n=215)	Ruxolitinib (n=217)	p-value
Responder, n (%)	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	-
Proportion difference: stratified CMH method (95% CI)	[redacted]		[redacted]

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat

Figure 8. Change in spleen volume and spleen response rate (≥35%) at Week 24 (SIMPLIFY-1; ITT)(61)



Abbreviations: CI = confidence interval; ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib; SRR = spleen response rate

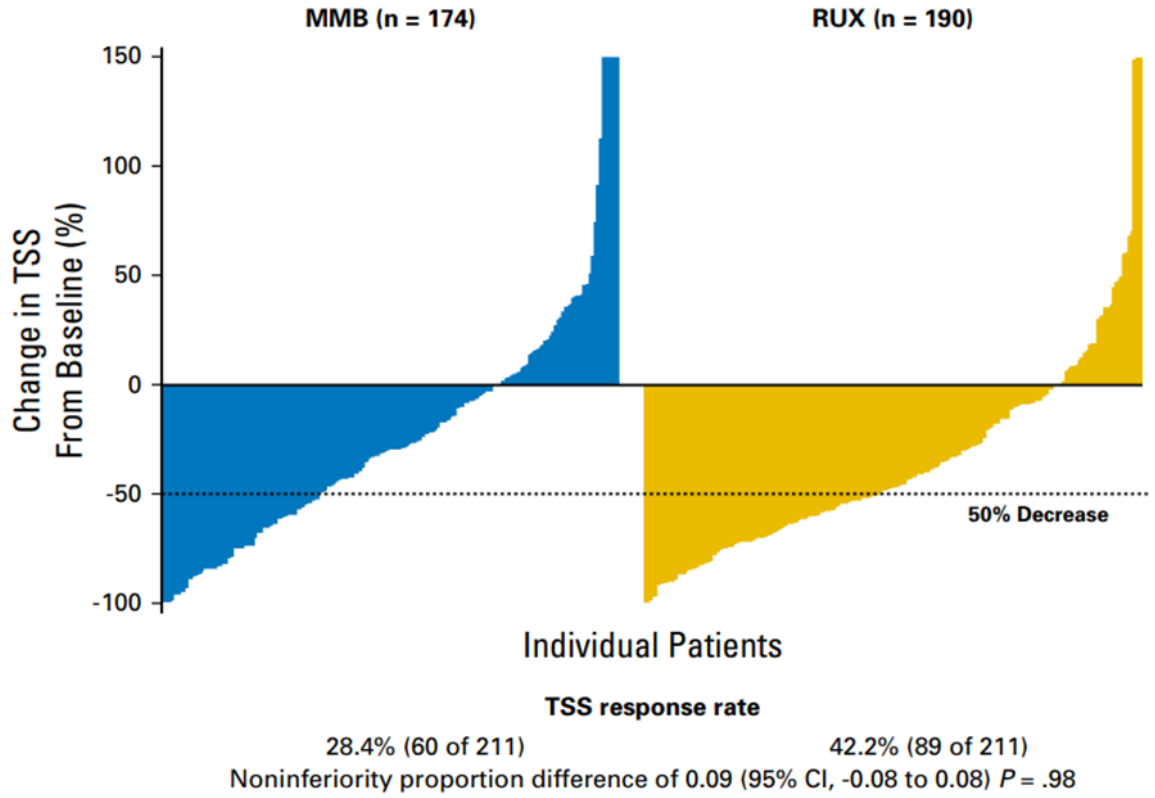
A total of 85.6% in the momelotinib group (184 of 215) and 94.0% in the ruxolitinib group (204 of 217) had spleen volume measurements at both baseline and Week 24.(62) The lower rate of discontinuation in the ruxolitinib group at Week 24 was mainly driven by the lower rate of low-grade AEs in this group, likely due to the protocol-defined, ruxolitinib oriented dose modification schema. Please see Section D.1.2 for data on patient discontinuation in SIMPLIFY-1. The mean percent change in spleen volume at Week 24 was [redacted] in the momelotinib group and [redacted] in the ruxolitinib group.(62) However, the observed difference in the mean percent change between the two groups was not statistically significant.(62)

Results from the open-label phase indicated that patients continued to receive a benefit with momelotinib treatment after 24 weeks. In the ITT population, [redacted] of patients in the momelotinib group and [redacted] of patients in the ruxolitinib group (including those who switched from ruxolitinib to momelotinib after Week 24) had a spleen response at any time during the double-blind or open-label phase.(62) Spleen responses (achieved during the double-blind or open-label phase) were durable, with a median response duration of [redacted] in the momelotinib group and [redacted] in the ruxolitinib group.(62, 65)

B.2.7.1.2 Secondary endpoint: TSS response rate

In the secondary endpoint of TSS response rate (Myeloproliferative Neoplasm Symptom Assessment Form [MPN-SAF]), fewer patients had a reduction of ≥50% in TSS from baseline at Week 24 in the momelotinib group (28.4%) than the ruxolitinib group (42.2%).(61) The non-inferiority proportion difference between treatment groups was 0.00 (95% CI: -0.08, 0.08; Figure 9). As the lower bound of the two-sided 95% CI was not >0, the non-inferiority of momelotinib to ruxolitinib was not shown for this endpoint (p=0.98).(61) The mean absolute change in TSS from baseline at Week 24 was [redacted] in the momelotinib group and [redacted] in the ruxolitinib group.(62)

Figure 9. Change in TSS from baseline and TSS response rate (≥50% reduction) at Week 24 (SIMPLIFY-1; ITT)(61)



Abbreviations: CI = confidence interval; ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib; TSS = Total Symptom Score

The dichotomous response design of this endpoint was problematic for several reasons; notably, baseline symptom severity was not an inclusion criterion or stratification factor, leading to imbalanced TSS scores across treatment arms (see Section B.2.13.1.1 for more information). In light of this, a post-hoc analysis of the cumulative distribution function of absolute change in MPN-SAF TSS from baseline to Week 24 in symptomatic patients (baseline TSS ≥10) was conducted, which revealed comparable results in the momelotinib and ruxolitinib arms (Figure 10).(48)

Figure 10. Cumulative distribution function of absolute change in MPN-SAF TSS from baseline to Week 24 in the SIMPLIFY-1 symptomatic population(62)

Abbreviations: MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; TSS = total symptom score

On analysis of individual symptom scores, similar improvements were observed in patients treated with momelotinib and ruxolitinib across symptom domains (Figure 11).(62)

Figure 11. Median change from baseline in individual MPN-SAF symptom scores at Week 24 (SIMPLIFY-1; ITT)(62)

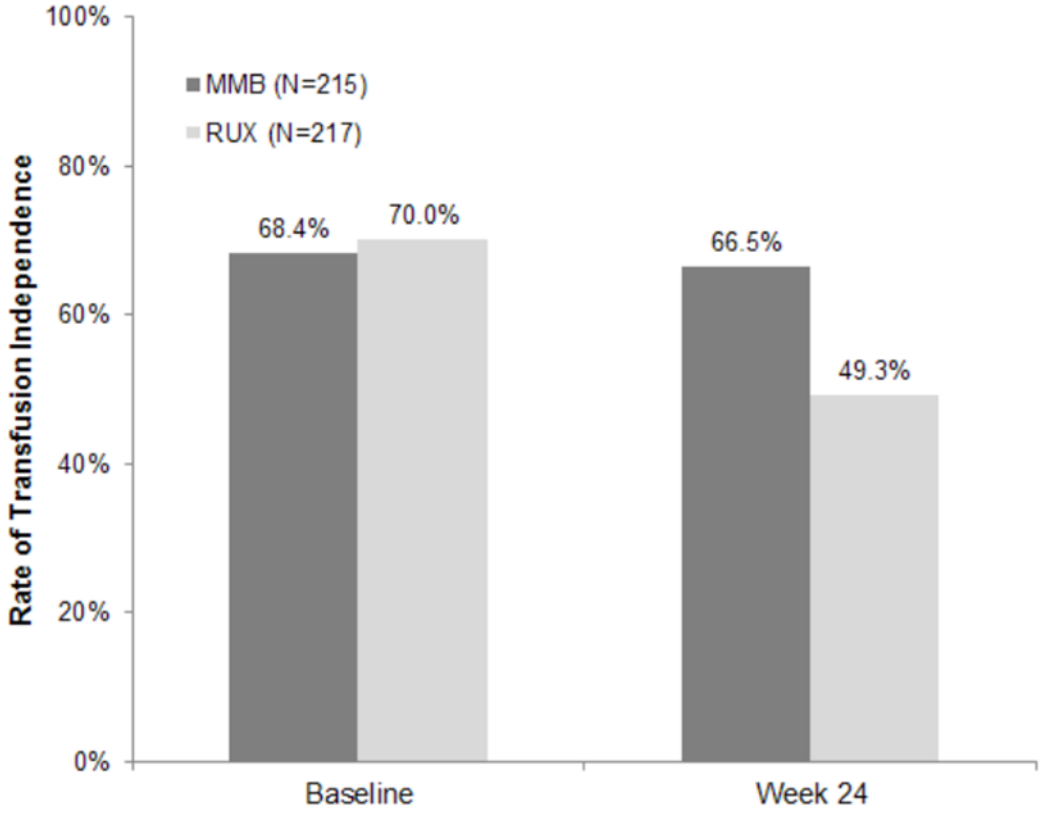
Abbreviations: ITT = intent-to-treat; MMB = momelotinib; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; RUX = ruxolitinib

As non-inferiority was not achieved in the secondary endpoint of TSS response rate, only nominal significance was reported for subsequent endpoints in the statistical hierarchy.(61)

B.2.7.1.3 Secondary endpoint: TI rate

The secondary endpoint of TI rate was defined as the proportion of patients who had no RBC transfusions and no Hb levels <8 g/dL in the previous 12 weeks.(61) A higher proportion of patients in the momelotinib group (66.5%) versus the ruxolitinib group (49.3%) were TI at Week 24 (Figure 12).(61) The TI rate at Week 24 in the momelotinib group was similar to the baseline (68.4%), but represented an approximate 20% absolute reduction from baseline (70.0%) in the ruxolitinib group.(62) The difference between treatment groups was nominally significant (proportion difference [stratified CMH]: [redacted]; nominal p<0.001).(62)

Figure 12. TI rate at baseline and Week 24 (SIMPLIFY-1; ITT)(62)

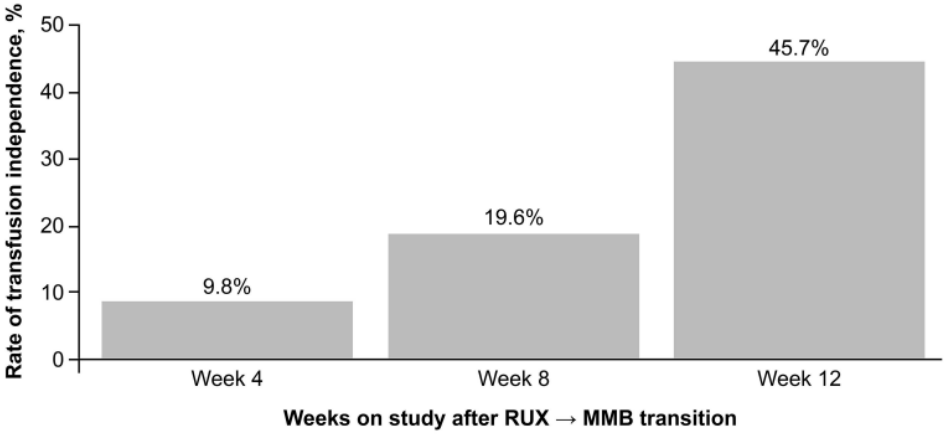


Abbreviations: ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib; TI = transfusion-independence

Furthermore, the median rate of RBC transfusions through Week 24 was nominally significantly lower in the momelotinib group (0 units/month) versus the ruxolitinib group (0.4 units/month; nominal p<0.001).(61)

Following crossover to momelotinib at Week 24, patients originally randomised to ruxolitinib-experienced a rapid improvement in transfusion burden.(65) Nearly half of patients who were not TI on ruxolitinib at Week 24 became TI by Week 12 of momelotinib treatment in the open-label phase (Figure 13).(65)

Figure 13. TI rate after transition to momelotinib at Week 24, among non-TI ruxolitinib-randomised patients, in the open-label phase (SIMPLIFY-1; ITT; n=92)(65)

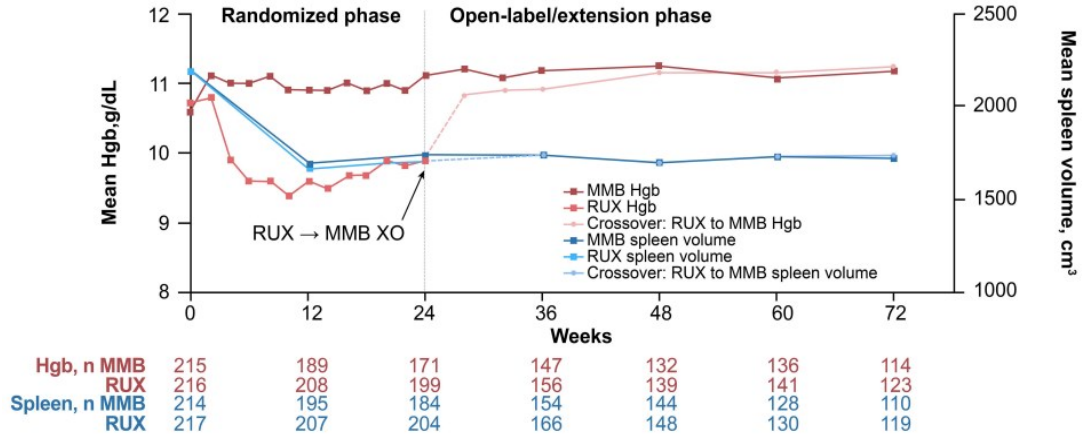


Abbreviations: ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib; TI = transfusion-independence

B.2.7.1.4 Exploratory secondary endpoint: changes in Hb levels over time

In the randomised treatment phase, there was a notable difference in Hb levels between groups; patients treated with momelotinib experienced an increase in mean Hb levels whereas patients treated with ruxolitinib-experienced a decrease (Figure 14).(65) Following immediate transition to momelotinib at Week 24, patients originally randomised to ruxolitinib-experienced a rapid increase in mean Hb levels (~1 g/dL) after 4 weeks.(65) Hb levels were maintained at a similar level to those of patients originally randomised to momelotinib for the duration of the open-label phase.(65) Furthermore, the spleen volume reductions achieved in the randomised phase were maintained with momelotinib treatment for the entirety of the 48-week open-label phase, regardless of initial treatment.(65)

Figure 14. Mean Hb levels and spleen volume over time in the double-blind and open-label phases (SIMPLIFY-1; ITT)(65)



Abbreviations: Hgb = haemoglobin; ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib

B.2.7.1.5 Exploratory secondary endpoint: changes in platelet levels over time

Changes in platelet counts over time in SIMPLIFY-1 highlighted the low myelosuppressive potential of momelotinib.(65) Despite similar baseline values in the two groups, platelet counts were maintained in the momelotinib group but dropped decreased in the ruxolitinib group (Figure 15).(65) Furthermore, following crossover from ruxolitinib to momelotinib at Week 24, platelet levels recovered and were comparable to those of patients treated with momelotinib from baseline by Week 48.(65)

Figure 15. Mean platelet levels over time in the double-blind and open-label phase (SIMPLIFY-1; ITT)(65)

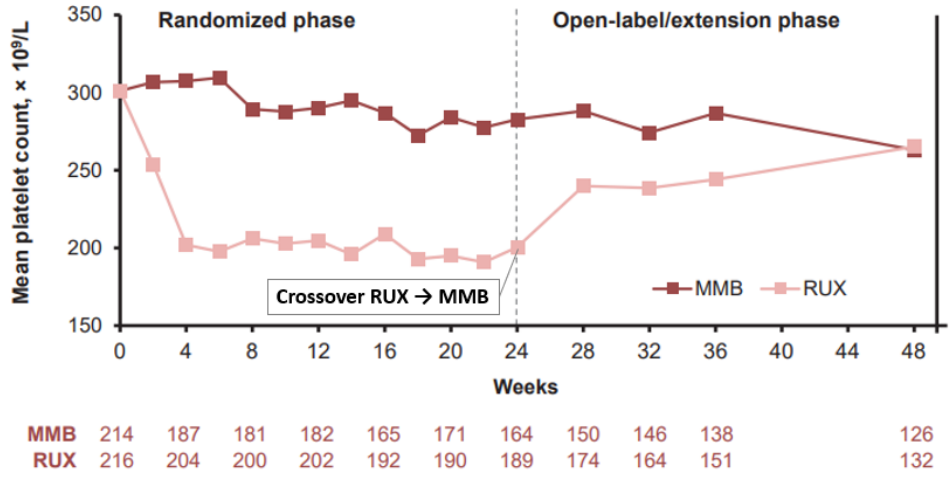


Figure adapted from Mesa et al. 2023
Abbreviations: ITT = intent-to-treat; MMB = momelotinib; PLT = platelet; RUX = ruxolitinib

B.2.7.1.6 Exploratory secondary endpoint: OS

SIMPLIFY-1 demonstrated comparable OS in JAKi-naïve patients treated with momelotinib compared with ruxolitinib.(11, 62) OS was assessed in the safety analysis set at the Week 24 interim analysis. A total of [redacted] patients in the momelotinib group and [redacted] patients in the ruxolitinib group had died by Week 24 [redacted](62) At Week 24 and each subsequent analysis, survival was similar between groups (hazard ratios [HR] for momelotinib versus ruxolitinib;

Table 21):(62)

- Week 24 analysis of initial randomised treatment phase [redacted](62)
- Interim Week 48 OS analysis, at which point all patients in the extension phase who were originally randomised to receive ruxolitinib had been receiving momelotinib for 24 weeks [redacted](62)
- Final analysis up to 5 years from randomisation [redacted](62)

Table 21. OS for the combined randomised and extended treatment phases in SIMPLIFY-1(62)

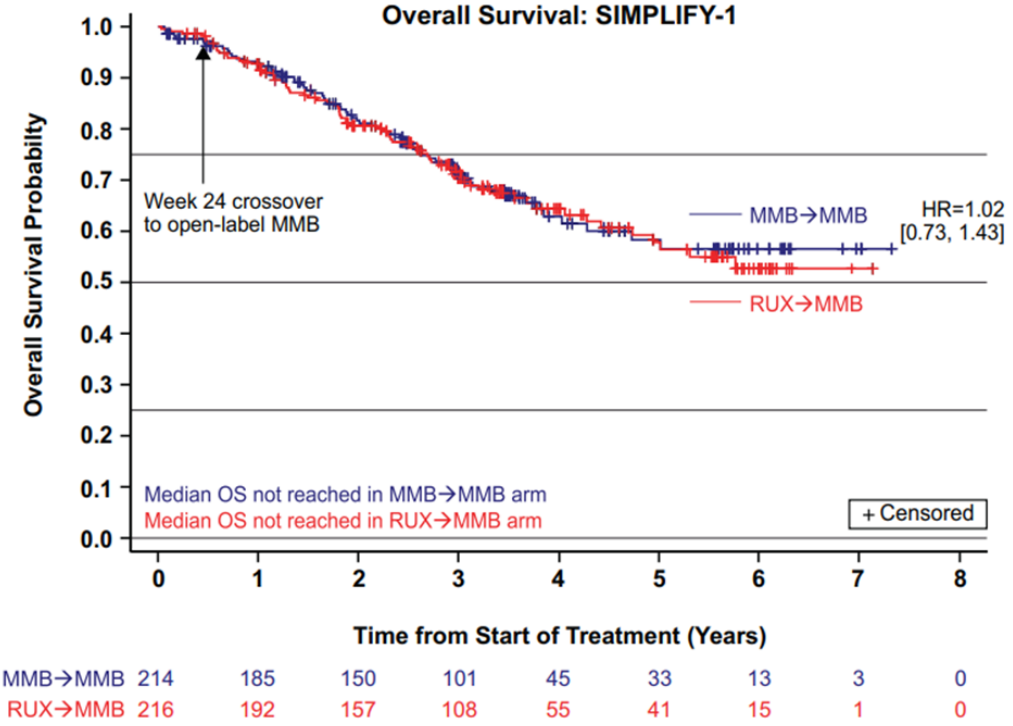
	Week 24 interim analysis		Week 48 interim analysis		Final analysis	
	Momelotinib (n=214)	Ruxolitinib (n=216)	Momelotinib (n=214)	Ruxolitinib (n=216)	Momelotinib (n=214)	Ruxolitinib (n=216)
Patients with event						
Death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimate of OS (months)						
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-rank test p-value	[redacted]		[redacted]		[redacted]	
Stratified HR	[redacted]		[redacted]		[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; NR = not reached; OS = overall survival

A long-term post-hoc analysis compared OS in ITT patients randomised to momelotinib versus patients randomised to ruxolitinib who switched to momelotinib after Week 24.(11) Median follow-up was 3.43 years in the momelotinib group, during which 66 (30.8%) patients died, and 3.47 years in patients randomised to ruxolitinib who switched to momelotinib, during which 73 (33.8%) patients died. Median OS was not reached in either treatment arm. At this point when all patients

had been receiving momelotinib since Week 24, survival was similar between treatment groups (HR: 1.02; 95% CI: 0.73, 1.43; Figure 16).(11) However, these findings demonstrate that durable survival was observed on extended treatment with momelotinib, regardless of starting therapy.(11)

Figure 16. OS from baseline through open-label phase (SIMPLIFY-1; ITT)(11)



Abbreviations: HR = hazard ratio; ITT = intent-to-treat; MMB = momelotinib; OS = overall survival; RUX = ruxolitinib

The 2-year OS rate was also similar between groups (81.6% for patients with momelotinib and 80.6% for patients with ruxolitinib then momelotinib; Table 22).(11)

Table 22. OS rates at 2, 4 and 6 years (SIMPLIFY-1; ITT)(11)

Study treatment	OS rate		
	2-year	4-year	6-year
Momelotinib	81.6%	62.9%	56.5%
Ruxolitinib	80.6%	64.4%	52.7%

Abbreviations: ITT = intent-to-treat; OS = overall survival

B.2.7.1.7 Exploratory endpoints: Health-related quality of life

SIMPLIFY-1 included a range of MF-specific patient-reported outcome (PRO) endpoints to capture the effects of treatment on clinically relevant symptoms and additional endpoints using both generic and MF-specific PRO tools to assess momelotinib's impact on patient HRQoL. Momelotinib demonstrated a comparable

benefit to ruxolitinib at Week 24 across all the PRO tools used. For more details of each assessment tool outcomes, see below.

As described in Section B.2.7.1.2, there was comparable benefit with momelotinib and ruxolitinib for individual symptoms at baseline and Week 24 as measured by MPN-SAF score.(62)

SF-36: The Short Form (SF)-36 v2 was used to assess patient's health status across 8 domains; physical functioning, role physical, bodily pain, general health, vitality, social function, role-emotional, and mental health.(62) Two summary scores (physical and mental component) characterise a patient's physical and mental health state and are presented in

Table 23.(62)

In SIMPLIFY-1, median percent (Q1 to Q3) improvement from baseline at Week 24 for the physical component summary [redacted]) in the momelotinib group compared with [redacted] in the ruxolitinib group indicating improvement in HRQoL in each group. The difference between treatment groups was not statistically significant [redacted].(62) The median percentage (Q1 to Q3) improvement from baseline to Week 24 in the mental component summary was [redacted]in the momelotinib group and [redacted] in the ruxolitinib group indicating improvement in HRQoL in each group.(62) The difference between treatment groups was not statistically significant [redacted].(62)

Table 23. SF-36 physical and mental components in SIMPLIFY-1 (ITT population)(62)

	Physical component summary		Mental component summary	
	Momelotinib (n=215)	**Ruxolitinib (n=217)**	**Momelotinib (n=215)**	**Ruxolitinib (n=217)**
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24				
Median (Q1, Q2)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
Percentage change from baseline at Week 24				
Median (Q1, Q2)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; SF-36 = Short Form 36-item

EQ-5D VAS: The median (Q1 to Q3) percentage change in EQ-5D VAS score at Week 24 was [redacted] in the momelotinib group compared with [redacted] in the ruxolitinib group [redacted] Table 24).(62) The difference was not statistically significant.

Table 24. EQ-5D VAS in SIMPLIFY-1 (ITT population)(62)

	Momelotinib (n=215)	**Ruxolitinib (n=217)**
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; EQ-5D = EuroQol 5 dimension; SD = standard deviation; VAS = visual analogue scale

PGIC: The PGIC is a single question to assess patient's impression of change in MF symptoms since the start of study treatment.(62) PGIC includes 7 categories ranging from "very much improved" to "very much worse".(62) Improvements in symptoms were reported by the majority of patients in both the momelotinib and ruxolitinib group [redacted].(62) Worsening of symptoms were reported by [redacted] of patients in the momelotinib group and [redacted] of patients in the ruxolitinib group (Table 25).(62) No differences between treatment groups were statistically significant.

Table 25. PGIC during the double-blind phase in SIMPLIFY-1 (ITT)

	Momelotinib	Ruxolitinib	Proportion difference (95% CI)
Any timepoint in double-blind phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]
Week 24 at double-blind phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PGIC = Patients' Global Impression of Change

During the open-label stage, improvement in symptoms was reported by [redacted] of patients who remained on momelotinib, and [redacted] of patients who switched from ruxolitinib to momelotinib.(62) Worsening of symptoms was reported by [redacted] of patients who remained on momelotinib, and [redacted] of patients who switched from ruxolitinib to momelotinib.(62)

HRQoL utility analysis: An analysis was conducted to investigate utility values for use in the economic modelling of momelotinib. Data from PROs and individual HRQoL questionnaires were merged to create a dataset containing treatment received, EQ-5D-5L UK utilities, EQ-5D VAS and transfusion status. Regression models were fitted to estimate utility values, accounting for repeated measures at the patient level. Analyses were conducted on pooled data sets as well as individual trials to assess the impact of variables (including treatment arm) on utility.(73)

In SIMPLIFY-1, no evidence of a treatment effect on utility was observed, thus there was no clear case for a differential effect of either treatment (either positive or negative).(73) The results of the analysis are presented in Table 26.(73)

Table 26. LMM Regression of EQ-5D-5L utility on key clinical measures and treatment arm (SIMPLIFY-1)(73)

	LMM regression model						
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Reference group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]			[redacted]	[redacted]		[redacted]
TD	[redacted]			[redacted]	[redacted]		[redacted]
TSS Change		[redacted]		[redacted]		[redacted]	[redacted]
100cm Normalised Spleen Volume Change			[redacted]		[redacted]	[redacted]	[redacted]
Ruxolitinib (compared with momelotinib)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Likelihood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Akaike Information Criterion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Absolute Error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Root Mean Square Error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*p<0.05; **p<0.01; ***p<0.001
Columns 1 to 3 present simple models of individual measures, columns 4 to 6 include 2/3 of the measures, and column 7 includes all measures. All models include an arm variable.
Abbreviations: EQ-5D = EuroQol 5 dimension; LMM = linear mixed models; TD = transfusion-dependent; TSS = total symptom score

B.2.7.2 SIMPLIFY-2 (NCT02101268)

B.2.7.2.1 Primary endpoint: spleen response rate

The primary endpoint in SIMPLIFY-2, spleen response rate, was defined as the percentage of patients with a ≥35% reduction in spleen volume from baseline at Week 24, as assessed by magnetic resonance imaging or computed tomography scans.(23)

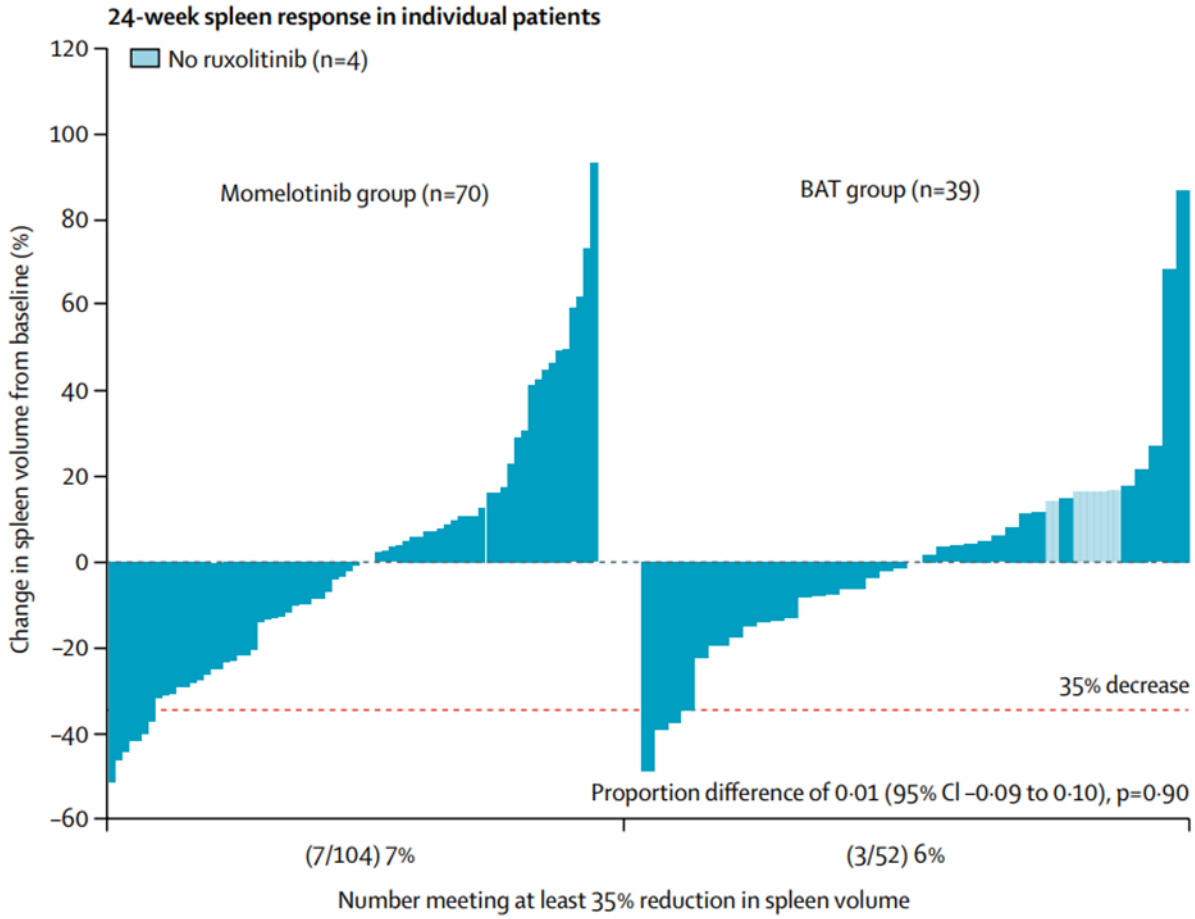
The proportion of patients who achieved a response at Week 24 in the momelotinib group (6.7%) was similar to the proportion of patients in the BAT group (5.8%).(63) The proportion difference between treatment groups was 0.01 (95% CI: -0.09, 0.10; Figure 17).(63) Thus, the primary endpoint was not met, with momelotinib not deemed superior to BAT (p<0.90; Table 27).(63)

Table 27. Analysis of spleen response rate (≥35% reduction in spleen volume) at Week 24 (SIMPLIFY-2; ITT)(63)

	Momelotinib (n=104)	**BAT (n=52)**	**p-value**
Responder, n (%)	7 (6.7%)	3 (5.8%)	
95% CI	0.0275, 0.1338	0.0121, 0.1595	-
Proportion difference: stratified CMH method (95% CI)	0.01 (-0.09, 0.10)		0.90

Abbreviations: BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat

Figure 17. Change in spleen volume and spleen response rate (≥35%) at Week 24 (SIMPLIFY-2; ITT)(23)



Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat

A total of 67.3% in the momelotinib group (70 of 104) and 75.0% in the BAT group (39 of 52) had spleen volume measurements at both baseline and Week 24. The mean percent change in spleen volume at Week 24 was [redacted] in the momelotinib group and [redacted] in the BAT group. However, the observed difference in the mean percent change between the two groups was not statistically significant.(63)

The failure to achieve the primary endpoint of superiority in spleen response rate in this study may have been influenced by some inadvertent study design features:(63)

- The BAT arm was largely composed of ruxolitinib-treated patients (88.5%). The SIMPLIFY-2 statistical analysis plan was designed with a BAT treatment effect based on the BAT arm of the COMFORT-2 study (as described in Section B.2.5.2.1), in which no JAKi were included as part of BAT and no BAT patients achieved a spleen response. Notably, all BAT

patients achieving a response in SIMPLIFY-2 were treated with ruxolitinib.(63)

- Spleen volume response rates in both arms were lower than expected at the time of study design, which can be explained by the lack of a ruxolitinib washout period prior to randomisation. The absence of a washout period likely resulted in continued saturation of JAK-STAT signalling pathways, preventing further spleen volume reduction. Notably, this lack of spleen volume response was not observed in other trials of JAKi, in which a washout period was implemented prior to randomisation (i.e., MOMENTUM, JAKARTA-2).(64, 74)

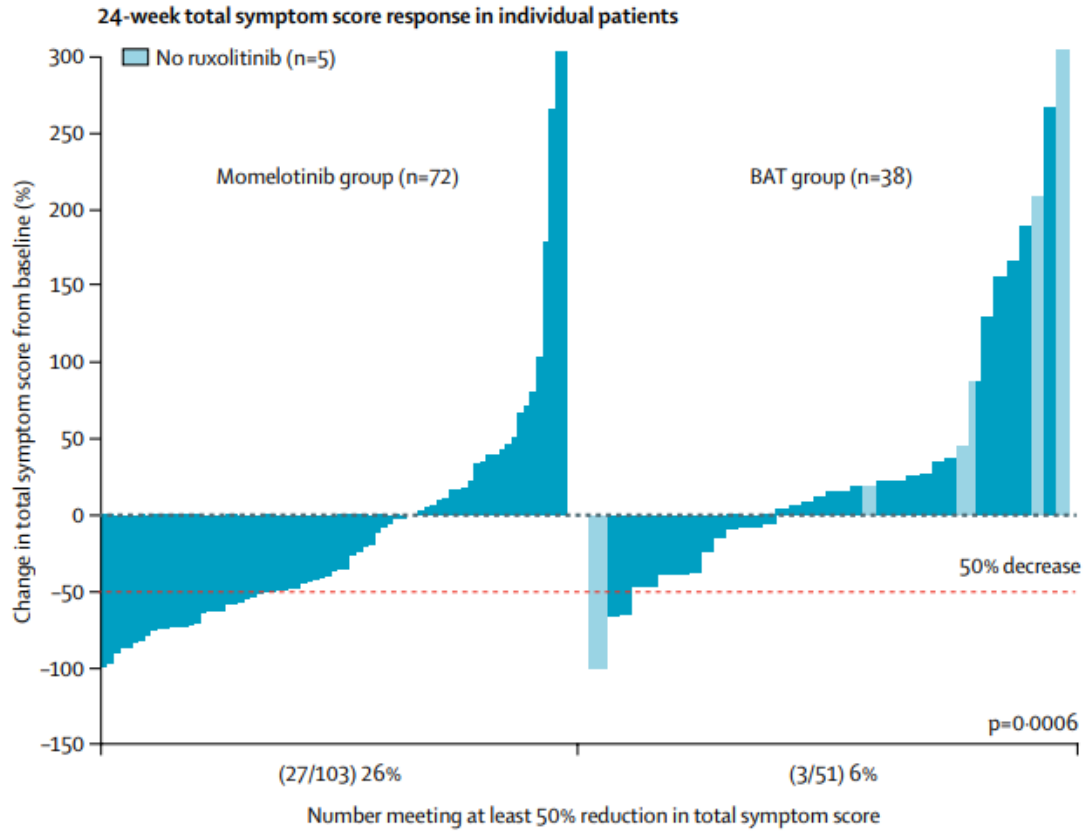
Clinical experts at the advisory board in November 2022 agreed that the failure to meet the primary endpoint was due to study design choices and lack of washout period.(32)

As superiority was not achieved in the primary endpoint of spleen response rate, only nominal significance was reported for subsequent endpoints in the statistical hierarchy.(23)

B.2.7.2.2 Secondary endpoint: TSS response rate

In the secondary endpoint of TSS response rate (MPN-SAF), more patients had a reduction of ≥50% in TSS from baseline at Week 24 in the momelotinib group (26.2%) than the BAT group (5.9%; Figure 18). The proportional difference between treatment groups was [redacted] nominal p<0.001).(23, 63)

Figure 18. Change in TSS from baseline to Week 24 and TSS response at Week 24 (SIMPLIFY-2; ITT)(23)



Abbreviations: BAT = best available therapy; ITT = intent-to-treat; TSS = total symptom score

On assessment of the cumulative distribution function of absolute change in MPN-SAF TSS from baseline to Week 24 in symptomatic (TSS ≥10) patients from SIMPLIFY-2, momelotinib showed a greater proportion of patients in the improvement levels vs BAT (Figure 19).(48)

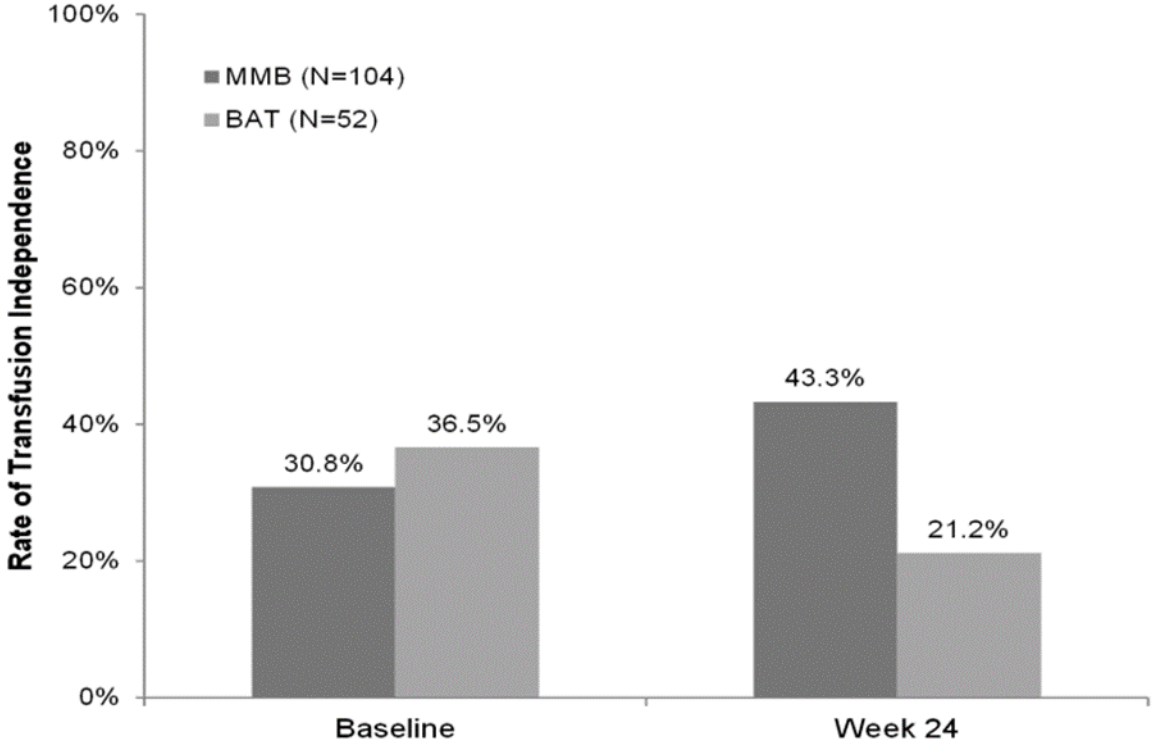
Figure 19. Cumulative distribution function of absolute change in MPN-SAF TSS from baseline to Week 24 in the SIMPLIFY-2 symptomatic population(63)

Abbreviations: MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; TSS = total symptom score

B.2.7.2.3 Secondary endpoints: transfusions and TI rate

The rate of RBC transfusions was lower in the momelotinib group (median 0.5 units/month) than the BAT group (median 1.2 units/month) through Week 24 (nominal p=0.39).(23) A higher proportion of patients in the momelotinib group (43.3%) versus the BAT group (21.2%) were TI at Week 24 (nominal p=0.0012; Figure 20).(63) Overall, the proportion of patients who were TI increased by 12.5% in the momelotinib group and decreased by 15.3% in the BAT group from baseline to Week 24.(63)

Figure 20. TI at baseline and Week 24 (SIMPLIFY-2; ITT)(63)



Abbreviations: BAT = best available therapy; ITT = intent-to-treat; MMB = momelotinib

B.2.7.2.4 Exploratory endpoint: changes in Hb levels over time

On analysis of mean change in Hb levels from baseline to Week 24, levels increased by [redacted] in the momelotinib group and decreased by [redacted] in the BAT group (Figure 21).(63) This represented statistically significant least square mean differences between groups of:(63)

- Mean difference: [redacted]g/dL [redacted]
- Difference in mean percent change: [redacted]

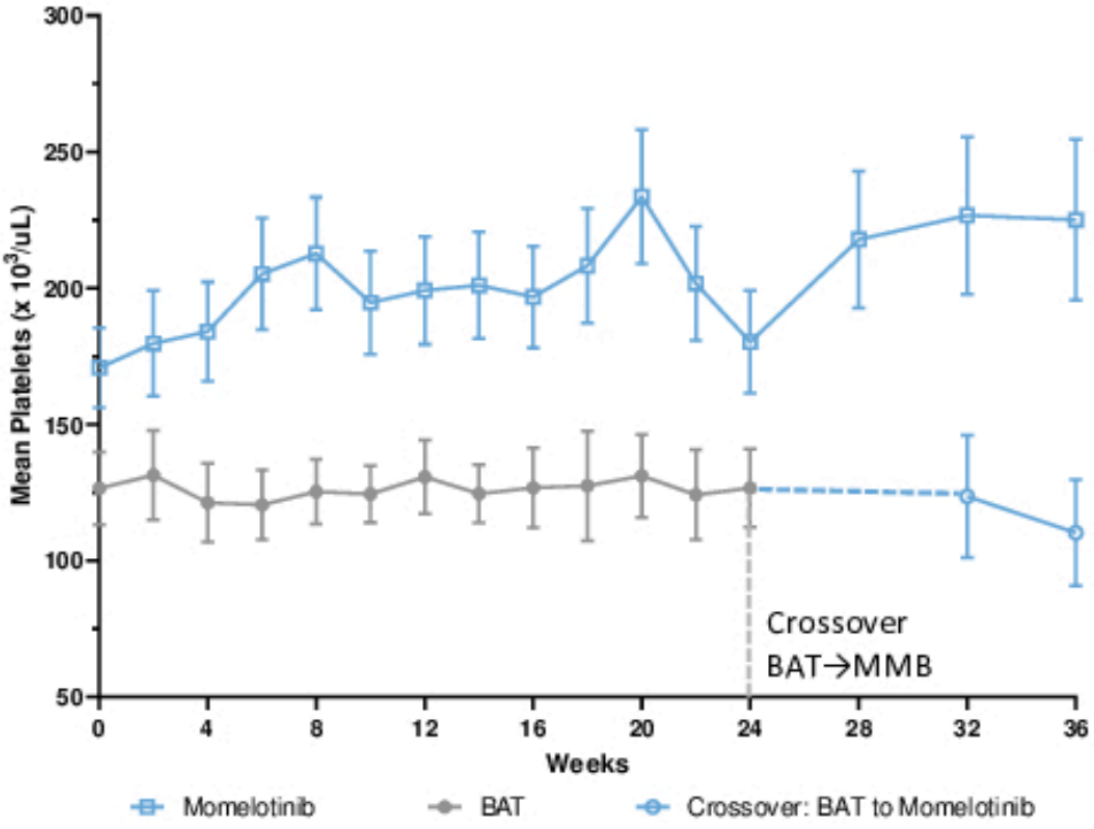
Figure 21. Mean (SE) Hb levels over time in the randomised treatment and extension phase (SIMPLIFY-2: ITT)(63)

Abbreviations: BAT = best available therapy; Hgb = haemoglobin; ITT = intent-to-treat; MMB = momelotinib; SE = standard error

B.2.7.2.5 Exploratory endpoint: changes in platelet levels over time

In a prespecified exploratory endpoint, mean platelet levels improved over time from baseline with momelotinib, highlighting its low myelosuppressive potential.(63, 75) Further, higher platelet levels were observed with momelotinib vs BAT throughout the randomised treatment phase (Figure 22).(63, 75)

Figure 22. Mean (SE) platelet levels over time in the randomised treatment and extension phase (SIMPLIFY-2; ITT)(75)



Abbreviations: BAT = best available therapy; ITT = intent-to-treat; MMB = momelotinib; SE = standard error

B.2.7.2.6 Exploratory endpoint: OS

SIMPLIFY-2 demonstrated favourable OS in current or prior ruxolitinib-treated patients receiving momelotinib versus BAT.(11, 63) OS was assessed in the safety analysis set at the Week 24 interim analysis. A total of [redacted]) patients in the momelotinib group and [redacted]) of patients in the BAT group had died by Week 24 (median OS [redacted] in the momelotinib group; [redacted] in the BAT group).(63) A trend towards improved survival was observed in this initial randomised treatment phase [redacted]).(63) After Week 24, patients originally randomised to receive BAT could switch to momelotinib in the extension phase (Section B.2.4.1.2). Another interim OS analysis was conducted at Week 48, at which point all patients in the extension phase who were originally randomised to receive BAT had been receiving momelotinib for 24 weeks.(63) The trend towards improved survival was maintained for patients randomised to momelotinib vs BAT [redacted](63) At the final analysis (up

to 5 years from randomisation),

[redacted]

[redacted].(63)

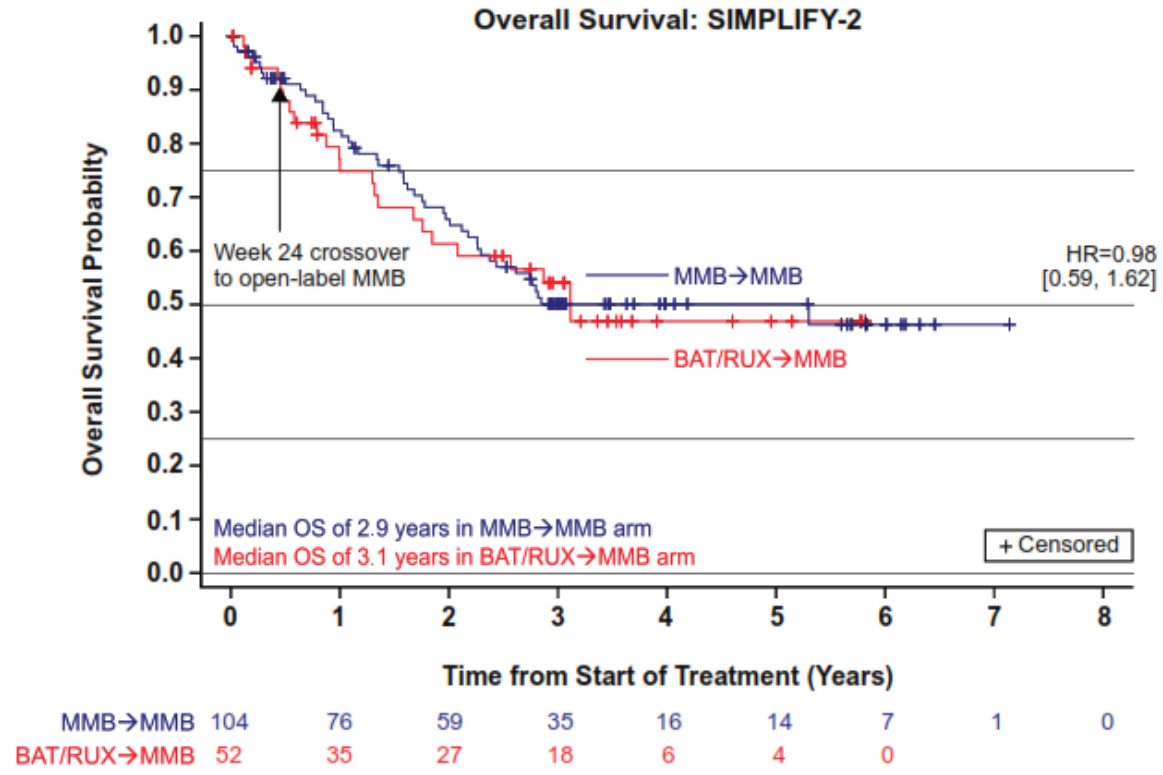
Table 28. OS for the combined randomised and extended treatment phases in SIMPLIFY-2(63)

	Week 24 interim analysis		Week 48 interim analysis		Final analysis	
	Momelotinib (n=104)	BAT (n=52)	Momelotinib (n=104)	BAT (n=52)	Momelotinib (n=104)	BAT (n=52)
Patients with event						
Death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimate of OS (months)						
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stratified log-rank test p-value	[redacted]		[redacted]		[redacted]	
Stratified HR	[redacted]		[redacted]		[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival

A long-term post-hoc analysis compared OS in ITT patients randomised to momelotinib versus patients randomised to BAT who switched to momelotinib after Week 24. Median follow-up was 3.07 years in the momelotinib arm, during which 47 (45.2%) patients died, and 3.22 years in patients randomised to BAT who switched to momelotinib, during which 23 (44.2%) patients died.(11) Median OS in the momelotinib arm was 2.9 years (95% CI: 2.3, not estimable [NE]) and 3.1 years (95% CI: 1.8, NE) in patients randomised to BAT who switched to momelotinib after Week 24. No significant differences between groups were observed (HR: 0.98; 95% CI: 0.59, 1.62; Figure 23).(11) However, these findings demonstrate that durable survival was observed on extended treatment with momelotinib, regardless of starting therapy.(11)

Figure 23. OS from baseline through extension phase (SIMPLIFY-2; ITT)(11)



Abbreviations: BAT = best available therapy; HR = hazard ratio; ITT = intent-to-treat; MMB = momelotinib; OS = overall survival; RUX = ruxolitinib

The 2-year OS rate was also similar between groups (65.8% for patients with momelotinib and 61.2% for patients with BAT then momelotinib).(11)

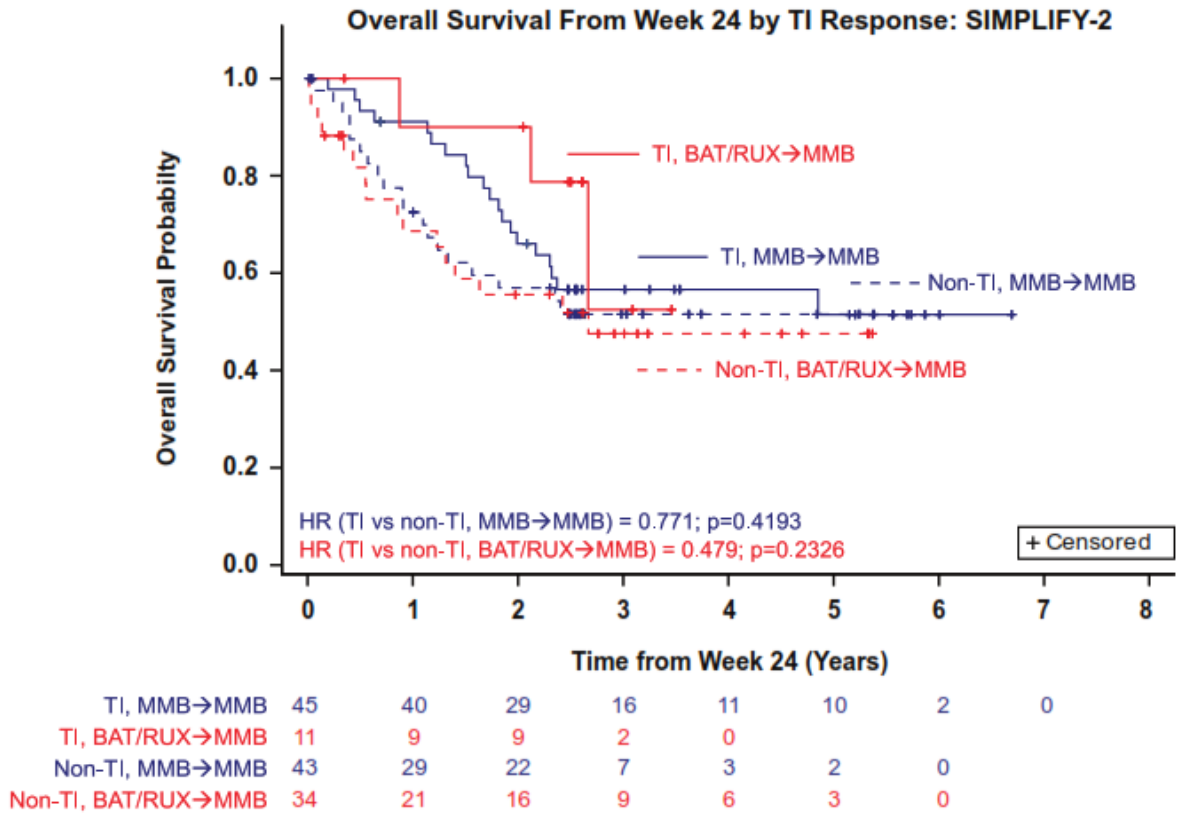
In a crossover-adjusted OS analysis (methods described in Section B.2.7.1.6), The RPSFT-adjusted HR was [redacted] indicating that the risk of death was lower in patients treated with momelotinib as those treated with BAT [redacted].(76)

Figure 24. OS adjusted for treatment switching (SIMPLIFY-2)(76)

Abbreviations: BAT = best available therapy; HR = hazard ratio; MMB = momelotinib; OS = overall survival

In a post-hoc subgroup analysis, TI at Week 24 was associated with a non-significant trend toward longer survival in patients randomised to receive momelotinib by univariate analysis (HR: 0.771; p=0.4193; Figure 25).(11) Patients with TI response at Week 24 (n=45) had a 2-year OS rate of 66.1% compared with 57.0% for patients without TI response (n=43).(11) See Section B.2.8 for more information on subgroup analyses.

Figure 25. OS from baseline by TI response through extension phase (SIMPLIFY-2; ITT)(11)



Abbreviations: BAT = best available therapy; HR = hazard ratio; ITT = intent-to-treat; MMB = momelotinib; OS = overall survival; RUX = ruxolitinib; TI = transfusion-independence

TI was also a statistically significant baseline predictor of OS in multivariate regression analysis of SIMPLIFY-2 (HR: 0.226 [TI vs not]; p=0.0005).(11) TI (p=0.0002) and higher Hb levels (p=0.0003) were also significant predictors of greater survival on univariate analysis.(11)

Time varying regression results also demonstrate that patients who were not TI had an increased risk of death at all timepoints [redacted](77) Please see Appendix M.1.2.3 for more information.

These results are also evident in previously published studies in MF patients. In a targeted literature review, GSK identified 22 studies that provide data on survival and transfusion status.(78) Feasibility assessment concluded that a meta-analysis was not feasible due to heterogeneity in endpoint definitions across studies. However, investigation of multivariate relationships based on reported HRs or HRs derived from digitised Kaplan-Meier (KM) curves shows that TD was associated with higher

mortality in the large majority of studies (Figure 26).(78) For most studies, the cited HR relates to the mortality risk associated with being TD at a particular timepoint (typically baseline). See Appendix M1.5 for more information.

Figure 26. Multivariate analysis of survival and TD(78)

Abbreviations: HR = hazard ratio; RBC = red blood cell; TD = transfusion-dependence

B.2.7.2.7 Exploratory endpoint: health-related quality of life

As discussed in Section B.2.7.2.2, more patients had a reduction of ≥50% in TSS from baseline at Week 24 in the momelotinib group (26.2%) than the BAT group (5.9%).(23, 63) There was a numerically larger median percentage change from baseline to Week 24 in the momelotinib compared with BAT for physical function component summary and mental health component summary.(63) Furthermore, as measured by the PGIC, a higher proportion of patients ( ) reported an improvement in symptoms in the momelotinib group compared with the BAT group ( ).(63)

SF-36: In SIMPLIFY-2, the median maximum percentage change from baseline in the physical functioning component summary was in the momelotinib group compared with in the BAT group.(63) Therefore, there was a numerical improvement in physical component in the momelotinib group compared with the

BAT group, however, this difference was not statistically significant using the stratified Wilcoxon rank sum test ([redacted]).(63)

The median maximum percentage change from baseline in the mental health component was [redacted] in the momelotinib group and [redacted] in the BAT group, this difference was not statistically significant ([redacted]), therefore there was no difference between treatment groups.(63)

The results of SF-36 summary component scores in SIMPLIFY-2 are presented in Table 29. A nominally significant improvement in physical component summary in change from baseline and percentage change from baseline to Week 24.

Table 29. SF-36 physical and mental components in SIMPLIFY-2 (ITT population)(63)

	Physical component summary		**Mental component summary**	
	Momelotinib (n=104)	**BAT (n=52)**	**Momelotinib (n=104)**	**BAT (n=52)**
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24				
Median (Q1, Q2)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
Percentage change from baseline at Week 24				
Median (Q1, Q2)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation

EQ-5D: The EQ-5D was used to assess a patient's health status across five dimensions; mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.(63) No significant differences were observed in absolute or percentage change from baseline to Week 24 between treatment groups (Table 30).(63)

Table 30. EQ-5D VAS in SIMPLIFY-2 (ITT population)(63)

	Momelotinib (n=104)	BAT (n=52)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
p-value	[redacted]	
Percentage change from baseline at Week 24		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation

PGIC: In the randomised treatment phase, a higher proportion of patients reported an improvement in symptoms in the momelotinib group ([redacted]) compared with the BAT group ([redacted]).(63) This difference was nominally statistically significant ([redacted]).(63) A lower proportion of patients reported worsening of symptoms in the momelotinib group ([redacted]) compared with the BAT group ([redacted]).(63) This difference was nominally statistically significant ([redacted]) (Table 31).

Table 31. PGIC during the double-blind phase in SIMPLIFY-2 (ITT)(63)

	Momelotinib (n=104)	BAT (n=52)	Proportion difference (95% CI)
Any timepoint in randomised treatment phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]
Week 24 at double-blind phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat

During the evaluation phase, an improvement in symptoms was reported by [redacted] of patients who continued with momelotinib and by [redacted] of patients who switched from BAT to momelotinib.(63) These results demonstrate more than half of patients who entered the evaluation phase continued to report improvement in MF symptoms.(63) Worsening of symptoms was reported by [redacted] of patients who continued on momelotinib and [redacted] of patients who switched from BAT to momelotinib.(63)

HRQoL utility analysis: An analysis was conducted to investigate utility values for use in the economic modelling of momelotinib. Data from PROs and individual HRQoL questionnaires were merged to create a dataset containing of, treatment received, EQ-5D-5L UK utilities, EQ-5D VAS and transfusion status. Regression models were fitted to estimate utility values, accounting for repeated measures at the patient level. Analyses were conducted on pooled data sets as well as individual trials to assess the impact of variables (including treatment arm) on utility.(73)

In SIMPLIFY-2, BAT had a lower utility with a meaningful decrement, however statistical significance was not reached, which may be due to the limited sample size. There was evidence of a significant effect of transfusion status on utility in all models. The results of the HRQoL utility analysis are presented in Table 32.(73)

Table 32. LMM regression of EQ-5D-5L utility on key clinical measures and treatment arm (SIMPLIFY-2)(73)

	LMM regression model						
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Reference group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]			[redacted]	[redacted]		[redacted]
TD	[redacted]			[redacted]	[redacted]		[redacted]
TSS Change		[redacted]		[redacted]		[redacted]	[redacted]
100cm Normalised Spleen Volume Change			[redacted]		[redacted]	[redacted]	[redacted]
Best Available Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Likelihood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Akaike Information Criterion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Absolute Error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Root Mean Square Error	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*p<0.05; **p<0.01; ***p<0.001
Columns 1 to 3 present simple models of individual measures, columns 4 to 6 include 2/3 of the measures, and column 7 includes all measures. All models include an arm variable.
Abbreviations: EQ-5D = EuroQol 5-Dimensions; LMM = linear mixed models; TD = transfusion-dependent; TSS = total symptom score

B.2.7.3 MOMENTUM (NCT04173494)

B.2.7.3.1 Coprimary endpoint: TSS response rate

The coprimary endpoint in MOMENTUM, TSS response rate, was defined as the percentage of patients with a ≥50% reduction in MF-SAF TSS from baseline at Week 24.(64) MF-SAF is a validated PRO measure which was considered appropriate to replace the MPN-SAF used in SIMPLIFY-1 and SIMPLIFY-2.(79)

The proportion of patients who achieved a response at Week 24 in the momelotinib group (24.6%) was higher than the proportion of patients in the danazol group (9.2%). The proportion difference between treatment groups was [redacted]. Thus, the primary endpoint was met, demonstrating the superiority of momelotinib to danazol (p=0.0095; Table 33 and Figure 27).(64, 67)

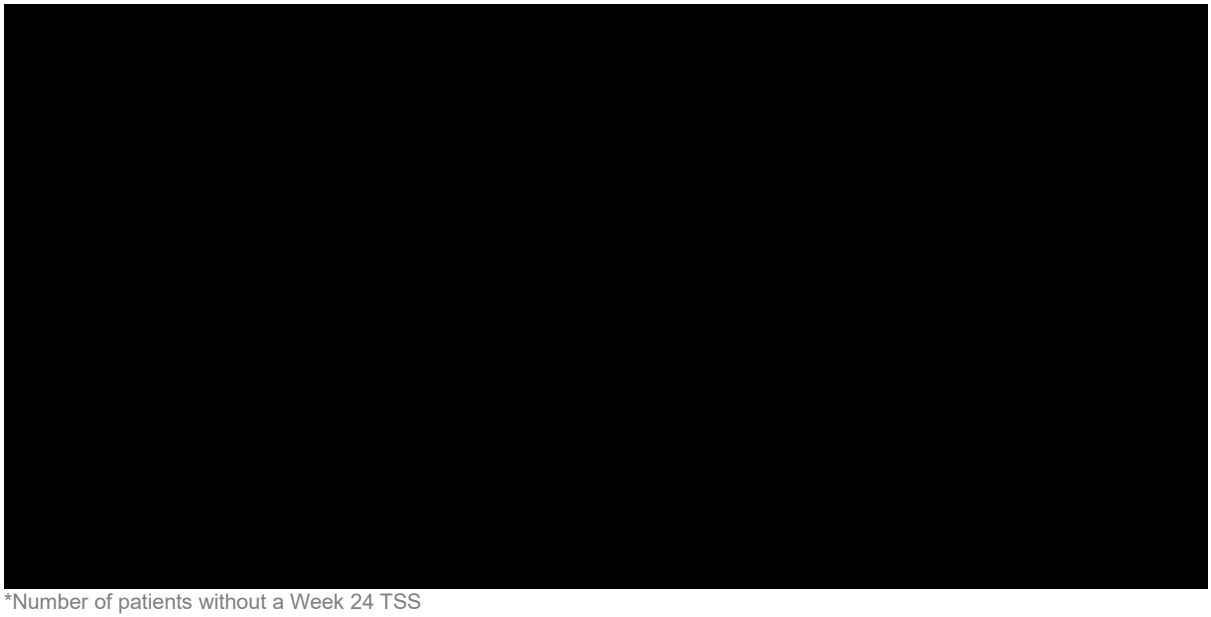
All sensitivity and subgroup analyses of MF-SAF TSS response rate were consistent with the overall results in the ITT population, and results were robust when analysed as a continuous variable using MMRM, demonstrating the appropriateness of this measure to evaluate symptom response in MF.(67)

Table 33. Analysis of MF-SAF TSS response rate at Week 24 (MOMENTUM; ITT) (64, 67)

	Momelotinib (n=130)	**Danazol (n=65)**	**p-value**
Responder, n (%)	32 (24.6)	6 (9.2)	-
Response rate 95% CI	17.5, 32.9	3.5, 19.0	-
Treatment difference: stratified CMH method (95% CI)	15.67% (5.54, 25.81)		0.0095

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; MF-SAF = Myelofibrosis Symptom Assessment Form; TSS = total symptom score

Figure 27. Percent change from baseline in MF-SAF TSS at Week 24 for each patient (MOMENTUM; ITT)(67)



*Number of patients without a Week 24 TSS
Abbreviations: DAN = danazol; ITT = intent-to-treat; MF-SAF = Myelofibrosis Symptom Assessment Form; MMB = momelotinib; TSS = total symptom score

B.2.7.3.2 Coprimary endpoint: TI rate

In the coprimary endpoint, a higher proportion of patients in the momelotinib group (30.0%) versus the danazol group (20.0%) were TI at Week 24, with a non-inferiority difference of [redacted]). As momelotinib demonstrated non-inferiority to danazol, a test for superiority was conducted (though not included in the statistical hierarchy), and the treatment difference was [redacted]).(72)

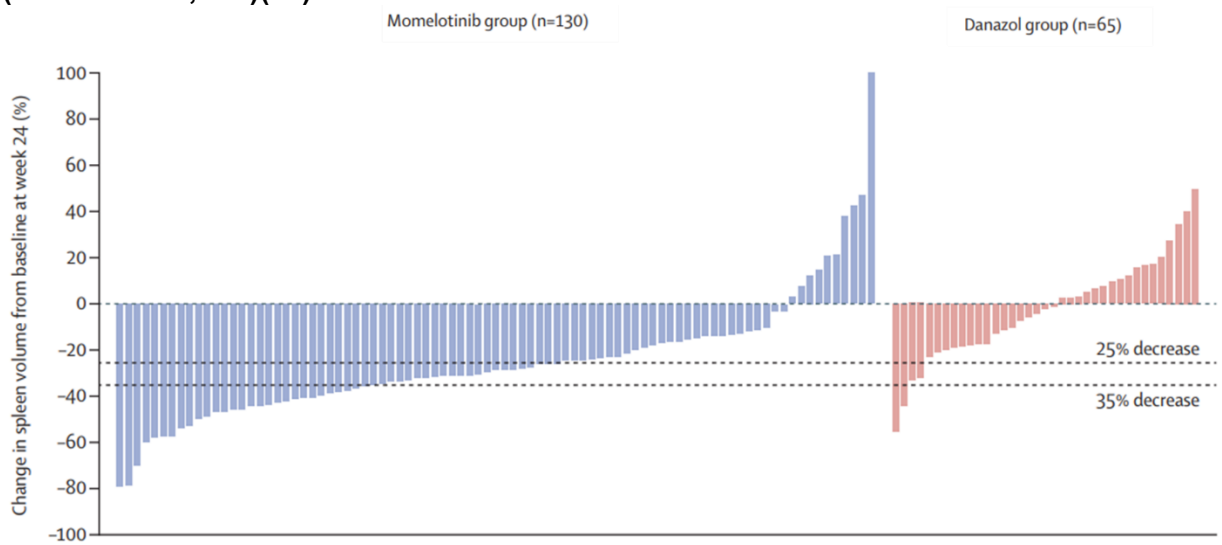
Among evaluable TI patients at Week 48, TI response rates was 57% in the momelotinib group (who continued on momelotinib) and 60% in the danazol group (who crossed over to momelotinib) were responders.(80) At any time during the open-label period by Week 48, TI response rates were 52% in the momelotinib group and 56% in the danazol group (who crossed over to momelotinib).(80) No statistical testing was conducted for the Week 48 analyses.

B.2.7.3.3 Key secondary endpoints: spleen response rate

Momelotinib achieved statistically significant superiority over danazol in the key secondary endpoints of ≥25% and ≥35% spleen response rate at Week 24. The

≥25% response rate in the momelotinib arm was 39.2% versus 6.2% in the danazol group, representing a treatment difference of [redacted] p<0.0001).(64)(72) The ≥35% response rate in the momelotinib arm was 22.3% versus 3.1% in the danazol group, representing a treatment difference of [redacted] p=0.0011; Figure 28).(72)

Figure 28. Percentage change of spleen volume from baseline to Week 24 (MOMENTUM; ITT)(64)



Abbreviations: ITT = intent-to-treat

B.2.7.3.4 Key secondary endpoint: mean TSS change

Statistically significant superiority for momelotinib over danazol was demonstrated for the key secondary endpoint of mean TSS change from baseline at Week 24, indicating better symptomatic improvement with momelotinib vs danazol (−11.5 versus −3.9, respectively; least squares mean difference −6.2; 95% CI: −10.0, −2.4; p=0.0014).(64)(72)

B.2.7.3.5 Exploratory endpoint: changes in Hb levels over time

During the double-blind phase (baseline to Week 24), both momelotinib and danazol caused increases in mean Hb concentration.(64) However, patients in the momelotinib group exhibited a greater increase in Hb that was sustained over time compared with patients who received danazol (Figure 29).(64) For patients who switched from danazol to momelotinib in the open-label phase, Hb levels further increased.(64)

Figure 29. Mean Hb levels over time in MOMENTUM (double-blind and open-label phase)(67)

Abbreviations: BL = baseline; DAN = danazol; Hgb = haemoglobin; MMB = momelotinib

The proportion of patients with increases in Hb from baseline at Week 24 was consistently greater with momelotinib vs danazol in each incremental Hb category during the entire randomised treatment phase (Table 34).(67)

Table 34. Rates of Hb responses at ≥1, ≥1.5 and ≥2 g/dL from baseline during the 24-week randomised treatment phase(67)

Hb response rate	Momelotinib (n=130)	Danazol (n=65)
Increases of ≥1 g/dL, n (%)	[redacted]	[redacted]
Response rate (95% CI)	[redacted]	[redacted]
Treatment difference by stratified CMH (95% CI)	[redacted]	
p-value	[redacted]	
Increases of ≥1.5 g/dL, n (%)	[redacted]	[redacted]
Response rate (95% CI)	[redacted]	[redacted]
Treatment difference by stratified CMH (95% CI)	[redacted]	
p-value	[redacted]	
Increases of ≥2 g/dL, n (%)	[redacted]	[redacted]
Response rate (95% CI)	[redacted]	[redacted]
Treatment difference by stratified CMH (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Hb = haemoglobin

B.2.7.3.6 Exploratory secondary endpoint: changes in platelet levels over time

Analysis of changes in platelet levels over time in MOMENTUM confirmed the low myelosuppressive effect of momelotinib observed in SIMPLIFY-1 and SIMPLIFY-2, with platelet levels maintained through 48 weeks (Figure 30).(67) Mean platelet counts were similar in the momelotinib and danazol groups at baseline, and patients switching from danazol to momelotinib post-Week 24 had similar counts as those randomised to, and continuing, momelotinib.(67)

Figure 30. Mean (SE) platelet levels over time in the randomised treatment and extension phase (MOMENTUM; ITT)(67)

Abbreviations: BL = baseline; DAN = danazol; ITT = intent-to-treat; SE = standard error; MMB = momelotinib

B.2.7.3.7 Exploratory secondary endpoint: OS

Median OS was not reached in either treatment arm at the end of the 24-week double-blind treatment phase; patients treated with momelotinib exhibited a non-significant trend toward improved OS compared with patients in the danazol arm (HR: 0.73; 95% CI: 0.38, 1.41; p=0.35; Figure 31).(64) In the momelotinib group, the median follow-up was 275 days (range: 41 to 476) with 81% of patients in the momelotinib group censored.(64) In the danazol group, the median follow-up was 295 days (range: 26 to 523) with 75% of patients censored.(64) It should be noted that all patients randomised to danazol who entered the open-label treatment phase

([redacted] patients completing 24 weeks) opted to switch to momelotinib, despite the option being available to remain on danazol.(67)

Survival rates at 24-week were nominally higher in the momelotinib group (88%; 95% CI: 81, 93) compared with the danazol group (80%; 95% CI: 68, 88; HR: 0.51; p=0.0719).(64) Based on analysis of cumulative incidence of non-COVID-19 deaths up to Week 24, treating COVID-19 deaths as competing events, OS was significantly improved with momelotinib (HR: 0.33; 95% CI: 0.14, 0.76; p=0.010).(64)

Figure 31. OS from baseline through the open-label period (MOMENTUM: ITT)(67)

Abbreviations: CI = confidence interval; DAN = danazol; HR = hazard ratio; ITT = intent-to-treat; MMB =momelotinib; NC = not computable; OS = overall survival

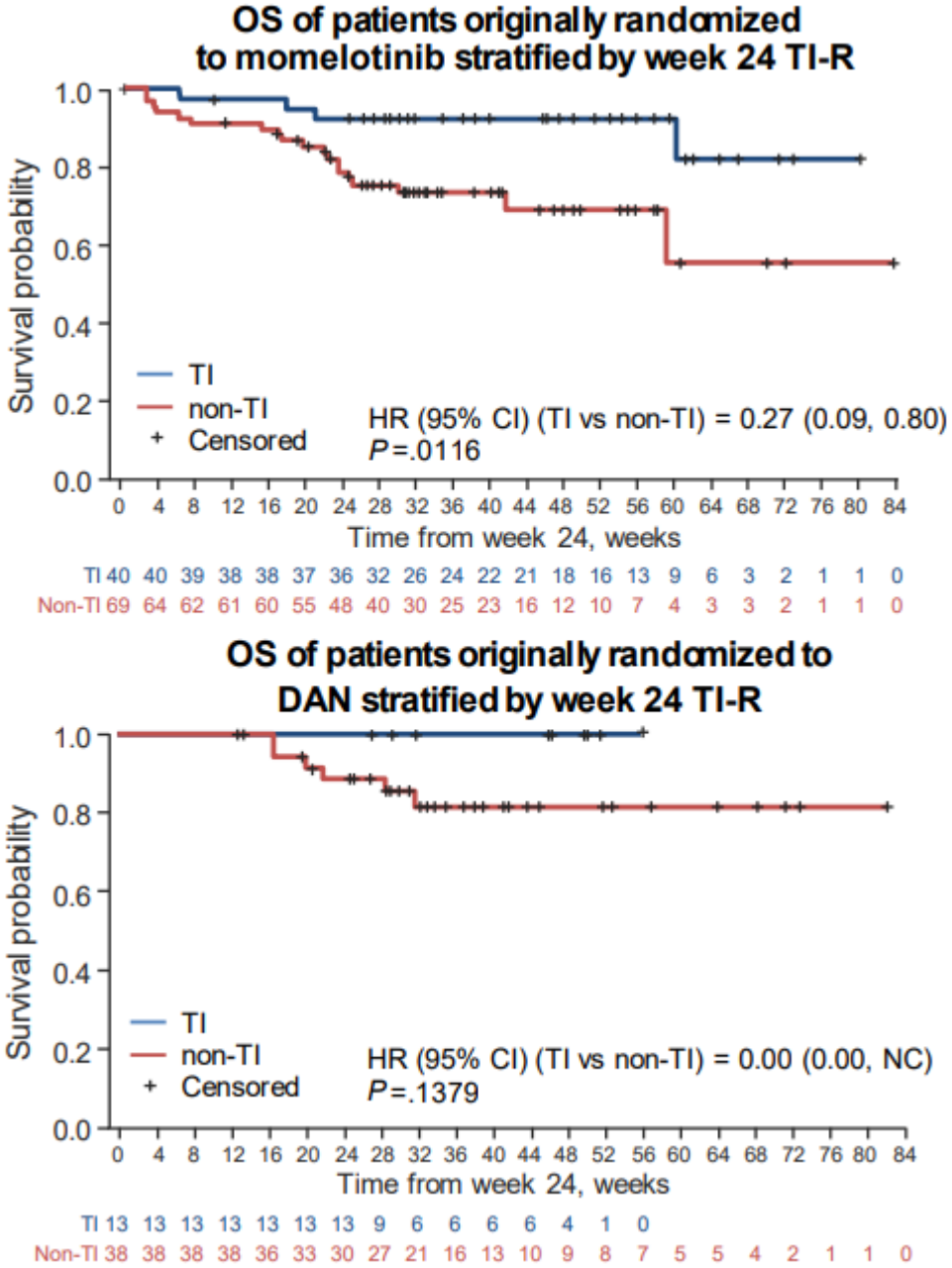
In a crossover-adjusted OS analysis (methods described in Section B.2.7.1.6), The RPSFT-adjusted HR was [redacted] indicating that the risk of death was lower in patients treated with momelotinib as those treated with danazol ([redacted]; Figure 32).(76)

Figure 32. OS adjusted for treatment switching (MOMENTUM)(76)

Abbreviations: DAN = danazol; HR = hazard ratio; MMB = momelotinib; OS = overall survival

In a post-hoc subgroup analysis, TI at Week 24 was associated with significantly longer OS in patients randomised to receive momelotinib (; Figure 33).(81)

Figure 33. OS from baseline by TI response through open-label phase (MOMENTUM; ITT)(81)



Abbreviations: DAN = danazol; HR = hazard ratio; ITT = intent-to-treat; NC = not calculable; OS = overall survival; TI = transfusion-independence; TI-R = transfusion-independence response; TR = transfusion-requiring

B.2.7.3.8 Exploratory endpoint: Health-related quality of life

As discussed in B.2.7.3.1, the primary endpoint of TSS was met, demonstrating superiority of momelotinib to danazol for treatment of MF symptoms. Momelotinib also improved patient-reported fatigue from baseline to Week 24 as measured by mean EORTC QLQ-C30 score. In addition, the mean change from baseline at Week

24 for EQ-5D VAS was greater in the momelotinib group compared with the danazol group.

Patient-reported fatigue: Patient-reported fatigue numerically improved in both treatment groups as demonstrated by reductions from baseline in mean disease-related fatigue and mean cancer-related fatigue (Table 35).(67) There was a numerically greater reduction in MF-SAF mean fatigue score from baseline at Week 24 in the momelotinib group [redacted]) compared with the danazol group [redacted]).(67) The least squares mean difference was [redacted] indicating that any differences were not significant.(67) There was a significantly greater reduction in mean EORTC QLQ-C30 score in the momelotinib group [redacted]) compared with the danazol group [redacted]). The least squares mean difference [redacted]).(67)

Descriptive analyses of proportion of responders based on meaningful change threshold were performed for MSFAF fatigue (defined as ≥3) and EORTC QLQ-C30 (defined as >9).(67) The proportion of responders was numerically greater in the momelotinib group compared with the danazol group for both MF-SAF fatigue ([redacted]) and EORTC QLQ-C30 ([redacted]).(67)

Table 35. Change from baseline at Week 24 in disease-related fatigue and cancer-related fatigue (ITT)(67)

Change from baseline at Week 24	Momelotinib (n=130)	Danazol (n=65)
Disease-related fatigue by MF-SAF		
Baseline MF-SAF fatigue item score, mean (SD)	[redacted]	[redacted]
Change from baseline at Week 24		
Least squares mean (SE)[a]	[redacted]	[redacted]
Least squares mean difference (SE)[a]	[redacted]	
95% CI[a]	[redacted]	
p-value[b]	[redacted]	
Cancer-related fatigue by EORTC QLQ-C30		
Baseline EORTC QLQ-C30	[redacted]	[redacted]
Change from baseline at Week 24		
Least squares mean (SE)[a]	[redacted]	[redacted]
Least squares mean difference (SE)[a]	[redacted]	
95% CI[a]	[redacted]	
p-value[b]	[redacted]	

[a]Based on MMRM adjusted for baseline stratification factors
[b]p-value for LSM difference between arms from MMRM

Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ITT = intent-to-treat; MF-SAF =Myelofibrosis Symptom Assessment Form; SD = standard deviation; SE = standard error

EQ-5D: The mean change from baseline at Week 24 for EQ-5D VAS was numerically greater in the momelotinib group ([redacted]) compared with the danazol group ([redacted]; Table 36).(67) The least squares mean difference was [redacted]), indicating that any differences were not significant.(67)

Table 36. EQ-5D VAS in MOMENTUM (ITT population)(67)

	Momelotinib (n=130)	Danazol (n=63)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (SE)	[redacted]	
95% CI	[redacted]	
p-value	[redacted]	
Percentage change from baseline at Week 24		
Mean (SD)	[redacted]	[redacted]

Abbreviations: CI = confidence interval; EQ-5D = EuroQol 5-Dimensions; ITT = intent-to-treat; SD = standard deviation; SE = standard error; VAS = visual analogue scale

B.2.8 Subgroup analysis

As described in Section B.2.4, the pre-planned and post-hoc subgroup analyses described in Table 37 were undertaken for SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM. Subgroup analyses of the primary and secondary efficacy endpoints were generally consistent with the primary analysis across all three studies.(62, 63, 67)

As described below, momelotinib demonstrated similar benefits in post-hoc analysis of subgroups of patients with intermediate-2 or high-risk (int-2/HR) MF and anaemia as the primary analysis.(62, 63, 67) To demonstrate robustness of results regardless of how 'anaemia' is defined, results are reported for both Hb<10 g/dL and Hb<12 g/dL populations. All relevant subgroups referred to within this section are restricted to int-2/HR MF patients only, therefore int-2/HR with Hb<12 g/dL subgroup will be referred to as the Hb<12 g/dL subgroup, and similarly, the int-2/HR with Hb<10 g/dL will be referred to as the Hb<10 subgroup. An overview of additional subgroup results is presented in Appendix E.

Please note, however, the trials were not powered to show significance between subgroups. All subgroup analyses were exploratory with no multiplicity adjustment.

Table 37. Comparative summary of trial subgroup methodology

Trial	SIMPLIFY-1 (NCT01969838)(62, 82, 83)	SIMPLIFY-2 (NCT02101268)(63, 82)	MOMENTUM (NCT04173494)(67)
Pre-planned subgroups	• Age (<65 years or ≥65 years) • Gender (male or female) • Race (white or all other races) • Baseline spleen volume (< median or ≥ median) • Baseline TSS (quartiles: < Q1, ≥ Q1 and < median, ≥ median and < Q3, ≥ Q3) • Baseline TD (defined as requiring ≥4 units of transfusion or a Hb <8 g/dL in the 8 weeks prior to randomisation) • Baseline Hb (<8 g/dL or ≥8 g/dL) • Baseline platelet count (<100, ≥100 and ≤200, >200 [10^9/L]) • IPSS prognostic category (int or HR) • MF disease status (PMF, post-PV MF, or post-ET MF) • JAK2V617F mutation (positive or negative, based on medical history) • Graphical region (Western Europe, Eastern Europe, or Asia)	• Age (<65 years or ≥65 years) • Gender (male or female) • Race (white or all other races) • Baseline spleen volume (< median or ≥ median) • Baseline Hb (<8 g/dL or ≥8 g/dL) • DIPSS prognostic category (int or HR) • MF disease status (PMF, post-PV MF, or post-ET MF) • JAK2V617F mutation (positive or negative, based on medical history) • Duration of ruxolitinib received prior to randomisation (≥12 weeks or <12 weeks) • Highest dose of ruxolotinib received since randomisation (≥20mg twice daily or <20mg twice daily [BAT arm only])	• Transfusion status (TI/TR/TD) at baseline • Transfusion status (TI/non-TI) at baseline • Age (<65 years or ≥65 years) • Sex (male or female) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other) • Baseline platelet count (<50, ≥50 but ≤150, >150 but ≤300, >300; ≤150, >150; ≤200, >200 [10^9/L]) • Baseline MF-SAF TSS (<22, ≥22) • Baseline spleen volume (< median or ≥ median) • RBC transfusions or whole blood units transfused in the 8-week period prior to randomisation (0, 1 to 4, ≥5 units) • Baseline Hb (<8 or ≥8 g/dL) • Baseline glomerular filtration rate (30 to 60; ≥60mL/min) • DIPSS prognostic category (int or HR) • MF disease status (PMF, post-PV MF, or post-ET MF) • JAK2 mutation (positive, negative, unknown) • Prior JAKi total daily dose received immediately before enrolment (0, <20mg ruxolitinib twice daily or 200mg fedratinib, ≥20mg ruxolitinib twice daily or >200mg fedratinib) • Geographic region (Asia, Australasia, Europe, North America) • Duration of JAKi treatment received before randomisation (<12 weeks, ≥12 weeks) • Receiving ongoing JAKi at screening (yes, no)

Trial	SIMPLIFY-1 (NCT01969838)(62, 82, 83)	SIMPLIFY-2 (NCT02101268)(63, 82)	MOMENTUM (NCT04173494)(67)
Post-hoc subgroups	• Baseline TI • Baseline non-TI • Baseline TSS (≥10) • Baseline Hb (<10 g/dL, <12 g/dL and ≥12 g/dL) • Baseline TSS ≥10 AND Hb <10 g/dL • Baseline platelet count (≤150, >150; ≤300, >300 [10^9/L]) • Week 24 TI response: no RBC transfusions ≥12 weeks, with Hb ≥8 g/dL • Week 24 spleen response: ≥35% spleen volume reduction vs baseline • Week 24 symptom response: ≥50% reduced in MF-SAF total symptoms score vs. baseline • Week 24 TI response: baseline Hb • Week 24 TI response: baseline platelet count • Week 24 TI response: baseline transfusion status	• Baseline TI • Baseline non-TI • Baseline TSS (<10 or ≥10) • Baseline Hb (<10 g/dL or ≥10 g/dL) • Baseline TSS ≥10 AND Hb <10 g/dL • Baseline platelet count (<100, <150, ≥100; ≤200, >200 [10^9/L]) • Week 24 TI response: no RBC transfusions ≥12 weeks, with Hb ≥8 g/dL • Week 24 spleen response: ≥35% spleen volume reduction vs baseline • Week 24 symptom response: ≥50% reduced in MF-SAF total symptoms score vs. baseline	N/A

Abbreviations: DIPSS = Dynamic International Prognostic Scoring System; ET = essential thrombocythemia; Hb = haemoglobin; IPSS = International Prognostic Scoring System; JAKi = Janus kinase inhibitor; MF = myelofibrosis; MF-SAF = Myelofibrosis Symptoms Assessment Form; PMF = primary myelofibrosis; PSA = prostate-specific antigen; PV = polycythemia vera; RBC = red blood cell; TD = transfusion-dependence; TI = transfusion-independence; TR = transfusion-requiring; TSS = total symptom score

B.2.8.1 Post-hoc analysis of int-2/HR anaemic populations

B.2.8.1.1 SIMPLIFY-1

Baseline characteristics: The baseline characteristics for SIMPLIFY-1 int-2/HR and Hb <10 g/dL and int-2/HR and Hb <12 g/dL subgroups are presented Table 38.(62)

Table 38. Baseline characteristics for SIMPLIFY-1 Hb <10 g/dL subgroup and Hb <12 g/dL subgroup (double-blind treatment phase)(62)

	Int-2/HR and Hb <10 g/dL		Int-2/HR and Hb <12 g/dL	
Characteristic	**Momelotinib (n=84)**	**Ruxolitinib (n=90)**	**Momelotinib (n=137)**	**Ruxolitinib (n=143)**
Risk category, n (%)				
Intermediate-2	[redacted]	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]
TSS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean Hb, g/dL (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Hb ≥8 g/dL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean platelet count, x10^3/µL	[redacted]	[redacted]	[redacted]	[redacted]
TI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ET = essential thrombocythemia; Hb = haemoglobin; HR =high-risk; int-2 = intermediate-2; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation; TD = transfusion-dependent; TI = transfusion-independent; TSS = total symptom score

Endpoints: The SIMPLIFY-1 subgroup analysis of Hb <10 g/dL and Hb <12 g/dL were consistent with the results from the primary analysis (Table 39).(62)

In the Hb <10 g/dL subgroup, the proportion of patients who had a spleen response at Week 24 in the momelotinib group ([redacted]) was similar to the proportion of patients in the ruxolitinib group ([redacted]).(62) The proportion difference between treatment groups was [redacted]).(62) In the Hb <12 g/dL subgroup, the proportion of patients who achieved a spleen response at Week 24 in the momelotinib group ([redacted]) was similar to the proportion of patients in the ruxolitinib group ([redacted]).(62) The non-inferiority proportion difference between treatment groups was [redacted]), indicating that momelotinib was non-inferior to ruxolitinib.(62)

In both subgroups (Hb <10 g/dL and Hb <12 g/dL), a higher proportion of patients were TI in momelotinib group ([redacted], respectively) compared with the ruxolitinib group ([redacted], respectively), these differences were nominally significant (proportion difference [stratified CMH]: [redacted] and proportion difference [stratified CMH]: [redacted], respectively).(62)

In both subgroups (Hb <10 g/dL and Hb <12 g/dL), TSS response rate was lower in the momelotinib group ([redacted] and [redacted], respectively) compared with the ruxolitinib group ([redacted], respectively). However, the non-inferiority proportion difference was [redacted] and [redacted], respectively), therefore non-inferiority of momelotinib to ruxolitinib was not shown for the same reason as the primary analysis.(62)

In the Hb <10 g/dL subgroup, the mean RBC transfusion rate was lower in the momelotinib group ([redacted]) compared with the ruxolitinib group ([redacted]).(62) Similarly, in the Hb <12 g/dL subgroup the mean RBC transfusion rate was lower in the momelotinib group ([redacted]) compared with the ruxolitinib group ([redacted]).(62)

Table 39. Summary of prespecified efficacy endpoints in SIMPLIFY-1 (int-2/HR anaemic populations)(62)

Trial	Int-2/HR and Hb <10 g/dL			Int-2/HR and Hb <12 g/dL		
	Momelotinib	Ruxolitinib	Proportion difference (95% CI)	Momelotinib	Ruxolitinib	Proportion difference (95% CI)
Primary efficacy endpoint						
Spleen response rate, i.e., the proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoints						
MPN-SAF TSS response rate, i.e., the proportion of patients with a ≥50% reduction in mean MPN-SAF TSS at Week 24 compared with baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TI rate i.e., the proportion of patients who had no RBC transfusions or no Hb levels <8 g/dL in the previous 12 weeks at Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD rate i.e., the proportion of patients who had 4 units of RBC transfusions or Hb levels <8 g/dL in the previous 12 weeks at Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; LSM = least squares mean; Hb = haemoglobin; MF-SAF = Myelofibrosis Symptoms Assessment Form; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment; RBC = red blood cell; TSS = total symptom score

B.2.8.1.2 SIMPLIFY-2

Baseline characteristics: The baseline characteristics for SIMPLIFY-2 int-2/HR and Hb <10 g/dL subgroup and int-2/HR and Hb <12 g/dL subgroup are presented in Table 40.

Table 40. Baseline characteristics for SIMPLIFY-2 Hb <10 g/dL subgroup and Hb <12 g/dL subgroup (double-blind treatment phase)(63)

	Int-2/HR and Hb <10 g/dL		Int-2/HR and Hb <12 g/dL	
Characteristic	**Momelotinib (n=61)**	**BAT (n=32)**	**Momelotinib (n=77)**	**BAT (n=34)**
Risk category, n (%)				
Intermediate-2	[redacted]	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]
TSS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean Hb, g/dL (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Hb ≥8 g/dL, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean platelet count, $x10^3/\mu L$	[redacted]	[redacted]	[redacted]	[redacted]
TI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ET = essential thrombocythemia; Hb = haemoglobin; HR = high-risk; int-2 = intermediate-2; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation; TD = transfusion-dependent; TI = transfusion-independent; TSS = total symptom score

Endpoints: The SIMPLIFY-2 subgroup analysis of Hb <10 g/dL and Hb <12 g/dL were consistent with the results from the primary analysis (Table 41).(63)

In both groups (Hb <10 g/dL and Hb <12 g/dL) the spleen response rate was higher in the momelotinib group ([redacted], respectively) compared with the BAT group ([redacted], respectively), however the proportion differences were [redacted] and [redacted], therefore momelotinib was not superior to BAT, similar to the primary analysis.(63)

In both groups (Hb <10 g/dL and Hb <12 g/dL), the proportion of patients with a ≥50% reduction in mean MPN-SAF TSS at Week 24 compared with baseline was higher in the momelotinib group ([redacted] and [redacted], respectively) compared with the BAT group ([redacted] and [redacted], respectively).(63) The proportion difference was [redacted] in the Hb <10 g/dL subgroup and [redacted] in the Hb <12 g/dL subgroup.(63)

In the Hb <10 g/dL, the mean RBC transfusion rate was similar between the momelotinib groups ([redacted]) and the BAT group ([redacted]).(63) In the

Hb <10 g/dL subgroup and Hb <12 g/dL subgroup, the proportion of patients who were TI was over double in the momelotinib group ([redacted] and [redacted], respectively) compared with the BAT group ([redacted] and [redacted], respectively).(63) In the Hb <10 g/dL subgroup the proportion difference was [redacted] between treatment groups.(63) In the Hb <12 g/dL subgroup the proportion difference was [redacted] between the treatment groups.(63)

Table 41. Summary of prespecified efficacy endpoints in SIMPLIFY-2 (int-2/HR anaemic populations)(63)

Trial	Int-2/HR and Hb <10 g/dL			Int-2/HR and Hb <12 g/dL		
	Momelotinib	BAT	Proportion difference (95% CI)	Momelotinib	BAT	Proportion difference (95% CI)
Primary endpoint						
Spleen response rate, i.e., the proportion of patients with ≥35% reduction in spleen volume from baseline at 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary endpoints						
MPN-SAF TSS response rate, i.e., the proportion of patients with a ≥50% reduction in mean MPN-SAF TSS at Week 24 compared with baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TI rate i.e., the proportion of patients who had no RBC transfusions or no Hb levels <8 g/dL in the previous 12 weeks at Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD rate i.e., the proportion of patients who had 4 units of RBC transfusions or Hb levels <8 g/dL in the previous 12 weeks at Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; CI = confidence interval; Hb = haemoglobin; HR = high-risk; int = intermediate; MF-SAF = Myelofibrosis Symptoms Assessment Form; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment; RBC = red blood cell; TSS = total symptom score

B.2.9 Meta-analysis

An SLR and meta-analysis by Sureau et al. 2021 assessed the efficacy and tolerability of JAKi, using data from RCTs comparing momelotinib, ruxolitinib, fedratinib and pacritinib with placebo/BAT in patients with MF.(84) The study found that momelotinib was associated with a significant improvement in reducing spleen volume compared to placebo (momelotinib OR 0.92, 95% CI: 0.68, 1.25 versus ruxolitinib; placebo OR 0.02, 95% CI: 0, 0.07 versus ruxolitinib). However, no statistically significant difference was demonstrated between fedratinib, momelotinib, and ruxolitinib on this criterion. The results also showed significantly fewer anaemia grade 3/4 AEs with momelotinib treatment compared with ruxolitinib (OR 0.32, 95% CI: 0.19, 0.50).(84)

Overall, the study suggests that momelotinib could be a valuable treatment option for MF patients experiencing splenomegaly.(84)

B.2.10 Indirect and mixed treatment comparisons

Not applicable.

The clinical trial program for momelotinib presents head-to-head data for all relevant comparators for the decision problem in JAKi-naïve patients (comparison versus ruxolitinib from SIMPLIFY-1) and JAKi-experienced patients (comparison versus BAT from SIMPLIFY-2). Therefore, no indirect or mixed treatment comparison was performed.

B.2.11 Adverse reactions

This section presents pooled safety analyses including patients from SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM. For individual trial safety results please see Appendix F.

B.2.11.1 Pooled safety analysis

To characterise the long-term safety of momelotinib, patients from SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM continued to receive momelotinib in the extended access study (XAP).(66) The total follow-up time was 1,261 patient-years in 725

patients.(66) The median duration of momelotinib exposure was 11.3 months (range: 0.1 to 90.4 months).(66) Throughout the duration of treatment, the dose intensity of momelotinib was maintained at a high level (Table 42).(66)

Table 42. Dose intensity of momelotinib throughout duration of treatment(66)

	Momelotinib overall (N=725)
Duration of exposure, median (range), months[a]	11.3 (0.1, 90.4)
Duration of exposure for ≥60 months, n (%)	88 (12.1)
Relative dose intensity, median (range), %	97.3 (0, 247)

[a]The duration of exposure was 20.3 months; the maximum duration of exposure was approximately 7.5 years

Overall, grade ≥3 nonhaematologic treatment-emergent AE (TEAEs) were infrequent, and grade ≥3 haematologic TEAEs such as thrombocytopenia and anaemia were experienced by 16.4% and 14.8% of patients (respectively, Table 43).(66)

Table 43. TEAEs experienced by the overall momelotinib population (XAP)(66)

	Any grade AE, n (%)	**Grade ≥3 AE, n (%)**
Diarrhoea	194 (26.8)	19 (2.6)
Nausea	141 (19.4)	8 (1.1)
Fatigue	127 (17.5)	18 (2.5)
Cough	126 (17.4)	5 (0.7)
Dizziness	112 (15.4)	4 (0.6)
Abdominal pain	102 (14.1)	13 (1.8)
Pyrexia	102 (14.1)	9 (1.2)
Headache	101 (13.9)	6 (0.8)
Asthenia	96 (13.2)	8 (1.1)
Pruritus	90 (12.4)	5 (0.7)
Dyspnoea	89 (12.3)	15 (2.1)
Peripheral sensory neuropathy	89 (12.3)	5 (0.7)
Urinary tract infection	88 (12.1)	18 (2.5)
Pneumonia	83 (11.4)	61 (8.4)
Constipation	81 (11.2)	1 (0.1)
Edema peripheral	75 (10.3)	5 (0.7)
Arthralgia	73 (10.1)	2 (0.3)
Upper respiratory tract infection	73 (10.1)	3 (0.4)
Thrombocytopenia	181 (25.0)	119 (16.4)
Anaemia	170 (23.4)	107 (14.8)
Neutropenia	49 (6.8)	38 (5.2)
Peripheral neuropathy	107 (14.8)	9 (1.2)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event; XAP = Extended Access Program

Fatal AEs were reported in 14.1% of patients (n=102), with pneumonia (n=9, 1.2%), acute myeloid leukaemia (AML; n=6, 0.8%) and sepsis (n=5, 0.7%) being most

commonly reported.(66) Frequently and clinically important AEs did not increase in incidence over time (Table 44).(66)

Table 44. Clinically important AEs over time (XAP)(66)

n (%)	24 weeks (n=725)	25 to 48 weeks (n=510)	49 to 96 weeks (n=367)	97 to 144 weeks (n=213)	145 to 192 weeks (n=150)	193 to 240 weeks (n=109)	241 to 288 weeks (n=93)	≥289 weeks (n=64)
Any AE	663 (91.4)	371 (72.7)	280 (76.3)	159 (74.6)	99 (66.0)	60 (55.0)	51 (54.8)	20 (31.3)
All infections	263 (36.3)	133 (26.1)	121 (33.0)	64 (30.0)	38 (25.3)	22 (20.2)	20 (21.5)	8 (12.5)
Opportunistic infections	13 (1.8)	7 (1.4)	9 (2.5)	8 (3.8)	3 (2.0)	0	4 (4.3)	1 (1.6)
Malignancies	38 (5.2)	21 (4.1)	23 (6.3)	13 (6.1)	12 (8.0)	3 (2.8)	7 (7.5)	3 (4.7)
AML/leukemic transformation	12 (1.7)	1 (0.2)	6 (1.6)	1 (0.5)	2 (1.3)	0	0	0
NMSC	9 (1.2)	14 (2.7)	10 (2.7)	5 (2.3)	3 (2.0)	1 (0.9)	3 (3.2)	3 (4.7)
MACE	20 (2.8)	9 (1.8)	18 (4.9)	8 (3.8)	4 (2.7)	1 (0.9)	2 (2.2)	1 (1.6)
Thromboembolism	25 (3.4)	12 (2.4)	19 (5.2)	8 (3.8)	6 (4.0)	2 (1.8)	3 (3.2)	2 (3.1)

Abbreviations: AE = adverse event; AML = acute myeloid leukaemia; MACE = major adverse cardiovascular event; NMSC = nonmelanoma skin cancer; XAP = Extended Access Prgram

Of all patients in the pooled analysis, 36.1% had ≥1 AE leading to dose adjustments (dose reduction/interruption) of momelotinib.(66) The most common AEs leading to dose adjustment was thrombocytopenia (10.5%) and infections and infestations (including pneumonia, 7.0%).(66) The most common AE leading to discontinuation were infections and infestations (4.0%) and thrombocytopenia (3.7%).(66) AEs leading to discontinuation for each individual trial are included in Section F.

B.2.12 Ongoing studies

No studies are awaiting read-out; any further publication will be based on existing completed trials. The following relevant analyses are expected to be presented at congresses in 2023:

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- Clinical outcomes with momelotinib versus ruxolitinib in patients with myelofibrosis and anaemia: subgroup analysis of SIMPLIFY-1. SOHO 2023 poster.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The pivotal clinical studies (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM) collectively show that momelotinib has clinical benefits for patients with MF, such as reduced spleen size, decreased anaemia and transfusion burden, improved MF-associated symptoms, and durable survival.(11, 23, 61, 64) These benefits were observed in patients with anaemia and thrombocytopenia, regardless of prior JAKi treatment. In SIMPLIFY-1, momelotinib was non-inferior to ruxolitinib in the primary endpoint of spleen response rate at Week 24.(61) Spleen volume reductions were clinically meaningful and durable in the open-label phase, including in those who crossed over to momelotinib from ruxolitinib after Week 24.(62) Furthermore, patients who crossed over to momelotinib from ruxolitinib/BAT in both SIMPLIFY-1 and SIMPLIFY-2 experienced rapid improvements in anaemia, maintained symptom control and did not experience safety concerns or ruxolitinib withdrawal effect.(65) Together, these results affirm that the immediate transition to momelotinib from ruxolitinib is tolerable by patients, without the need for tapering or a washout period.(65) In the primary endpoint of SIMPLIFY-2, momelotinib was not superior to BAT, likely due to lack of washout period and high use of JAKi in the comparator arm.(23) In contrast, MOMENTUM showed statistically significant superiority of momelotinib over danazol for the primary endpoint of TSS response rate and secondary endpoint of spleen response rate.(64) The results of SIMPLIFY-1 and SIMPLIFY-2 support the MOMENTUM results and together demonstrate that momelotinib provides clinical benefits for MF patients in terms of spleen volume, symptoms and anaemia, across different stages and treatment histories.(62, 63, 67)

B.2.13.1.1 SIMPLIFY-1

SIMPLIFY-1 demonstrated that momelotinib is non-inferior to ruxolitinib in terms of splenic response in a JAKi-naïve population. Non-inferiority in a secondary endpoint of symptom response was not achieved, though analysis of the cumulative distribution of absolute change in TSS, plus individual item analyses, indicated comparable response between momelotinib and ruxolitinib. Certain aspects of the study design may have impacted the assessment of symptom response. There are several explanations why non-inferiority was not met for this endpoint, including:

- Baseline severity on the MPN-SAF TSS was not an inclusion criterion or stratification factor in the SIMPLIFY-1 trial; consequently, imbalances occurred between treatment groups in terms of symptom severity(48)
- A higher proportion of patients were categorised as having 'severe' symptoms in the momelotinib group ([redacted]) compared with the ruxolitinib group ([redacted]). Similarly, for 'moderate' symptoms ([redacted] versus [redacted], respectively)(85)
- Furthermore, patients with missing TSS at Week 24 were counted as non-responders.(48) A higher proportion of the momelotinib group were considered non-responders due to missing data at Week 24 ([redacted]) compared with the ruxolitinib group ([redacted])(62)

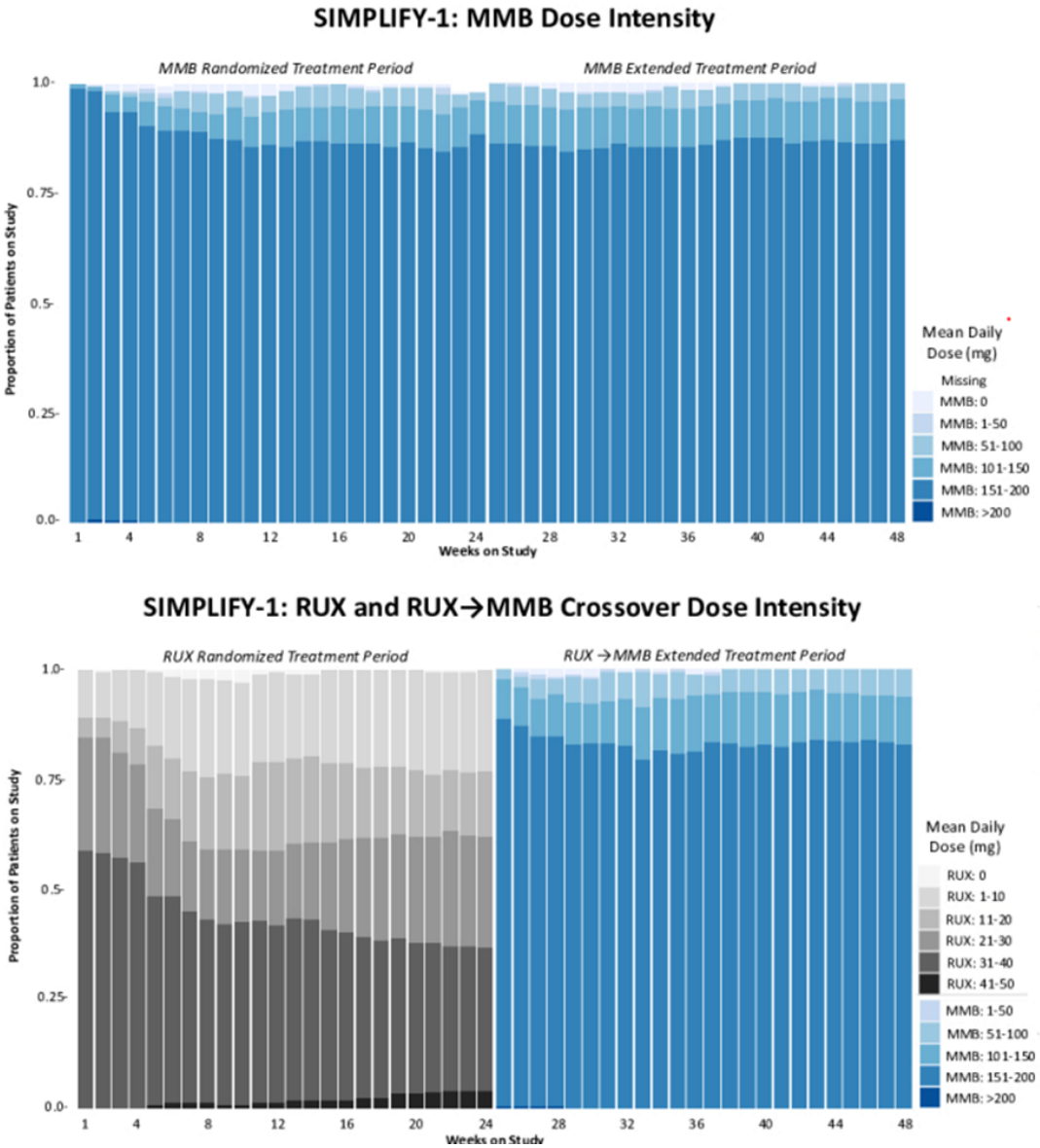
Patients generally had low symptom scores at baseline, with median individual symptom scores ranging from 2 to 4, out of a possible 10. TSS response is difficult to detect with low baseline scores, due to natural variability in symptoms over time.(62) For example, at low baseline scores, small absolute increases over the study period lead to large percentage increases, regardless of the resulting level of symptom severity. In SIMPLIFY-1, a similar proportion of patients met the derived meaningful change threshold with an improvement of at least 8 points within 24 weeks of momelotinib or ruxolitinib treatment (overall population: [redacted]; symptomatic population; [redacted]).(86)

Clinical experts from the advisory board in November 2022 also acknowledged a percentage reduction in TSS was not as meaningful in clinical practice since large, clinically meaningful improvements in the individual components may be achieved that might not be well reflected in the averaged total scores.(33) Additionally, the

clinical experts considered the demonstration of non-inferior spleen response by momelotinib a positive result, which was not undermined by not meeting the percentage change in symptom response secondary endpoint; the rationale being that many patients treated with momelotinib also experienced substantial improvements in symptom scores.(32, 33)

Furthermore, momelotinib demonstrated efficacy in spleen and anaemia endpoints; the treatment effect of momelotinib was robust regardless of baseline Hb levels and platelet counts (which were both maintained from baseline); ruxolitinib efficacy, on the other hand, was negatively impacted by low baseline platelet counts (Appendix E.1.1.1 and Appendix E.1.1.5).(87) The haematological profile of momelotinib enabled the maintenance of therapeutic dose intensities, in contrast to ruxolitinib treatment which necessitated greater dose tapering due to toxicities (Appendix F.1.1) and affected efficacy in patients with pre-existing low platelet counts (Figure 34).(87, 88)

Figure 34. Momelotinib and ruxolitinib dose intensity in the randomised treatment and extended phase (SIMPLIFY-1)(88)



Abbreviations: MMB = momelotinib; RUX = ruxolitinib

A higher proportion of patients in the momelotinib group (66.5%) versus the ruxolitinib group (49.3%) were TI at Week 24. The TI rate was maintained in the momelotinib group from baseline to Week 24 (68.4% to 66.5%); however, in the ruxolitinib group, the TI rate dropped approximately 20% from baseline to Week 24 (70.0% to 49.3%).(62) Using a separate measure of transfusion-free response, which omits the Hb component of TI rate, similar results were observed: the transfusion-free response rate at Week 24 was [redacted] in the momelotinib group versus [redacted] in the ruxolitinib group.(62)

Overall efficacy profiles, in terms of spleen response, TSS and TI at Week 24 (Figure 35), show that momelotinib provides comparable holistic benefits to ruxolitinib in JAKi-naïve patients, with:(62)

- [redacted] of the momelotinib group and [redacted] of the ruxolitinib group achieving ≥1 of these endpoints
- [redacted] of the momelotinib group and [redacted] of the ruxolitinib group achieving all 3 endpoints

Figure 35. Rates of spleen response, TSS response and TI at Week 24 (SIMPLIFY-1; ITT)(62)

Abbreviations: ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib; TI = transfusion-independence; TSS = total symptom score

Durable survival was observed on extended treatment with momelotinib, regardless of starting therapy, with TI at baseline and TI response at Week 24 being independent predictors of OS.(11) This was also observed in post-hoc analysis accounting for treatment crossover after Week 24.(76) Overall, the efficacy data presented suggests that momelotinib may provide similar or greater holistic benefits compared to ruxolitinib in JAKi-naïve patients. Of note, patients who switched immediately from ruxolitinib to momelotinib at Week 24 experienced maintenance of spleen response, symptom control, and a rapid increase in Hb levels.(65)

Momelotinib was generally well-tolerated. Although a higher number of patients prematurely discontinued treatment due to AEs compared with the ruxolitinib group ([redacted]),(62) this may be explained by a much greater number of patients having dose adjustment or interruption in the ruxolitinib group ([redacted] vs [redacted] in the momelotinib group), which is aligned with clinical practice in the UK. No notable differences in AEs were observed in patients with/without anaemia or with/without thrombocytopenia, and fewer patients treated with momelotinib experienced anaemia [redacted] and thrombocytopenia (18.7% vs 29.2%) events than those treated with ruxolitinib. Moreover, no evidence of new or progressive toxicity was observed in patients who switched from ruxolitinib to momelotinib in the open-label phase. Note that no ruxolitinib tapering was required and switching to momelotinib was not associated with any rebound effect or other safety signal.(65) Momelotinib was well-tolerated with continued treatment, and a lower occurrence of AEs was observed at 48 weeks versus 24 weeks. Patients who switched from ruxolitinib to momelotinib at Week 24 did not experience safety concerns or withdrawal effects. These findings provide strong evidence for the safety and tolerability of momelotinib in JAKi-naïve patients with MF, with no new safety signals observed.(62)

B.2.13.1.2 SIMPLIFY-2

In SIMPLIFY-2, a similar proportion of patients in the momelotinib (7%) and BAT comparator arm (6%) had a ≥35% reduction in spleen volume, thus statistical superiority was not demonstrated for the primary endpoint. This was likely due to treatments administered and certain study design features in SIMPLIFY-2. At the time of protocol development, BAT treatments were anticipated to comprise hydroxyurea, steroids or ESAs, or ruxolitinib at a subtherapeutic dose.(23) Subsequently, however, ruxolitinib dosing guidelines became widely available.(23) Along with increased clinical experience, this led to patients frequently continuing on ruxolitinib at therapeutic doses despite them experiencing AEs (30.8% of patients received ruxolitinib >5 mg BID and ≤10 mg BID, 25.0% of patients received ≤5 mg BID, 19.2% of patients received >10 mg BID and <20 mg BID and 11.5% of patients received ≥20 mg BID).(23) Thus, the large majority of patients in the BAT group

received ruxolitinib (88.5%), in contrast to what was expected when the study was designed.(23) Both being JAK1/2i, momelotinib and ruxolitinib may not be expected to show statistically significant differences in terms of spleen response rate, given that the relationship between the JAK/STAT pathway and splenomegaly is well-established.(89)

Another confounding factor was the lack of washout period in SIMPLIFY-2, which can explain the low spleen response rates observed in this study.(23) Patients entering the study had either suboptimal responses or haematological toxicity with ruxolitinib, but were not necessarily ruxolitinib-refractory.(23) Given there was no treatment washout period, the trial effectively becomes a switch trial, and patients would not be expected to experience a large reduction in spleen volume from having an active treatment at baseline.

These explanations for the primary endpoint result have been corroborated by expert clinicians at an advisory board.(32) Furthermore, the low response rates observed in each treatment arm in SIMPLIFY-2 have not been replicated in comparable clinical trials that included washout periods prior to receiving study drug with momelotinib (MOMENTUM) or other JAKi (JAKARTA-2).(64, 74)

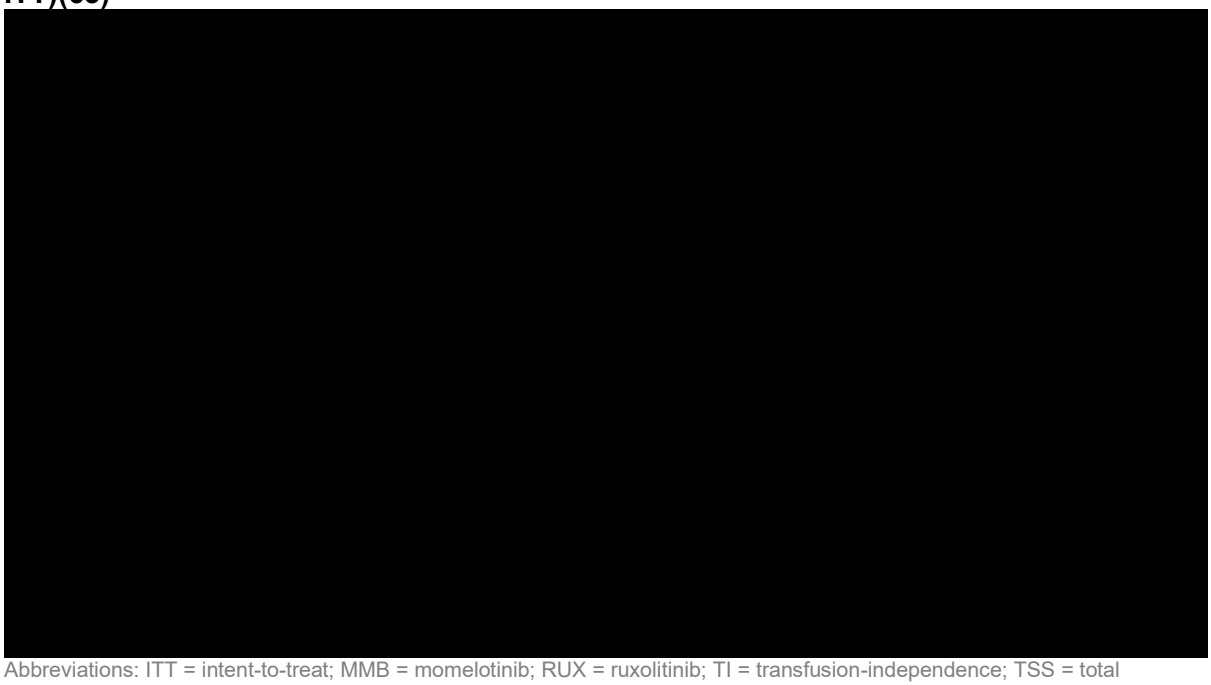
However, considering the totality of efficacy evidence, such as symptom and anaemia benefits, and OS duration, momelotinib appeared to offer a greater overall benefit in more advanced, JAKi-experienced patients than BAT. While statistical significance could not be claimed for any secondary analysis due to the primary endpoint result, momelotinib demonstrated nominal statistical significance across all key secondary endpoints. Of note, symptomatic improvement was observed with momelotinib, along with improvements in several haematological endpoints, such as:

- Improvements in Hb and platelet levels
- Improved TI vs BAT (and from baseline)
- Reduced TD vs BAT (and from baseline)

On analysis of overall efficacy profiles (Figure 36), the proportion of patients achieving 1 of the spleen response, TSS and TI at Week 24 endpoints in the momelotinib group was approximately double that of the BAT group ([redacted]

[redacted]). The rate of response in any 2 endpoints was approximately 5-fold higher in the momelotinib group compared with the ruxolitinib group ([redacted].(63)

Figure 36. Rates of spleen response, TSS response and TI at Week 24 (SIMPLIFY-2; ITT)(63)



Abbreviations: ITT = intent-to-treat; MMB = momelotinib; RUX = ruxolitinib; TI = transfusion-independence; TSS = total symptom score

Furthermore, OS with momelotinib was comparable to BAT. While OS in the extended phase is biased due to crossover from BAT, numerically improved survival was observed in the randomised treatment phase. Post-hoc analyses adjusting for crossover also observed numerically improved survival.(76) Other post-hoc analyses indicated that momelotinib may have a survival benefit driven by improvements in TI rate.(11) Further analyses that accounted for changes in transfusion status over time found that TI in JAKi-experienced patients is a significant independent predictor of improved survival.(77)

The use of ruxolitinib as the major component of BAT and lack of washout period contributed to the failure to demonstrate superiority of momelotinib over BAT. It is because of these clinical trial design features that SIMPLIFY-2 is well placed to demonstrate the comparative clinical effectiveness of momelotinib in JAKi-experienced patients in England, who are very likely to be continuing ruxolitinib therapy.

In addition, momelotinib treatment was found to be generally well-tolerated in JAKi-experienced patients, with no notable differences in AEs between thrombocytopenic and non-thrombocytopenic patients, or between patients with Hb levels above or below 10 g/dL. There was no evidence of new or progressive toxicity in patients who switched from BAT to momelotinib during the extension phase. Overall, the study provided strong evidence for the safety and tolerability of JAKi-experienced patients with MF.(63)

B.2.13.1.3 MOMENTUM

Although danazol is an anaemia treatment rather than an active MF therapy, the MOMENTUM study showed that momelotinib has a definitive treatment effect on symptoms and splenomegaly in JAKi-experienced patients which could not be demonstrated in SIMPLIFY-2 (as described above in Section B.2.13.1.2). In the MOMENTUM trial, momelotinib demonstrated statistically significant superiority over danazol for the primary endpoint of TSS response rate, as well as statistically significant improvements in spleen response rate (both at ≥25% and ≥35% thresholds).

Momelotinib also demonstrated superiority over this active anaemia treatment across a range of anaemia-related endpoints, confirming the impact of ACVR1 inhibition on anaemia. Momelotinib showed a significantly higher rate of zero RBCT or whole blood unit transfusions, plus other benefits in anaemia response, such as longer median times to transfusions, higher proportions of patients with Hb increases, and lower cumulative transfusion risk versus danazol. Analysis of 48-week data demonstrated an increase in the proportion of patients achieving a late TI response in those continuing momelotinib treatment (57%) compared to the 24-week analysis (30%).(80, 90) Clinical experts at the advisory board were particularly impressed by the rapid increase in Hb with momelotinib.(32)

Consistent with SIMPLIFY-2, there was a trend in improved survival with momelotinib versus comparator, particularly within the initial 24-week randomised treatment phase. TI at Week 24 was associated with significantly longer survival in patients randomised to momelotinib ([redacted]).(72) TI at Week 24 was also

associated with a trend towards longer survival in patients randomised to danazol who crossed over to momelotinib after Week 24.(81) Consistent with results for SIMPLIFY-2, further post-hoc analyses to account for changes in transfusion status over time found that TI (versus non-TI) was a statistically significant independent predictor of improved survival.(77)

The study also demonstrated the favourable safety profile of momelotinib compared with danazol and was consistent with the previous safety findings of SIMPLIFY-1 and SIMPLIFY-2. Overall, the study suggests that momelotinib has a positive benefit-risk profile in anaemic and symptomatic patients with MF previously treated with JAKi.(67)

B.3 Economic Value

JAKi-naïve

Model Overview

- In line with the decision problem and as described in Section B.1 of this submission, the relevant comparator for momelotinib in JAKi-naïve population is ruxolitinib. With SIMPLIFY-1 trial results demonstrating the non-inferiority of momelotinib compared to ruxolitinib, a NICE recommended therapy within the same therapeutic class, the economic value of momelotinib in a JAKi-naïve population is demonstrated in a standalone cost-comparison evaluation. This approach was discussed and agreed with NICE and other relevant submission stakeholders at the decision problem meeting.
- For the cost-comparison analysis, momelotinib was compared against ruxolitinib from an NHS and PSS perspective over a 10-year time horizon, with costs discounted at 3.5% annually in line with the NICE reference case. Time on momelotinib and ruxolitinib treatment was assumed equal for the base-case analysis, with a constant discontinuation rate derived from SIMPLIFY-1 and applied to both treatment arms over time, and patients then moving to BAT (based on SIMPLIFY-2) following discontinuation. Costs included in the model were those expected to differ between treatment arms: namely drug acquisition, subsequent treatment, red blood cell transfusion, iron chelation therapy (ICT) and adverse event costs. Various scenario analyses were performed to test key input assumptions and alternatively data sources.

Results

- Following application of the proposed patient access scheme (PAS) price discount for momelotinib, total costs over 10 years for momelotinib were then reduced to [redacted] compared to £326,021 for ruxolitinib, representing a cost saving of [redacted] for momelotinib. Furthermore, when applying the proposed PAS price, momelotinib also continued to demonstrate cost savings over ruxolitinib across all scenario analyses performed.

JAKi-experienced

Model Overview

- Momelotinib is expected to provide additional health benefits to JAKi-experienced patients with potentially greater treatment costs versus the standard of care. Therefore, consistent with the reference case, a modelled cost-effectiveness/-utility analysis is required to suitably assess whether momelotinib represents value-for-money to the NHS. This was also discussed and agreed with NICE and other relevant submission stakeholders at the decision problem meeting.
- As transfusion status was identified as a key differentiator in clinical outcomes between momelotinib and ruxolitinib in the SIMPLIFY-2 trial, a Markov model was developed including health states based on transfusion dependency status (TI, transfusion-requiring [TR], TD) and death. An NHS and PSS perspective was

adopted for the model along with a lifetime time horizon (33 years) and 3.5% discount rate in line with the NICE reference case. Momelotinib was compared against BAT, with BAT defined based on the BAT comparator in the SIMPLIFY-2 trial.

- Health state membership was determined based on transfusion status distribution and overall survival (OS) data from SIMPLIFY-2. For the first 24 weeks, transfusion status was determined using treatment specific distributions from SIMPLIFY-2, and assuming equivalent OS between comparator arms as no statistically significant differences in OS were observed over the first 24 weeks. As patients in the SIMPLIFY-2 trial crossed over from BAT to momelotinib at 24 weeks, OS extrapolations based on Week 24 transfusion status only, and derived from the momelotinib arm of SIMPLIFY-2, were applied to the proportion of patients in each transfusion state at 24 weeks for each treatment arm. After 24 weeks, pooled transfusion status transition probabilities were then applied independently of OS to inform costs and utilities for those remaining alive over time.
- For momelotinib, time on treatment data were used to inform drug related costs (acquisition, administration, AEs) with patients discontinuing assumed to receive BAT excluding ruxolitinib. Per expert advice, ruxolitinib re-treatment as part of BAT is not expected for patients discontinuing momelotinib in a JAKi-experienced population. All BAT arm patients remaining alive were assumed to remain on treatment over time.
- Drug acquisition, drug administration, adverse event, monitoring, disease management, subsequent treatment and terminal care costs were included in the model. Unit costs were primarily sourced from relevant UK data sources (BNF, eMIT, NHS reference costs, PSSRU), with RBCT unit costs informed from the literature and prior NICE appraisals for myelofibrosis therapies. RBCT units per cycle and adverse event probabilities were sourced directly from SIMPLIFY-2, with other monitoring and disease management frequencies based on clinical expert feedback.
- EQ-5D-3L health state utility values were derived from a mixed effects model based on cross-walked EQ-5D-5L data from SIMPLIFY-2. Adverse event disutilities were sourced from available literature and prior NICE appraisals for myelofibrosis therapies.
- Probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA), as well as scenario analysis, was performed to explore uncertainty around model inputs, data sources and key assumptions in the model.
- A subgroup analysis was also performed for the Hb <10 g/dL population from SIMPLIFY-2 to test the impact of using an alternative definition for anaemia. Available subgroup specific data were applied from SIMPLIFY-2 for transition probabilities, OS, treatment discontinuation and transfusion units per cycle.

Results

- Momelotinib was dominant over BAT in the base-case and PSA, as well as all scenario analyses conducted. Momelotinib was also either dominant or cost-effective (incremental NMB <£0) at a £30,000 per QALY threshold across all DSA parameter variations following application of the proposed PAS discount.
- For the Hb <10 g/dL subgroup analysis, momelotinib produced an ICER of [redacted] per QALY compared to BAT at list price, indicating cost-effectiveness at both £20,000 and £30,000 per QALY thresholds. Following application of the proposed PAS price discount, momelotinib became dominant over BAT.

Overall conclusions

- When applying the proposed PAS discount, momelotinib results in cost savings to the NHS when used as an alternative to ruxolitinib for a JAKi-naïve population, and was highly cost-effective against BAT for a JAKi-experienced population across all scenario, sensitivity and subgroup analyses performed. This was largely driven by the reduced need for RBCTs and the associated management costs, as well as potential OS gains over BAT, driven by increased TI rates versus BAT as observed in SIMPLIFY-2.
- Momelotinib is therefore expected to be a valuable and cost-effective treatment option for either JAKi-naïve or JAKi-experienced patients with MF, reducing the need for TD and its associated economic and health implications.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify cost-effectiveness studies relevant to the decision problem from the published literature, specifically in adult patients with MF. Details of the methods used to identify and select the relevant studies are described in Appendix G.

The review identified eight publications comprising one cost-effectiveness and seven cost-utility evaluations in MF. None of these publications related to momelotinib. Two of the publications were identified in full-text format, one in abstract format, and five were models reported in HTA submissions (NICE [n=2], CADTH [n=2], SMC [n=1]).(91-98) An overview of the identified studies is provided in

Table 45.

Full details of the SLR search strategy, methodology and results, as well as critical appraisals of each publication are presented in Appendix G.

As no existing economic evaluations of momelotinib were identified in the cost-effectiveness SLR, *de novo* models were developed for the purposes of this submission.

Table 45. Model characteristics and results

Study Author, Year	Country	Summary Of Model	LYs and QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per LY or QALY Gained)
Ruxolitinib					
Vandewalle et al, 2016(92)	Portugal	Cost-effectiveness analysis, discrete event simulation model Study objective: To assess the long-term survival benefits and disease management costs with ruxolitinib versus BAT Horizon: lifetime Discount rate: 5% Currency/year (perspective): €/ NR (healthcare system)	Ruxolitinib versus BAT • LY gain: 2.43 • QALY gain: NR	Ruxolitinib versus BAT Incremental cost: €97,052	Ruxolitinib versus BAT ICER: €40,000/LY
Smith et al, 2022(93)	US	Cost-utility analysis, Markov model Study objective: To assess the cost-effectiveness of ruxolitinib versus BAT Horizon: lifetime Discount rate: 3% Currency/year (perspective): US$/2021 (healthcare system)	Ruxolitinib versus BAT • LY gain: NR • QALY gain: 2.86	Ruxolitinib versus BAT Incremental cost: $680,848	Ruxolitinib versus BAT ICER: $238,474/QALY
Gomez-Casares et al, 2018(91)	Spain	Cost-utility analysis, decision tree and Markov model Study objective: To assess the cost-effectiveness of ruxolitinib versus BAT in MF patients Horizon: 15 years Discount rate: 3% Currency/year (perspective): €/2016 (societal)	Ruxolitinib versus BAT • LY gain: 2.58 • QALY gain: 2.18	Ruxolitinib versus BAT Incremental cost: €121,539	Ruxolitinib versus BAT ICER: €55,616/QALY

Study Author, Year	Country	Summary Of Model	LYs and QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per LY or QALY Gained)
H02, NICE, 2016(27)	UK	Cost-utility analysis, discrete event simulation model Study objective: To appraise the clinical and cost-effectiveness of ruxolitinib versus BAT within its marketing authorisation for treating MF Horizon: lifetime Discount rate: 3.5% Currency/year (perspective): £/2015 (healthcare system)	Ruxolitinib versus BAT • LY gain: 3.81 • QALY gain: 2.51	Ruxolitinib versus BAT Incremental cost: £112,682	Ruxolitinib versus BAT ICER: £44,831/QALY
H03, CADTH, 2013(96)	Canada	Cost-utility analysis Study objective: To assess the cost-utiity of ruxolitinib versus BAT Horizon: lifetime Discount rate: NR Currency/year (perspective): CAD/2013 (healthcare system)	Ruxolitinib versus BAT • LY gain: NR • QALY gain: 0.82	Ruxolitinib versus BAT Incremental cost: CAD83,246	Ruxolitinib versus BAT ICER: CAD101,207/QALY
H05, SMC, 2015(98)	Scotland, UK	Cost-utility analysis, discrete event simulation model Study objective: To assess health economic evidence using a lifetime analysis comparing ruxolitinib versus BAT for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF, post-PV MF or post-ET MF Horizon: lifetime	Ruxolitinib versus BAT • LY gain: NR • QALY gain: 1.99	Ruxolitinib versus BAT Incremental cost: £98,982	Ruxolitinib versus BAT ICER: £49,774/QALY

Study Author, Year	Country	Summary Of Model	LYs and QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per LY or QALY Gained)
		Discount rate: NR Currency/year (perspective): £/2015 (NR)			
Fedratinib					
H01, NICE, 2021(51)	UK	Cost-utility analysis, discrete event simulation model Study objective: To establish the comparative efficacy and cost of fedratinib and BAT Horizon: lifetime Discount rate: 3.5% Currency/year (perspective): £/2020 (healthcare system)	<u>Fedratinib versus BAT</u> • LY gain: 0.848 • QALY gain: 0.615	<u>Fedratinib versus BAT</u> Incremental cost: £8,545	<u>Fedratinib versus BAT</u> ICER: £13,905/QALY
H04, CADTH, 2022(97)	Canada	Cost-utility analysis, discrete event simulation model Study objective: To assess the cost-effectiveness of fedratinib among 2 subgroups: patients without prior exposure to JAK inhibitors (JAKi-naïve patients) and patients previously exposed to ruxolitinib (ruxolitinib-experienced patients) Horizon: lifetime Discount rate: 1.5% Currency/year (perspective): CAD/2019 (healthcare system)	<u>Fedratinib versus BAT</u> • JAKI-naïve patients QALY gain:1.85 • Ruxolitinib-experienced patients QALY gain: 0.7 <u>Fedratinib versus ruxolitinib</u> • JAKI-naïve patients QALY gain: 0.04	<u>Fedratinib versus BAT</u> • JAKI-naïve patients incremental cost: CAD316,043 • Ruxolitinib-experienced patients incremental cost: CAD44,027 <u>Fedratinib versus ruxolitinib</u> • JAKI-naïve patients incremental cost: CAD94,080	<u>Fedratinib versus BAT</u> • JAKI-naïve patients ICER: CAD2,242,600/QALY • Ruxolitinib-experienced patients ICER: CAD63,636/QALY <u>Fedratinib versus ruxolitinib</u> • JAKI-naïve patients ICER: CAD2,119,620/QALY

Abbreviations: CAD = Canadian dollar; CADTH = Canadian Agency for Drugs and Technologies in Health; BAT = best available therapy; ET = essential thrombocytopenia; ICER = incremental cost-effectiveness ratio; JAK = Janus kinase; JAKi = Janus kinase inhibitor; LY = life year; MF = myelofibrosis; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; PMF = primary myelofibrosis; PV = polycythemia vera; QALY = quality-adjusted life year; SLR = systematic literature review; SMC = Scottish Medicines Consortium; US = United States; UK = United Kingdom

B.3.2 Economic evaluation of momelotinib in JAKi-naïve patients

B.3.2.1 Population

The following cost-comparison evaluation is to support the reimbursement of momelotinib in JAKi-naïve patients int-2/HR myelofibrosis and anaemia. Evidence from the SIMPLIFY-1 trial is used to support this cost-comparison. The SIMPLIFY-1 trial enrolled patients beyond the scope of the population proposed for appraisal; namely, patients with int-1 risk disease were included if they had evidence of splenomegaly, and there was no specific inclusion criterion relating to anaemia. Nevertheless, the SIMPLIFY-1 trial is considered the most suitable evidence source to support this evaluation as a randomised, controlled, head-to-head trial assessing momelotinib against the relevant comparator.

B.3.2.2 Modelling approach

As detailed in Section B.3.1, the SLR of economic evaluations in myelofibrosis did not identify any studies assessing momelotinib in the UK or elsewhere. As such, a *de novo* cost-comparison model was developed for the purposes of this appraisal to estimate the economic value of momelotinib versus ruxolitinib in patients with myelofibrosis.

B.3.2.2.1 Time horizon

For the JAKi-naïve cost-comparison model, a time horizon of 10 years was considered. By this time point, any relevant cost differences (e.g. acquisition costs, iron chelation therapy [ICT] and RBC transfusions) are small enough to be considered nominal. A discount rate of 3.5% per annum was applied in line with the NICE reference case.

B.3.2.2.2 Model description

The cost-comparison model was developed in Microsoft Excel. The analysis considered all relevant costs that may differ substantially between patients receiving momelotinib and ruxolitinib. As such, the cost-comparison analysis included drug acquisition costs, blood transfusions, AEs, and concomitant and subsequent therapies.

Other costs, such as resource use for disease management, are expected to be identical among patients receiving momelotinib and those receiving ruxolitinib throughout treatment. Therefore, these costs were not included in the analysis.

Patients were assumed to enter either the momelotinib or ruxolitinib treatment arm, and accrue the associated drug costs over time. Patients are assumed to discontinue initial JAKi monotherapy at a constant rate derived from SIMPLIFY-1 trial data. Following discontinuation of momelotinib or ruxolitinib monotherapy, patients in both arms move on to treatment with BAT. The BAT arm is assumed to contain ruxolitinib as one of its components; the proportional composition of the BAT arm was based on data from SIMPLIFY-2. Mortality is not explicitly modelled, with OS assumed to be identical between the momelotinib and ruxolitinib arms. This is supported by survival outcomes from SIMPLIFY-1, in which OS was comparable between the momelotinib and ruxolitinib arms. A post-hoc crossover-adjusted OS analysis from SIMPLIFY-1 provided further support for the comparable survival benefits of momelotinib and ruxolitinib (Section B.2.7.1.6).

A comparison of features of the cost-comparison model versus cost-effectiveness models used in prior MF NICE appraisals is shown in Table 46.

Table 46. Features of the cost-comparison analysis vs cost-effectiveness models in prior NICE appraisals

	Previous appraisals		**Current appraisal**	
Factor	**TA386(27)**	**TA756(51)**	**Chosen values**	**Justification**
Cycle Length	Weekly cycle length	Weekly cycle length	28-days and annually	Aligned with treatment cycle lengths for momelotinib and ruxolitinib
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NICE reference case
Time horizon	35 years	35 years	10 years	Given assumption of clinical equivalence for the cost-comparison model, 10 years expected to be sufficiently long to capture momelotinib and ruxolitinib time on treatment, after which no differences are expected between treatment arms.
Discounting	3.5%	3.5%	3.5%	NICE reference case
Population	Int-2/HR MF	Int-2/HR MF who have received ruxolitinib (and ruxolitinib is no longer suitable)	Adult patients with MF who are JAKi-naïve and are candidates for JAKi therapy.	The SIMPLIFY-1 head-to-head trial enrolled MF patients with int-1 and non-anaemic patients. However, costs of momelotinib and ruxolitinib treatment are not

	Previous appraisals		Current appraisal	
Factor	**TA386(27)**	**TA756(51)**	**Chosen values**	**Justification**
				expected to differ between population subgroups relating to disease risk or concomitant anaemia
Model type	DES	DES	Cost-comparison model	Results of SIMPLIFY-1 trial indicating non-inferiority between momelotinib and ruxolitinib. NICE early scientific advice. Clinical and health economic expert feedback.
Source of costs	BNF, NHS reference costs, PSSRU and published literature	TA386- updated using 2019, NHS reference cost, MIMS and eMIT.	BNF, eMIT, NHS reference costs, PSSRU, published literature (including prior NICE appraisals)	NICE reference case and suitable publications identified from literature reviews or prior NICE appraisals

Abbreviations: BNF = British National Formulary; DES = discrete event simulation; eMIT = drugs and pharmaceutical electronic market information tool; HR = high-risk; int = intermediate; JAKi = Janus kinase inhibitor; MF = myelofibrosis; MIMS = Monthly Index of Medical Specialties; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit

B.3.2.2.2.1 Momelotinib/ruxolitinib discontinuation

Time to discontinuation or death (TTDD) is derived from the SIMPLIFY-1 trial and informs the movement of patients from momelotinib or ruxolitinib monotherapy to BAT. TTDD data for momelotinib are mature, with data available up to 4.6 years; however, ruxolitinib TTDD was only captured during the RT period of the trial, prior to momelotinib crossover in the ET phase. The 24 weeks of comparative data available show a slightly higher discontinuation rate in the momelotinib arm ([redacted]) compared to the ruxolitinib arm ([redacted]).(62) However, most discontinuations were due to grade 1-3 AEs, which could be managed with a dose de-escalation schema which disproportionately favoured ruxolitinib. Ruxolitinib could be titrated to lower subtherapeutic doses, as evidenced by [redacted] of patients receiving a dose ≤10mg twice daily and [redacted] receiving less than the recommended 20mg twice daily at Week 24. This compares to [redacted] of patients treated with momelotinib being maintained on the recommended 200 mg daily. Additionally, within SIMPLIFY-1 the protocol allowed for ruxolitinib dosing to be adjusted on up to 5 occasions before mandatory unblinding, compared to only 3 occasions with momelotinib.

In real-world use, without the influence of trial protocols on discontinuation, it is expected that discontinuation would be more comparable for momelotinib and

ruxolitinib monotherapy. For the modelling of costs within the cost-comparison model, TTDD is assumed equal for momelotinib and ruxolitinib monotherapies, with a constant discontinuation rate of approximately 5.9% per month (~48-week median TTDD). Clinical experts have advised that when ruxolitinib monotherapy begins to fail, patients move on to BAT, which is comprised primarily of dose-adjusted ruxolitinib in combination with other treatments and supportive therapies, as well as non-ruxolitinib supportive measures. Following momelotinib discontinuation, it is unclear whether post-momelotinib BAT would contain ruxolitinib, given the lack of evidence supporting sequential ruxolitinib treatment following momelotinib, and potential NHS access barriers. In the cost-comparison model, it is, therefore, conservatively assumed that all patients discontinuing first line momelotinib receive subsequent treatment with ruxolitinib-containing BAT (an assumption tested in scenario analyses).

B.3.2.3 Intervention and comparator acquisition costs

B.3.2.3.1 Momelotinib

The list price of momelotinib is £5,650 per 30 tablet pack for 200mg, 150mg and 100mg doses. Drug acquisition costs for momelotinib are captured over the model time horizon. Wastage was assumed to not occur for momelotinib as tablets are administered orally and doses are assumed to align with tablet strengths described above. In addition, as patients are expected to receive either 100mg, 150mg or 200mg doses of momelotinib, and the price per tablet is set to be equal across pack types, the average acquisition cost per 28-day cycle is £5,273.33 per patient. This corresponds to an annual cost of £68,788.75 per patient.

Pending approval of a PAS simple discount of [redacted] to the list price for all strengths, the acquisition cost of momelotinib to the NHS would be [redacted] per 30-tablet pack, or [redacted] per cycle. This corresponds to an annual cost of [redacted] per patient.

Acquisition costs for momelotinib at list price and net price are outlined in Table 47 and Table 48, respectively.

Table 47. Drug acquisition cost and dosing information for momelotinib [List price]

Unit size per tablet (mg)	Dosing regimen	Quantity per pack	Cost per pack	Treatment cost per 28-days	Cost per year
100	Once daily	30	£5,650.00	£5,273.33	£68,788.75
150	Once daily	30	£5,650.00	£5,273.33	£68,788.75
200	Once daily	30	£5,650.00	£5,273.33	£68,788.75

Table 48. Drug acquisition cost and dosing information for momelotinib [PAS price]

Unit size per tablet (mg)	Dosing regimen	Quantity per pack	Cost per pack	Treatment cost per 28-days	Cost per year
100	Once daily	30	[redacted]	[redacted]	[redacted]
150	Once daily	30	[redacted]	[redacted]	[redacted]
200	Once daily	30	[redacted]	[redacted]	[redacted]

B.3.2.3.2 Ruxolitinib

Drug costs for ruxolitinib are sourced from the BNF. The cost per pack for each strength is outlined in Table 49. Flat pricing is in place for all strengths except 5mg, which is half the cost of the 10mg, 15mg and 20mg strength packs.

Table 49. Drug acquisition cost and dosing information for ruxolitinib

Unit size per tablet (mg)	Dosing regimen	Quantity per pack	Cost per pack	Treatment cost per 28-days
5	**Twice daily**	**56**	**£1,428.00**	**£1,428.00**
10	**Twice daily**	56	£2,856.00	£2,856.00
15	**Twice daily**	56	£2,856.00	£2,856.00
20	**Twice daily**	56	£2,856.00	£2,856.00

Drug acquisition costs for ruxolitinib are captured and included in the CCM over the 10-year model time horizon, based on the twice daily recommended dosing regimen. To derive the average treatment cost for ruxolitinib-treated patients, the ratio of 5mg usage to 10mg, 15mg and 20mg usage is required to account for the differing treatment costs. Frequent ruxolitinib dose adjustments typically occur following treatment initiation, as observed in SIMPLIFY-1 (See Figure 34 for ruxolitinib and momelotinib weekly dose intensity over the trial period). Therefore, following visual inspection of Figure 34, it is assumed that dose adjustments are made in the initial 12 weeks of therapy, after which the ratio of 5mg dosing to other strengths remains fixed. Dose shares for each strength of ruxolitinib up to, and following, Week 12 are presented in Table 50. As a conservative assumption, no wastage is assumed for ruxolitinib despite dose titration being more frequent for ruxolitinib than momelotinib,

inevitably resulting in some loss of tablets. The acquisition cost per 28-days for ruxolitinib at each dose, as well as dose distribution before and after 12 weeks, is shown in Table 51. The weighted average acquisition cost per 28-day treatment cycle for ruxolitinib was £2,591.53 for the first 12 weeks of the CCM and £2,573.83 per 28-day treatment cycle thereafter. This results in an annual ruxolitinib treatment cost of £33,628 per patient in year 1 and £33,575 per patient in subsequent years.

Table 50. Dosing regimens of ruxolitinib and associated costs per patient and cycle

Dose	Cost per unit	Dose share overall	Dose share (weeks 0 to 12)	Dose share (after Week 12)	Average cost per 28 days (weeks 0 to 12)	Average cost per 28-days (after Week 12)	Annual cost (year 1)	Annual cost (year 2+)
0	£0	1%	1.10%	0.30%	£2,592	£2,574	£33,628	£33,575
5 mg BD	£1,428	20%	17.28%	21.74%				
10 mg BD	£2,856	15%	13.70%	16.20%				
15 mg BD	£2,856	21%	19.20%	22.70%				
20 mg BD	£2,856	42%	48.00%	36.00%				
25 mg BD	£4,284	2%	0.80%	2.90%				

Abbreviations: BD = twice daily

Table 51. Acquisition costs of the intervention and comparator technologies

	Momelotinib [List price]	Momelotinib [PAS price]	Ruxolitinib
Pharmaceutical formulation	Tablet	Tablet	Tablet
(Anticipated) care setting	Secondary care. Treatment administered at home.	Secondary care. Treatment administered at home.	Secondary care. Treatment administered at home.
Acquisition cost (excluding VAT) *	£5,650	[redacted]	£2,856 (10mg, 15mg and 20mg packs) £1,428 (5mg pack)
Method of administration	Oral	Oral	Oral
Doses	30	30	28
Dosing frequency	Once daily	Once daily	Twice daily
Dose adjustments	Yes, in response to AEs	Yes, in response to AEs	Yes, required dependant on blood platelet concentration and in response to AEs
Average length of a course of treatment	N/A: Chronic therapy	N/A: Chronic therapy	N/A: Chronic therapy
Average cost of a course of treatment (acquisition costs only)	£68,788.75 annually	[redacted] annually	£33,628 annually (year 1) £33,575 annually (year 2+)
(Anticipated) average interval between courses of treatment	N/A: Re-treatment not expected following discontinuation or death	N/A: Re-treatment not expected following discontinuation or death	N/A: Re-treatment not expected following discontinuation or death
(Anticipated) number of repeat courses of treatment	N/A: Re-treatment not expected following discontinuation or death	N/A: Re-treatment not expected following discontinuation or death	N/A: Re-treatment not expected following discontinuation or death

Abbreviations: AE = adverse event; N/A = not applicable; PAS = patient access scheme; VAT = value added tax

B.3.2.4 Disease management costs

Costs associated with blood transfusions, including supportive ICT, and adverse effects of treatments are applied to patients receiving both ruxolitinib and momelotinib, as well as patients who discontinue and are managed with BAT.

Red blood cell transfusions

A cost per RBC transfusion unit of £371.70 from NICE TA756 (2019 costs), originally inflated from £235 based on Varney and Guest, was inflated to 2022 costs using PSSRU NHSCII inflation data to generate a cost per RBC transfusion unit of £399.77.(51) In the original study, the cost per RBC transfusion unit was estimated by dividing the NHS hospital resource use attributable to blood transfusions, plus the total costs incurred by the blood transfusion services, by the estimated number of transfusions. Hospital resource use encompasses costs related to hospital stays, managing blood transfusion-related complications, and staff attendance at blood transfusion committee meetings. Blood transfusion services encompass collecting, testing, processing and issuing blood products.(99)

In SIMPLIFY-1 the mean rate of RBC transfusions was lower in the momelotinib arm (0.5 units/month) compared to the ruxolitinib arm (1 unit/month). When adjusted for strata, the mean rate of RBC transfusion units was [redacted] lower in the momelotinib arm compared to the ruxolitinib arm (rate ratio: [redacted]; p<0.001). This corresponds to an adjusted mean transfusion rate of [redacted] units per month for momelotinib patients compared to [redacted] units per month for ruxolitinib-treated patients. The RBC transfusion rate associated with BAT, derived from the BAT arm of SIMPLIFY-2, is [redacted] units per month. In line with expectations, the BAT RBC transfusion rate is higher than momelotinib but lower than ruxolitinib monotherapy, reflecting the expected reduced transfusion burden following transition to non-ruxolitinib therapies or add-on of anaemia treatments. These rates of transfusion are outlined in Table 52. A comparison of unadjusted transfusion rates for a patient population with Hb <12 g/dL, at baseline shows a similar trend in transfusion rates to the ITT population. The impact of applying these unadjusted rates are explored in a scenario analysis.

The rate of transfusion for patients discontinuing initial momelotinib or ruxolitinib therapy and receiving maintenance BAT is also reported.

Table 52. Rates of RBC transfusions by treatment

	SIMPLIFY 1 ITT		SIMPLIFY 1, Hb <12 g/dL		SIMPLIFY-2
	Momelotinib	Ruxolitinib	Momelotinib	Ruxolitinib	BAT
RBC transfusion rate in RT phase					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) units per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusion rate in RT phase, adjusted for strata					
Mean (95% CI)	[redacted]	[redacted]	N/A		[redacted]
Rate ratio (95% CI)	[redacted]				-
p-value	[redacted]				-

Abbreviations:BAT = best available therapy; CI = confidence interval; Hb = haemoglobin; ITT = intent-to-treat; N/A = not applicable; RBC = red blood cell; RT = randomised treatment; SD = standard deviation

The RBC transfusion rates reported above were applied to the cost per unit of blood to estimate the annual cost of RBC transfusion for each intervention and BAT (Table 53).

Table 53. Annual cost of RBC transfusion by treatment

	RBC transfusion rate (units/month)	Annual cost of RBC transfusions
Momelotinib	[redacted]	[redacted]
Ruxolitinib	[redacted]	[redacted]
BAT	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; RBC = red blood cell

Iron chelation therapy

Experts advised that patients requiring regular RBC transfusions would be indicated for ICT to mitigate complications resulting from iron overload with repeated transfusions. Clinicians advised that deferasirox is the most used ICT for patients with MF. Deferasirox is dosed per kg and taken daily. The cost of treating a patient with defersirox is £653 per 28-days at a dose of 21 mg/kg/day (Table 54), based on the mean baseline weight of the SIMPLIFY-1 trial population (72.5kg).

Table 54. Cost of ICT

Treatment	Cost per pack	Cost per mg	Dose	Cost per person per 28 days
Deferasirox 360mg	£165.45	£0.02	21mg/kg/day	£653.07

Abbreviations: ICT = iron chelation therapy

There is limited guidance on the use of ICT in patients with MF requiring RBC transfusions. Use is expected to become more widespread in TR MF; following a UK advisory board (2023), clinicians noted that guidance on ICT use is expected in upcoming UK MF treatment guidelines.(32) Use of ICT was not well captured in SIMPLIFY-1 concomitant therapies given the relatively short-duration of the randomised treatment phase of the trial. Therefore, it is assumed that patients having a high transfusion burden after 24 weeks of JAKi treatment would be considered for ICT. At the end of the randomised treatment phase of SIMPLIFY-1, [redacted] of the momelotinib arm and [redacted] of the ruxolitinib arm were categorised as transfusion dependant having received ≥4 RBC transfusion units in the previous 8 weeks. According to clinicians, approximately 37% of patients with a high transfusion burden would be treated with ICT.(32) The proportion of patients receiving ICT with BAT is assumed equal to those receiving ruxolitinib. The mean cost of ICT per year is [redacted], [redacted] and [redacted] for momelotinib, ruxolitinib and BAT-treated patients, respectively (Table 55).

Table 55. ICT treatment cost per person and per treatment group

	Cost of ICT per 28-days	Proportion with high transfusion burden (SIMPLIFY-1)*	Proportion with high transfusion burden receiving ICT	Estimated ICT use per treatment group	Average annual ICT cost
Momelotinib	£653.07	[redacted]	37%	[redacted]	[redacted]
Ruxolitinib/ BAT**		[redacted]		[redacted]	[redacted]

*Defined as the proportion at the end of the 24-week randomised treatment phase of SIMPLIFY-1 requiring ≥4 units of RBCs in the prior 8 weeks. **BAT ICT usage assumed equal to ruxolitinib.
Abbreviations: BAT = best available therapy; ICT = iron chelation therapy

B.3.2.5 Adverse event costs

AEs considered in the economic analyses are grade 3/4 AEs with incidence ≥5% in any treatment arm of SIMPLIFY-1 or SIMPLIFY-2 (Table 56). In the SIMPLIFY-1 trial, anaemia, thrombocytopenia, asthenia, and neutropenia were the most common grade 3/4 AEs. Unit costs for thrombocytopenia, asthenia and neutropenia are based on hospitalisation-related NHS reference cost codes. As anaemia is likely to be managed primarily through RBC transfusions, management of grade 3/4 anaemia is assumed to require a single outpatient visit at a haematology service. Derivation of AE costs for each event is described further in Section B.3.3.6.4.

While abdominal pain is a grade 3/4 AE reported in >5% in BAT patients in SIMPLIFY-2, it is assumed that no additional cost is associated with the management of abdominal pain. Abdominal pain can be a symptom of MF resulting from splenomegaly and is, therefore, assumed to be captured within disease management costs.

Table 56. Incidence of grade 3/4 AEs in any treatment arm of SIMPLIFY-1/-2

Adverse event	Adverse event rate		
	Momelotinib	Ruxolitinib	BAT
Anaemia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; BAT = best available therapy

The corresponding annual rate and associated costs of these AEs, as applied in the CCM, are illustrated in Table 57.

Table 57. Annual rate and associated costs of grade 3/4 AEs

AE	Annual AE rate			AE Cost
	Momelotinib	Ruxolitinib	BAT	
Anaemia	[redacted]	[redacted]	[redacted]	£194.02
Thrombocytopenia	[redacted]	[redacted]	[redacted]	£948.22
Asthenia	[redacted]	[redacted]	[redacted]	£13.73
Neutropenia	[redacted]	[redacted]	[redacted]	£1,303.42
Abdominal pain	[redacted]	[redacted]	[redacted]	£0

Abbreviations: AE = adverse event; BAT = best available therapy

B.3.2.6 Subsequent treatment costs

As described in Section B.3.2.2.2, both momelotinib- and ruxolitinib-treated patients receive BAT following discontinuation. For the ruxolitinib arm, discontinuation of ruxolitinib monotherapy and initiation of BAT, which also contains ruxolitinib, reflects the fact that ruxolitinib, when administered as a first JAKi, is rarely discontinued completely in the UK, but rather dose-modified as described in Section B.1.4.3.2. Following discontinuation of momelotinib, as described in Section B.3.2.2.2, it is assumed that patients move on to treatment with BAT. Despite the absence of clinical evidence to support momelotinib to ruxolitinib sequencing, clinicians have advised that, in practice, they would look to use ruxolitinib in a proportion of initially-momelotinib-treated patients if available. It was noted that this may be more relevant to JAKi-naïve patients, and would not be considered for all patients, especially

patients approaching end-of-life. In the base-case scenario, we conservatively assume that all patients discontinuing momelotinib move onto BAT, which includes ruxolitinib. The composition of BAT, with and without ruxolitinib, and the associated costs, are outlined in Table 102 in Section B.3.3.6.5. BAT without ruxolitinib is derived by reallocating the 88.5% use of ruxolitinib across all other BAT therapies, based on their relative proportional use within BAT from SIMPLIFY-2.

B.3.2.7 Uncertainties in the inputs and assumptions

To avoid unnecessary complexity, only the costs which were expected to differ between momelotinib and ruxolitinib patients were consider in the analysis. As such, the only costs included as part of the cost-comparison economic evaluation include momelotinib and ruxolitinib acquisition costs, RBC transfusion costs, ICT costs, AE costs and the cost of subsequent therapies. Other aspects of the natural progression of MF which are omitted from the evaluation due to assumed equivalence between arms include costs associated with mortality and end-of-life care, and costs associated with leukemic transformation of MF.

Uncertainties associated with the model inputs were explored through sensitivity analyses outlined in B.3.2.9; however, the key assumptions made in the model base-case are as follows:

- Patients are assumed to enter either the momelotinib or ruxolitinib treatment arm, and accrue costs associated with either treatment. Patients discontinue initial JAKi treatment at a constant rate derived from SIMPLIFY-1 data. Following discontinuation of momelotinib or ruxolitinib monotherapy, patients in both arms move on to BAT. For modelling of costs within the CCM, discontinuation is assumed equal for momelotinib and ruxolitinib monotherapies. Additionally, ruxolitinib is assumed to be a component of BAT for both arms.

- OS is assumed to be identical between the momelotinib and ruxolitinib arms. This is supported by exploratory survival outcomes from SIMPLIFY-1.

- The percentage of patients needing ICT was not well captured in SIMPLIFY-1, therefore it is assumed that patients with a high transfusion burden after 24 weeks of JAKi treatment would be considered for ICT. The proportion of patients requiring ≥4 RBC transfusion units in the prior 8 weeks was used to inform the cost of ICT, with 37% of this group assumed to require ICT based on clinical expert feedback.(32) Exclusion of ICT costs was therefore explored in scenario analysis to test the impact of ICT costs on the results.

- The cost of ICT was derived through the recommended guidance for deferasirox. A dosing of 21mg/kg/day was utilised as the midpoint of the recommended dose range of 14-28 mg/kg/day, with the mean weight of participants in SIMPLIFY-1 being applied to derive the average cost per patient. The lower bound of this range (14 mg/kg/day) was also tested in scenario analysis.

- There is potential uncertainty as to whether patients would necessarily receive ruxolitinib following momelotinib as a first line JAKi therapy, with a current absence of evidence to support momelotinib to ruxolitinib treatment sequencing. It was conservatively assumed that 88.5% of patients would receive ruxolitinib following discontinuation of momelotinib as per the distribution of therapies within the BAT comparator arm of SIMPLIFY-2, with removal of ruxolitinib (and redistribution to other BAT therapies) explored in scenario analysis.

B.3.2.8 Base-case results

The base-case cost-comparison results based on momelotinib list price and the proposed momelotinib PAS price over 10 years are presented in Table 58 and Table 59, respectively.

For the list price analysis, momelotinib increased total costs by [redacted] per patient over 10 years compared to ruxolitinib.

Following application of the proposed PAS price discount, drug acquisition costs are [redacted] lower per patient in the momelotinib arm compared to the ruxolitinib arm.

Aside from acquisition cost, momelotinib reduced ICT, RBC transfusion and AE costs by [redacted], [redacted] and [redacted] per patient compared to ruxolitinib. However, we are aware ruxolitinib also has a confidential PAS in place therefore the true difference in acquisition costs is unknown. The resulting total incremental costs per patient were [redacted] lower over 10 years for momelotinib compared to ruxolitinib.

Overall, the cost-comparison analysis indicates that momelotinib is cost saving against ruxolitinib in the JAKi-naïve population.

Table 58. Base-case cost-comparison results [List price]

Technology	Drug acquisition cost	Subsequent medicine cost	ICT cost	RBC transfusion cost	AE costs	Total costs	Incremental costs
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-

Abbreviations: AE = adverse event; ICT = iron chelation therapy; RBC = red blood cell

Table 59. Base-case cost-comparison results [PAS price]

Technology	Drug acquisition cost	Subsequent medicine cost	ICT cost	RBC transfusion cost	AE costs	Total costs	Incremental costs
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-

Abbreviations: AE = adverse event; ICT = iron chelation therapy; PAS = patient access scheme; RBC = red blood cell

B.3.2.9 Sensitivity and scenario analysis

B.3.2.9.1 Deterministic and probabilistic sensitivity analysis

Deterministic and probabilistic sensitivity analyses were not deemed appropriate to conduct due to the simplicity of the cost-comparison model. Extensive scenario analyses were conducted to explore uncertainty in the model results (see following section).

B.3.2.9.2 Scenario analysis

Several scenario analyses investigating the cost-comparison key model inputs and assumptions were conducted. The results of the scenario analyses are presented in Table 60 (momelotinib list price) and Table 61 (momelotinib PAS price), with the following scenarios explored:

- Three-year time horizon with no discontinuation applied
- Alternative RBC transfusion cost per unit source (Agrawal 2006)
- Removal of ICT costs and lower ICT dosing for deferasirox of 14 mg/kg/day
- Utilising discontinuation data and unadjusted RBC transfusion rates of a JAKi-naïve population with Hb<12 g/dL
- Ruxolitinib treatment discontinuation informed by constant extrapolation of observed discontinuation from the 24 Week SIMPLIFY-1 trial period
- Application of the 95% CI upper bound of the adjusted RBC transfusion rate ratio from SIMPLIFY-1 ([redacted])
- Exclusion of ruxolitinib from BAT subsequent treatment for momelotinib

As shown in Table 61, incremental costs increased for the momelotinib list price analyses when using a shorter three-year time horizon and no treatment discontinuation from [redacted] to [redacted]. This reflects a scenario exploring the cost differences between patients on treatment over the 3 years. Incremental costs were also slightly increased when removing ICT costs ([redacted]) and lowering the dose of ICT ([redacted]), with reducing the impact of ICT costs favouring ruxolitinib given the

higher proportion of ruxolitinib patients with a high transfusion burden in SIMPLIFY-1 (and therefore higher ICT costs). Use of the 95% CI upper bound of the adjusted rate ratio from SIMPLIFY-1 also slightly increased incremental total costs ([redacted]). Conversely, excluding ruxolitinib from BAT subsequent treatment costs for the momelotinib arm (and redistributing among other BAT therapy options from SIMPLIFY-2) had a substantial impact on the results, leading to a large cost saving for momelotinib compared to ruxolitinib (reduction in total costs of [redacted]) due to ruxolitinib therapy being the most expensive component of BAT from SIMPLIFY-2. Otherwise, incremental costs for momelotinib versus ruxolitinib were slightly reduced compared to the base-case analysis through use of a slightly higher RBC transfusion unit cost from Agrawal 2006 (from [redacted] to [redacted]), applying Hb <12 g/dL population data for treatment discontinuation and RBC transfusion rates ([redacted]), or when utilising a less conservative constant discontinuation probability for ruxolitinib derived from available SIMPLIFY-1 trial data ([redacted]).

As highlighted in Table 61, the scenario analyses showed that momelotinib remained cost saving compared to ruxolitinib across all scenarios when applying the list price for ruxolitinib and PAS price discount for momelotinib. Incremental cost savings increased substantially when excluding ruxolitinib from the BAT subsequent treatment composition for momelotinib (from [redacted] to [redacted]). Sizeable increases in cost savings were also observed when applying a three-year time horizon without applying treatment discontinuation data for either treatment arm ([redacted]) and when assuming ruxolitinib discontinuation rates based on extrapolation of available data from SIMPLIFY-1 ([redacted]). Similar to the list price results, other scenarios had a more minor impact on the resulting incremental costs for momelotinib compared to ruxolitinib, with slight increases in cost savings (to [redacted]) when applying an alternative source of RBC transfusion unit cost data (Agrawal 2006), and slight reductions in cost savings when excluding ICT costs ([redacted]), lowering the ICT dose to 14 mg/kg/day ([redacted]), applying TTD and RBC transfusion unit data for the Hb <12 g/dL population instead of the ITT population ([redacted]) and using the 95% CI upper bound of the RBC transfusion rate ratio for momelotinib vs ruxolitinib from SIMPLIFY-1 ([redacted]).

Table 60. Cost-comparison scenario analysis results: 10-year time horizon [List price]

#	Base-case input	Scenario analysis description	Technology	Acquisition cost	Subsequent medicine cost	ICT cost	RBC transfusion costs	AE costs	Total Costs	Incremental costs
1	Ten-year time horizon with equivalent TTD	Three-year time horizon with no TTD	Ruxolitinib	£93,888	£0	£1,744	£20,245	£893	£116,771	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	RBC transfusion cost source: Varney and Guest, 2003; TA756	Agrawal et al. 2006	Ruxolitinib	£42,175	£219,056	£5,157	£67,161	£2,126	£335,675	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Inclusion of ICT costs	Removal of ICT costs	Ruxolitinib	£42,175	£219,056	£0	£57,507	£2,126	£320,864	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	ICT dose: 21 mg/kg	ICT dose: 14 mg/kg	Ruxolitinib	£42,175	£219,056	£3,438	£57,507	£2,126	£324,302	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	TTD and RBC transfusion rates from S1 ITT population	TTD and unadjusted RBC transfusion rates from Hb<12 population	Ruxolitinib	£39,361	£221,674	£5,157	£57,423	£2,120	£325,735	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Equivalent TTD rates between momelotinib and ruxolitinib	Ruxolitinib d/c: constant extrapolation of S1 ruxolitinib d/c	Ruxolitinib	£146,610	£121,845	£5,157	£58,551	£2,354	£334,519	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	RBC transfusion rate ratio: [redacted]	RBC transfusion rate ratio: [redacted]	Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Momelotinib subsequent treatment costs include ruxolitinib	Momelotinib subsequent treatment costs do not include ruxolitinib	Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; Hb = haemoglobin; ICT = iron chelation therapy; ITT = intent-to-treat; PAS = patient access scheme; RBC = red blood cell; TTD = time to discontinuation

Table 61. Cost-comparison scenario analysis results: 10-year time horizon [PAS price]

#	Base-case input	Scenario analysis description	Technology	Acquisition cost	Subsequent medicine cost	ICT cost	RBC transfusion costs	AE costs	Total Costs	Incremental costs
1	Ten-year time horizon with equivalent TTD	Three-year time horizon with no TTD	Ruxolitinib	£93,888	£0	£1,744	£20,245	£893	£116,771	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	RBC transfusion cost source: Varney and Guest, 2003; TA756	Agrawal et al. 2006	Ruxolitinib	£42,175	£219,056	£5,157	£67,161	£2,126	£335,675	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Inclusion of ICT costs	Removal of ICT costs	Ruxolitinib	£42,175	£219,056	£0	£57,507	£2,126	£320,864	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	ICT dose: 21 mg/kg	ICT dose: 14 mg/kg	Ruxolitinib	£42,175	£219,056	£3,438	£57,507	£2,126	£324,302	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	TTD and RBC transfusion rates from S1 ITT population	TTD and unadjusted RBC transfusion rates from Hb <12 g/dL population	Ruxolitinib	£39,361	£221,674	£5,157	£57,423	£2,120	£325,735	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Equivalent TTD rates between momelotinib and ruxolitinib	Ruxolitinib d/c: constant extrapolation of S1 ruxolitinib d/c	Ruxolitinib	£146,610	£121,845	£5,157	£58,551	£2,354	£334,519	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	RBC transfusion rate ratio: [redacted]	RBC transfusion rate ratio: [redacted]	Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Momelotinib subsequent treatment costs include ruxolitinib	Momelotinib subsequent treatment costs do not include ruxolitinib	Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-
			Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; Hb = haemoglobin; ICT = iron chelation therapy; ITT = intent-to-treat; PAS = patient access scheme; RBC = red blood cell; TTD = time to discontinuation

B.3.3 Economic evaluation of momelotinib in JAKi-experienced patients

No existing economic evaluations of momelotinib (momelotinib) were identified in the cost-effectiveness SLR (Section B.3.1); therefore, a *de novo* cost-effectiveness model was developed.

Three NICE TAs related to myelofibrosis were identified in a pragmatic literature search: two for ruxolitinib and one for fedratinib (ruxolitinib TA289, ruxolitinib TA386(27) [an update of ruxolitinib TA289], and fedratinib TA756).(51) Additionally, two publications by Wade et al. were identified (Wade 2013(100) and 2017(101)). Wade et al. (2013) reviewed TA289, the original NICE TA for ruxolitinib, and Wade et al. (2017) reviewed TA386, the updated ruxolitinib TA. Both economic models used as part of TA386 and TA756 were complex, based on a discrete event simulation (DES) approach.

The Evidence Review Group (ERG) deemed the DES model structure appropriate for TA386, but noted that it required many assumptions, which only allowed uncertainty to be explored on a univariate basis. Conversely, the ERG deemed the DES model structure in TA756 unnecessarily complicated given the limitations of the available clinical evidence, and questioned its value when OS was modelled independently from response and time in previous health state. The NICE Committee agreed with this and reiterated that a simpler model structure might have been more robust given the lack of evidence to inform such a complex model. A summary of TA386 and TA756 is provided in Table 62.

Table 62. Summary of TA386 and TA756

TA386 summary(27, 100, 101)	TA756 summary(51)
• A DES model was used to model the progressive nature of MF, which was deemed appropriate, though complex and with many assumptions made • Ruxolitinib non-responders were assumed to move to BAT after 24 weeks. For the first 24 weeks a mortality benefit for non-responders was assumed with no evidence to back up this assumption	• A DES model was used to model the progressive nature of MF, with patients split into two groups (responders and non-responders) based on response assessment at Week 24, which was retrospectively applied to Weeks 0-24 o The ERG and Committee felt that the model was unnecessarily complicated given the immaturity of the data, and suggested a simpler approach, such as a partitioned survival model, would have been more robust

TA386 summary(27, 100, 101)	TA756 summary(51)
• In clinical practice, response to ruxolitinib is seen relatively quickly; therefore, the stopping rule of 24 weeks may be applied earlier • Evidence for the use of ruxolitinib in patients with lower risk disease was not as robust, as the evidence presented focused on high-risk patients • Overall, the Committee concluded there was sufficient evidence to show ruxolitinib increased OS compared with BAT Overall, ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with PMF, PPV-MF, PET-MF, in those with int-2/HR disease, and if the Company provides ruxolitinib with the discount agreed in the PAS.	• In the original model, a stopping rule was applied, with patients moving from fedratinib to BAT following disease progression ○ The Committee did not believe a stopping rule would apply in practice and suggested 89% of patients should continue on fedratinib in the model (in line with the proportion remaining on ruxolitinib in the BAT arm) • Overall, the Committee concluded that, although fedratinib was likely to increase OS compared with BAT, the OS benefit was highly uncertain based on the evidence presented Overall, fedratinib is recommended for use within the CDF as an option for treating disease-related symptoms of splenomegaly or symptoms of PMF, PPV-MF, or PET-MF in adults. It is recommended only if patients have previously had ruxolitinib and the conditions in the managed access agreement for fedratinib are followed.

Abbreviations: BAT = best available therapy; CDF = Cancer Drugs Fund; ERG = Evidence Review Group; HR = high-risk; int = intermediate; MF = myelofibrosis; OS = overall survival; PMF = primary myelofibrosis; PPV-MF = post-polycythaemia vera myelofibrosis; PET-MF = post essential thrombocythemia myelofibrosis.

B.3.3.1 Patient population

The cost-effectiveness analysis of momelotinib is restricted to a JAKi-experienced population with int-2/HR MF and baseline Hb <12 g/dL. The population is restricted to int-2/HR disease given the absence of JAKi access for int-1 risk patients in England, resulting in momelotinib use in JAKi-experienced patients inevitably being limited to int-2/HR. As described in Section B.1, the base-case population excludes patients with Hb>12 on the basis that they are unlikely to require treatment for their anaemia. While it is unlikely that all patients with Hb <12 g/dL would be considered moderately or severely anaemic, clinicians have advised that restriction to a lower Hb threshold would omit patient groups with clinically relevant treatment-requiring anaemia. However, subgroup analyses are also presented for an Hb <10 g/dL population.

Baseline age of 67.4 years and 60.0% proportion of males were applied in the model. These data were sourced from the ITT population of SIMPLIFY-2, as it provided a larger sample size and no differences in these parameters were expected by subgroup.

All analyses referred to in the following cost-effectiveness evaluation relate to patients with int-2/HR MF, unless the full SIMPLIFY-2 ITT population is specified.

Accordingly, the int-2/HR with Hb <12 g/dL population is referred to throughout this section as the base-case Hb<12 g/dL population. Similarly, int-2/HR with Hb <10 g/dL subgroup will be referred to as the Hb <10 g/dL subgroup.

B.3.3.2 Model structure

B.3.3.2.1 Type of model

A cohort-based Markov model was constructed in Microsoft® Excel to estimate costs and QALYs in patients treated with momelotinib or BAT, over a lifetime horizon. Health economics experts consulted as part of an advisory board in May 2023 agreed that a Markov model structure was appropriate.(32)

The JAKi-experienced CEM structure allows changes in transfusion status to be captured, using patient level data to inform transition probability matrices from the SIMPLIFY-2 trial data.

DES models were used in previous NICE submissions for MF (TA386 and TA756). However, in TA756, the ERG and Committee described the model as unnecessarily complex and suggested that a simpler structure would have been more robust given the lack of evidence to inform a DES model. In the scientific advice received from NICE on the early momelotinib CEM, health economic experts encouraged consideration of simpler model structures, noting that they may be more intuitive for demonstrating momelotinib's impact on transfusion status. Additionally, the level of data required for a DES is unlikely to be available for ruxolitinib or BAT due to treatment crossover at 24 weeks in SIMPLIFY-1 and SIMPLIFY-2. Patient level data from the COMFORT trials, that were used in TA386, are also not available.

A partitioned survival model (PSM) framework was not deemed appropriate because:

- The health states will not follow the typical progression modelled in a PSM, i.e., unidirectional movement from stable disease to progressed disease.

- In SIMPLIFY-1 and SIMPLIFY-2, reversal from TD to TI was observed. Additionally, multiple movements between different transfusion status states are expected. A PSM structure would not allow all possible transitions between health states to be incorporated (i.e., reversal from TD to TI, or multiple movements in both directions between TI/TR/TD states, which is expected based on the movements between groups seen in the SIMPLIFY trials).
- In a PSM, endpoints are independent of each other when extrapolated beyond the trial period; due to independent extrapolation, no link between endpoints (e.g., no link between mortality and transfusion status) would be assumed. Based on the results of SIMPLIFY-1, SIMPLIFY-2, and COMFORT, this assumption would lack clinical plausibility and validity.
- Excluding the NICE appraisals for ruxolitinib (TA356) and fedratinib (TA756), four of the remaining six published models identified in the systematic literature review also adopted a similar DES approach to those used in the NICE appraisals. The remaining two models (Smith et al, 2022(93) and Gomez-Casares et al, 2018(91)), adopted simpler Markov modelling frameworks with on treatment, off-treatment and dead health states. However, this model structure does not allow for differentiation of patients based on transfusion status, which was identified as a key differentiator in clinical outcomes for momelotinib compared to BAT in SIMPLIFY-2.

B.3.3.2.2 Time horizon

The base-case time horizon of 33 years was selected based on the average age of 67.4 years in the SIMPLIFY-2 trial population, and was expected to be sufficiently long to capture costs and health outcomes over the lifetime of the average patient (with the average cohort age reaching 100 years by the end of the model).

B.3.3.2.3 Model schematic and health states

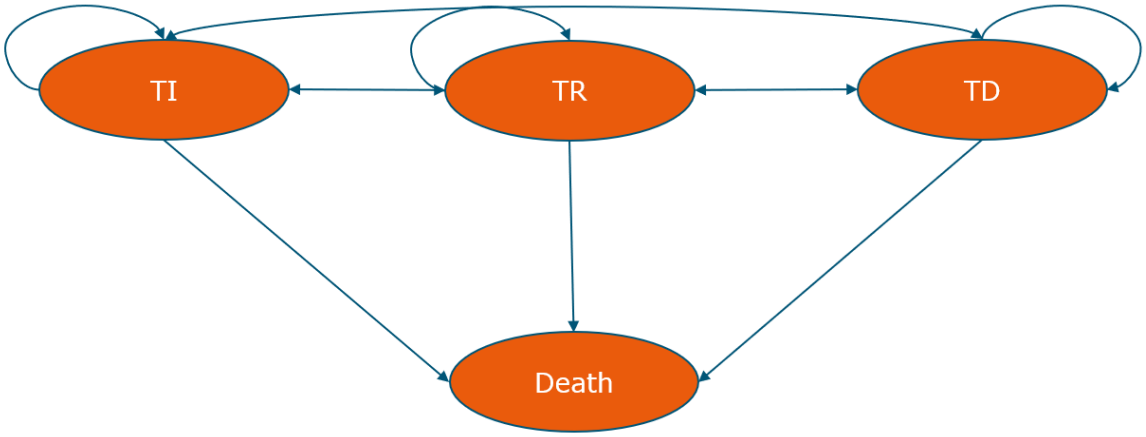
The CEM model structure is illustrated in Figure 37. A Markov model was used, including three transfusion status health states (TI, TR, TD), and death.

Health state definitions were aligned with those used in the momelotinib trials, defined as:

- TI: An absence of RBC transfusions and no haemoglobin level <8 g/dL in the three prior model cycles (12 weeks),
- TD: At least four units of RBC transfusions, or a haemoglobin level <8 g/dL in the two prior model cycles (8 weeks),
- TR: Not meeting the TI or TD criteria.

As described in Section B.1.4.1.4 and B.1.4.2.2, approximately one third of patients are anaemic upon diagnosis, and nearly half of patients become TD one year after diagnosis.(102) Transfusion status is a valid and meaningful measure of response to MF treatment; feedback from a UK clinical expert advisory board meeting in November 2022 noted that “becoming TI was considered the most clinically relevant anaemia endpoint in the momelotinib clinical trials, followed by resolution of anaemia symptoms and no longer requiring supportive measures, like darbepoetin”.(33) Analysis of momelotinib trial data showed that requirement for transfusions was an independent predictor of HRQoL. The analysis also indicated that TI was correlated with other measures of disease improvement, such as spleen size reduction. These are further described in Section B.2.7.1.7. At a separate advisory board meeting, held in May 2023, clinical experts agreed that a lower mortality risk is expected for JAKi-experienced patients who are TI versus those who are not TI, supported by the DIPSS Plus prognostic scoring tool wherein transfusion status is included as an independent prognostic indicator.(32) Therefore, in order to appropriately capture the clinical and economic benefit of TI, health states were defined by transfusion status. Defining the health states by transfusion status allows the model to best capture health outcomes that are meaningful in clinical practice, through maintaining TI or improved anaemia management achieved by patients who transition from TR (or TD) to TI.

Figure 37. JAKi-experienced: Markov model structure diagram



Abbreviations: JAKi = Janus kinase inhibitor; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

A cycle length of 4 weeks was chosen as the most appropriate cycle length to account for: a 12-week rolling assessment, daily dosing of treatments included in the model, and follow-up period time points in the SIMPLIFY-2 trial of 30 days, 12 W weeks, and 6 months. For each cycle, patients can either remain in the same transfusion state, transition to a different transfusion health state or move to the 'death' health state, which is an absorbing health state.

AML was a rare AE in SIMPLIFY-1(62) and SIMPLIFY-2(63) (five [1.2%] and three patients [2.1%], respectively). The inclusion of a health state defined by AML was not considered necessary due to the low incidence and uncertainty associated with generating transition probabilities from a low frequency of events. SIMPLIFY-2 results showed that momelotinib had a non-statistically significant treatment effect on leukaemia-free survival versus BAT. To simplify the modelling approach as recommended through NICE Scientific Advice, and to reflect the same approach as in TA756, progression to AML is not explicitly modelled. Patient mortality associated with AML was expected to be captured within the OS for each health state (defined by transfusion status) and associated costs are assumed to be captured within end-of-life costs.

Previous CEM structures in MF have defined health states based on other clinical endpoints such as SRR and TSS response.(27, 51) Use of such health states have

facilitated the application of differing utility weights to responders and non-responders, and have also been used to predict treatment discontinuation based on assumptions relating to MF disease progression. The model structure presented in this submission deviates from this approach as the effect of momelotinib on RBC transfusion requirements and treatment effect on TI is the main difference between momelotinib and BAT relevant for decision making. As described in Section B.2.7.2.1 no significant incremental spleen response was observed in patients receiving momelotinib compared to BAT. In addition, the impact of symptom improvement on HRQoL is captured in the utility weights assigned to each health state. As SIMPLIFY-2 TTDD data is mature, assumptions linked to response might not be appropriate to predict treatment discontinuation given TTDD data immaturity.

B.3.3.2.4 Features of the economic analysis

Features of the economic analysis compared with previous appraisals are presented in Table 63. The features described are primarily related to the JAKi-experienced CEM.

Table 63. Features of the cost-effectiveness analysis

	Previous appraisals		**Current appraisal**	
Factor	**TA386(27)**	**TA756(51)**	**Chosen values**	**Justification**
Cycle Length	Weekly cycle length	Weekly cycle length	4 weeks	Aligned with treatment cycle lengths for momelotinib and ruxolitinib, and 4-week deemed sufficiently short to capture SIMPLIFY-2 trial outcomes and health state transitions over time
Perspective	NHS/PSS	NHS/PSS	NHS/PPS	NICE reference case
Time horizon	35 years	35 years	Lifetime (33 years)	Lifetime horizon in line with NICE reference case
Discounting	3.5%	3.5%	3.5%	NICE reference case
Population	Int-2/HR MF	Int-2/HR MF who have received ruxolitinib (and ruxolitinib is no longer suitable)	Int-2/HR PMF or post-PV/-ET MF with moderate to severe anaemia, who have previously been treated with a JAKi	Int-1 risk MF patients cannot currently access initial JAKi earlier in the pathway. Therefore, all JAKi-experienced patients will have int-2/HR MF. This approach [redacted].

	Previous appraisals		Current appraisal	
Factor	**TA386(27)**	**TA756(51)**	**Chosen values**	**Justification**
Model type	DES	DES	Markov model	NICE TA756 ERG and committee feedback. NICE early scientific advice. Clinical and health economic expert feedback.
Source of utilities	COMFORT-I trial (MF-8D) and assumption	JAKARTA-2 trial (MF-8D)	SIMPLIFY-2 trial (EQ-5D-5L cross-walked to EQ-5D-3L)	EQ-5D-3L utilities for each transfusion status health state from available trial data and applied in line with NICE reference case.
Source of costs	BNF, NHS reference costs, PSSRU and published literature	TA386- updated using 2019, NHS reference cost, MIMS and eMIT.	BNF, eMIT, NHS reference costs, PSSRU, published literature (including prior NICE appraisals)	NICE reference case and suitable literature identified from literature reviews or prior NICE appraisals

Abbreviations: BNF = British National Formulary; CEM = cost-effectiveness model; DES = discrete event simulation; eMIT = drugs and pharmaceutical electronic market information tool; EQ-5D = EuroQol 5-dimensions; ERG = Evidence Review Group; ET = essential thrombocythemia; HR = high-risk; int = intermediate; JAKi = Janus kinase inhibitor; MF = myelofibrosis; MF-8D = myelofibrosis 8-dimensions instrument; MIMS = Monthly Index of Medical Specialties; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PMF = primary myelofibrosis; PV = polycythemia vera; PSS = Personal Social Services; PSSRU = Personal Social Services Research Unit

B.3.3.3 Intervention technology and comparators

The intervention is momelotinib at a dose of either 100mg, 150mg or 200mg once daily, administered orally.

Based on the NICE methods guide, comparators should be established care in England.(60) Both ruxolitinib and fedratinib are approved and recommended by NICE for the treatment of myelofibrosis. However, fedratinib is reimbursed by NHS England via the CDF and is not available via routine commissioning;(51) it is therefore not included as a comparator in the model. Ruxolitinib is the only approved JAKi myelofibrosis therapy in England that is reimbursed via routine commissioning.(27) Ruxolitinib is recommended by NICE as an option for treating disease-related splenomegaly or symptoms in adults with PMF, post-PV MF or post-ET MF in patients with int-2/HR disease only.(27)

Apart from fedratinib, there are no treatments recommended by NICE for JAKi-experienced patients. JAKi-experienced patients may discontinue ruxolitinib if not optimally managed; however, based on clinical advice supported by BSH guidelines,(47) ruxolitinib discontinuation does not routinely happen in practice.

Instead, patients are treated with BAT, which is a mixture of dose-adjusted ruxolitinib and/or established clinical practice (Section B.2.5.2.1). This was confirmed at a clinical advisory board in in November 2022,(33) aligning with the advice received by the submitting company during TA756 and adopted during that appraisal. Therefore, BAT as described in SIMPLIFY-2 is considered the most relevant comparator for JAKi-experienced patients.(103) The composition of BAT in SIMPLIFY-2 is presented in Table 64.(63)

Table 64. Composition of BAT in SIMPLIFY-2(63)

	Proportion	n
Ruxolitinib	88.5%	46
Hydroxyurea	23.1%	12
Prednisone / prednisolone	11.5%	6
Danazol	5.8%	3
Erythropoiesis-stimulating agent	3.8%	2
No therapy	3.8%	2
Anagrelide	1.9%	1
Aranesp	1.9%	1
Aspirin	1.9%	1
Thalidomide	1.9%	1

Abbreviations: BAT = best available therapy

B.3.3.4 Clinical parameters and variables

B.3.3.4.1 Input sources for clinical efficacy

Efficacy data (transition probabilities, OS, TTD) for the JAKi-experienced base-case population included in the CEM were derived from SIMPLIFY-2, given the availability of direct comparative data for both momelotinib and BAT from the trial.

B.3.3.4.2 Transition probabilities

The model health states for the JAKi-experienced population are described in Section B.3.3.2.3. Efficacy is incorporated in the CEM through the achievement and maintenance of TI. Transfusion-related efficacy data for momelotinib and BAT are derived from SIMPLIFY-2 patient level data. Data were analysed to generate transition counts and subsequently transition probabilities for the first six cycles (up to Week 24). Transition probabilities are used only to inform movement between TI, TR and TD health states. Different definitions were used for the transition probability derivation compared to those used to derived transfusion status data reported in the

SIMPLIFY-2 CSR, in order to account for missing data relating to Hb results or death/withdrawal during the trial period.

Mortality risk, which informs movement to the death state, is modelled separately, and described in further detail in Section B.3.3.4.3. Patients who died or withdrew from the trial early are included in the transition counts until the cycle prior to death or withdrawal. Patients with a missing Hb record in any cycle are assumed to have an unchanged transfusion status from their previous cycle.

Due to the definition of TI used in the trials, requiring 12 weeks of data to be available for assessment, the first transfusion status measurements after baseline were not available until Week 12 in the trials. In the absence of data between baseline and Week 12, it was assumed that for cycle 0-1 (Week 0-4) and cycle 1-2 (Week 4-8) patients would experience no change from baseline transfusion status following treatment initiation. Changes observed in the trial within the first 12 weeks are applied only in cycle 3 (Week 8-12).

Patient level data for deriving transition probabilities are available only for the first 6 cycles reflecting the 24-week randomised treatment period of SIMPLIFY-2. From cycle 7 onwards, a modified transition probability matrix from cycle 6 is applied for the duration of the model to both treatment arms. It assumes the movement of patients between states during cycle 6 is reflective of subsequent movements, with an alternative approach (average of cycles 4-6 transition probabilities) explored in scenario analysis. The application of transition probabilities, and therefore movement between states, beyond cycle 6 informs the accruement of health state specific costs and HRQoL, mortality is unaffected given its basis in the Week 24 transfusion status.

As no efficacy data is available beyond Week 24 it is conservatively assumed that neither momelotinib nor BAT patients experienced improvement in transfusion status beyond Week 24. While the proportion of patients who are TI decreased for BAT patients over the duration of SIMPLIFY-2, it increased for momelotinib patients with recent data from the MOMENTUM trial indicating momelotinib-treated patients may experience further improvement beyond Week 24.(64) This assumption was implemented by modifying the cycle 6 transition probability matrix applied for future

cycles to prevent backward movement to 'better' health states following Week 24, i.e., TR or TD patients cannot move to the TI health state and TD patients cannot move to the TR health state. Less conservative alternative assumptions (assuming no movement after 24 weeks, capping backward transition probabilities by equivalent forward transition probabilities) were then explored in scenario analyses to explore the impact of allowing some improvement in transfusion status. Pooled momelotinib and BAT transition counts were also used to derive the matrix for cycles 7+ to maximise the sample size and to ensure neither treatment arm is disproportionately advantaged or disadvantaged by the lack of data following Week 24. This also ensures that health state membership in future model cycles is not biased by treatment specific results observed specifically for health state transitions between 20 to 24 weeks in SIMPLIFY-2.

The baseline distribution of patients in each health state upon entering the model is set to be equal in both treatment arms and derived as the pooled baseline distribution across both treatment arms from SIMPLIFY-2. Pooled baseline health state distribution data (as well as momelotinib and BAT specific data from SIMPLIFY-2) are presented in Table 65. The transition probability matrices for momelotinib and BAT in the base-case Hb <12 g/dL population for the first six cycles are presented in Table 66 to Table 70. Baseline health state distribution and transition probabilities applied for the Hb <10 g/dL subgroup analysis are presented in Appendix N.1.3.

Table 65. Mean baseline health state distribution for base-case population

Health state	Pooled momelotinib and BAT	Momelotinib	BAT
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 66. Transition probability matrix for baseline to cycle 1 (Week 0-4), and cycle 1 to cycle 2 (Week 4-8)

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	100%	0%	0%	100%	0%	0%
TR	0%	100%	0%	0%	100%	0%
TD	0%	0%	100%	0%	0%	100%

Abbreviations: BAT = best available therapy;TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 67. Transition probability matrix for cycle 2 to cycle 3 (Week 8-12)

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 68. Transition probability matrix for cycle 3 to cycle 4 (Week 12-16)

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 69. Transition probability matrix for cycle 4 to cycle 5 (Week 16-20)

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 70. Transition probability matrix for cycle 5 to cycle 6 (Week 20-24)

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 71 presents the transition probability matrices for momelotinib and BAT used to extrapolate transfusion health state membership beyond 24 weeks, derived from the transition probability matrix in Table 70 but conservatively assuming no

backwards movement. Pooled data were applied in the base-case analysis, with treatment specific estimates applied in scenario analyses. Alternative transition probability extrapolation matrices explored in scenario analyses are presented in Table 72, Table 73 and Table 74.

Table 71. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – base-case probabilities using cycle 6 transition probabilities and assuming no improvement in transfusion status

	Pooled momelotinib + BAT (base-case)			Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: extrapolate based on cycle 6 transition probabilities but assuming no movement to better health states
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

Table 72. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – average of cycle 4-6 transition probabilities scenario analysis

	Pooled Momelotinib + BAT		
From/to health state	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

Note: extrapolate based on average of cycle 4-6 probabilities
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

Table 73. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – no change in transfusion status after Week 24 scenario analysis

	Pooled Momelotinib + BAT		
From/to health state	**TI**	**TR**	**TD**
TI	100%	0%	0%
TR	0%	100%	0%
TD	0%	0%	100%

Note: extrapolate assumed no movement to better health states
BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

Table 74. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – cap probability of improvement in transfusion status by probability of worsening transfusion status scenario analysis

	Pooled Momelotinib + BAT		
From/to health state	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

Note: extrapolate based on cycle 6 transition probabilities but assuming no movement to better health states
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

B.3.3.4.3 Survival

In SIMPLIFY-2, no significant differences in mortality were observed between treatment arms in the first 24 weeks. Comparison of survival outcomes between treatment arms after 24 weeks was confounded due to patients in the BAT arm crossing over to momelotinib at Week 24. As such, pooled mortality across the momelotinib and BAT arms is used to estimate mortality risk in the first 24 weeks in the model, following which mortality is based on transfusion status at 24 weeks. Figure 25 in Section B.2.7.2.6 demonstrates that transfusion status at 24 weeks in SIMPLIFY-2 was predictive of survival, which was further validated by clinical experts who stated that patients who were TD at 24 weeks would have poorer long-term survival outcomes than those who were TI. This relationship between requirement for RBC transfusions after 6 months of treatment and OS has similarly been described in other predictive models in MF external to momelotinib, such as a recent prognostic (RR6) developed for MF to predict survival after 6 months for ruxolitinib.(59)

In the CEM, a TI mortality risk based on TI survival from Week 24 is then applied to the TI state. Similarly, a non-TI mortality risk from Week 24 is applied to both TR and TD states beyond Week 24. This involves extrapolation of two separate OS curves, one of which is applied to TI patients and the other to non-TI (TR and TD). While clinicians have advised that patients requiring more frequent transfusions may have poorer survival prognosis, the evidence to support this is not conclusive. Prognostic models such as the DIPSS+ and RR6 predict poorer survival based on any requirement for RBC transfusions to manage anaemia in MF. Furthermore, SIMPLIFY-2 survival outcomes supported a difference in survival stratified by TI and

non-TI while the TR sample size trial was too small to determine any meaningful difference in survival between TR and TD from Week 24. Expert clinical feedback confirmed that applying the same mortality risk to TD and TR was most appropriate and reflective of available evidence.(32) The same health state mortality risk is applied to both BAT and momelotinib arms, with differences in survival between treatment arms in the model driven by differences in transfusion status at 24 weeks.

Patients who crossed over from BAT to momelotinib were excluded from the survival analyses to avoid confounding results due to change in transfusion status following momelotinib initiation. Therefore, the momelotinib only arm is used to estimate TI and non-TI OS curves from Week 24.

In line with NICE Decision Support Unit guidelines, the following six parametric distributions are fitted to the KM data of TI and non-TI survival using the 'flexsurv' package in R: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma.(104) Curves are fitted to the OS KM curves for each momelotinib TI and non-TI cohort for the base-case Hb <12 g/dL population from SIMPLIFY-2. This was also investigated for other relevant population groups from SIMPLIFY-2 (ITT, Hb <10 g/dL subgroup) as a validation exercise to help select the most appropriate parametric models according to internal consistency between population groups.

For each set of TI and non-TI OS curves, the proportional hazards (PH) assumption was tested via assessment of log-cumulative hazard plots and Schoenfeld residuals to determine whether TI and non-TI OS were appropriate to model using a single parametric model or using independent parametric fits. In line with NICE DSU guidance, the PH assumption was deemed inappropriate if the log-cumulative hazard plots crossed or appeared non-parallel, or if the Schoenfeld residuals plot produced a p-value <0.05, or showed a fitted residuals line that appeared non-parallel to the 0 line.

The best fitting distribution was then chosen according to statistical fit (AIC [Akaike Information Criterion] and BIC [Bayesian Information Criterion]), visual inspection of the fitted curves against the KM data to ensure the survival distributions closely predict the observed OS events, and plausibility based on clinical expert feedback.

Importantly, models were also selected on the basis of internal consistency between population groups, assuming that the ITT populations survival should be comparable or greater to the base-case Hb <12 g/dL population, but greater than the Hb <10 g/dL subgroup, given the importance of Hb <10 g/dL as a negative predictor of survival. Review and discussion of the ITT and Hb <10 g/dL subgroup OS data, and associated parametric models, is included in Appendix N.1.2. Additionally, internal consistency was considered between TI and non-TI extrapolations within population groups, with patients who are TI at 24 weeks expected to have improved long-term survival expectations over those who were non-TI.

Lower AIC and BIC values indicate parametric survival models with better statistical fit. In order to better categorise parametric models based on statistical fit relative to the model with the lowest AIC/BIC values, modified Burnham/Anderson(105) and modified Kass/Raftery(106, 107) rules of thumb were adopted for AIC and BIC, respectively, similar to those applied in NICE TA612, NICE TA640 and NICE TA883 (Table 75).(108-110)

Table 75. Modified Burnham/Anderson criteria for AIC and modified Kass/Raftery criteria for BIC

AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
0 to 4	Good	0-10	Reasonable
4 to 7	Reasonable		
7 to 10	Inferior		
>10	Poor	>10	Poor

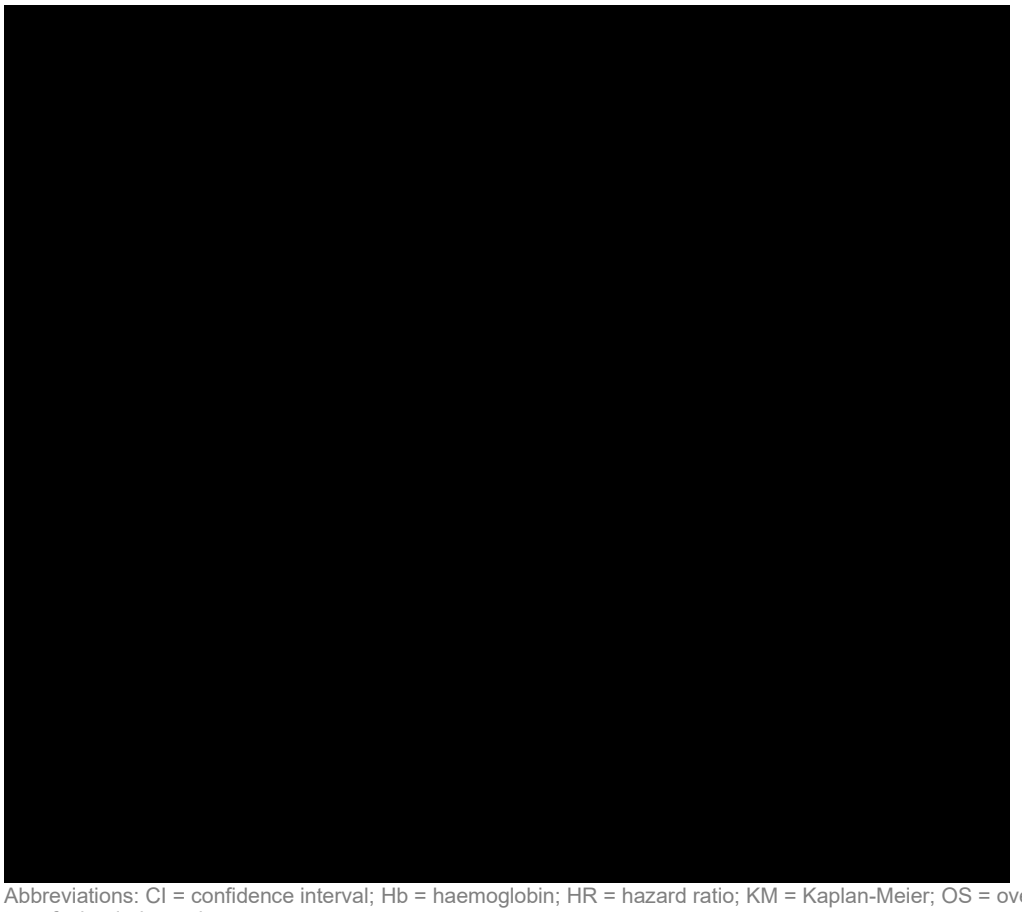
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

All OS curves derived from clinical trial data are capped by age- and sex-matched general population mortality for England sourced from Office for National Statistics national life tables, such that the clinical trial risk of mortality per cycle does not fall below the per cycle risk of mortality adjusted from the general population.(111)

Non-TI OS curves are capped by TI OS such that the risk of mortality per cycle does not fall below TI OS risk of mortality per cycle, with clinical experts at a May 2023 advisory board indicating that it would not be plausible for TR or TD OS to be greater than TI OS.(32) All plots below present OS curves *prior* to capping by general

population or TI mortality (for the non-TI curves). TI and non-TI OS KM curves and associated number at risk are presented in Figure 38.

Figure 38. TI and non-TI OS KM curves from Week 24 and number at risk, SIMPLIFY-2 momelotinib only (base-case Hb <12 g/dL population)



Abbreviations: CI = confidence interval; Hb = haemoglobin; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; TI = transfusion-independent

Prior to the fitting of parametric models for the base-case Hb <12 g/dL population, log-cumulative hazard plot and Schoenfeld residual plots were generated to assess whether the PH assumption holds (Figure 39 and Figure 40, respectively).

Figure 39. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 40. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

While the p-value from the Schoenfeld residuals test (>0.05) suggested a PH assumption may be reasonable, given the log-cumulative hazard plots for TI and non-TI cohorts are not clearly parallel and the fitted residuals line on the Schoenfeld residuals plot is clearly non-parallel to the 0 line, the PH assumption was assumed to be unsuitable for the base-case Hb <12 g/dL population, with independent parametric fits explored.

Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 76 for each pure momelotinib arm parametric model for the base-case Hb <12 g/dL population, for those who are TI at Week 24. The log-normal model produced the best statistical fit with the lowest AIC and BIC.

Table 76. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	5	[redacted]	3
Weibull	[redacted]	3	[redacted]	4
Gompertz	[redacted]	6	[redacted]	5
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	1	[redacted]	1
Generalised gamma	[redacted]	4	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independence

AIC and BIC relative fit classifications for the base-case TI models are shown below in Table 77. Statistical fit differences were fairly uninformative for differentiating between parametric models, with all other parametric models within 4 AIC points and 10 BIC points of the log-normal.

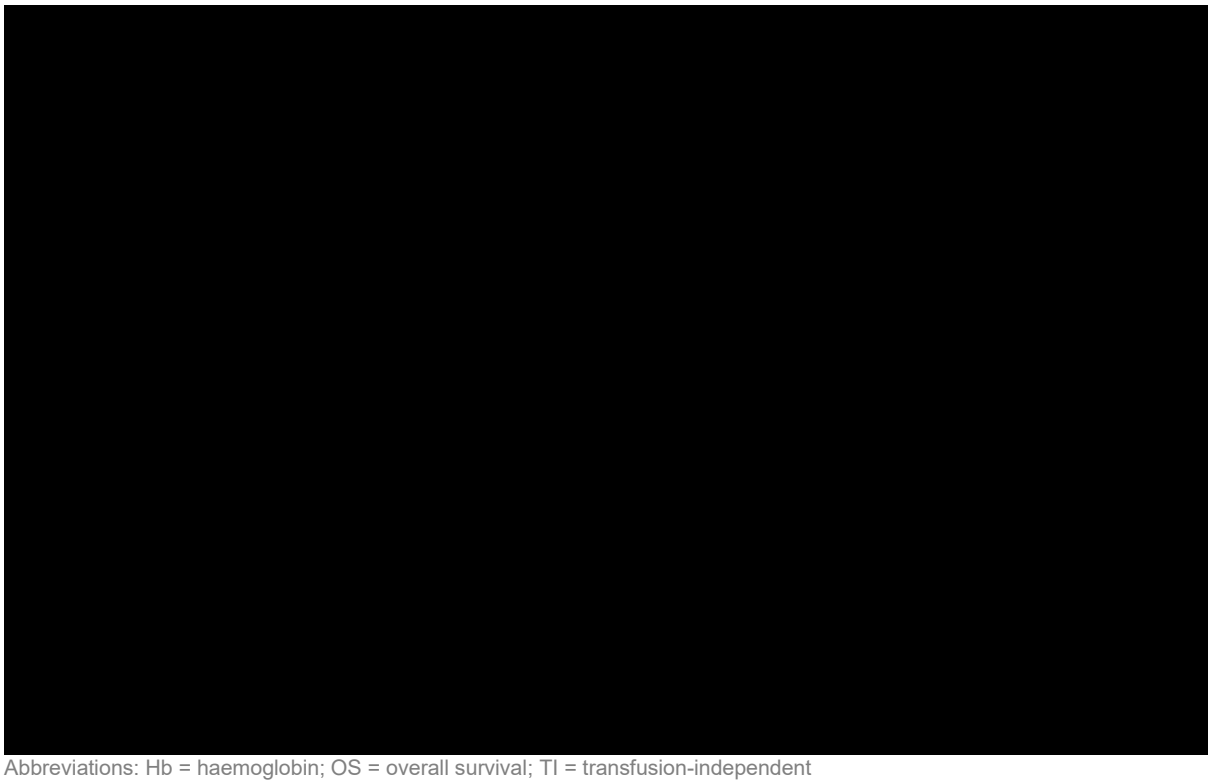
Table 77. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Good	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	-	[redacted]	-
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independence

Figure 41 and Table 78 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Gompertz) to [redacted] (exponential) at 5 years and [redacted] (Gompertz) to [redacted] (generalised gamma) at 10 years across parametric models.

Figure 41. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, TI, from Week 24 (base-case Hb<12 g/dL population)



Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 78. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Visual fit assessment was again inconclusive, with most parametric models appearing to produce reasonable visual fits to the data, albeit with the exponential model appearing to underpredict the KM curve for most of the first 2-years of follow-up.

Furthermore, additional considerations in the selection of the most appropriate curve for those who were TI at 24 weeks were:

1. Internal consistency:

    a) TI patients are expected to have greater or comparable long-term survival to non-TI patients. Therefore, Weibull and Gompertz models are not considered plausible, since they produced 10-year survival estimates ([redacted] and [redacted], respectively) which were lower than all parametric models for the non-TI parametric extrapolations.

    b) It is assumed that landmark survival of the base-case Hb <12 g/dL population at 5 and 10 years is expected to be similar or lower than the ITT group and greater than the corresponding Hb <10 g/dL population. On this basis, the exponential ([redacted]) and generalised gamma ([redacted]) models were also excluded on the basis that they produced higher long-term survival than all ITT TI parametric models Appendix N.1.1).

2. Clinical expectation for TI survival: At a clinical-HEOR advisory board, clinicians were shown two blinded parametric survival curves reporting estimated survival based on transfusion status for the full SIMPLIFY-2 population from Week 24. Parametric model 1 reported 5- and 10-year TI survival to be [redacted] and [redacted], respectively, while parametric model 2 reported 5- and 10-year survival to be [redacted] and [redacted], respectively. Clinicians choose parametric model 1 as a reasonable model choice while the alternative model was not considered likely given that more patients are expected to be alive 10 years. While this advice related to the ITT population rather than the base-case Hb <12 g/dL population, survival estimates are expected to be comparable or slightly lower for this subgroup.

Both the log-logistic and log-normal models produced 10-year survival estimates which were not contradicted by TI or non-TI extrapolations for other population groups, and were also in line with clinical expectations for TI patient survival. The

log-normal model was selected based on slightly better statistical fit, in the absence of other clear criteria to differentiate between parametric models. Log-logistic was then explored via scenario analysis.

For the Hb <10 g/dL subgroup analysis, the log-logistic model was used to model TI OS after 24 weeks. Further details on the model selection process for the Hb <10 g/dL subgroup are presented in Appendix N.1.2 and Appendix N.1.3.

Survival extrapolation for Non-TI patients

The group of non-TI Hb <12 g/dL patients at Week 24 was the same patient group as the non-TI ITT population. This is since patients who were non-TI at 24 weeks in SIMPLIFY-2 belonged to the base-case Hb <12 g/dL population. Therefore, the following discussion of non-TI survival extrapolations are equally applicable to the base-case Hb <12 g/dL and the ITT population OS data.

AIC and BIC statistics are shown in Table 79 for each pure momelotinib arm parametric model for the base-case Hb <12 g/dL population (non-TI). The exponential model produced the best statistical fit with the lowest AIC and BIC.

Table 79. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	6	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

AIC and BIC relative fit classifications for the base-case Hb <12 g/dL population TI models are shown in Table 80. Compared to the exponential model, all models produced good relative fits based on AIC (<4-point difference) and reasonable relative statistical fits according to BIC (<10-point difference).

Table 80. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	-	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 42 and Table 81 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between 24.02% (Weibull) and 31.02% (log-normal) at 5 years, and 4.41% (Weibull) to 15.16% (log-normal) at 10 years, across parametric models.

Figure 42. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 81. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In line with the statistical fit results, all parametric models appeared to produce reasonable visual fits to the KM curve.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have greater OS than patients who are TR or TD (i.e., non-TI), and that they would expect few patients in the TD health state to be alive after 10 years.(32) In addition, clinical experts noted that patients who are TI would have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations between TI and TR/TD patients.

While not explicit in terms of specific survival expectations at 10 years for TI and non-TI groups, this suggested that the exponential and Weibull models produced more clinically plausible extrapolations for the ITT or base-case Hb <12 g/dL population non-TI cohorts (assuming similar survival expectations between both population groups) than other parametric models, with the remaining parametric models (Gompertz, log-logistic, log-normal, generalised gamma) all producing 10-year survival estimates ([redacted] to [redacted]) similar to or potentially greater than the most plausible parametric models (log-logistic, log-normal, generalised gamma) for the ITT TI group ([redacted] to [redacted]; see Appendix N.1.1).

Based on the criteria above, the exponential model was considered the best overall parametric model fit to base-case Hb <12 g/dL non-TI OS data, with a marginal improvement over the Weibull model in terms of statistical fit (lower AIC/BIC). The Weibull model was then explored in scenario analysis.

For the Hb <10 g/dL subgroup analysis, the Weibull model was used to model non-TI OS after the first 24 weeks. Additional information on the model selection process for the Hb <10 g/dL subgroup are presented in Appendix N.1.2 and Appendix N.1.3.

B.3.3.4.4 Time to discontinuation or death

TTDD was used to estimate the proportion of patients remaining alive and on treatment over time in the JAKi-experienced CEM, with those off-treatment determined by the difference in TTDD compared to overall OS across health states. TTDD was capped by overall OS to prevent the proportion of patients on treatment being greater than those remaining alive. Similar to the JAKi-naïve CCM, this is primarily used to determine drug specific costs (i.e., drug acquisition, administration

and adverse event costs), though also used for a scenario analysis where BAT specific health state utilities are applied to patients discontinuing momelotinib.

No discontinuation is assumed for the BAT comparator as this is composed of all subsequent treatments. Therefore, if any individual element of BAT is discontinued, it will only be replaced with another element of BAT. This aligns with how the comparator arm was modelled for NICE TA756 and was validated by clinicians at an advisory board,(32) who confirmed that the average composition of these therapies is not expected to change significantly over time. As the TTDD curve applied for momelotinib contained death events, TTDD extrapolations were capped by the sum of OS across each health state to prevent the proportion on treatment over time being higher than the proportion alive.

TTDD data for the base-case Hb <12 g/dL population, derived from SIMPLIFY-2, were analysed and assessed in line with methodology used to analyse OS data (Section B.3.3.4.3). However, given the availability of complete data, TTDD curves for momelotinib were primarily selected based on statistical and visual fit. TTDD for the pure momelotinib arm is presented in Figure 43 for the base-case Hb <12 g/dL population.

Figure 43. Pure momelotinib TTDD KM curves from baseline and number at risk, SIMPLIFY-2 (base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; TTDD = time to treatment discontinuation or death

AIC and BIC statistics are shown in Table 82 for each pure momelotinib arm TTDD parametric model for the base-case Hb <12 g/dL population. The generalised gamma model produced the best statistical fit with the lowest AIC and BIC.

Table 82: Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 TTDD parametric distributions, overall cohort, from baseline (base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	3	[redacted]	2
Weibull	[redacted]	4	[redacted]	4
Gompertz	[redacted]	2	[redacted]	3
Log-logistic	[redacted]	6	[redacted]	6
Log-normal	[redacted]	5	[redacted]	5
Generalised gamma	[redacted]	1	[redacted]	1

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; TTDD = time to treatment discontinuation or death

AIC and BIC relative fit classifications for the Hb <12 g/dL TTDD models for momelotinib are shown in Table 83. The exponential, Weibull and Gompertz models all appeared to be reasonable relative statistical fits compared to the generalised gamma (4-7 AIC difference, <10 BIC difference). However, the log-logistic and log-normal models were poor relative statistical fits compared to the generalised gamma (as well as the exponential, Weibull and Gompertz models) with a >10 difference in both AIC and BIC.

Table 83. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 TTDD parametric distributions, TI, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Reasonable	[redacted]	Reasonable
Gompertz	[redacted]	Reasonable	[redacted]	Reasonable
Log-logistic	[redacted]	Poor	[redacted]	Poor
Log-normal	[redacted]	Poor	[redacted]	Poor
Generalised gamma	[redacted]	-	[redacted]	-

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; TI = transfusion-independent; TTD = time to treatment discontinuation or death

Figure 44 shows TTDD estimates for each distribution over time up to 5 years overlayed with the TTDD KM curve, which reaches close to 0% of patients on treatment at ~3.5 years.

Figure 44. Pure momelotinib TTDD parametric curves from baseline, SIMPLIFY-2, (base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; TTDD = time to treatment discontinuation or death

In terms of visual fit, the log-normal and log-logistic both produced poor visual fits to the observed data with underpredictions of the KM curve up to ~2.5 years, and substantial overpredictions of the tail of the KM curve. Exponential and Weibull models both produced similar extrapolations, with underpredictions of the KM curve between ~0.5 years and ~3 years, and slightly over-predicting the tail. The generalised gamma and Gompertz models appeared to produce the best overall visual fits to the curve, though the generalised gamma underpredicted the beginning of the KM curve (sharp drop in predicted TTDD from baseline). The models also slightly overpredicted (generalised gamma) and underpredicted (Gompertz) the middle section of the KM curve, with the generalised gamma producing a slightly closer fit to the tail.

Given the availability of complete survival data for the momelotinib KM curve, the Gompertz model was selected based on statistical and visual fit to the KM curve. While the generalised gamma model produced the best statistical fit, the model produced a likely implausible sharp drop in TTDD at the beginning of the curve and was therefore excluded from consideration. Aside from the Gompertz and generalised gamma models, the exponential and Weibull models produced the next best statistical and visual fits, with the exponential model explored in scenario analysis (given the improved statistical fit and similar visual fit to the Weibull model).

The Gompertz model was also used to model TTDD for momelotinib for the Hb <10 g/dL subgroup analysis. Additional information on the model selection process for the Hb <10 g/dL subgroup are presented in Appendix N.1.2 and Appendix N.1.3.

B.3.3.4.5 Adverse events

In the SIMPLIFY-1 and SIMPLIFY-2 trials, thrombocytopenia and anaemia were the most common grade 3/4 AEs. Grade 3/4 AEs with >5% incidence in any treatment arm of the SIMPLIFY-1 or SIMPLIFY-2 trials are included in the models. These adverse event estimates were converted to rates per cycle and applied for the duration of treatment in each model (see Section B.3.3.6.4).

ITT population data was used to increase the sample sizes available for informing AE estimates, given the risk of AEs is not expected to vary substantially in the base-case Hb <12 g/dL population.

Table 84. Incidence of grade 3/4 AEs in any treatment arm in SIMPLIFY-2 applied in CEM

Adverse event	Momelotinib	BAT
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]

Abbreviations: AE= adverse event; BAT = best available therapy; CEM = cost-effectiveness model

AE disutilities and management costs applied to these AEs are described in B.3.3.5.4 and Section B.3.3.6.4, respectively.

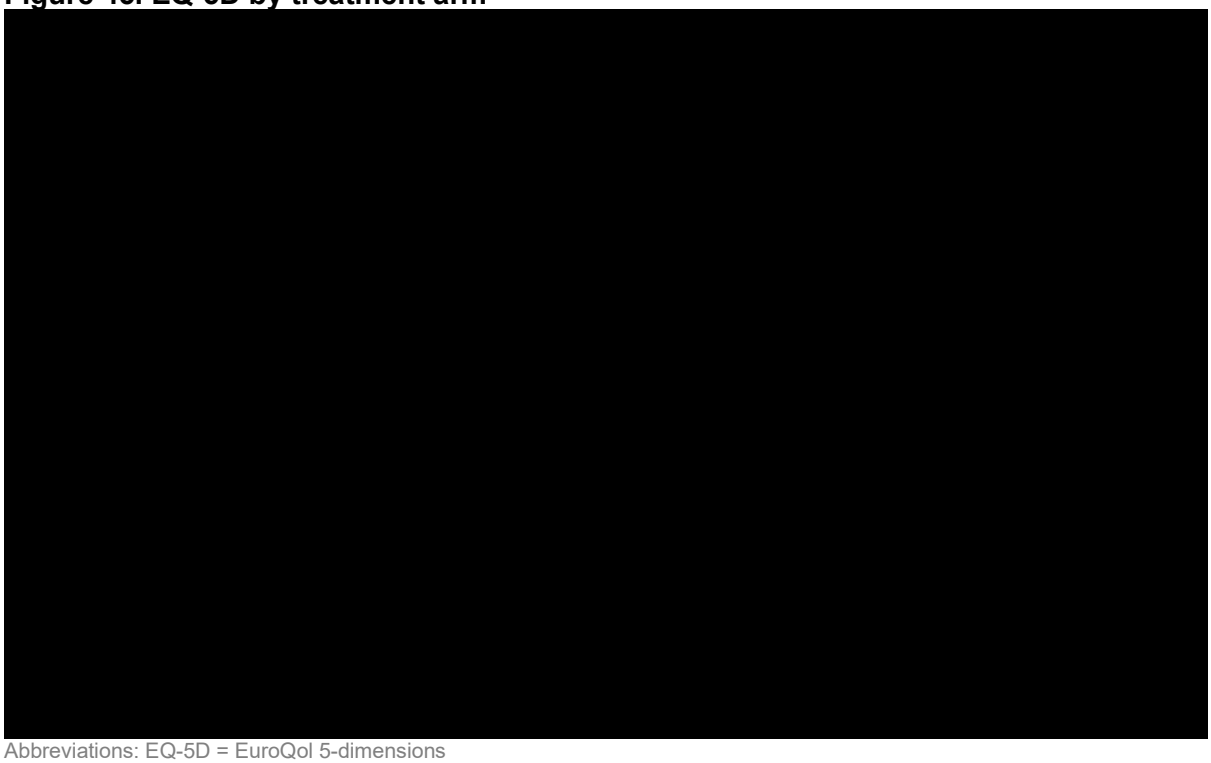
B.3.3.5 Measurement and valuation of health effects

B.3.3.5.1 Health-related quality of life data from clinical trials

During the SIMPLIFY trials, patients completed EuroQol-5 dimension-5 level (EQ-5D-5L) questionnaires during clinic visits, based on the availability of country specific value sets or country specific reimbursement requirements. These responses are available in raw form, with individual scores for each of the five dimensions, which were then used to calculate EQ-5D index scores using the 'eq5d' package in R.

This process took the five-dimension scores, alongside age and sex, to calculate EQ-5D-5L index scores before using a crosswalk algorithm by Hernandez-Alava et al to map the EQ-5D-5L data to EQ-5D-3L responses based with the NICE Decision Support Unit recommended UK value set.(112-115) Analysis of EQ-5D scores by treatment arm indicate a small improvement in the momelotinib arm over the 24-week treatment period, while mean utility scores for the BAT arm show a decreasing trend as illustrated in Figure 45.

Figure 45. EQ-5D by treatment arm



Abbreviations: EQ-5D = EuroQol 5-dimensions

Much of the HRQoL benefit attributable to momelotinib is captured by the treatment effect on becoming of maintaining TI, although some numerical (but not statistically significant) improvement in HRQoL was also observed for momelotinib over BAT among those who were TI or TD (see Section B.3.3.5.6). Becoming or maintaining TI is associated with improved HRQoL compared to patients who are TD or TR. This is supported by analysis of EQ-5D scores from the SIMPLIFY-2 trial demonstrating that being TD or TR was and statistically significant predictor of poorer HRQoL, even when other response criteria were controlled for. This reflects the symptomatic burden of anaemia which causes fatigue, palpitations, bone pain and weakness.(40) Transfusion status-defined health state utility values (HSUVs) are therefore applied in the model to capture this difference in HRQoL in each health state (TI, TR, TD), and to align with the model structure described in Section B.3.3.2.

Further details on how utility values were derived from the SIMPLIFY-2 trial are presented in Section B.3.3.5.2 and Section B.3.3.5.6.

B.3.3.5.2 Mapping

As stated in Section B.3.3.5.1, EQ-5D-5L data collected from the SIMPLIFY-2 trial were mapped onto the UK EQ-5D-3L valuation set using a crosswalk algorithm published by Hernández Alava et al.(116) Using these mapped data, EQ-5D-3L HSUVs were estimated (see Section B.3.3.5.6).

B.3.3.5.3 Health-related quality of life studies

An SLR was conducted to identify HRQoL studies reporting in adult patients with MF. Details of the methods used to identify and select the relevant studies are described in Appendix H. A total of 40 unique studies, reported across 84 records, report HRQoL data. However, only five publications across three trials and one observational study were identified that report utilities. These are described in Appendix H.1.4. None reported utility weights stratified by transfusion status and were therefore not considered for the analysis as they could not be applied to the health states considered in the economic model (TI/TR/TD).

In addition, utility values for UK economic evaluations of ruxolitinib have been reported (Table 85).(51) The majority of utilities used in fedratinib UK economic evaluations are unavailable due to redaction. Like the studies identified in the SLR, these utility values represent different health states to those utilised for the economic model for momelotinib, and therefore were excluded from consideration for use in the CEM.

Table 85. Utility values in prior JAKi appraisals (as reported in the fedratinib NICE appraisal TA756)(51)

State	Assignment	Utility value: mean (standard error)	95% CI	Reference
Ruxolitinib (TA356)				
Baseline utility	Baseline utility use for first 4 weeks after patient first receives treatment	0.732 (0.073, [assumed 10% of mean])	0.577 – 0.862	Ruxolitinib SMC DAD65 (reported in TA756)
Response	Change from baseline at 4 weeks if patient receiving JAKi is classified as a responder	0.153 (0.015, [assumed 10% of mean])	0.124 – 0.184	Ruxolitinib SMC DAD65 (reported in TA756)

State	Assignment	Utility value: mean (standard error)	95% CI	Reference
Non-response	Change from baseline at 4 weeks if patient receiving JAKi is classified as a non-responder	0.037 (0.004, [assumed 10% of mean])	0.030 – 0.045	Ruxolitinib SMC DAD65 (reported in TA756)
BAT	Change from baseline	0	0	Ruxolitinib SMC DAD65 (reported in TA756) No response was allowed for BAT patients in model
Worsening utility	Utility of patients receiving BAT is reduced every 24 weeks by this utility decrement.	0.025 (0.003, [assumed 10% of mean])	0.020 – 0.030	Ruxolitinib SMC DAD65 (reported in TA756)
AML	Decrement applied to patient utility upon transitioning to AML	0.257 (0.026, [assumed 10% of mean])	0.208 – 0.309	TA3867 (reported in TA756)
Fedratinib (TA756)				
Baseline utility	NR	NR	NR	-
Response	NR	NR	NR	-
Non-response	NR	NR	NR	-
Loss of response	NR	NR	NR	-
AML	Utility value for patients who transition to AML health state	0.530 (0.053, [assumed 10% of mean])	0.426 – 0.633	Pan et al. 2010 (reported in TA756)
Palliative care	Utility value for patients who transition to end-of-life health state who do not die	0.530 (0.053, [assumed 10% of mean])	0.426 – 0.633	Capped at the value of the lowest utility (AML)

Abbreviations: AML = acute myeloid leukaemia; BAT = best available therapy; CI = confidence interval; DAD = detailed advice document; JAK = Janus kinase; JAKi = JAK inhibitor; NICE = National Institute for Health and Care Excellence; NR = not reported (redacted); SMC = Scottish Medicines Consortium

B.3.3.5.4 Adverse events

Given the use of treatment independent health state utilities, adverse event disutilities were included in the base-case analysis, with disutilities input values sourced from the literature and prior NICE MF appraisals (Table 86). Utility decrements are applied per cycle, proportionate to the rate of each AE for each treatment arm (see Section B.3.3.6.4).

Table 86. Disutility values due to AEs

AE	Disutility	Source
Anaemia	0.090	Beusterien et al. 2010 Wehler 2018 Referenced in TA813
Thrombocytopenia	0.050	Assumption, consistent with TA813 and TA426
Asthenia	0.090	Beusterien et al. 2010 (assumed equal to anaemia)

AE	Disutility	Source
		Referenced in TA756
Neutropenia	0.050	Assumption, consistent with TA813 and TA426
Abdominal pain	0.110	Tielemans et al. 2013, disutility for "gastrointestinal symptoms", consistent with TA756(51)

Abbreviations: AE = adverse event

B.3.3.5.5 Age-adjustment of utilities

In line with NICE guidance, age-adjustment of HSUVs was performed using a multiplicative approach. For each health state, a utility multiplier was generated by dividing the original utility value by an age-matched general population utility estimate, according to the baseline age of the SIMPLIFY-2 trial arms (see Table 87). General population utility estimates by age and sex were sourced from Hernandez-Alava et al.(116)

Assuming the same proportional decrement in utility compared to the general population for each age, each health state utility multiplier was then applied to the original general population utility curve to generate health state utility curves by age, which were then applied in the model to account for decreasing utility expected with increasing age values.

B.3.3.5.6 Health-related quality of life data used in the cost-effectiveness analysis

For the cost-effectiveness analysis for the JAKi-experienced population, EQ-5D-3L utilities derived from SIMPLIFY-2 (cross-walked from EQ-5D-5L) were applied.

When the cross-walked EQ-5D-3L utilities were analysed using mixed effects models (to account for multiple observations being available for each patient), regression analyses found that health states based around transfusion status, TSS score, and spleen volume were all predictive of patient HRQoL. However, once accounting for any individual endpoint, model fit was not improved by the addition of other endpoints, i.e., once transfusion status was controlled for, TSS or spleen volume did not further improve the fit. As such, HSUVs were calculated based solely on transfusion status, in line with the economic model structure.

For SIMPLIFY-2, the effect of the treatment arm in the trial was unclear, with fewer than 200 observations available to help inform the utility analyses. Although the coefficient attached to treatment did not reach statistical significance, the magnitude of the difference between TI and TD treatment specific values made it difficult to conclude that a treatment effect (beyond the impact on transfusion status) is not present. As such, values are presented below in Table 87 for both treatment independent utilities, i.e., based only on transfusion status, as well by transfusion status and treatment arm. Reference ages for each treatment arm are also shown, which were used to perform age-adjustment of the utility values (see Section B.3.3.5.5).

To estimate the values including the coefficient for treatment arm, bootstrapping was performed using LME's inbuilt 'bootMer' function. This allows for the incorporation of the random effects from the model, as the impact of this is not numerically calculable. 1000 bootstraps were performed, and the mean and standard errors calculated across the sample. The resulting values suitable for use in economic models are given in the table below.

Further details on the utility analyses performed are presented in GSK Myelofibrosis HRQoL analysis report.(73)

Table 87. EQ-5D-3L health state utilities derived from SIMPLIFY-2 trial

Health state	Utility value (SE)		
	Treatment independent	Momelotinib	BAT
Reference age, years*	67.4	66.4	69.4
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

*Reference age values are used to compare each set of treatment independent and treatment specific HSUVs to age-matched
Abbreviations: general population estimates to perform age-adjustment of utilities.
BAT = best available therapy; EQ-5D-3L = EuroQol 5-dimensions 3-levels; SE = standard error; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Given the uncertainty around the differential utility of momelotinib and BAT in SIMPLIFY-2, treatment independent health state utilities were explored in the base-case analysis, with treatment specific utilities explored in scenario analysis. An additional scenario analysis was also performed using the treatment specific utilities where BAT treatment specific utilities were applied to patients discontinuing momelotinib.

B.3.3.6 Cost and healthcare resource use identification, measurement and valuation

B.3.3.6.1 Drug acquisition

The list price of momelotinib is £5,650 per 30 tablet pack for 200 mg, 150 mg and 100 mg doses, resulting in an average treatment cost of £5,273.33 per cycle. Pending approval of a patient access scheme (PAS) simple discount of [redacted] to the list price for all strengths, the acquisition cost for momelotinib to the NHS reduces to [redacted] per 30 tablet pack, or [redacted] per cycle. Acquisition costs for momelotinib at list price and at net price are outlined in Table 88 and Table 89, respectively.

Table 88. Drug acquisition cost and dosing information for momelotinib [List price]

Unit size per tablet (mg)	Dosing regimen	Quantity per pack	Cost per pack	Cost per 4-week cycle
100	Once daily	30	£5,650.00	£5,273.33
150	Once daily	30	£5,650.00	£5,273.33
200	Once daily	30	£5,650.00	£5,273.33

Table 89. Drug acquisition cost and dosing information for momelotinib [PAS price]

Unit size per tablet (mg)	Dosing regimen	Quantity per pack	Cost per pack	Cost per 4-week cycle
100	Once daily	30	[redacted]	[redacted]
150	Once daily	30	[redacted]	[redacted]
200	Once daily	30	[redacted]	[redacted]

Abbreviations: PAS = patient access scheme

As per the SIMPLIFY-2 protocol, subjects in the BAT treatment arm received treatment at doses and schedules determined by the investigator in accordance with standard of care. Therapy was changed at any time during the study except during the screening period. Regimens for BAT included but were not limited to chemotherapy (e.g., hydroxyurea), anagrelide, corticosteroid, haematopoietic growth factor, immunomodulating agent, androgen (danazol), interferon, and may include no active myelofibrosis treatment.(117) The composition of therapies comprising BAT, based on the RT phase of SIMPLIFY-2, is presented in Table 90.(63) Summation of all therapies exceed 100% and some treatments were used in combination with others.

Table 90. Medications received by BAT group (SIMPLIFY-2)

BAT therapy	Therapy usage
Ruxolitinib – 5mg BID	17.3%

BAT therapy	Therapy usage
Ruxolitinib – 10mg BID	35.3%
Ruxolitinib – 15mg BID	20.7%
Ruxolitinib – 20mg BID	15.1%
Hydroxyurea (hydroxycarbamide)	23.1%
Prednisone/prednisolone	11.5%
ESA (assumed as epoetin alfa)	3.8%
No therapy	3.8%
Anagrelide	1.9%
Aranesp (darbepoetin alfa)	1.9%
Aspirin	1.9%
Thalidomide*	1.9%

*Dalteparin is coadministered with Thalidomide, therefore it is used for the same proportion of patients.
Abbreviations: BAT = best available therapy; BID = twice daily; ESA = erythropoiesis-stimulating agent

The mean or median doses could not be estimated from the SIMPLIFY-2 trial for BAT treatments, except for ruxolitinib, due to the complexity of treatment regimens and variability in regimens across subjects. For all treatments except ruxolitinib, the lowest dose from the Summary of Product Characteristics (SmPC) was assumed. UK clinical validation was sought during a myelofibrosis health technology assessment advisory board held by GSK on 31st May 2023 to confirm dosing in SIMPLIFY-2 was aligned with UK clinical practice.(32) Clinicians felt that the therapies used in the BAT arm from SIMPLIFY-2 are broadly aligned with UK clinical practice, but suggested alternative doses for hydroxyurea and ESAs.(32) Therefore, these doses were amended to align with clinical expert responses. Per the SmPC for thalidomide, thromboprophylaxis is assumed to be administered concomitantly to the treatment. This thromboprohylaxis is assumed to be dalteparin at a dose of 5000 IU once daily, as recommended in The Clatterbridge Cancer Centre NHS Foundation Trust protocol.(118)

Costing information for this and BAT therapies administered in SIMPLIFY-2 are outlined in Table 91. All drug acquisition costs were sourced from the BNF or eMiT, with the exception of danazol which was sourced from available UK pharmacy pricing data at a cost of £11.21 per 10 capsules.(119-121)

Based on the distribution shown in Table 90 and cost per cycle estimates in Table 91, the weighted average total acquisition cost per cycle for BAT was £2,396.04.

Table 91. Dosing and acquisition cost for each therapy in the JAKi-experienced BAT arm

BAT therapy	Unit size	Dose per admin	Admin per cycle	Dosing source	Cost per unit	Cost per cycle (including wastage*)	Cost source
Ruxolitinib – 5mg BID	5mg	5mg	56	GSK(63)	£25.50	£1,428.00	BNF(122)
Ruxolitinib – 10mg BID	10mg	10mg	56	GSK(63)	£51.00	£2,856.00	BNF(122)
Ruxolitinib – 15mg BID	15mg	15mg	56	GSK(63)	£51.00	£2,856.00	BNF(122)
Ruxolitinib – 20mg BID	20mg	20mg	56	GSK(63)	£51.00	£2,856.00	BNF(122)
Hydroxyurea (hydroxycarbamide)	500mg	1,000mg	28	GSK(32)	£0.10	£5.60	eMIT(120)
Prednisone/prednisolone	5mg	15mg	28	EMC(123)	£0.01	£0.90	eMIT(120)
Danazol	200 mg	600 mg	28	GSK(32)	£1.12	£94.16	United Pharmacies UK(119)
ESA (assumed as epoetin alfa)	40,000 IU	40,000 IU	4	GSK(32)	£265.48	£1,061.92	BNF(124)
No therapy	0	0	0	NA	£0.00	£0.00	NA
Anagrelide	0.5mg	1mg	28	EMC(125)	£0.26	£14.77	eMIT(120)
Aranesp (darbepoetin alfa)	60mcg	400mcg	4	GSK(32)	£88.09	£2,349.07	BNF(126)
Aspirin	75mg	75mg	28	EMC(127)	£0.01	£0.26	eMIT(120)
Thalidomide	50mg	200mg	28	EMC(128)	£10.29	£1,152.32	eMIT(120)
Dalteparin*	5000 IU	5000 IU	28	Clatterbridge Cancer Centre protocol and EMC(118, 129)	£2.82	£79.04	BNF(130)

*Coadministered with thalidomide
Abbreviations: BAT = best available therapy; BNF = British National Formulary; EMC = Electronic Medicines Compendium; eMIT = electronic market information tool; ESA = erythropoiesis-stimulating agent; NA = not applicable;

As momelotinib and all BAT therapies were generally anticipated to be administered at fixed dosage levels either equivalent to or divisible by the number of mg per unit for each dose size available, drug wastage was not included in the analysis. Wastage may be expected in practice for darbepoetin alfa and deferasirox, an ICT, as they are weight-based therapies, however, wastage is not considered in the base-case analysis. This is a simplifying assumption and expected to be a conservative given that these therapies constitute a greater cost burden on the BAT arm than the momelotinib arm.

B.3.3.6.2 Drug administration

For oral treatments, such as momelotinib and ruxolitinib, no treatment administration costs are assumed.

In the BAT arm for the JAKi-experienced model, epoetin alfa, darbepoetin alfa, and dalteparin are administered via subcutaneous (SC) injection using pre-filled syringes. Patients receiving these treatments are assumed to incur a one-off administration cost for attending a training session to receive education and support with SC administration. The training session is assumed to take place in a hospital with a nurse (Band 6) and last for 20 minutes. It is assumed that patients will be able to self-administer treatments after attending the training session, so will incur no further administration costs. The one-off training cost is applied to the proportion of patients who receive SC injections as part of BAT in the model during cycle one.

Hourly costs for hospital nurse time are sourced from the PSSRU 2021/22.[89] To account for the time that nurses spend on non-patient-related activities, hourly costs were converted to a 'cost per hour of patient-related work', using methods reported in Ball and Philippou (2014).(131) This approach has previously been accepted by NICE as an appropriate methodology.(132)

On average, Band 6 hospital nurses spend 41% of time on patient care; when the ratio of time spent on patient care to other activities is 1:1:44 (0.59 / 0.41 = 1.44), each hour spent with a patient requires 2.44 paid hours (1 / 0.41 = 2.44).(133) Hourly costs per working hour are therefore multiplied by 2.44 for hospital nurses to derive

the cost per hour of patient-related work. Table 92 shows the administration costs for SC injection applied in the model.

Table 92. Administration cost for therapies administered through SC injection

Resource	Cost per hour (£)	Cost per hour of patient-related work (£)	Cost per appointment time (£)
Training session by a hospital nurse for patients who receive SC (Band 6 [20-minute appointment])	£53.00	£147.94	£49.31

Abbreviations: SC = subcutaneous

B.3.3.6.3 Monitoring and disease management costs

Resource use and costs associated with blood transfusions and ICT are applied to patients in both models. A cost per RBC transfusion unit of £371.70 from NICE TA756 (2019 costs), originally inflated from £235 based on Varney and Guest, was inflated to 2022 costs using PSSRU NHSCII inflation data to generate a cost per RBC transfusion unit of £399.77.(134) In the original study, the cost per RBC transfusion unit was estimated by dividing the NHS hospital resource use attributable to blood transfusions, plus the total costs incurred by the blood transfusion services, by the estimated number of transfusions. Hospital resource use encompasses costs relating to hospital stay, managing blood transfusion-related complications, and staff attendance at blood transfusion committee meetings. Blood transfusion services encompass collecting, testing, processing and issuing blood products.(99) Iron chelation was assumed to be administered as deferasirox at a dose of 21 mg/kg per day; based on a cost per 360 mg tablet of £5.52 from eMIT(120) and average patient weight of 76.2 kg in SIMPLIFY-2, a cost per patient per 4-week cycle of £686.40 was calculated.

In line with the JAKi-naïve cost-comparison model, alternative costs of £466.18 per RBC transfusion unit inflated from Agrawal 2006, exclusion of ICT costs and a lower dose of 14 mg/kg/day for deferasirox were each explored in scenario analysis.(42)

The number of units transfused per cycle for TI, TR and TD health states within the CEM were obtained from post-hoc analysis of patients meeting these health state definitions at Week 24. RBC transfusion rates were derived by analysing the number of units transfused in TD patients in the prior 8 weeks, similarly, the number of units

transfused in the prior 12 weeks was required to derive the transfusion rate of TR patients. The rates were derived as units per month which were then converted to numbers of RBC transfusion units per 4-week cycle. RBC transfusion units per 4-week cycle used in the Hb <10 g/dL subgroup analysis are provided in Appendix N.1.2.

Table 93. Mean number of RBC transfusion units transfused per patient from Week 0-24

Health state	Mean RBC transfusions in unit per month (SD)	Mean number of units per 4-week cycle
TI	0	0
TR	0.90 (0.39)	0.83
TD	3.00 (2.50)	2.77

Abbreviations: RBC = red blood cell; SD = standard deviation; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

A scenario analysis was also performed based on the feedback obtained from a healthcare resource use (HCRU) questionnaire sent to six consultants as part of a UK Clinical and HEOR advisory board in May 2023. The average number of RBC units per transfusion for this scenario was 0.66 per cycle for TR patients and 2.10 per cycle for TD patients.

Additional monitoring and disease management associated with blood test monitoring and follow-up appointments at a haematology clinic were included. The resource use for blood test monitoring, follow-up haematology appointments, and iron chelation for the JAKi-experienced CEM was obtained from a HCRU questionnaire sent to six consultants as part of a UK Clinical and HEOR advisory board in May 2023. The average of their responses was calculated and converted to a per cycle unit of time. The resource use for iron chelation corresponds to the proportion of patients receiving ICT.

The resource use figures for the JAKi-experienced CEM, stratified by transfusion health state, are summarised in Table 94.

Table 94. Monitoring and disease management resource use per cycle - JAKi-experienced CEM (base-case Hb <12 g/dL population)

Resource	Resource use per cycle		
	TI	TR	TD
Blood test monitoring	0.27	0.79	2.00
Follow-up haematology appointment	0.31	0.58	1.25

Resource	Resource use per cycle		
	TI	TR	TD
Iron chelation (deferasirox)*	0.00%	14.17%	37.08%
RBC transfusion units	0.00	0.83	2.77

*Resource use for iron chelation corresponds to the proportion of patients receiving ICT.
Abbreviations: CEM = cost-effectiveness model; JAKi = Janus kinase inhibitor; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

For the unit cost for blood test monitoring, HRG code DAPS03 for integrated blood services was used, costing £2.39. For follow-up appointments at a haematology, HRG code WF01A (non-admitted face-to-face attendance, follow-up, non-consultant led) was used, costing £163.44. Total monitoring and disease management costs per cycle are calculated as the unit cost multiplied by the frequency of resource use per cycle, shown in Table 95.

Table 95. Total cost of monitoring and disease management per cycle per health state – JAKi-experienced CEM (base-case Hb <12 g/dL population)

Resource	Total cost per cycle		
	TI	TR	TD
Blood test monitoring	£0.64	£1.89	£4.77
Follow-up haematology appointment	£50.40	£95.34	£204.31
Iron chelation (deferasirox)*	£0.00	£97.24	£752.50
RBC transfusion	£0.00	£332.12	£1,107.06
Total resource use costs per cycle	**£182.28**	**£625.54**	**£2,076.94**

Abbreviations: CEM = cost-effectiveness model; JAKi = Janus kinase inhibitor; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

B.3.3.6.4 Adverse events

Unit costs for anaemia, thrombocytopenia, asthenia, and neutropenia are sourced from the NHS Cost Collection.(135) It is assumed that no additional cost is associated with the management of abdominal pain. Abdominal pain is a symptom of MF resulting from splenomegaly and is assumed to be captured within disease management costs.

Anaemia

Grade 3/4 anaemia corresponds to a reduction in Hb to less than 8 g/dL per CTCAE definitions.(136) It is assumed that incidences of grade 3/4 anaemia is most often managed with RBC transfusions per Pan-London Haemato-Oncology Clinical Guidelines.(103) In the base-case, it is assumed that these AEs only require a haematologist visit and that any AE management costs in addition to the RBC transfusion costs already included in the model are captured within these costs. An

average cost per outpatient clinical haematology visit of £194.02 was applied, derived from NHS reference costs and based on total outpatient attendances.

However, this is likely to underestimate the management of JAKi-experienced patients requiring more complex care as a result of treatment-related AEs. Alternative costing of anaemia has been undertaken and explored in scenario analysis. In this method, a weighted average cost for anaemia was calculated based on NHS activity reported for non-elective long stay, non-elective short stay, day case, and regular day or night admission patients across all reported CC scores. The weighted average unit cost for iron deficient anaemia (CC score 0-14) is presented in Table 96. The unit costs and activity associated with each HRG code was sourced from the NHS Cost Collection for the year 2021/22.(135)

Table 96. Weighted average unit cost of anaemia

	HRG code	2021/22 unit cost (£)	Activity
Non-elective long stay	SA04G (CC score 14+)	£4,037.18	5,542
	SA04H (CC score 10-13)	£2,980.26	4,442
	SA04J (CC score 6-9)	£2,586.82	4,067
	SA04K (CC score 2-5)	£2,088.50	2,987
	SA04L (CC score 0-1)	£1,474.70	993
Non-elective short stay	SA04G (CC score 14+)	£736.06	2,875
	SA04H (CC score 10-13)	£700.14	4,282
	SA04J (CC score 6-9)	£650.48	7,491
	SA04K (CC score 2-5)	£578.21	11,271
	SA04L (CC score 0-1)	£490.23	7,554
Day case	SA04G (CC score 14+)	£374.02	754
	SA04H (CC score 10-13)	£378.65	2,845
	SA04J (CC score 6-9)	£368.25	9,348
	SA04K (CC score 2-5)	£359.42	20,496
	SA04L (CC score 0-1)	£344.50	21,056
Regular day or night admission	SA04G (CC score 14+)	£387.39	106
	SA04H (CC score 10-13)	£363.21	242
	SA04J (CC score 6-9)	£378.35	614
	SA04K (CC score 2-5)	£393.41	1,812
	SA04L (CC score 0-1)	£410.55	3,623
Weighted average cost (£)	**£854.33**		

Abbreviations: CC = complexity and comorbidity split; HRG = Health Resource Group

Thrombocytopenia

A weighted average cost for thrombocytopenia was calculated based on NHS activity reported for non-elective long stay, non-elective short stay, day case, and regular day or night admission patients across all reported CC scores. The weighted

average unit cost for thrombocytopenia (CC score 0-8) is presented in Table 97. The unit costs and activity associated with each HRG code was sourced from the NHS Cost Collection for the year 2021/22.(135)

Table 97. Weighted average unit cost of thrombocytopenia

	HRG code	2021/22 unit cost (£)	Activity
Non-elective long stay	SA12G (CC score 8+)	£5,092.95	1,143
	SA12H (CC score 5-7)	£3,281.44	564
	SA12J (CC score 2-4)	£3,143.05	613
	SA12K (CC score 0-1)	£2,558.57	291
Non-elective short stay	SA12G (CC score 8+)	£796.44	735
	SA12H (CC score 5-7)	£673.05	612
	SA12J (CC score 2-4)	£658.87	1,071
	SA12K (CC score 0-1)	£683.02	788
Day case	SA12G (CC score 8+)	£314.60	1,036
	SA12H (CC score 5-7)	£295.27	1,303
	SA12J (CC score 2-4)	£433.35	3,142
	SA12K (CC score 0-1)	£386.47	3,362
Regular day or night admission	SA12G (CC score 8+)	£278.05	306
	SA12H (CC score 5-7)	£259.90	533
	SA12J (CC score 2-4)	£270.97	962
	SA12K (CC score 0-1)	£338.55	1,364
Weighted average cost (£)	**£948.22**		

Abbreviations: CC = complexity and comorbidity split; HRG = Health Resource Group

Asthenia

The unit cost for asthenia was sourced from the fedratinib TA756 and inflated to a 2022 value using PSSRU inflation indices, giving a cost of £13.73.(51) Table 98 summarises the cost details.

Table 98. Unit cost of asthenia

Source	Cost (£)	Year	Cost inflated to 2022 (£)
Fedratinib TA756	£12.00	2014	£13.73

Neutropenia

A weighted average cost for neutropenia was calculated based on NHS activity reported for non-elective long stay, non-elective short stay, day case, and regular day or night admission patients across all reported CC scores. The weighted average unit cost for neutropenia (taken as the cost for other haematological or splenic disorders, CC score 0-6) is presented in Table 99. The unit costs and activity associated with each HRG code was sourced from the NHS Cost Collection for the year 2021/22.(135)

Table 99. Weighted average unit cost of neutropenia

	HRG code	2021/22 unit cost (£)	Activity
Non-elective long stay	SA08G (CC score 6+)	£4,105.12	1,136
	SA08H (CC score 3-5)	£2,870.29	359
	SA08J (CC score 0-2)	£2,928.55	247
Non-elective short stay	SA08G (CC score 6+)	£658.65	716
	SA08H (CC score 3-5)	£578.07	733
	SA08J (CC score 0-2)	£456.39	1,260
Day case	SA08G (CC score 6+)	£432.00	442
	SA08H (CC score 3-5)	£567.79	540
	SA08J (CC score 0-2)	£398.88	918
Regular day or night admissions	SA08G (CC score 6+)	£234.94	99
	SA08H (CC score 3-5)	£359.50	116
	SA08J (CC score 0-2)	£361.75	274
Weighted average cost (£)	**£1,303.42**		

Abbreviations: CC = complexity and comorbidity split; HRG = Health Resource Group

Total adverse event costs

For each adverse event, the total cost per cycle was estimated as the event rate per cycle multiplied by the unit cost. The total adverse event costs per cycle per patient are presented in Table 101.

AE incidence figures reported in SIMPLIFY-2 are in Section B.3.3.4.5. The adverse event probabilities for the JAKi-experienced base-case population are presented in Table 100, which were converted to per cycle estimates and applied each cycle to those remaining on treatment over time. Adverse event costs per cycle are presented in Table 101.

Table 100. SIMPLIFY-2 adverse event rates per cycle

	Momelotinib	BAT
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]

Abbreviations: BAT = best available therapy

Table 101. JAKi-experienced total adverse event costs per patient per cycle

Adverse event	Momelotinib	BAT
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain*	[redacted]	[redacted]
Total	[redacted]	[redacted]

Please note, the total cost of AEs for each population/subgroup is influenced by the number of patients in each health state over time (TI, TR, TD). The costs presented align with the base-case transition probabilities.
*No costs assumed for abdominal pain AEs.
Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

B.3.3.6.5 Subsequent treatment

As stated in Section B.3.3.4.4, patients in the BAT arm are assumed not to discontinue BAT, as validated by clinical experts and as modelling during TA756. In addition, BAT also includes 'No therapy' and supportive therapies. However, subsequent treatment costs are included for momelotinib to account for treatment costs accrued following discontinuation, with a proportion of these patients assumed to be treated with BAT therapies following momelotinib discontinuation. At the clinical-HEOR advisory board clinicians were asked whether re-treatment with ruxolitinib would form part of BAT therapies following momelotinib discontinuation in a previously JAKi-treated population. Clinicians stated that for JAKi-experienced patients, patients likely would not be able to access ruxolitinib re-treatment following momelotinib. This is not expected for two reasons: i) Patients may not be suitable for re-treatment with a previously trialled JAKi, and ii) NHS funding is not available for ruxolitinib re-treatment following initial discontinuation.(32, 137) The second reason was also alluded to as a reason for poor uptake of fedratinib use within the NHS and a rationale for patients being maintained on ruxolitinib with or without additional therapies despite loss of response or incidence of AEs.(32) However, in the questionnaire sent to clinicians they were asked to quantify in a JAKi-experienced population the "proportion of patients discontinuing momelotinib who will be retreated with a JAKi". The mean response to this question was 39% [range 0%-80%; interquartile range: 21.3%-60.0%]. While this is expected to relate to subsequent treatment with fedratinib which is currently only reimbursed through the CDF and so is out of scope for this technology appraisal, a scenario analysis was explored whereby 39% of patients following momelotinib discontinuation are able to re-access ruxolitinib through the NHS.

The original constitution of BAT therapies from SIMPLIFY-2, along with no ruxolitinib and 39% ruxolitinib BAT compositions are outlined in Table 102. BAT without ruxolitinib and BAT with 39% ruxolitinib distributions are derived by reallocating ruxolitinib use across all other BAT therapies, according to their proportional distribution in the original BAT distribution from SIMPLIFY-2, assuming that these patients only receive one of the alternative BAT therapies.

Table 102. BAT subsequent treatment distributions

Subsequent therapy	Original SIMPLIFY-2 BAT composition	BAT composition excluding ruxolitinib (base-case)	BAT composition with 39% ruxolitinib (scenario)
Ruxolitinib - 5mg BID	17.3%	0.0%	7.6%
Ruxolitinib - 10mg BID	35.3%	0.0%	15.6%
Ruxolitinib - 15mg BID	20.7%	0.0%	9.1%
Ruxolitinib - 20mg BID	15.1%	0.0%	6.7%
Hydroxyurea	23.1%	59.7%	43.5%
Prednisone / prednisolone	11.5%	29.8%	21.8%
Danazol	5.8%	14.9%	10.9%
Erythropoiesis-stimulating agent (assumed as epoetin alfa)	3.8%	9.9%	7.3%
No therapy	3.8%	9.9%	7.3%
Anagrelide	1.9%	5.0%	3.6%
Aranesp (darbepoetin alfa)	1.9%	5.0%	3.6%
Aspegic	1.9%	5.0%	3.6%
Thalidomide	1.9%	5.0%	3.6%

Abbreviations: BAT = best available therapy; BID = twice daily

As noted in Section B.3.3.4.4, the proportion of patients who discontinue treatment is determined using extrapolated TTDD curves and OS curves. TTDD is capped by OS to prevent the proportion on treatment over time being higher than the proportion alive; the difference between TTDD and overall OS is then used to determine the proportion of patients who are alive but have discontinued momelotinib, and incur subsequent treatment costs (both drug acquisition and administration, where relevant) based on the post-momelotinib BAT distributions described above and BAT drug acquisition costs described in Section B.3.3.6.1. The total subsequent treatment acquisition and administration cost per 28-day cycle applied for momelotinib was £308.00 for cycle 1 and £299.70 for cycles 2 onwards for the base-case analysis. For the 39% ruxolitinib scenario analysis, costs per cycle were £1,230.23 for the first cycle and £1,223.91 per cycle thereafter.

B.3.3.6.6 Terminal care

To represent the increased cost of providing care to patients near the end of their lives, the JAKi-experienced CEM incorporates a terminal care cost. This is applied as a one-off cost at death in the model to all patients who enter the death state at each cycle.

In line with the fedratinib TA756 submission, the end-of-life cost was sourced from Table 5 in Round et al. 2015,(138) taken as the sum of the average health care and

social care costs for patients with cancer; this cost is presented in Table 103.(51) As the paper uses cost year 2013/14, the terminal care cost was inflated to cost year 2021/22 in line with the cost year used in the model based on PSSRU inflation data, which gave an overall value of £6,959.00. This cost accounts for increased inpatient, outpatient, and GP appointments, increased A&E attendance, and increased home care and nursing home use.

Table 103. Terminal care cost

Category	2013/14 cost	2022 cost
Health care	£4,254.00	£4,866.61
Social care	£1,829.00	£2,092.39
Total end-of-life cost	£6,083.00	£6,959.00

B.3.3.7 Severity

The QALY shortfall was calculated assuming a mean cohort age of 67 years and 60% male, as applied in the JAKi-experienced CEM. The total expected QALYs for patients MF treated with current standard of care was based on the BAT arm of the base-case Hb <12 g/dL population. The total expected QALYs in patients with the disease on current standard of care (BAT) were then compared to the general population QALYs to calculate the absolute and proportional shortfall; total (discounted) BAT QALYs of 2.084 were generated compared to 9.733 for a general population cohort of the same baseline age and proportion male. Based on the above, the absolute QALY shortfall is estimated to be 7.649 and the proportional shortfall is estimated to be 78.6%. Therefore, a QALY weight of 1.0 was applied for the appraisal.

Table 104. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	60.0% male	B.3.4.1
Starting age	67.4 years	B.3.4.1

Abbreviations: QALY = quality-adjusted life year.

Table 105. Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment (BAT)	Absolute QALY shortfall	Proportional QALY shortfall
9.733	2.084	7.649	78.6%

Abbreviations: BAT = best available therapy; QALY = quality-adjusted life year.

B.3.3.8 Uncertainty

Deterministic and probabilistic sensitivity analyses were conducted in order to explore parameter uncertainty. Scenario analyses were also conducted to explore uncertainty regarding selection of key data sources and model assumptions.

B.3.3.8.1 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was conducted with a Monte-Carlo simulation using 1,000 iterations in which parameter values were randomly drawn from probability distributions assigned to each relevant model parameter, defined using the parameter value and associated uncertainty data.

The parameter inputs used in PSA are shown in Table 106. Broadly speaking, the following probability distributions were adopted in the PSA for each input type:

- Beta distributions for inputs confined by the interval 0 to 1 (such as proportions) and HSUVs
- Gamma distributions for costs and resource use frequencies, as well as parameters bounded to positive values (such as baseline age)
- Dirichlet for transition probabilities
- Multivariate normal distributions for time to event parameters

Standard errors (SE) were used to inform the distributions of input parameters where available. Where SEs or 95% confidence intervals were not available for parameters (or not estimable from other measures of uncertainty), SE values were assumed to be equal to 10% of the mean.

B.3.3.8.2 Deterministic sensitivity analyses

The one-way sensitivity analysis (OWSA) involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter was assessed. The OWSA was conducted by allocating a ‘low’ value and a ‘high’ value to each parameter; the low value was the lower bound of the 95% CI, the high value was the upper bound of the 95% CI. In the absence of CI data, the

standard error assumed to be 10% of the mean value as for the PSA. A tornado diagram was then used to graphically present the parameters which had the greatest impact on the results.

B.3.3.8.3 Scenario analyses

A set of exploratory scenarios analyses were conducted to test structural and parametric uncertainty. These scenarios were relevant to the assumptions made in the model development, and are described below in Table 116 and Table 117.

B.3.3.9 Summary of base-case analysis inputs and assumptions

B.3.3.9.1 Summary of base-case analysis inputs

Table 106 presents the inputs for the JAKi-experienced model analysis.

Table 106. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Baseline age	67.4	6.74 (Gamma)	B.3.3.1
Percentage male	60.0%	0.06 (Beta)	B.3.3.1
Baseline proportion of patients in health state - TI	22.5%	- (Dirichlet)	B.3.3.4.2
Baseline proportion of patients in health state - TR	15.2%	- (Dirichlet)	B.3.3.4.2
Baseline proportion of patients in health state - TD	62.4%	- (Dirichlet)	B.3.3.4.2
BAT overall proportion on ruxolitinib	88.5%	4.4% (Beta)	B.3.3.3
BAT proportion of ruxolitinib on 5mg	19.6%	2.0% (Beta)	B.3.3.6.1
BAT proportion of ruxolitinib on 10mg	39.9%	4.0% (Beta)	B.3.3.6.1
BAT proportion of ruxolitinib on 15mg	23.4%	2.3% (Beta)	B.3.3.6.1
BAT proportion of ruxolitinib on 20mg	17.1%	1.7% (Beta)	B.3.3.6.1
Administration cost per cycle with BAT cycle 1	£3.79	£0.38 (Gamma)	B.3.3.6.2
Resource use cost - blood test monitoring	£2.39	£0.24 (Gamma)	B.3.3.6.3
Resource use cost - follow-up haematology appointment	£163.44	£16.34 (Gamma)	B.3.3.6.3
Resource use cost – RBC transfusion	£399.77	£39.98 (Gamma)	B.3.3.6.3
Resource use cost - iron chelation	£686.40	£68.64 (Gamma)	B.3.3.6.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
AE cost - anaemia	£194.02	£19.40 (Gamma)	B.3.3.6.4
AE cost - thrombocytopenia	£948.22	£94.82 (Gamma)	B.3.3.6.4
AE cost - asthenia	£13.73	£1.37 (Gamma)	B.3.3.6.4
AE cost - neutropenia	£1,303.42	£130.34 (Gamma)	B.3.3.6.4
Blood test monitoring resource use per cycle - TI	0.27	0.03 (Gamma)	B.3.3.6.3
Blood test monitoring resource use per cycle - TR	0.79	0.08 (Gamma)	B.3.3.6.3
Blood test monitoring resource use per cycle - TD	2.00	0.20 (Gamma)	B.3.3.6.3
Follow-up haematology appointment resource use per cycle - TI	0.31	0.03 (Gamma)	B.3.3.6.3
Follow-up haematology appointment resource use per cycle - TR	0.58	0.06 (Gamma)	B.3.3.6.3
Follow-up haematology appointment resource use per cycle - TD	1.25	0.13 (Gamma)	B.3.3.6.3
Iron chelation resource use per cycle - TR	14.17%	0.71% (Beta)	B.3.3.6.3
Iron chelation resource use per cycle - TD	37.08%	1.85% (Beta)	B.3.3.6.3
Terminal care cost	£6,959.00	£695.90 (Gamma)	B.3.3.6.6
Mean RBC transfusion units per month - TR	0.90	0.12 (Gamma)	B.3.3.6.3
Mean RBC transfusion units per month - TD	3.00	0.31 (Gamma)	B.3.3.6.3
Health state utility: TI	[redacted]	[redacted] (Beta)	B.3.3.7
Health state utility: TR	[redacted]	[redacted] (Beta)	B.3.3.7
Health state utility: TD	[redacted]	[redacted] (Beta)	B.3.3.7
Adverse event disutility - anaemia	0.090	0.009 (Beta)	B.3.3.5.4
Adverse event disutility - thrombocytopenia	0.050	0.005 (Beta)	B.3.3.5.4
Adverse event disutility - asthenia	0.090	0.009 (Beta)	B.3.3.5.4
Adverse event disutility - neutropenia	0.050	0.005 (Beta)	B.3.3.5.4
Adverse event disutility – abdominal pain	0.110	0.011 (Beta)	B.3.3.5.4
Momelotinib adverse event total cost	[redacted]	[redacted] (Gamma)	B.3.3.6.4
BAT adverse event total cost	[redacted]	[redacted] (Gamma)	B.3.3.6.4
TI OS (after 24 weeks)	Log-normal distribution	- (Multivariate normal)	B.3.3.4.3
Non-TI OS (after 24 weeks)	Exponential distribution	- (Multivariate normal)	B.3.3.4.3
Momelotinib TTDD	Gompertz distribution	- (Multivariate normal)	B.3.3.4.4

Abbreviations: BAT = best available therapy; Non-TI = non-transfusion-independent; OS = overall survival; RBC = red blood cell; SE = standard error; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTDD = time to treatment discontinuation or death.

B.3.3.9.2 Assumptions

Assumptions associated with the CEM are presented in Table 107.

Table 107. Main assumptions in the economic model – JAKi-experienced CEM

Category	Assumption	Justification
Population	The SIMPLIFY-2 trial is assumed to be representative of a patient population with myelofibrosis treated in UK clinical practice	The SIMPLIFY-2 trial populations include patients with myelofibrosis with prior experience in JAKi (ruxolitinib) and ruxolitinib is routinely available in the UK.
Clinical effectiveness	Treatment efficacy data for momelotinib and BAT and by transfusion status is informed by the SIMPLIFY-2 trial	Outcomes associated with transfusion status were identified by key opinion leaders and clinical experts in a UK advisory board meeting as a clinically meaningful and relevant assessment of anaemia management in MF patients in UK clinical practice.
	Treatment discontinuation of momelotinib and BAT	For the JAKi-experienced population, if a patient discontinues momelotinib, they are assumed to receive a BAT distribution as subsequent treatment derived from the same composition of BAT therapies as those used in SIMPLIFY-2, with 0% ruxolitinib applied for the base-case analysis (and 39% ruxolitinib tested in scenario analysis). Patients in the BAT arm of the CEM are assumed to remain on BAT over time, and hence no TTD curves are applied for the BAT comparator in the model.
Morbidity and mortality	Treatment specific OS curves are not applied in the JAKi-experienced CEM, as comparator data for BAT from SIMPLIFY-2 are only available for 24 Weekd. Health state specific OS curves (based on transfusion status) are applied after 24 weeks, derived from SIMPLIFY-2 trial data. A difference in mortality, over the model time horizon, is expected between momelotinib and comparators due to a greater proportion of patients in momelotinib arm in the TI health state, compared to BAT, over the first 24 weeks of the SIMPLIFY-2 trial.	Momelotinib showed statistically significant improvements in transfusion status compared to BAT in the SIMPLIFY-2 trial. Differences in overall survival status were observed in the SIMPLIFY-2 trial, with clinical experts confirming an expectation that TI patients would have improved survival over time compared to non-TI patients.
	The same OS data for “non-TI” patients was applied to both TR and TD health states in the model.	Limited sample sizes of patients were available to inform TR OS extrapolations from 24 weeks, with TR parametric models producing implausible extrapolations (e.g., crossings with the TI curve). Based on clinical expert feedback, TR and TD OS data were combined to create a “non-TI” OS curve and applied to both health states in the model.

Category	Assumption	Justification
	TI and non-TI OS parametric survival curves from 24 weeks are applied independently of transfusion status transition probabilities	TI and non-TI OS KM data is expected to reflect future movement between TI and non-TI health states that may have occurred in the SIMPLIFY-2 trial, and therefore OS parametric models are applied directly to the proportion of patients in health state at the end of the first 24 weeks. To avoid any potential underestimation of costs or overestimation of QALYs gained for patients remaining alive after 24 weeks, cycle 6 transition probabilities SIMPLIFY-2, conservatively restricted to prevent improvement in transfusion status, are used to derive future distributions of TI, TR and TD health states.
	Equivalent health state transition probabilities are applied after the first 24 weeks.to both therapies to determine the distribution of health states for those remaining alive	Conservative assumption; alternative assumptions tested in scenario analysis
Cost and resource use inputs	Grade 3/4 anaemia AEs are costed based on a clinical haematologist outpatient visit	Cost of managing grade 3/4 anaemia expected to be partially captured through RBC transfusion costs already included in the model. However, as this is likely to underestimate the management of JAKi-experienced patients requiring more complex care as a result of treatment-related AEs, higher anaemia AE costs are explored in scenario analysis
	End-of-life costs are applied as a one-off cost in the cycle at which patients die	Patients accrue end-of-life care costs before they die and therefore they are applied in the cycle of death
Quality of life inputs	EQ-5D-3L utility scores are derived from SIMPLIFY-2	In line with the NICE reference case[104]
	Treatment-agnostic HSUVs are applied in the base-case analysis	While moderate numerical improvements in quality of life were observed for momelotinib over BAT for the TI and TD health states, differences were not statistically significant. Impact of treatment specific health state utilities explored in scenario analysis

Abbreviations: AE = adverse event; BAT = best available therapy; CEM = cost-effectiveness model; EQ-5D-3L = EuroQol 5-dimensions 3-levels; HSUC = health state utility values; JAKi = Janus kinase inhibitor; KM = Kaplan-Meier; MF = myelofibrosis; NICE = National Institute for Health and Care Excellence; OS = overall survival; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

B.3.3.10 Base-case results

B.3.3.10.1 Base-case incremental cost-effectiveness analysis results

Disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix J.

Total costs, LYs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT for the JAKi-experienced model population are presented in Table 108. Momelotinib decreased total costs against BAT by [redacted]; it also produced an increase in both total life years (0.464) and QALYs (0.346). BAT was therefore dominated by momelotinib.

The incremental net monetary benefit was [redacted] and [redacted] at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as shown in Table 109.

Results based on applying a PAS price discount of [redacted] are provided in Table 110. Incremental total cost savings for momelotinib were reduced further to [redacted] and momelotinib therefe remained dominant over BAT as in the list price results. The incremental net monetary benefit values increased to [redacted] and [redacted] for £20,000 and £30,000 per QALY thresholds (Table 111), respectively, after application of the PAS discount.

Table 108. Base-case results for momelotinib vs BAT in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.355	2.062	-	-	-	-	-
Momelotinib	[redacted]	3.819	2.408	[redacted]	0.464	0.346	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; QALY = quality-adjusted life year

Table 109. Net monetary benefit in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	2.062	-	-	-	-
Momelotinib	[redacted]	2.408	[redacted]	0.346	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; QALY = quality-adjusted life year

Table 110. Base-case results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.355	2.062	-	-	-	-	-
Momelotinib	[redacted]	3.819	2.408	[redacted]	0.464	0.346	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 111. Net monetary benefit in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	2.062	-	-	-	-
Momelotinib	[redacted]	2.408	[redacted]	0.346	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; PAS = patient access scheme; QALY = quality-adjusted life year

B.3.3.11 Exploring uncertainty

B.3.3.11.1 Probabilistic sensitivity analysis

The probabilistic mean values for total costs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT generated through the PSA are presented in Table 112. Momelotinib generated a probabilistic average of 0.379 incremental QALYs gained and [redacted] lower incremental costs over a lifetime horizon compared with BAT, resulting in momelotinib dominating BAT (with higher total mean QALYs and lower total mean costs). Probabilistic mean incremental QALYs were slightly higher than the deterministic model incremental QALYs (0.379 vs 0.346) with slightly larger probabilistic mean total cost savings compared to the deterministic based case (lower total costs for momelotinib of [redacted] vs [redacted]).

The corresponding incremental cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are presented in Figure 46 and Figure 47, respectively. At a willingness to pay (WTP) threshold of £0, £20,000 and £30,000 per QALY, momelotinib has a

[redacted].

Table 112. PSA results for momelotinib vs BAT in JAKi-experienced patients [List price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean Incremental Costs (£) versus BAT	Mean Incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	2.032			
Momelotinib	[redacted]	2.411	[redacted]	0.379	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 46. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 47. Momelotinib versus BAT CEAC – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor

PSA results following application of the PAS price discount are presented in Table 113. Probabilistic mean incremental total QALYs for momelotinib were 0.377 and probabilistic mean incremental total costs were further reduced with momelotinib to [redacted]. The corresponding ICEP and CEAC are presented in Figure 48 and Figure 49, respectively.

[redacted]

Table 113. PSA results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean incremental costs (£) versus BAT	Mean incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	2.056			
Momelotinib	[redacted]	2.433	[redacted]	0.377	Dominant

Note: These results were produced using version 1.3 of the model. The nature of PSA means that these results are never exactly reproducible.
Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year.

Figure 48. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [PAS price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 49. Momelotinib versus BAT CEAC – base-case JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

B.3.3.11.2 Deterministic sensitivity analysis

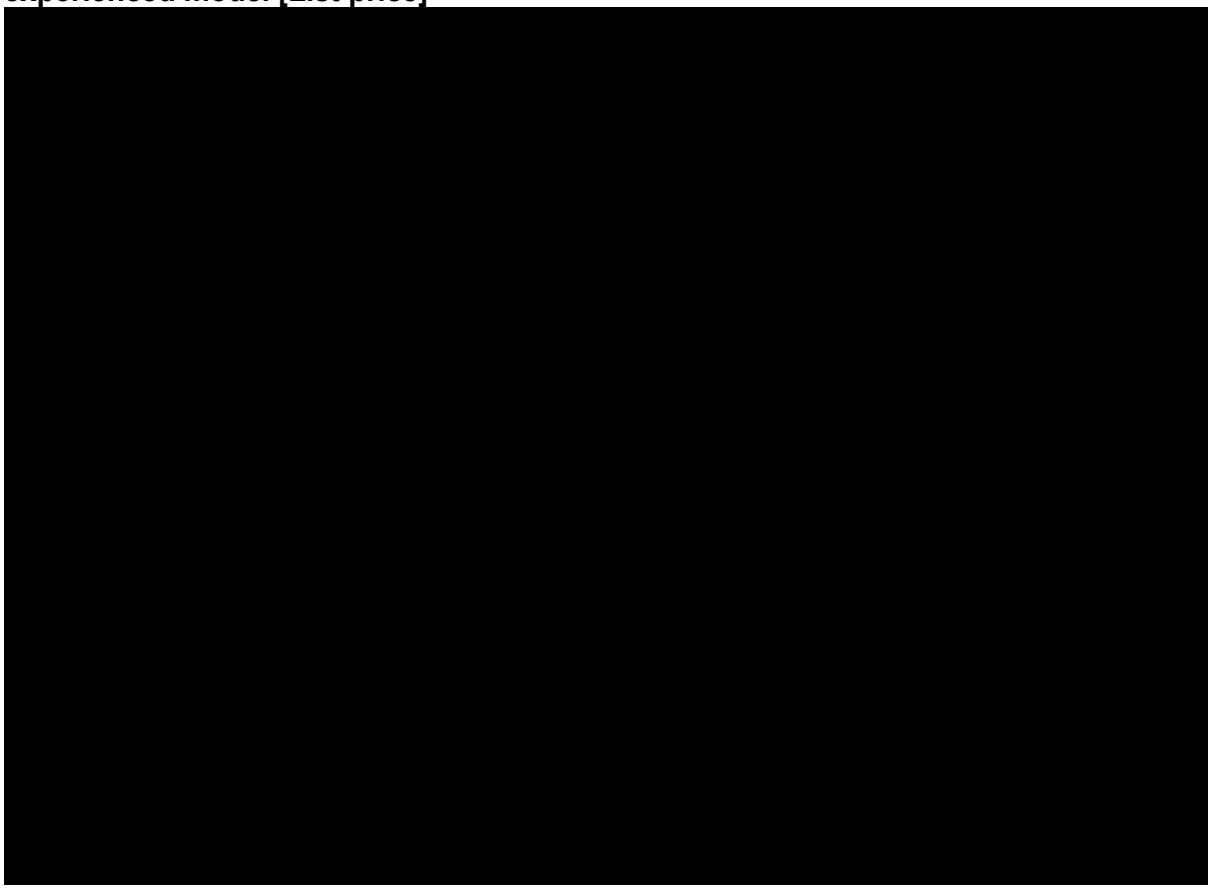
The parameters in the model with single input values were varied individually in deterministic sensitivity analysis (DSA). Upper and lower values were based on the confidence intervals or estimated confidence intervals based on other uncertainty data. In the absence of appropriate uncertainty data to inform the confidence intervals, the upper and lower values for the DSA were derived from assuming the SE values to be 10% of the mean base-case value, as for the PSA. Each parameter was set to the upper and lower bounds to test the impact of each individual parameter on the results.

A DSA tornado diagram presenting the top 20 most sensitive parameters for the momelotinib versus BAT cost-effectiveness results for the JAKi-experienced model population in descending order of sensitivity is shown in Figure 50. As the base-case results indicated that momelotinib was dominant over BAT, results are presented in terms of NMB at a WTP threshold of £30,000 per QALY.

The key drivers of cost-effectiveness were OS parameters (for both the non-TI and TI states), the overall proportion on ruxolitinib with the BAT comparator, and utilities for the TD health state for both BAT and momelotinib. Some slight sensitivity was also observed around the momelotinib TTD model parameters, proportion of BAT patients on a low 5mg dose of ruxolitinib and TI utility values, with all other inputs generating relatively small variations in the incremental NMB results.

The 10 most impactful set of tabulated results from the sensitivity analysis (in terms of NMB) are presented in Table 114. Across all parameter variations, only the upper bound variation of the non-TI OS exponential model parameter and lower bound variation in TI log-normal model parameters resulted in incremental NMB values below £0.

Figure 50. Base-case DSA tornado diagram for momelotinib vs BAT – JAKi-experienced model [List price]



Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; OS = overall survival; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

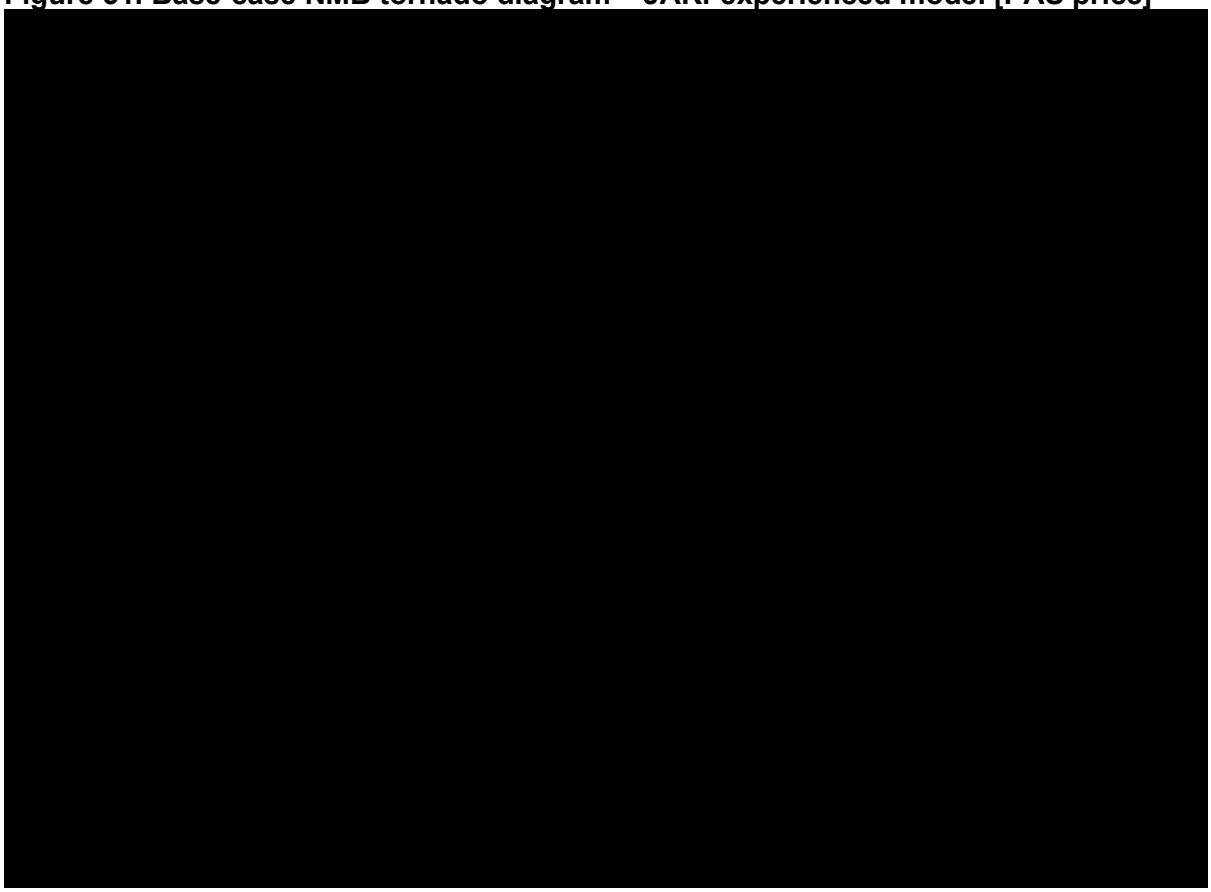
Table 114. Tabulated DSA results (top 10) for momelotinib versus BAT – JAKi-experienced model [List price]

Variable	LB NMB value	UB NMB value	Difference
JAKi-experienced - momelotinib and BAT OS - TD, base-case Hb <12 g/dL population	[redacted]	[redacted]	[redacted]
JAKi-experienced - momelotinib and BAT OS - TI, base-case Hb <12 g/dL population	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on ruxolitinib (%)	[redacted]	[redacted]	[redacted]
JAKi-experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi-experienced momelotinib utility: TD	[redacted]	[redacted]	[redacted]
JAKi-experienced - momelotinib TTD - overall cohort, base-case Hb <12 g/dL population	[redacted]	[redacted]	[redacted]
BAT 2L proportion of ruxolitinib on 5mg (%)	[redacted]	[redacted]	[redacted]
JAKi-experienced momelotinib utility: TI	[redacted]	[redacted]	[redacted]
JAKi-experienced BAT utility: TI	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; TD = transfusion-dependent; TI = transfusion-independent; TTD = time to treatment discontinuation; UB = upper bound

DSA results following application of the PAS discount are available in Figure 51 and Table 115. Similar results were observed as for the results without the PAS discount in terms of which parameters produced the most variation around the base-case incremental NMB estimate, albeit with incremental NMB values greater than [redacted] in all cases and therefore indicating momelotinib to be cost-effective against BAT for all parameter variations producing.

Figure 51. Base-case NMB tornado diagram – JAKi-experienced model [PAS price]



Abbreviations: BAT = best available therapy; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; NMB = net monetary benefit; PAS = patient access scheme; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 115. Tabulated DSA results (top 10) for momelotinib versus BAT (NMB) – JAKi-experienced model [PAS price]

Variable	LB value	UB value	Difference
JAKi-experienced - momelotinib and BAT OS - TD, base-case Hb <12 g/dL population	[redacted]	[redacted]	[redacted]
JAKi-experienced - momelotinib and BAT OS - TI, base-case Hb <12 g/dL population	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on ruxolitinib (%)	[redacted]	[redacted]	[redacted]
JAKi-experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi-experienced momelotinib utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of ruxolitinib on 5mg (%)	[redacted]	[redacted]	[redacted]
JAKi-experienced - momelotinib TTD - overall cohort, base-case Hb <12 g/dL population	[redacted]	[redacted]	[redacted]
JAKi-experienced momelotinib utility: TI	[redacted]	[redacted]	[redacted]
JAKi-experienced BAT utility: TI	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; PAS = patient access scheme; TD = transfusion-dependent; TI = transfusion-independent; TTD = time to treatment discontinuation; UB = upper bound

B.3.3.11.3 Scenario analysis

Scenarios exploring alternative long-term extrapolations and data source of survival parameters, cure assumptions, utilities and, along with shorter model time horizons and lower discount rates, are summarised in Table 116.

Scenario analysis results are most sensitive to use of subsequent ruxolitinib (following discontinuation of momelotinib) and a shorter time horizon (5-year) (scenarios 1 and 12), where they generated the greatest NMB decreases of [redacted] and [redacted] compared to BAT and for which momelotinib was no longer dominant over BAT. The ICERs in these scenarios were [redacted] per QALY when assuming 39% of patients on ruxolitinib after discontinuing momelotinib as a result of increasing the costs of subsequent treatment for momelotinib, and [redacted] when using a shorter time horizon of 5 years.

The incremental NMB results were also somewhat sensitive to variations in assumptions around transition probability extrapolations for determining transfusion health state distribution over time, with both costs and QALYs impacted as a result of increased resource use costs and lower health state utilities for TR and TD compared to TI. Applying a less conservative assumption of no health state movement after 24 weeks increased the NMB by [redacted] compared to the base-case analysis, with use of treatment specific cycle 6 probabilities reducing the NMB by [redacted] (albeit with momelotinib remaining dominant over BAT). Other transition probability scenarios had a more modest impact on the results, generating ~4% variations in the NMB.

Application of alternative models for OS had a relatively modest impact on the results, with use of the Weibull model for non-TI patients having a slightly larger impact on the NMB (reduction of [redacted]) than the log-logistic model for TI OS (reduction of [redacted]).

As anticipated, given the numerically higher utility values observed for momelotinib-specific TI and TD health state utilities compared to BAT, application of treatment specific utilities instead of treatment independent utilities increased the cost-effectiveness of momelotinib compared to BAT, with an increase of [redacted] in the NMB,

although this increased in NMB was reduced to [redacted] when also assuming patients discontinuing momelotinib have BAT specific health state utilities.

All other scenario analyses had minimal impacts on the NMB values, with ≤2% variation from the base-case NMB estimate.

Table 116. Scenario analysis results for momelotinib versus BAT – JAKi-experienced model [List price]

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
-	**Base-case**	[redacted]	0.346	[redacted]	N/A	Dominant
1	5-year time horizon	[redacted]	0.179	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	0.266	[redacted]	[redacted]	Dominant
3	Discount rate (cost and health outcomes) of 1.5%	[redacted]	0.396	[redacted]	[redacted]	Dominant
4	TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.342	[redacted]	[redacted]	Dominant
5	TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.429	[redacted]	[redacted]	Dominant
6	TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.350	[redacted]	[redacted]	Dominant
7	TP extrapolation: Treatment specific transition probabilities	[redacted]	0.308	[redacted]	[redacted]	Dominant
8	TI OS: log-logistic	[redacted]	0.307	[redacted]	[redacted]	Dominant
9	Non-TI OS: Weibull	[redacted]	0.363	[redacted]	[redacted]	Dominant
10	Momelotinib TTDD: exponential	[redacted]	0.346	[redacted]	[redacted]	Dominant
11	Apply KOL RBC transfusion unit data	[redacted]	0.346	[redacted]	[redacted]	Dominant
12	Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.346	[redacted]	[redacted]	[redacted]
13	Exclude terminal care costs	[redacted]	0.346	[redacted]	[redacted]	Dominant
14	Treatment specific HSUVs	[redacted]	0.407	[redacted]	[redacted]	Dominant
15	Scenario 15 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.359	[redacted]	[redacted]	Dominant
16	Higher anaemia AE cost	[redacted]	0.346	[redacted]	[redacted]	Dominant
17	Alternative RBC	[redacted]	0.346	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
	transfusion unit costs (Agrawal 2006)					
18	Exclude ICT costs	[redacted]	0.346	[redacted]	[redacted]	Dominant
19	Reduce deferasirox (ICT) dose to 14 mg/kg/day	[redacted]	0.346	[redacted]	[redacted]	Dominant

Abbreviations: AE = adverse event; BAT = best available therapy; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; JAKi = Janus kinase inhibitor; KOL = key opinion leader; N/A = not applicable; NMB = net monetary benefit; OS = overall survival; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TP = transition probability; TTDD = time to treatment discontinuation or death

Table 117 presents the scenario analysis including momelotinib PAS price. The directional impact on the NMB results was similar to the list price scenarios, albeit with the magnitude of the proportional change from the base-case NMB reduced as a result of lowering momelotinib drug acquisitions costs. Following application of the PAS discount, momelotinib dominated BAT across all scenarios (including 39% ruxolitinib post-momelotinib and 5-year time horizon scenarios).

Table 117. Scenario analysis results for momelotinib versus BAT – JAKi-experienced model [PAS price]

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER incremental (£/QALY)
-	**Base-case**	[redacted]	0.346	[redacted]	N/A	Dominant
1	5-year time horizon	[redacted]	0.179	[redacted]	[redacted]	Dominant
2	10-year time horizon	[redacted]	0.266	[redacted]	[redacted]	Dominant
3	Discount rate (cost and health outcomes) of 1.5%	[redacted]	0.396	[redacted]	[redacted]	Dominant
4	TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.342	[redacted]	[redacted]	Dominant
5	TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.429	[redacted]	[redacted]	Dominant
6	TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.350	[redacted]	[redacted]	Dominant
7	TP extrapolation: Treatment specific transition probabilities	[redacted]	0.308	[redacted]	[redacted]	Dominant
8	TI OS: log-logistic	[redacted]	0.307	[redacted]	[redacted]	Dominant
9	Non-TI OS: Weibull	[redacted]	0.363	[redacted]	[redacted]	Dominant
10	Momelotinib TTDD: exponential	[redacted]	0.346	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER incremental (£/QALY)
11	Apply KOL RBC transfusion unit data	[redacted]	0.346	[redacted]	[redacted]	Dominant
12	Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.346	[redacted]	[redacted]	Dominant
13	Exclude terminal care costs	[redacted]	0.346	[redacted]	[redacted]	Dominant
14	Treatment specific HSUVs	[redacted]	0.407	[redacted]	[redacted]	Dominant
15	Scenario 15 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.359	[redacted]	[redacted]	Dominant
16	Higher anaemia AE cost	[redacted]	0.346	[redacted]	[redacted]	Dominant
17	Alternative RBC transfusion unit costs (Agrawal 2006)	[redacted]	0.346	[redacted]	[redacted]	Dominant
18	Exclude ICT costs	[redacted]	0.346	[redacted]	[redacted]	Dominant
19	Higher anaemia AE cost	[redacted]	0.346	[redacted]	[redacted]	Dominant

Abbreviations: AE = adverse event; BAT = best available therapy; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; JAKi = Janus kinase inhibitor; KOL = key opinion leader; N/A = not applicable; NMB = net monetary benefit; OS = overall survival; PAS = patient access scheme; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TP = transition probability; TTDD = time to treatment discontinuation or death

B.3.3.12 Subgroup analysis

Subgroup analysis was performed for the Hb <10 g/dL population to explore the benefits of momelotinib compared to BAT when applying a more restrictive interpretation to clinically relevant anaemia.

Total costs, LYs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT for the Hb <10 g/dL subgroup population are presented in Table 118. Momelotinib generated [redacted] more total costs against BAT, as well as increases in incremental life years and QALYs of 0.132 and 0.129, respectively. Compared to BAT, momelotinib generated an ICER of [redacted] per QALY gained.

The incremental net monetary benefit was [redacted] and [redacted] at £20,000 and £30,000 per QALY WTP thresholds, respectively, as shown in Table 119.

Results based on applying a proposed PAS price discount of [redacted] are provided in Table 120. Momelotinib reduced total costs by [redacted]. The

incremental net monetary benefit values were increased to [redacted] and [redacted] for £20,000 and £30,000 per QALY thresholds (Table 121), respectively.

Table 118. Base-case results for momelotinib vs BAT in Hb <10 g/dL subgroup [List price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	2.666	1.648	-	-	-	-	-
Momelotinib	[redacted]	2.798	1.777	[redacted]	0.132	0.129	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; QALY = quality-adjusted life year

Table 119. Net monetary benefit in Hb <10 g/dL subgroup [List price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.648	-	-	-	-
Momelotinib	[redacted]	1.777	[redacted]	0.129	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; QALY = quality-adjusted life year

Table 120. Base-case results for momelotinib vs BAT in Hb <10 g/dL subgroup [PAS price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	2.666	1.648	-	-	-	-	-
Momelotinib	[redacted]	2.798	1.777	[redacted]	0.132	0.129	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 121. Net monetary benefit in Hb <10 g/dL subgroup [PAS price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.648	-	-	-	-
Momelotinib	[redacted]	1.777	[redacted]	0.129	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; PAS = patient access scheme; QALY = quality-adjusted life year

B.3.3.13 Benefits not captured in the QALY calculation

A key innovation of momelotinib which is not fully captured in the QALY calculation is that it prevents the need to treat MF with interventions which exacerbate a key symptom of MF itself (anaemia). There are significant practical and ethical issues involved in prescribing a treatment which will make a disease symptom worse in the course of managing another set of disease manifestations (and these issues are more involved than for a simple unrelated 'side effect' of a treatment). Because of the innovative mechanism of action of ACVR1 inhibition, momelotinib avoids this ethical issue.

In addition, fatigue is known to be poorly captured by generic utility measures like EQ-5D that inform economic analyses in technology appraisals, and therefore the potential QALY benefits of momelotinib may be underestimated.

B.3.3.14 Validation

B.3.3.14.1 Technical quality control of the model

The CEM was assessed for conceptual validity using the AdViSHE framework.(139) Before finalisation, the CEM was subject to a rigorous quality assessment checklist. Technical validation was based on relevant checklists from the TECH-VER framework.(140) The CEM was also assessed against the GSK's internal quality assessment guidelines for CEM. The final CEM was reviewed by all necessary stakeholders from GSK.

B.3.3.14.2 External validation

The model approach, assumptions and outputs were validated through consultation with 6 UK clinical experts and two UK health economists.(32) Feedback from this session was incorporated into the final model, including for informing the OS modelling approach, transition probability extrapolation and other key model assumptions. Resource use data were also collected based on UK clinical expert feedback and used to inform monitoring and disease management costs in the CEM.

B.3.3.14.3 OS outcomes

In a comparable NICE appraisal, TA756, evaluating fedratinib use in JAKi-experienced patients mean life expectancy generated for BAT from the economic analysis was 28.7 months and 34.9 months in the company and ERG preferred base-case analyses, respectively.(51) This compares to 45.5 months (based on undiscounted life years gained) for the BAT comparator in the present economic analysis. While the predicted life years were higher than in TA756, this is expected given differences in positioning and populations being appraised in each instance. JAKARTA-2, the pivotal trial informing the use of fedratinib in JAKi-experienced patients, enrolled patients who were resistant or intolerant to ruxolitinib and had a life expectancy of 6 months, which is more reflective of positioning closer to end-of-life treatment. This contrasts to the much broader population enrolled into SIMPLIFY-2, where patients were enrolled if they had experienced haematological toxicity with prior JAKi therapy.

Survival outcomes are also consistent with the NICE TA386 appraisal of ruxolitinib, with both momelotinib and BAT discounted total life years, 3.82 and 3.36 respectively, being lower than predicted for ruxolitinib in a healthier JAKi-naïve patient population (5.96 life years).

B.3.3.14.4 Clinical outcomes from the model

Trial data at Week 24 and CEM outcomes at Week 24 were compared. The analysis plan for the SIMPLIFY-2 trial resulted in all withdrawals, fatalities and missing observations being categorised as non-TI and TD, and as noted in Section B.3.3.4.2 transition probabilities for informing health state occupancy for the first 6 cycles were derived to account for these. Furthermore, health state occupancy over the initial 6 cycles is influential in generating overall costs and QALYs. TI state occupancy at Week 24 is particularly influential given that lower costs, higher HRQoL and improved survival are associated with these outcomes. In both arms it is assumed that TI response is maximised at Week 24 and deteriorates in extrapolations used to derive health state distributions after Week 24 for the base-case analysis.

The proportions of patients being TI at baseline and at Week 24 in each arm are presented in Table 122, as reported in SIMPLIFY-2 trial results for the base-case population and as predicted by the model. The proportion of the momelotinib arm categorised as TI increased [redacted] during the trial period ([redacted] to [redacted]). In the BAT arm, this proportion decreased [redacted] ([redacted] to [redacted]).

The predicted TI responses at Week 24 are also outlined in Table 122. Predicted TI change from baseline (CFB) in the momelotinib arm is comparable to the SIMPLIFY-2 results ([redacted] predicted versus [redacted] observed). However, the predicted TI CFB in the BAT arm ([redacted]) is less than that observed in SIMPLIFY-2 ([redacted]). In summary, the modelled Week 24 TI rates for the momelotinib arm are reflective of the trial results, while the BAT comparator may be disproportionately favoured by the derived transition probabilities.

Table 122. TI at baseline and Week 24 for the base-case population (comparison of CEM and trial results)

Treatment arm	TI (SIMPLIFY-2)			TI (CEM-predicted)		
	Baseline	Week 24	Absolute CFB	Baseline	Week 24	Absolute CFB
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; CEM = cost-effectiveness model; CFB = change from baseline; TI = transfusion-independence

B.3.4 Interpretation and conclusions of economic evidence

When applying the proposed PAS discount, momelotinib results in cost savings to the NHS when used as an alternative to ruxolitinib in a JAKi-naïve population, and was highly cost-effective compared to BAT in a JAKi-experienced population across all scenarios and sensitivity analyses performed. Momelotinib was also dominant over BAT for the Hb <10 g/dL subgroup, showing consistency in cost-effectiveness regardless of how anaemia is defined.

The need for RBC transfusions to manage disease- or treatment-driven anaemia constitutes a substantial economic burden to the NHS. Existing JAKis, such as ruxolitinib, are associated with a decline in red blood cell counts and haemoglobin levels, resulting in increased rate of RBC transfusions to maintain adequate haemoglobin levels. This is demonstrated by the drop in TI rate from 70.0% at

baseline to 49.3% at Week 24 in the ruxolitinib arm of SIMPLIFY-1, compared to TI rates being maintained on momelotinib (68.4% at baseline and 66.5% at Week 24).

Much of the economic benefit of momelotinib to the NHS in JAKi-naïve patients is a result of the reduction in RBC transfusion costs compared to ruxolitinib. The sensitivity analysis described in Section B.3.2.9.2 explored different assumptions related to RBC transfusion requirements. When applying the proposed PAS price discount, using the upper bound of the 95% confidence interval of transfusion rate ratio still results in momelotinib producing a positive economic impact compared to ruxolitinib in the JAKi-naïve population. Momelotinib also remained cost saving compared to ruxolitinib when applying more conservative ICT costing assumptions (removal of ICT costs, lower ICT dose).

A key strength to the cost-comparison analysis is the availability of head-to-head pivotal trial data, which included a representative JAKi-naïve population, and which accurately captured the transfusion burden in each treatment arm. The relatively large sample size (n=432), given the rarity of the disease, minimised uncertainty in the RBC transfusion rate reduction because of momelotinib, compared with ruxolitinib. This resource-impact treatment effect is supported by other anaemia-related outcomes, such as improved Hb and TI response which was replicated across all momelotinib trials. In addition, we conducted robust scenario analyses assessing a range of assumptions. This allowed for any uncertainties to be robustly tested.

Limitations of the cost-comparison analysis include the omission of natural progression components of the disease, such as leukemic transformation and mortality. Although it was considered acceptable to simplify the cost-comparison analysis given the comparable mortality and transformation risks in each arm, it did result in quite high total treatment costs when the analysis horizon in set to 10 years. As described in Section B.1.4.2.1, unfortunately most patients with MF do not live for 10 years following diagnosis. Furthermore, as momelotinib is currently not available in clinical practice, it is unclear whether the NHS will allow for the use of ruxolitinib following momelotinib discontinuation considering the lack of evidence supporting its

sequencing. However, a very conservative approach was considered in the base-case results with the cost impact of excluding JAKi sequencing explored in scenario analysis.

In JAKi-experienced patients who have experienced haemotological AEs on an initial JAKi therapy, switching to momelotinib has been shown to maintain any initial splenic response while delivering greater health outcomes through improved TI. As well as a reduction in costs, TI is also associated with improved HRQoL and, furthermore, a predictor of better survival outcomes. The cost-effectiveness analysis has demonstrated, across sensitivity analyses and a range of scenario analyses, that momelotinib is associated with greater QALY gains and lower overall costs in a JAKi-experienced population compared to BAT.

In addition, subsequent treatment costs account for a substantial proportion of overall costs. As described previously, current practice is such that patients rarely completely discontinue ruxolitinib, even where there is a suboptimal response or emergence of AEs or haematological toxicity. Clinicians have advised that it is preferable to reduce to lower doses of ruxolitinib doses as part of BAT rather than discontinue entirely. As reflected in the mature momelotinib discontinuation data, this is less likely to occur with momelotinib, likely due to limited dosing flexibility with momelotinib compared to ruxolitinib. Where momelotinib would be used in a JAKi-experienced population, clinicians have advised that they would be unlikely to re-treat with ruxolitinib even if it were accessible. Momelotinib's cost-effectiveness in the JAKi-experienced population is therefore supported by a reduction in suboptimal yet expensive JAKi usage.

Similar to the JAKi-naïve evaluation, the JAKi-experienced evaluation is supported by a randomised controlled trial against a relevant comparator reflective of English clinical practice. As described in Section B.2.6.1, the attributes of SIMPLIFY-2 which contributed to its failure to demonstrate a superior splenic response over BAT, resulted in a comparator arm which was better placed for informing comparative effectiveness. As such, the economic evaluation and supporting cost-effectiveness model was developed to capture costs and outcomes resulting from differences in

transfusion needs, which has been identified as main difference between momelotinib and BAT which is relevant for decision making.

The lack of comparator data beyond Week 24, when all BAT patients crossed over to momelotinib in the pivotal trial, presents a limitation in the modelling approach, requiring the use of Week -24 TI response to predict OS. In addition, the modelling approach is heavily reliant on patient level data which resulted in the application of very conservative assumptions to model health state occupancy beyond Week 24. However, to explore the impact of these limitations, a range of scenario analyses have been undertaken and which have supported the base-case results in terms of consistently indicating cost-effectiveness for momelotinib.

Momelotinib is therefore expected to be a valuable and cost-effective treatment option for either JAKi-naïve or JAKi-experienced patients with myelofibrosis, reducing the need for TD and its associated costs, HRQoL and mortality implications.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Summary of Information for Patients (SIP)

August 2023

File name	Version	Contains confidential information	Date
ID6141_Momelotinib_in_myelofibrosis_STA_SIP_8Aug2023	1	Yes	8 August 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open access IJTAHC journal article

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Momelotinib *(no approved brand name at time of submission)*

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The population that is being appraised by NICE is patients who have myelofibrosis and are impacted by symptoms of the disease (including an enlargement of their spleen), and who also have anaemia (low red blood cells) which requires treatment which is impacting quality of life. Because of the way we have presented our evidence, in this submission we separate this population into two distinct groups of people: 1. People who have not previously been treated with similar therapies to momelotinib, such as ruxolitinib (Jakavi®) and fedratinib (Inrebic®) 2. People who have already tried these similar therapies but have not responded all that well to them or have experienced side effects, and so might benefit from a different treatment option.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Momelotinib is not yet an approved treatment. It expected to be approved by the UK's medicine's regulator, the MHRA, in early 2024.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

MPN Voice have spoken at an internal GSK UK meeting to raise awareness of myeloproliferative neoplasms and convey how a diagnosis and then living with this disease can impact someone's life. A fee for honoraria services was paid for this activity.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Disease background and symptoms:

Myelofibrosis (MF) is a rare blood cancer, which can cause scarring ('fibrosis') of the bone marrow.(1) This scarring results in inflammation around the body, which leads to symptoms such as tiredness and fatigue, night sweats, intense itching, bone pain, fever and general problems in concentrating. It is part of a group of blood cancers called 'Myeloproliferative Neoplasms' (MPNs), which mean cancers affecting the bone marrow.

This scarring prevents the bone marrow from performing its usual job, which is to create new blood cells. The body can compensate by instead making some new red blood cells in organs such as the spleen. However, the spleen is not as efficient as the bone marrow, and it also tends to swell or enlarge in order to carry out this function. An enlarged spleen, known as 'splenomegaly', leads to symptoms such as tummy (abdominal) swelling, pain, lack of appetite, shortness of breath (dyspnoea), and diarrhoea (loose and/or more frequent bowel movements).

Because the body is not producing enough healthy red blood cells, it cannot transport enough oxygen around the body which can lead to tiredness (fatigue) and a lower quality of life. The specific name for this symptom is 'anaemia', and it affects many people when they have MF. Unfortunately, some existing MF therapies which work well to treat other symptoms of MF may cause anaemia or make it worse.

Although red blood cells are most commonly affected by this scarring of the bone marrow, other types of blood cells can also be affected. These include white blood cells, which fight infections and support the immune system, and platelets which help the blood to clot when needed. Disrupting the production of these cells can cause serious complications such as infections, blood clots which cause blockages around the body (thrombosis), bleeding, and heart/blood circulation complications.

Epidemiology:

MF is a very rare disease. The number of new cases ('incidence') of MF has been estimated at 0.60 per 100,000 persons per year in the UK.(2) The disease is more commonly diagnosed in men than women.(2)

The latest available data estimated the number of patients living with MF in the UK ('prevalence') is 3.2 per 100,000 persons.(2) Using these figures, the estimated total number of patients living with MF currently in the UK is 2,080.(3)

There are two kinds of MF. ‘Primary’ MF is where the bone marrow scarring is not caused by any other existing disease. ‘Secondary’ MF is where the bone marrow starts scarring because of another disease, most commonly ‘polycythaemia vera’ (PV) or ‘essential thrombocythemia’ (ET), which are both kinds of ‘Myeloproliferative Neoplasms’. ‘Primary’ MF is significantly more common than ‘Secondary’ MF, but from the point of view of a patient there is no difference in terms of how the disease is managed regardless of how the scarring starts. In this submission to NICE, we don’t distinguish between the different kinds of MF for this reason.

Mortality/morbidity data:

MF is a ‘progressive’ disease, meaning the scarring will typically get worse over the patient’s lifetime. This ultimately results in more severe symptoms and decreasing life expectancy over time. Studies suggest that around 30% of patients will receive their initial diagnosis when they have no symptoms at all (although around 50% of patients will receive their initial diagnosis when they have the most severe form of MF).(4-6) While every patient will experience this progression at a different rate, almost all patients will eventually experience symptoms which are impactful and debilitating to their lives.(7)

A key outcome which is very frequently experienced by patients with MF is a loss of ability to work; 57% of patients with MF experienced a negative impact on their work.(8)

Life expectancy at diagnosis can vary, and depends on a number of factors including age at diagnosis and severity of symptoms. Overall, patients with MF would expect an average survival of 5.75 years from diagnosis, but patients with the most severe disease at diagnosis might expect an average survival of 2.25 years.(5, 9)

Anaemia and MF:

As described above, anaemia is a common symptom of MF. In this submission we present evidence that patients with anaemia due to MF which requires treatment are particularly likely to benefit from momelotinib treatment. At diagnosis, approximately 38% of MF patients have anaemia and approximately a quarter of them will already be receiving red blood cell transfusions of donated, healthy red blood cells to treat it.(10) As the disease progresses, the number of patients with anaemia and those needing transfusions increases. Within one year of diagnosis up to 58% of patients develop anaemia and the number of patients who require blood transfusions nearly doubles.(10)

Anaemia, and the requirement for blood transfusions to treat it, is associated with shorter life expectancy compared with patients without anaemia.(11-13) Furthermore, red blood cell transfusions are associated with poor quality of life and costs to the healthcare system.(14-16) The need for blood transfusions creates an additional burden on patients. They have to attend hospital and spend up to four hours per transfused bag of blood. This can be disruptive to their daily life, including their work.(8, 17, 18) Blood transfusions also have risks associated with them; patients can development an immune response against donated blood, causing reactions such as: allergic-type reactions, fall in blood pressure (‘hypotensive reaction’), or raised body temperature. Each of these types of reactions can range from mild and easily managed, to severe requiring medical intervention or hospitalisation. Also, repeated blood transfusions may result in a

build-up of excessive iron in the body which can be toxic over time, leading to liver and heart issues.(19)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

MF is usually diagnosed when people visit their GP with symptoms. To confirm the diagnosis, there are a combination of tests such as physical examination, blood tests, imaging scans, bone marrow biopsy, and molecular testing.(20) In some rare cases where the patient doesn't have any symptoms and feels well, abnormal blood cell counts are flagged during a routine blood test and the patient will undergo further diagnostic tests.(20)

No change in diagnostic methods will occur following the introduction of momelotinib.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current MF treatments:

From the perspective of the patient, the most important treatment for MF is having their disordered bone marrow replaced with healthy blood stem cells from a donor. This procedure is called 'allogeneic-stem cell transplant' or sometimes 'allo-SCT'. The reason this is such an important treatment is that it is the only procedure available in MF which might cure the disease, rather than managing its symptoms. However, allo-SCT is a risky procedure and requires finding a donor who is a close genetic match to the patient. Even in genetically matched cases, there is still a risk of transplant rejection by the patient's body, which leads to serious complications. For these reasons, the treatment guidelines used in the UK only consider this treatment for patients with severe disease and predicted life expectancy of less

than 5 years.(12, 21) Therefore, only a small proportion of MF patients (around 5%) are likely to undergo allo-SCT.

Other treatments for MF are aimed at improving symptoms rather than reversing disease progression. Treatment is tailored to the patient based on assessment of their disease severity and presentation of symptoms.(4, 12, 21) In the submission we therefore refer to patients being on 'best available therapy' (BAT) if they are on a treatment regimen that is tailored to them, and which therefore potentially contains a complex mix of treatments. Many of the therapies used to treat MF symptoms were not designed specifically for MF. For example, many treatments used in MF are older drugs which have been identified over time as being able to provide some level of benefit to people with MF, depending on which symptoms they are presenting with. Examples of these established treatments include: hydroxycarbamide, prednisolone, thalidomide, radiotherapy, other chemotherapies, and surgical removal of the spleen (splenectomy).

Since 2016, patients in England and Wales have been able to access a new class of treatment for MF, a 'Janus Kinase Inhibitor' (JAKi). JAKis work by disrupting the production of chemicals in the body which make the signs and symptoms of the disease worse, and they therefore reduce spleen size and other associated symptoms of MF. The most common JAKi to receive in the NHS is ruxolitinib (branded as 'Jakavi'), however some patients may receive an alternative JAKi called fedratinib (branded as 'Inrebic'). Fedratinib is not yet routinely used in the NHS, but since 2021 some patients can access it through the Cancer Drugs Fund if they have previously been treated with ruxolitinib.

JAKis are not disease modifying (they do not remove scar tissue in the bone marrow which has already been created) but their impact on other important symptoms of MF means that they should reduce symptoms and improve life expectancy compared to the next best available therapies.(22-24) One important limitation of existing JAKis is that they do not improve MF-related anaemia, and in fact both existing JAKis may *worsen* anaemia, which can lead to treatment failure and further side effects.(13, 25-27)

For these reasons, and the significant cost of treating a patient with JAKis for a long period of time, treatment guidelines are to save JAKis for more severely progressed MF. In particular, ruxolitinib is recommended for patients with severe disease, enlarged spleen or general disease symptoms (as described above, fedratinib is only available through the Cancer Drugs Fund and so is not featured in these guidelines).(21, 28) The guidelines do not provide recommendations for patients whose disease does not respond (or is no longer responding) to ruxolitinib, or where patients experience various side effects from ruxolitinib treatment.(21) In practice most of these patients continue on ruxolitinib, either on a reduced dose, or in combination with other therapies to increase its effectiveness or help manage some of the side effect.(28)

For patients with anaemia, either due to MF or anaemia which is worsened with existing therapies, treatment options include:

- Erythropoiesis stimulating agents [ESAs]: These therapies mimic a natural hormone (erythropoietin) which encourages the bone marrow to produce more red blood cells. These therapies need to be injected.
- Steroid-like drugs, including androgens such as danazol, and corticosteroids such as prednisolone.

- Other drugs affecting the immune system (immunomodulating drugs).(12, 15) However, these treatments are not suitable for all patients, have limited long-term efficacy, are costly, and are associated with considerable side effects.(12, 15, 29-33)

Momelotinib:

Momelotinib is another kind of JAKi, and so we expect it will be used in the same way that other JAKis are currently used – which is to say, in MF patients who have severe disease, enlarged spleen or general disease symptoms (and who are not suitable for allo-SCT). Unlike currently approved JAKi treatments, momelotinib may be restricted to patients who have anaemia which requires treatment, since it may have an especially beneficial effect on the anaemia symptoms of MF due to its mechanism of action.

The NICE submission is divided into two parts depending on whether the patient has been treated with a JAKi before:

- **JAKi-naive -** Currently, patients who have not yet received treatment with a JAKi but are suitable candidates for the treatment will receive ruxolitinib. Momelotinib is an alternative JAKi that could be given instead to patients with anaemia which requires treatment.
- **JAKi-experienced –** Currently, patients who have previously received JAKi will typically be offered ruxolitinib at a reduced dose instead of a completely different treatment. Momelotinib works slightly differently to ruxolitinib and can be given at full dose in this population, so may be clinically more appropriate for some patients if they also have anaemia which requires treatment.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

GSK have gathered insights on lived patient experiences through an Expert Patient Council, social media listening exercises and exploration of the patient journey to identify how patients think, feel, and behave when diagnosed and treated for myelofibrosis.

Key findings included:

- Patients & health care professionals have difficulty identifying MF.
- Treatment plans are often full of uncertainty and patients & health care professionals can lose optimism as symptoms worsen.
- Symptoms can emerge and then reduce in complicated and unpredictable ways.
- Fatigue is the first symptom experienced by a majority of MF patients, leading to profound negative impact on quality of life (QoL).
- Anaemia is treated only when symptoms have worsened to the point of needing transfusions.

The substantial burden of symptoms caused by MF leads to a highly impaired QoL, with most patients with MF (83%) indicating that their symptoms reduced their QoL.(8) The cross-country Landmark health survey (Australia, Canada, Germany, Italy, Japan, UK) conducted online surveys with patients diagnosed with MF and treating physicians (April 2016 to October 2016).(8) The survey found that fatigue was the most common symptom, occurring in 54% of all patients with MF.(8) Other common symptoms in patients with MF:

- Tummy (abdominal) discomfort (30%)
- Shortness of breath/breathlessness (29%)
- Night sweats (29%)
- Difficulty sleeping (27%)

Most patients with MF indicated that their symptoms reduced their QoL (83%), with those with the most severe disease and highest symptom burden most likely to report impaired QoL. In terms of specific elements of QoL, a total of:(8)

- 58% required assistance from a caregiver
- 34% had felt worried or anxious about the disease
- 33% of patients had experienced emotional hardship due to their MF
- 11% received antidepressants to help manage their condition
- 9% received psychological therapy to help manage their condition

Both patients and physicians identified the improvement of symptoms (patients: 70%; physicians: 80%) as the most important treatment goal in MF, followed by a better QoL (patients: 61%; physician: 52%) and a delay in time to the disease returning (patients: 58%; physician: 43%).(8)

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

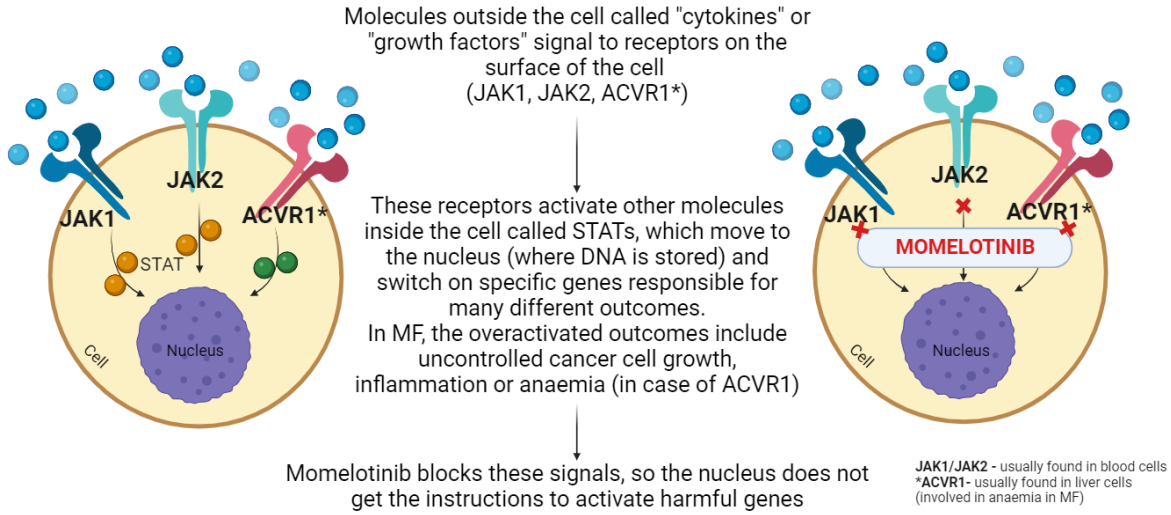
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

As described above, momelotinib is a 'Janus Kinase Inhibitor' (JAKi), like ruxolitinib and fedratinib.(34) JAKis work by blocking molecules in the body that signal cancer cells to multiply. An important impact of blocking the growth of these cancer cells is that it enables the spleen to return to a more healthy size, and reduces the symptoms of MF.(35)

However, unlike existing JAKis, momelotinib also blocks another signalling molecule in the body, 'activin A receptor type 1' (ACVR1). Overactivity of this results in too much iron being taken out of the blood, so there is less iron available to make haemoglobin (the substance which transports oxygen around the body in red blood cells). By blocking the ACVR1 molecule, momelotinib allows for the iron to be used to make red blood cells. Therefore, unlike other JAKis, momelotinib has the ability to improve anaemia in MF rather than making it worse.

Figure 1 demonstrates momelotinib's mechanism of action.

Figure 1. Momelotinib's mechanism of action(36)



Source: GSK internal material.
Abbreviations: ACVR1 = Activin A receptor, type I; DNA = deoxyribonucleic acid; JAK = Janus kinase; MF = myelofibrosis; STAT = signal transducer and activator of transcription

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐Yes

☒No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

N/A

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose is a 200 mg tablet taken by mouth, once daily. Momelotinib therapy can continue as long as the patient is benefitting and not experiencing side effects that would require them to stop treatment. Momelotinib is administered once daily, whereas ruxolitinib is administered twice daily.(37) Therefore, momelotinib can reduce the number of times a patient needs to take their treatment.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The evidence for momelotinib in adults with MF comprises the following clinical trials: • **SIMPLIFY-1** was a multicentre (Europe, including the UK, North America, Asia and Australia), randomised, double-blind phase 3 non-inferiority trial comparing momelotinib (n=215) versus ruxolitinib (n=217) in patients who had not yet been treated with a JAKi, and who were over 18 years with an enlarged spleen and a confirmed diagnosis of MF. The goal of this trial was to show that momelotinib was not worse than ruxolitinib ('non-inferiority'). Patients were enrolled into the study between December 2013 to September 2016.(38, 39) • **SIMPLIFY-2** was a multicentre (North America, Europe, including the UK, Middle East), randomised, open-label phase 3 superiority trial comparing momelotinib (n=104) versus best available therapy (BAT) (n=52) in patients who were over 18 years old who were currently receiving or had previously received ruxolitinib and had suboptimal response or blood-related side effects after receiving ruxolitinib.(40) BAT was administered according to

standard of care and investigator's discretion. The goal of this trial was to show momelotinib is better than BAT. Patients were enrolled into the study between June 2014 to July 2016.(40, 41)

- **MOMENTUM** was a multicentre (Europe, including the UK, North America, Asia and Australia), randomised, double-blind phase 3 trial evaluating the non-inferiority and superiority of momelotinib in patients aged 18 and over with a confirmed diagnosis of MF (n=130) compared with danazol (an anaemia treatment) (n=65) in JAKi-experienced, symptomatic and anaemic patients. The goal of this trial was to show momelotinib can improve symptoms and anaemia in a symptomatic, anaemic MF population. Patients were enrolled into the study between April 2020 to December 2021.(42, 43)

The three trials have been completed.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

We have tested momelotinib in three large clinical trials (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM). The results of the trials show that momelotinib can provide meaningful clinical benefits to patients with MF compared with current therapies.(38, 42, 43) Each trial looks at a number of different outcomes ('endpoints'), because the outcome that matters most to one patient may not matter at all to another. In general, we designed the trials so that they were most sensitive at detecting changes in outcomes we believed were most important to patients; these include reduction in spleen size, patient assessments of their MF symptoms and effects on anaemia.(26, 44-46)

SIMPLIFY-1 (JAKi-naïve patients):(38)

- SIMPLIFY-1 was designed to test whether momelotinib was **at least as good as** ruxolitinib in patients who had not been treated with a JAKi before. This is a slightly unusual approach, as most people are more familiar with trials that test whether a drug is **better** than another drug. The results from the SIMPLIFY-1 trial show that momelotinib is at least as good as ruxolitinib at reducing spleen size. Spleen size reduction is conventionally considered the most appropriate way of measuring whether MF therapies work or not. Other outcomes were also compared and overall the results indicated that ruxolitinib maybe more effective in some parts of the disease, while momelotinib is more useful in other areas. In terms of the outcomes we believe are most important to patients:

- Spleen size reduction was comparable between the two treatments (26.5% of patients who received momelotinib and 29.0% of patients who received ruxolitinib saw a reduction of at least 35% of the initial spleen size when they started the trial).(38, 39)
- Both the patients who were treated with momelotinib and the patients who were treated with ruxolitinib had an improvement in their symptoms, however more patients in the ruxolitinib group achieved a large reduction in their symptoms (28.4% for patients who received momelotinib and 42.2% for patients who received ruxolitinib). Further analysis of individual symptom scores found that similar improvements were observed in patients treated with momelotinib and ruxolitinib including abdominal (tummy) discomfort, pain under left ribs, early fullness, night sweats, itching, bone pain and tiredness.
- Momelotinib demonstrated improvements in the numbers of red blood cell markers compared with ruxolitinib. For example, haemoglobin is a chemical responsible for transporting oxygen around the body within red blood cells, and levels of haemoglobin increased in the momelotinib group and decreased in the ruxolitinib group. More patients who received momelotinib no longer required red blood cell transfusions when compared with those who received ruxolitinib.
- For further details on SIMPLIFY-1, see section B.2.4.1.1 in the submission.

SIMPLIFY-2 (JAKi-experienced patients):(41)

- SIMPLIFY-2 was designed to test whether momelotinib was **better** than the best available therapy used in the NHS (tailored to individual patients). As part of the best available therapy arm, 89% of patients received ruxolitinib. The other 11% of treatments used in the arm included hydroxyurea, prednisone/prednisolone, danazol, erythropoietin stimulating agent, anagrelide, aspirin, thalidomide or no therapy.
  - Spleen size reduction was comparable between the two treatments (6.7% of patients who received momelotinib and 5.8% of patients who received ruxolitinib saw a reduction of at least 35% in spleen size). Because the trial was designed to test whether momelotinib was **better** than the alternative, this is not a positive outcome like it was for SIMPLIFY-1, and part of our submission is spent explaining the technical reasons why we believe this result occurred (in brief; because we believe the momelotinib patients may still have had ruxolitinib in their system following their initial treatment).
  - A substantially greater number of patients in the momelotinib arm experienced a large reduction in MF symptoms compared to the comparator arm. 26.2% of patients treated with momelotinib compared to 5.9% of patients treated with BAT had a reduction in their symptom score of at least 50%.
  - As with SIMPLIFY-1, levels of haemoglobin increased in the momelotinib group and decreased by in the BAT group. More patients who received momelotinib no longer required red blood cell transfusions compared with patients who received BAT.
  - For further details on SIMPLIFY-2, see section B.2.4.1.2 in the submission.

MOMENTUM (JAKi-experienced patients):(42, 43)

- MOMENTUM was designed to test whether momelotinib was **better** than a treatment called danazol. Danazol is sometimes used in the NHS however is it mainly prescribed to help with anaemia symptoms in MF, rather than actively treating the broader signs and symptoms of MF. Because of this, we describe MOMENTUM results as being supportive of the SIMPLIFY-2 results in the submission. In general, the results from MOMENTUM were similar or slightly better than those reported in SIMPLIFY-2. In particular, MOMENTUM included many more patients with very low red blood cell counts (that is, anaemia) and low levels of white blood cells ('neutropenia') and platelets ('thrombocytopenia'), which makes us more confident when we say that momelotinib might be particularly suitable for patients with anaemia.
    - Momelotinib was more effective in reducing spleen size compared with danazol.
    - More patients who received momelotinib no longer required red blood cell transfusions compared with those who received danazol.
    - Patients who received momelotinib reported more of a reduction in their MF symptoms compared with those who received danazol.
    - Momelotinib demonstrated benefits in blood cell counts compared with danazol in patients with anaemia and low platelet counts (thrombocytopenia) before they started treatment.
    - For further details on MOMENTUM, see section B.2.4.1.3 in the submission.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient-reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials, the EQ-5D-5L questionnaire was administered to patients to measure health-related quality of life (HRQoL). The EQ-5D-5L is a frequently used HRQoL questionnaire comprising of five aspects of health: mobility, self-care, usual daily activities, pain/discomfort and anxiety/depression. Each aspect has five levels of severity: no problems, slight problems, moderate problems, severe problems and extreme problems. Results are measured at 1 for full health and 0 for health states considered equivalent to death.

The EQ-5D-5L Visual Analogue Scale (VAS) was also captured during the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials, which records the patient's self-rated-health on a vertical visual analogue scale, which is a scoring system where either end of the diagram is labelled 'The best health you can imagine' and 'The

worst health you can imagine'. The scale can record and assess the patient's perspective on their own health, providing valuable insights into their well-being or any changes in their condition over time.

Two additional HRQoL measures were available from the MOMENTUM study that were not captured in SIMPLIFY-1 or SIMPLIFY-2 trials; the MF-8D, and Patient-Reported Outcomes Measurement Information System (PROMIS) – 10b.

The MF-8D is a disease-specific measure developed from the Myelofibrosis Symptom Assessment Form (MF-SAF) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). This system takes 8 areas collected from the MF-SAF specifically relevant to myelofibrosis symptoms. This makes it highly suited to measuring HRQoL in MF patients, meaning it is important to understand its relationship with the more general measures such as the EQ-5D.

The PROMIS-10b provides an additional measure of patient HRQoL with a 10-question form to assess physical function. These questions had the option for a 5-point response ranging from 1 (unable to do) to 5 (without any difficulty). Given this scoring system, PROMIS-10b score can be interpreted positively where a higher score indicates better physical function.

All patient-reported outcomes collected within the three trials tend to agree with one another, which confirms that they are probably capturing the symptomatic burden of myelofibrosis well. Furthermore, the measures of patient-reported outcomes used in the trial tend to make sense given the underlying clinical activity (for example, needing more transfusions or having a larger spleen is associated with worse quality of life). Finally, disease-specific measurements reported by patients (such as the MF-8D and PROMIS-10b) tend to agree with other measurements such as the EQ-5D-5L, suggesting that all the measures were capturing outcomes that were important to patients.

Analysis of the results confirmed that there is a significant difference in the impact of not needing transfusions on myelofibrosis patients, emphasising the importance of 'transfusion independence' response achieved in the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials in capturing both the impact on health systems and the impact of patient quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The number of side effects of momelotinib compared to other treatments administered in the three clinical trials were recorded in the first 24 weeks of receiving any treatment. Then, to further understand the long-term safety of momelotinib, we recorded the number of side effects due to treatment from all three clinical trials (this is called a 'pooled safety analysis'). We also continued to monitor patients who had participated in the trials after they had ended treatment, in a follow-up extended access study. On average we followed these patients up for 11.3 months.(47) This is an important limitation of our approach, because we only follow up patients who took momelotinib long term, not any other treatment, so we can only consider results relating to momelotinib itself.

We were particularly interested in side effects which were severe or medically significant, which you will see referred to in the NICE submission as 'Grade ≥3'. These side effects are especially important because they can have a significant impact on patient quality of life. The most common Grade ≥3 side effects related to patients blood cells – 16.4% of patients experienced low platelet counts ('thrombocytopenia') and 14.1% of patients experienced low haemoglobin counts (anaemia).(47) Non-blood side effects were much rarer, and included:(47)

- Inflammation of the lung (pneumonia) was reported in 1.2% of patients
- Cancer of the white blood cells (acute myeloid leukaemia) was reported in 0.8% of patients
- Blood poisioning (sepsis) was reported in 0.7% of patients

These severe or medically significant side effects are similar in risk and severity to the side effects reported by the comparator drugs, such as ruxolitinib. However, the side effect profile of each drug will be different, and therefore different patients might prefer different treatment options.

The side effects from momelotinib were generally well tolerated. Around 2/3 of patients were able to take momelotinib without any need for dose adjustment, while the remaining 1/3 required at least one dose adjustment / interruption / discontinuation.(47) The most common side effects leading to dose adjustments were low platelet counts (thrombocytopenia, 10.5%) and infections (including pneumonia, 7.0%).(47) These were also the most common side effects leading to a complete discontinuation of momelotinib.(47)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

In patients who **have not** yet tried a JAKi, momelotinib offers several key benefits:

- Momelotinib works similarly to existing JAKis, controlling multiple symptoms and providing comparable spleen size reduction.
- Existing JAKi treatments are likely to make anaemia worse and increase the need for red blood cell transfusions. Momelotinib is less likely to do this.

- In our submission, we make the case that momelotinib is likely more cost effective for the NHS than currently used JAKis, because it is similarly effective but reduces the need for expensive red blood cell transfusions.

In patients who **have** tried a JAKi, momelotinib offers other benefits:

- Provides additional symptom benefit for patients whose disease is not optimally managed on best available therapy.
- Improves and maintains haemoglobin in anaemic patients. Fewer patients require regular transfusions ('transfusion independent') when taking momelotinib compared to best available therapy. It is known that repeated transfusions are linked with poorer quality of life and reduced life expectancy, therefore momelotinib is expected to improve survival outcomes and improve patients' quality of life.
- In patients who are unable take ruxolitinib (for example because the disease has stopped responding or the patient experiences intolerable side effects on ruxolitinib), momelotinib offers hope of symptom control which otherwise would not exist.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The main disadvantage of momelotinib is that it is a JAKi, and like other JAKis it is not a disease modifying treatment. Instead, momelotinib helps manage the effects of MF, such as the enlargement of the spleen, disease symptoms and anaemia.(38, 40, 42) Therefore, compared to stem cell transplant ('allo-SCT'), momelotinib has a clear disadvantage and we expect it to be rare that momelotinib would be recommended to a patient who could otherwise have allo-SCT. However, this is a drawback suffered by all JAKis (ruxolitinib and fedratinib) and so compared to other treatments in the same class this is not a specific disadvantage of momelotinib.

Across the three key clinical trials for momelotinib, there were some measurements (or endpoints) which momelotinib did not succeed in meeting.

- In patients who have not tried a JAKi, fewer patients experienced a large (≥50%) reduction in symptom score over the course of the trial on momelotinib compared to ruxolitinib
- In patients who have previously been treated with a JAKi, switching to momelotinib was not able to further reduce the spleen size significantly more than the comparator, best available therapy.

We believe there are technical reasons relating to the trial design that momelotinib did not perform as we expected for these outcomes, and in our submission to

NICE we make these technical arguments in Section B.2. However, it is reasonable to conclude that there is more uncertainty relating to these outcomes for momelotinib than the comparator; if these outcomes are of particular importance to a patient momelotinib may be at a disadvantage compared to the comparator.

Finally, as discussed above, patients experienced side effects on momelotinib. While overall we believe the side effect profile of momelotinib is generally well tolerated(38, 40, 42, 48) it is nevertheless true that certain side effects are more likely to be experienced with momelotinib than ruxolitinib, and vice versa. For patients who have a particular preference for ruxolitinib's side effect profile compared to momelotinib, momelotinib would be at a disadvantage.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

NICE request that manufacturers support their submissions with an economic model, trying to calculate whether the benefits of the drug to MF patients are worth the costs to the broader NHS. In this submission, we present two separate models for the value of momelotinib, depending on whether the patient has taken a JAKi before or not:

In the case where the patient has not taken a JAKi previously, the SIMPLIFY 1 trial was only designed to show that momelotinib was **at least as good as** ruxolitinib. Therefore, in our economic model we make a very conservative assumption that momelotinib is clinically the same as ruxolitinib, and that the only difference between them is the overall cost to the NHS. We model several sources of cost for patients treated on momelotinib and ruxolitinib: the cost to the NHS to purchase the

medicines themselves, the cost of the different side effects experienced on treatment, and the cost of blood transfusions expected on both treatments, for example. We conclude that momelotinib is likely to save the NHS several thousand pounds per year because patients require fewer expensive red blood cell transfusions when they are taking momelotinib.

In the case where the patient has taken a JAKi previously, the SIMPLIFY 2 trial was designed to show that momelotinib was **better** than best available therapy. Therefore, we do not need to make the assumption that momelotinib and best available therapy are clinically similar, and instead we can present a more conventional (but more complex) cost-effectiveness model. In the model, benefits are expressed in 'quality adjusted life years' (QALYs) which are a unit of measurement equivalent to one year of life lived in perfect health (so for example two years of life lived at 50% of perfect health is equivalent to one QALY). Our modelling approach, using evidence from SIMPLIFY-2, shows that momelotinib improves the quality of life of life people who would otherwise be managed on best available therapy. We also expect momelotinib to have a small but important benefit in increasing survival outcomes.

A key concept in cost-effectiveness analyses is the 'incremental cost-effectiveness ratio threshold', which is a number NICE publish whereby if a treatment can generate a QALY for less than this cost then it should be made available in the NHS. We conclude that in most cases momelotinib is likely to save the NHS money (since it still reduces the need for transfusions in the JAKi-experienced population), but that because it also provides more value to patients than best available therapy it would still be a good use of NHS resources even if it cost more money overall.

Because both models are trying to predict the lifetime impact of momelotinib on the basis of 24-week trials, some assumptions are inevitably made. In particular, we expect NICE to heavily scrutinise the way in which we demonstrate a link between transfusion independence and improved survival. However, we have looked at many alternative approaches to modelling this element of the treatment pathway and regardless of the approach adopted it does not change the overall conclusion that momelotinib represents good value for money for the NHS.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Momelotinib represents a significant advancement in the class of JAKi treatments for MF. In particular, momelotinib addresses a major unmet need from patients for a treatment which addresses their anaemia symptoms alongside the enlarged spleen and other aspects of the disease.

This is especially important in MF, where existing JAKis tend to exacerbate existing anaemia symptoms, which raises ethical issues for patients and clinicians since treating some symptoms of MF require worsening other symptoms of MF.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Fatigue is a symptom of MF, and can be made worse if the patient also has anaemia. Since chronic fatigue is recognised as a disability by the Equality Act, there are potentially major equality issues if NICE reject a medicine which would have a disproportionate impact on patients with chronic fatigue.

MF, particularly MF with anaemia, is an orphan condition, therefore, there is a major equality issue raised if the medicine is not approved for treatment within the NHS.

Section 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on MF

- https://www.mpnvoice.org.uk/
- https://www.cancerresearchuk.org/about-cancer/other-conditions/myelofibrosis
- https://bloodcancer.org.uk/understanding-blood-cancer/myelofibrosis-what/myelofibrosis/
- https://www.macmillan.org.uk/cancer-information-and-support/blood-cancer/myelofibrosis-mf
- Myelofibrosis (MF) - Leukaemia Care: https://www.leukaemiacare.org.uk/support-and-information/information-about-blood-cancer/blood-cancer-information/about-myeloproliferative-neoplasms-mpn/myelofibrosis-mf/

Further information about momelotinib

- https://www.gsk.com/en-gb/search/?q=momelotinib
- Clinical data:
    - SIMPLIFY-1: https://pubmed.ncbi.nlm.nih.gov/28930494/
    - SIMPLIFY-2: https://classic.clinicaltrials.gov/ct2/show/NCT02101268
    - MOMENTUM: https://pubmed.ncbi.nlm.nih.gov/33423550/ (trial design only)
    - Long term safety of momelotinib: https://pubmed.ncbi.nlm.nih.gov/37042865/
    - Follow-up survival analyses: https://pubmed.ncbi.nlm.nih.gov/35869266/

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Allogeneic-stem cell transplant (allo-SCT)	A treatment that uses stem cells from a donor to treat patients with blood cancers
Bone marrow	This is a soft, spongy tissue inside most bones where blood cells (e.g., red blood cells, white blood cells and platelets) are made.
Cancer Drugs Fund (CDF)	The CDF provides NHS patients access to cancer drugs while further evidence is collected to address clinical uncertainty (i.e., before drugs can be accepted for routine funding)
Chemotherapy	Treatment for cancer that uses chemical drugs to stop the growth of cancer cells
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.
Erythropoiesis-stimulating agents (ESAs)	Medicines that are injected under the skin to stimulate red blood cell production
Essential thrombocythemia (ET)	A rare myeloproliferative neoplasm characterised by a sustained elevation of platelet number
European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.

Fatigue	This is when you feel very tired, exhausted and lacking energy. It can be a symptom of the cancer itself or a side effect of treatment
Grade ≥3 adverse events	Severe or medically significant but not immediately life-threatening adverse event
Health economic model	A tool used to predict the costs and effects of a technology over a length of time or in patient groups not covered in a clinical trial.
Health Technology Assessment (HTA)	An assessment about the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared with existing ones. Reimbursing involves the payment that your hospital, doctor, diagnostic facility, or other healthcare providers receive for giving you a medical service.
Haemoglobin	The protein in red blood cells that transports oxygen
Haematology	The diagnosis, treatment and prevention of diseases of the blood and bone marrow
JAK1/JAK2	An enzyme that forms a communications pathways for messages travelling side cells
Liver	An organ in the upper abdomen that helps with digestion, removes waste products and worn-out cells from the blood
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country
Myelofibrosis (MF)	Fibrosis or scarring of the bone marrow, characterised by significant anaemia and an enlarged spleen
Myeloproliferative neoplasms	Diseases of the blood and bone marrow sometimes referred to as blood cancers
Night sweats	Severe hot flushes that occur at night and result in drenching sweat
Organomegaly	The abnormal enlargement of organs
Phase 3 (also called Phase III) clinical trial May include hundreds of people.	This phase tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III clinical trials only after they meet the goals of phase I and phase II clinical trials.

Placebo	A substance designed to have no therapeutic value
Platelet	Fragments of large bone marrow cells that help with blood clotting by clumping together.
Platelet count	The calculated number of platelets in a volume of blood. Normal platelet counts are 50 - 450 x 10^9 per litre)
Polycythaemia vera (PV)	A rare myeloproliferative neoplasm that results from an overproduction of red blood cells
Prognosis	This gives an idea about whether the disease can be cured and what may happen in the future.
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Radiotherapy	Treatment of cancer using radioactive energy to destroy cancer cells
Red blood cell (RBC)	The blood cell that carries oxygen. Red blood cells contain haemoglobin that allows them to carry oxygen.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment with a medication or other therapy. Side effects may be mild, moderate, or severe.
Spleen	An organ in the rib cage that helps filter blood cells and fight infection. It is often enlarged in patients with MF, and may be removed to treat the disease (splenectomy).
Splenectomy	A surgical procedure that partially or completely removes the spleen
Stem cells	The earliest type of cell and have the unique ability to develop into different types of cells. They may be used to replace cells that have been damaged or lost because of disease.
Thrombocytopenia	A condition where abnormally low level of platelets are observed.
Tolerated	The ability to put up with the side effects of treatment.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Harrison C, McLornan D. Myelofibrosis. Hematology. 2014;19(2):120-1.
2. Haematological Malignancy Research Network (HMRN) - Statistics. Haematological Malignancy Research Network (HMRN) - Statistics. 2023.
3. GSK. [Data on File] - NICE Scientific Advice. April, 14 2022.
4. Mead AJ, Butt NM, Nagi W, Whiteway A, Kirkpatrick S, Rinaldi C, et al. A retrospective real-world study of the current treatment pathways for myelofibrosis in the United Kingdom: the REALISM UK study. Ther Adv Hematol. 2022;13:20406207221084487.
5. 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;113(13):2895-901.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Clarification questions

September 2023

File name	Version	Contains confidential information	Date
ID6141 momelotinib EAG Clarification letter to PM [CON].docx	V1.0	Yes	15/9/2023

Section A: Clarification on effectiveness data

SIMPLIFY-1 primary endpoint

A1. Priority question: The SIMPLIFY-1 trial primary endpoint results provided in the company submission (CS) and clinical study report (CSR) do not match the results provided in the published paper (Mesa et al 2017) or those reported in the CS, Figure 8 (which do match the results reported in the published paper). See Table 1 (below) for the discrepancies. Please explain why these results differ and why the results only reported in the CS/CSR are marked confidential.

Table 1. SIMPLIFY-1 trial results at Week 24 requiring clarification

Outcome	Result reported in company submission in Table 1, p34, Table 19 and Table 20	Published paper and company submission, Figure 8
Spleen response rate (the proportion of patients with a ≥35% reduction in spleen volume	Momelotinib: 57 (26.5%) Ruxolitinib: 64 (29.5%) p=0.014	Momelotinib: 57 (26.5%) Ruxolitinib: 63 (29.0%) p=0.011

Data reported in the CSR and CS are based on the final analysis, whereas data reported in the Mesa et al 2017 publication are derived from the interim Week 24 data cut. Because the data from the final analysis (taken from the CSR) were not in the public domain at the time of writing the dossier, they have been marked as confidential. However, since the same final analysis was used in the Summary of Product Characteristics (SmPC), which will become public at the time of publishing this information, it is no longer necessary to mark this information up.

However, although the submission is accurate, there is a small imprecision in the published paper. One additional subject in the ruxolitinib arm who was a responder at Week 24, was incorrectly categorised in the interim analysis and, therefore, not captured in the publication. This response was captured correctly in the final analysis as reported in the final study report. This subject was also a responder at Week 12 and maintained response to Week 36. The reason for the subject not being captured correctly in the interim analysis is not known.

MOMENTUM trial results

A2. Priority question. Some of the results presented for the momelotinib arm of the MOMENTUM trial in the CS Table 19, Section B.2.7.3.2 and Section 2.7.3.3 do not match the results presented in the MOMENTUM CSR, namely the transfusion-independent (TI) rate and the spleen response rate (≥25% and ≥35%). Please provide the correct rates.

The correct rates for MOMENTUM transfusion-independence rate and spleen response rate (≥25% and ≥35%) are presented in company submission Table 19 (Section B.2.7.3.2). The reason for the discrepancy between the initial MOMENTUM study report and the CS is due to an error in the MOMENTUM data extraction which has since been identified corrected in the publication.(1, 2) According to the MOMENTUM protocol, active therapy for MF was prohibited during the randomised treatment period and the analyses of the primary and three of the five key secondary efficacy endpoints were to be adjusted for patients who received prohibited active MF therapy.(1) However, the analyst did not remove a filter from the prohibited concomitant medications dataset before it was extracted to Sierra Study Data Tabulation Model (SDTM) datasets for the interim data base lock (13 January 2022), resulting in the export of an incomplete dataset.(1) The error resulted in the correction of data for one patient.(1) The endpoints affected were transfusion-independence rate and spleen response rate (≥25% and ≥35%).(1) However, the updated data for these endpoints did not change the interpretation of the study results. Please see Table 2 for the original MOMENTUM data (strike through) and the corresponding corrected data, which is presented in the company submission.

Table 2. Overall summary of key secondary efficacy endpoints (original MOMENTUM CSR and corrected data, ITT population)(1)

	Momelotinib (N=130)	Danazol (N=65)
Transfusion-independence rate at Week 24		
Responder, n (%)	[redacted] 39 (30.0)	13 (20.0)
Response rate (95% CI)[a]	[redacted]	[redacted]
Non-inferiority test: Treatment arm difference for noninferiority (95% CI)[b]	[redacted]	
1-sided p-value	[redacted] 0.0116	

	Momelotinib (N=130)	Danazol (N=65)
Superiority test: Treatment arm difference by stratified CMH (95% CI)	[redacted]	
p-value[c]	[redacted]	
SRR at Week 24 based on ≥25% reduction in spleen volume		
Responder, n (%)	[redacted] 51 (39.2)	4 (6.2)
Response rate (95% CI)[a]	[redacted]	[redacted]
Treatment arm difference by stratified CMH (95% CI)	[redacted] 33.05 (22.59, 43.51)	
p-value	<0.0001	
SRR at Week 24 based on ≥35% reduction in spleen volume		
Responder, n (%)	~~30 (23.1)~~ 29 (22.3)	2 (3.1)
Response rate (95% CI)[a]	~~23.08 (16.14, 31.28)~~ 22.31 (15.48, 30.44)	3.08 (0.37, 10.68)
Treatment arm difference by stratified CMH (95% CI)	[redacted] 18.18 (9.77, 26.59)	
p-value	~~0.0006~~ [redacted]	

Note, text with a strikethrough is incorrect data. Correct data according to the MOMENTUM Amendment does not have a strikethrough.
a Exact binomial CI
b Delta = p(MMB) - 0.8 × p(DAN); 95% CI was stratum adjusted.
c Nominal p value outside of hierarchical testing for study wide type I error control.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CSR = clinical study report; ITT = intent-to-treat; SRR = spleen response rate

SIMPLIFY-1 trial and SIMPLIFY-2 trial leukaemia-free survival and overall survival analyses

A3. Priority question. Please provide the results of proportional hazards assessments (i.e., Schoenfeld residuals plots and tests) for leukaemia-free survival (LFS) and overall survival (OS) at Week 24 interim analysis, Week 48 interim analysis and final analysis from the SIMPLIFY-1 and SIMPLIFY-2 trials.

Per communication from NICE, this question has been retracted.

A4. In the CS, Appendix E, Table 13, Table 14, Table 19 and Table 20, please clarify the analyses timepoints (e.g., interim analysis, final analysis). Please also provide the median follow-up times for each set of results.

GSK confirm that the data in Appendix E, Table 13, Table 14, Table 19 and Table 20 were based on the final analysis population. All post-hoc analyses were conducted in

the intent-to-treat (ITT) population for SIMPLIFY-1 and SIMPLIFY-2. Median follow-up times for each analysis are provided in Table 3 and Table 4.(3, 4)

Table 3. Duration of follow-up (months) for LFS and OS analyses in SIMPLIFY-1 (ITT population)(3)

	Momelotinib	Ruxolitinib	Total
Int-2/HR and Hb <10 g/dL			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Int-2/HR and Hb <12 g/dL			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; ITT= intent-to-treat; LFS = leukaemia free; OS = overall survival

Table 4. Duration of follow-up (months) for LFS and OS analyses in SIMPLIFY-2 (ITT population)(4)

	Momelotinib	BAT	Total
Int-2/HR and Hb <10 g/dL			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Int-2/HR and Hb <12 g/dL			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = Best Available Therapy; Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; ITT= intent-to-treat; LFS = leukaemia free; OS = overall survival

A5. Please provide the methods used to conduct the cross-over adjusted OS analyses for the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials, particularly the differences between the three rank preserving structure failure time (RPSFT) approaches.

In SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM, patients were randomised to momelotinib or control (ruxolitinib, best available therapy, or danazol, respectively) arms and received their assigned treatment for 24 weeks. After Week 24, patients randomly assigned to the control arm were given the option to cross-over to receive momelotinib during the open-label treatment phase or discontinue the control treatment. However, estimates of overall survival (OS) and leukaemia-free survival (LFS) were confounded when patients were analysed according to their randomised treatment.

To adjust for the effect of cross-over and estimate the treatment effects of OS and LFS that would have been observed in the absence of cross-over, RPSFT analyses were performed. RPSFT models assume that each patient proceeds through disease progression towards their death at their own pace (accelerated failure time model) and that the investigational treatment slows this down by the same factor regardless of whether investigational therapy is given from randomisation or from the time of crossover ('common treatment effect'). The RPSFT applies this factor to patients who crossed over to understand which event time would have been observed had these patients not crossed over. This allows the effect in absence of crossover to be estimated.

Survival information over the entire study period, including the open-label phase, is used in the RPSFT model. Hazard ratios with their corresponding confidence intervals were reported. Median survival times were not reported as they were not reached in some cases. To handle censored patients without events, it is recommended to conduct adjusted analyses both with and without re-censoring, where re-censoring may be applied by censoring the counterfactual survival times at the earliest possible censoring time over all possible treatment trajectories.(5) In the RPSFT models, three different approaches were used to handle censored patients:

- Approach 1: RPSFT model without re-censoring

- Approach 2: RPSFT model with re-censoring applied to the data when fitting the RPSFT model
- Approach 3: RPSFT model with re-censoring applied to the comparator arm when computing the adjusted hazard ratio and plotting the Kaplan-Meier (KM) curve.

Two methods were applied to construct the confidence intervals; namely bootstrap method which additionally encodes the RPSFT model fitting uncertainty, and the ITT method which inflates the standard error to match the p-value of the ITT test.

A6. Please provide the methods used to conduct the time-varying OS analyses (CS, Appendix M.1.2.3) including the rationale for conducting these analyses and how the initial set of variables considered for inclusion in the regression model were chosen.

Data from SIMPLIFY-2 indicated an association between transfusion independence at week 24 and prolonged OS. However, these analyses did not adjust for additional prognostic factors or effect modifiers nor potential longitudinal changes in transfusion status over time.(6)

Treatment-agnostic time-varying OS analysis was conducted to investigate the prognostic influence of red-blood cell transfusion (RBCT) status, as well as other covariates, over time on OS.

The analysis was performed on the safety population of SIMPLIFY-2 (N=156), which examined momelotinib vs best available therapy in JAKi experienced patients.

Transfusion status was evaluated every 4 weeks. The following time-dependent and time-independent covariates were evaluated to determine their prognostic impact:

- Time-dependent covariates
    - RBCT status, categorized as either transfusion independent [TI; absence of RBC transfusion and no Hb level <8 g/dL in the prior 12 weeks] or non-TI [not satisfying the criteria for TI])

- Fixed baseline covariates:
    - Age
    - Sex
    - MF subtype
    - Eastern Cooperative Oncology Group status
    - JAK2 mutational profile
    - Total Symptom Score
    - Dynamic IPSS (DIPSS) score
    - Platelet counts
    - Baseline spleen volume (as assessed by central reading of magnetic resonance imaging/computed tomography scan).

An extended Cox model was used to generate an overall hazard ratio (HR) using all available follow-up times, and independent variables were retained if a backward variable selection method determined that they were significantly associated with OS (the remain criterion was set to 0.05).

A7. Please provide median follow-up times for the SIMPLIFY-1 trial and SIMPLIFY-2 trial OS and LFS final analyses (CS, Table 21 and Table 28; Appendix M Table 73 and Table 74).

See Table 5 and Table 6 for the median follow-up times for LFS and OS in SIMPLIFY-1 and SIMPLIFY-2.

Table 5. Duration of follow-up (months) for LFS and OS analyses in SIMPLIFY-1

	Momelotinib	**Ruxolitinib**	**Total**
LFS (ITT population)(3)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

	Momelotinib	Ruxolitinib	Total
OS (safety population)(7)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: ITT= intent-to-treat; LFS = leukaemia free; OS = overall survival

Table 6. Duration of follow-up (months) for LFS and OS analyses in SIMPLIFY-2

	Momelotinib	Ruxolitinib	Total
LFS (ITT population)(4)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
OS (safety population)(8)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; ITT= intent-to-treat; LFS = leukaemia free; NR = not reported; OS = overall survival

A8. Please clarify how median OS has been reached in the ruxolitinib arm of the SIMPLIFY-1 trial at the time of the final analysis (CS, Table 21), but has not been reached in the long-term post-hoc analysis (CS, p77).

The long-term post-hoc analysis presented in CS p77 and 78 was conducted in SIMPLIFY-1 patients but also included patients who enrolled in the ongoing open-label, extended access protocol (NCT03441113). Patients in the extended access protocol were required to have disease that did not progress and to have tolerated momelotinib treatment while enrolled in SIMPLIFY-1.(6) This led there to be additional follow-up time in the analysis compared with the final analysis presented in Table 21 of the CS:

- Final analysis (based on the CSR): median duration of follow up: [redacted] months ([redacted] years) in the momelotinib group and [redacted] months ([redacted] years) in patients randomised to ruxolitinib who switched to momelotinib.(7)

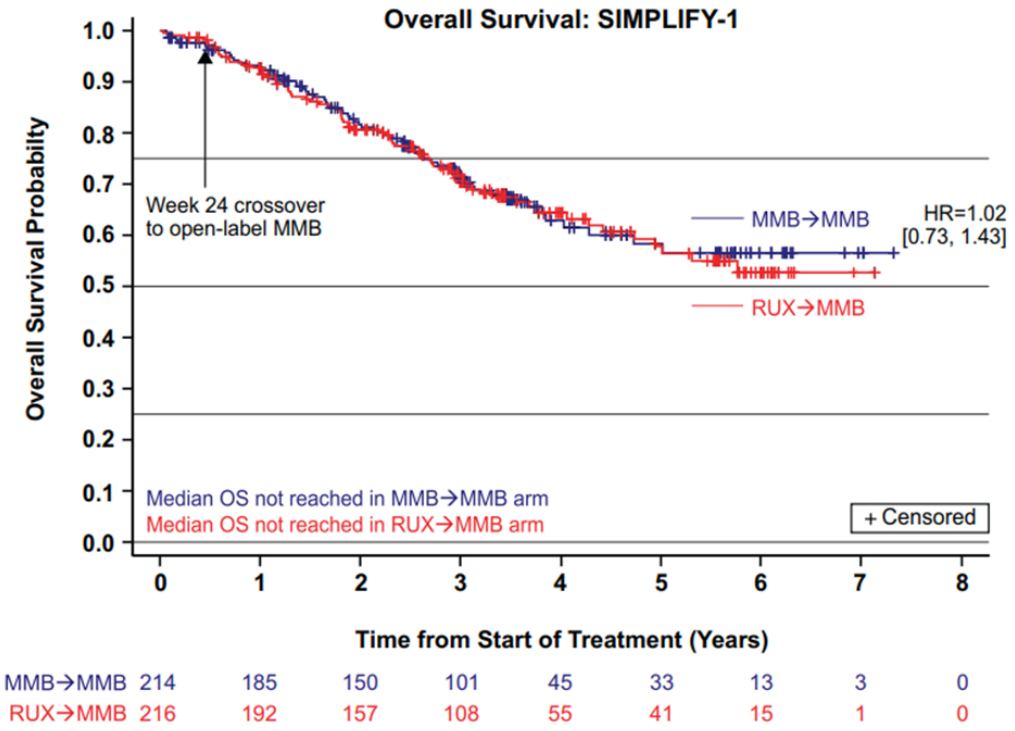
- Long-term post-hoc analysis (Mesa 2022): median duration of follow up: 3.43 years in the momelotinib group and 3.47 years in patients randomised to ruxolitinib who switched to momelotinib.(6)

In each analysis subjects who did not die or have leukemic transformation were censored at the last date known to be alive. Therefore, the longer follow-up in the post-hoc analysis led there to be additional patients at risk at longer time points in the post-hoc analysis compared with the final analysis and affected the calculation of median OS (Figure 1 and Figure 2).

Figure 1. OS at the final trial analysis presented in the CSR (SIMPLIFY-1)(7)

Abbreviations: CSR = clinical study report; MMB = momelotinib; N = number; OS = overall survival; RUX = ruxolitinib

Figure 2. Long-term OS follow-up (SIMPLIFY-1; CS Figure 16, p78)(6)



Abbreviations: CS = company submission; HR = hazard ratio; MMB = momelotinib; OS = overall survival; RUX = ruxolitinib

Health-related quality of life

A9. Please provide Eastern Cooperative Oncology Group performance status, Patient Global Impression scale, Myeloproliferative Neoplasm Symptom Assessment Form, EuroQol-5D-5L and Short Form-36 data for the intermediate-2/high-risk (int-2/HR) with haemoglobin (Hb)<10g/dL subgroup and for the int-2-HR with Hb<12g/dL subgroup.

SIMPLIFY-1: int-2/HR and Hb <10 g/dL

Table 7 presents the baseline ECOG PS for the int-2/HR and Hb <10 g/dL subgroup. The results of the int-2/HR and Hb <10 g/dL subgroup analysis for TSS (Table 8), SF-36 (Table 9), EQ-5D-5L (Table 10) and PGIC (Table 11) were consistent with the ITT population.(9)

Table 7. Baseline ECOG PS for the int-2/HR and Hb <10 g/dL subgroup (SIMPLIFY-1; ITT population)(10)

	Momelotinib (n=84)	Ruxolitinib (n=90)
Grade 0, n (%)	[redacted]	[redacted]
Grade 1, n (%)	[redacted]	[redacted]
Grade 2, n (%)	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]
Grade 5, n (%)	[redacted]	[redacted]

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat

Table 8. TSS (Myeloproliferative Neoplasm Symptom Assessment Form) in the int-2/HR and Hb <10 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Momelotinib (n=84)	Ruxolitinib (n=90)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; TSS = total symptom score

Table 9. SF-36 physical and mental components in the int-2/HR and Hb <10 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Physical component summary		Mental component summary	
	Momelotinib (n=84)	Ruxolitinib (n=90)	Momelotinib (n=84)	Ruxolitinib (n=90)
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	
Percentage change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	

	Physical component summary		Mental component summary	
	Momelotinib (n=84)	Ruxolitinib (n=90)	Momelotinib (n=84)	Ruxolitinib (n=90)
p-value	[redacted]		[redacted]	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; SF-36 = Short Form 36-item

Table 10. EQ-5D VAS in the int-2/HR and Hb <10 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Momelotinib (n=84)	Ruxolitinib (n=90)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; EQ-5D = EuroQol 5 dimension; SD = standard deviation; VAS = visual analogue scale

Table 11. PGIC in the int-2/HR and Hb <10 g/dL subgroup during the double-blind phase in (SIMPLIFY-1: ITT population)(9)

	Momelotinib (n=84)	Ruxolitinib (n=90)	Proportion difference[a] (95% CI)
Any timepoint in double-blind phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]
Week 24 at double-blind phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]

[a] Stratified CMH method
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PGIC = Patients' Global Impression of Change

SIMPLIFY-1: int-2/HR and Hb <12 g/dL

Table 12 presents the baseline ECOG PS for the int-2/HR and Hb <12 g/dL subgroup. Table 13 reports TSS for the int-2/HR and Hb <12 g/dL subgroup analysis. The results of the int-2/HR and Hb <12 g/dL subgroup analysis for SF-36 (Table 14), EQ-5D VAS (Table 15) and PGIC (Table 16) were consistent with the ITT population.(9)

Table 12. Baseline ECOG PS for the int-2/HR and Hb <12 g/dL subgroup (SIMPLIFY-1; ITT population)(10)

	Momelotinib (n=137)	Ruxolitinib (n=143)
Grade 0, n (%)	[redacted]	[redacted]
Grade 1, n (%)	[redacted]	[redacted]
Grade 2, n (%)	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]
Grade 5, n (%)	[redacted]	[redacted]

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat

Table 13. TSS (Myeloproliferative Neoplasm Symptom Assessment Form) in the int-2/HR and Hb <12 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Momelotinib (n=137)	Ruxolitinib (n=143)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; TSS = total symptom score

Table 14. SF-36 physical and mental components in the int-2/HR and Hb <12 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Physical component summary		Mental component summary	
	Momelotinib (n=137)	Ruxolitinib (n=143)	Momelotinib (n=137)	Ruxolitinib (n=143)
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
Stratified Wilcox Rank Sum p-value	[redacted]		[redacted]	
Percentage change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference	[redacted]		[redacted]	

	Physical component summary		Mental component summary	
	Momelotinib (n=137)	Ruxolitinib (n=143)	Momelotinib (n=137)	Ruxolitinib (n=143)
(95% CI)				
Stratified Wilcox Rank Sum p-value				

Abbreviations: CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; SF-36 = Short Form 36-item

Table 15. EQ-5D VAS in the int-2/HR and Hb <12 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Momelotinib (n=137)	Ruxolitinib (n=143)
Mean baseline value (SD)		
Change at Week 24 from baseline		
Mean (SD)		
Least squares mean difference (95% CI)		
Stratified Wilcoxon Rank Sum p-value		
Percentage change from baseline at Week 24		
Median (Q1, Q3)		
Mean (SD)		
Least squares mean difference (95% CI)		
Stratified Wilcoxon Rank Sum p-value		

Abbreviations: CI = confidence interval; ITT = intent-to-treat; EQ-5D = EuroQol 5 dimension; SD = standard deviation; VAS = visual analogue scale

Table 16. PGIC in the int-2/HR and Hb <12 g/dL subgroup during the double-blind phase (SIMPLIFY-1: ITT population)(9)

	Momelotinib (n=137)	Ruxolitinib (n=143)	Proportion difference[a] (95% CI)
Any timepoint in double-blind phase			
Improvement, n (%)			
Worsening, n (%)			
Week 24 at double-blind phase			
Improvement, n (%)			
Worsening, n (%)			

[a] Stratified CMH method
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PGIC = Patients' Global Impression of Change

SIMPLIFY-2: int-2/HR and Hb <10 g/dL

Table 17 presents the baseline ECOG PS for the int-2/HR and Hb <10 g/dL subgroup. Table 18 reports TSS for the int-2/HR and Hb <10 g/dL subgroup analysis. The TSS response rate was [redacted]% in the momelotinib group and [redacted]% in the BAT

group at Week 24 (proportion difference: [redacted]).(11) The results of the int-2/HR and Hb <10 g/dL subgroup analysis for SF-36 (Table 19) and EQ-5D VAS (Table 20) were consistent with the primary ITT analysis.(11) The results of the PGIC subgroup analysis of int-2/HR and Hb <10 g/dL are presented in Table 21.

Table 17. Baseline ECOG PS for the int-2/HR and Hb <10 g/dL subgroup (SIMPLIFY-2; ITT population)(12)

	Momelotinib (n=61)	BAT (n=32)
Grade 0, n (%)	[redacted]	[redacted]
Grade 1, n (%)	[redacted]	[redacted]
Grade 2, n (%)	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]
Grade 5, n (%)	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat

Table 18. TSS (Myeloproliferative Neoplasm Symptom Assessment Form) in the int-2/HR and Hb <10 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Momelotinib (n=61)	BAT (n=32)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; TSS = total symptom score

Table 19. SF-36 physical and mental components in the int-2/HR and Hb <10 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Physical component summary		Mental component summary	
	Momelotinib (n=61)	BAT (n=32)	Momelotinib (n=61)	BAT (n=32)
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
Stratified Wilcox Rank Sum p-value	[redacted]		[redacted]	
Percentage change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
Stratified Wilcox Rank Sum p-value	[redacted]		[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; SF-36 = Short Form 36-item

Table 20. EQ-5D VAS in the int-2/HR and Hb <10 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Momelotinib (n=61)	BAT (n=32)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; EQ-5D = EuroQol 5 dimension; SD = standard deviation; VAS = visual analogue scale

Table 21. PGIC in the int-2/HR and Hb <10 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Momelotinib (n=61)	BAT (n=32)	Proportion difference[a] (95% CI)
Any timepoint in double-blind phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]
Week 24 at randomised treatment phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]

[a] Stratified CMH method
Abbreviations: BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PGIC = Patients' Global Impression of Change

SIMPLIFY-2: int-2/HR and Hb <12 g/dL

Table 22 presents the baseline ECOG PS for the int-2/HR and Hb <12 g/dL subgroup. Table 23 reports TSS for the int-2/HR and Hb <12 g/dL subgroup analysis. The TSS response rate was [redacted]% in the momelotinib group and [redacted]% in the BAT group at Week 24 (proportion difference: [redacted]).(11) The results of the int-2/HR and Hb <12 g/dL subgroup analysis for SF-36 (Table 24) and EQ-5D-VAS (Table 25) was consistent with the primary ITT analysis.(11) Table 26 presents the results of PGIC for the subgroup analysis for the int-2/HR and Hb <12 g/dL.

Table 22. Baseline ECOG PS for the int-2/HR and Hb <12 g/dL subgroup (SIMPLIFY-2; ITT population)(12)

	Momelotinib (n=77)	BAT (n=34)
Grade 0, n (%)	[redacted]	[redacted]
Grade 1, n (%)	[redacted]	[redacted]
Grade 2, n (%)	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]
Grade 5, n (%)	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat

Table 23. TSS (Myeloproliferative Neoplasm Symptom Assessment Form) in the int-2/HR and Hb <12 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Momelotinib (n=77)	BAT (n=34)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; TSS = total symptom score

Table 24. SF-36 physical and mental components in the int-2/HR and Hb <12 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Physical component summary		Mental component summary	
	Momelotinib (n=77)	BAT (n=34)	Momelotinib (n=77)	BAT (n=34)
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
Stratified Wilcox Rank Sum p-value	[redacted]		[redacted]	
Percentage change from baseline at Week 24				
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]		[redacted]	
Stratified Wilcox Rank Sum p-value	[redacted]		[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; SF-36 = Short Form 36-item

Table 25. EQ-5D VAS in the int-2/HR and Hb <12 g/dL subgroup during the randomised treatment phase (SIMPLIFY-2: ITT population)(11)

	Momelotinib (n=77)	BAT (n=34)
Mean baseline value (SD)	[redacted]	[redacted]
Change at Week 24 from baseline		
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	
Percentage change from baseline at Week 24		
Median (Q1, Q3)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Least squares mean difference (95% CI)	[redacted]	
Stratified Wilcoxon Rank Sum p-value	[redacted]	

Abbreviations: BAT = best available therapy; CI = confidence interval; ITT = intent-to-treat; EQ-5D = EuroQol 5 dimension; SD = standard deviation; VAS = visual analogue scale

Table 26. PGIC in the int-2/HR and Hb <12 g/dL subgroup during the randomised treatment phase in (SIMPLIFY-2: ITT population)(11)

	Momelotinib (n=77)	BAT (n=34)	Proportion difference[a] (95% CI)
Any timepoint in randomised treatment phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]
Week 24 at randomised treatment phase			
Improvement, n (%)	[redacted]	[redacted]	[redacted]
Worsening, n (%)	[redacted]	[redacted]	[redacted]

[a] Stratified CMH method
Abbreviations: BAT = best available therapy; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PGIC = Patients' Global Impression of Change

Adverse events

A10. Fatal adverse events (AEs) were reported in 14.1% of patients (CS, p118). How many of these AEs were treatment-related?

The Company Submission (p.118) presents a pooled safety analysis of SIMPLIFY-1, SIMPLIFY-2 , MOMENTUM and those patients who transitioned from those studies to the XAP (long-term access study) which reported fatal adverse events (AEs) in 14.1% of patients, however the publication did not state how many AEs were treatment-related. The median duration of exposure to momelotinib patients in the final pooled analysis was 11.3 months (range 0.1, 90.4 months; n=725).(13)

Data for how many fatal AEs were related to momelotinib can be obtained from the CSRs. In SIMPLIFY-1, none of the fatal AEs were related to study treatment.(7) In SIMPLIFY-2, three patients had a fatal AE that was related to momelotinib (cardiac arrest, severe respiratory failure, and nephritis, one patient each).(8) In both SIMPLIFY-1 and SIMPLIFY-2, the causes of deaths in overall were consistent with the known principle causes of death in patients with MF.(7, 8) In MOMENTUM, two patients had fatal events (rotavirus gastroenteritis and staphylococcal pneumonia) considered by investigators to be related to momelotinib during the open-label phase.(14)

A11. In the SIMPLIFY-1 trial, "No notable differences in AEs were observed in patients with/without anaemia or with/without thrombocytopenia" (CS, p125). Similarly, in the SIMPLIFY-2 trial, "no notable differences in AEs were observed between thrombocytopenic and non-thrombocytopenic patients, or between patients with Hb levels above or below 10 g/dL" (CS, p128). Please provide full numerical details.

SIMPLIFY-1 AEs observed in patients with/without anaemia

In the overall exposed to momelotinib group, the safety profile of patients with baseline Hb <10 g/dL was similar to those with baseline Hb ≥10 g/dL (Table 27) with no notable differences in AEs.(7) Table 28 presents Grade 3 or 4 TEAEs reported in ≥5% of patients with Hb <10 g/dL and Hb ≥10 g/dL who were exposed to momelotinib overall.

Table 27. TEAEs reported in ≥5% of patients with Hb <10 g/dL and patients with Hb ≥10 g/dL who were exposed to momelotinib overall (SIMPLIFY-1)(7)

n (%)	Overall exposed to momelotinib	
	Hb <10 g/dL (n=171)	Hb ≥10 g/dL (n=240)
Any TEAE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

n (%)	Overall exposed to momelotinib	
	Hb <10 g/dL (n=171)	Hb ≥10 g/dL (n=240)
Peripheral sensory neuropathy	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Vitamin B1 deficiency	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hyperuricaemia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Leukocytosis	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Muscoskeletal pain	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]
Flushing	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]

Data not reported occurred in less in than 5% of patients of the analysis (as presented in the CSR).
Abbreviations: Hb = haemoglobin; NR = not reported; TEAE = treatment-emergent adverse event

Table 28. Grade 3 or 4 TEAEs in ≥5% of patients with Hb <10 g/dL and patients with Hb ≥10 g/dL who were exposed to momelotinib overall (SIMPLIFY-1)(7)

n (%)	Overall exposed to momelotinib	
	Hb <10 g/dL (n=171)	Hb ≥10 g/dL (n=240)
Any Grade 3 or 4 TEAE	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; TEAE = treatment-emergent adverse event

SIMPLIFY-1 AEs observed in patients with/without thrombocytopenia

In the overall exposed to momelotinib group, the safety profile was similar across patients with baseline platelets <100 x10^3/Ul, 100-200 x10^3/uL inclusive and >200 x10^3/uL (Table 29).(7) Table 30 presents Grade 3 or 4 AEs reported in ≥5% of patients with baseline platelets <100 x10^3/Ul, 100-200 x10^3/uL inclusive and >200 x10^3/uL who were exposed overall to momelotinib.

Table 29. TEAEs in ≥5% of patients with baseline platelet count <100 x10^3/uL, 100-200 x10^3/uL inclusive and >200 x10^3/uL who were exposed to momelotinib overall (SIMPLIFY-1)(7)

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=35)	Platelet count 100-200 x10^3/uL (n=123)	Platelet count >200 x10^3/uL (n=253)
Any TEAE	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]	[redacted]

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=35)	Platelet count 100-200 x10^3/uL (n=123)	Platelet count >200 x10^3/uL (n=253)
Anxiety	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]
Vitamin B1 deficiency	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]	[redacted]
Herpes simplex	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]
Hyperuricaemia	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=35)	Platelet count 100-200 x10^3/uL (n=123)	Platelet count >200 x10^3/uL (n=253)
Influenza	[redacted]	[redacted]	[redacted]
Iron deficiency	[redacted]	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]	[redacted]
Skin laceration	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increase	[redacted]	[redacted]	[redacted]

Data not reported occurred in less in than 5% of patients of the analysis (as presented in the CSR).
Abbreviations: NR = not reported; TEAE = treatment-emergent adverse event

Table 30. Grade 3 or 4 TEAEs in ≥5% of patients with baseline platelets <100 x10^3/uL, 100-200 x10^3/uL inclusive and >200 x10^3/uL who were exposed to momelotinib overall (SIMPLIFY-1)(7)

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=35)	Platelet count 100-200 x10^3/uL (n=123)	Platelet count >200 x10^3/uL (n=253)
Any Grade 3 or 4 TEAE	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]

Data not reported occurred in less in than 5% of patients in the subgroup analysis (as presented in the CSR).
Abbreviations: NR = not reported; TEAE = treatment-emergent adverse event

SIMPLIFY-2 AEs observed in patients with/without anaemia

In the overall exposed to momelotinib group, the safety profile of patients with baseline Hb <10 g/dL was similar to those with baseline Hb ≥10 g/dL (Table 31).(8) The Grade 3 or 4 AE profile was also similar, except for, and as can be expected, anaemia which was reported in a higher proportion of patients with Hb <10 g/dL at baseline (28.1%) compared with Hb ≥10 g/dL (12.5%; Table 32).(8)

Table 31. TEAEs reported in ≥10% of patients with Hb <10 g/dL and patients with Hb ≥10 g/dL who were exposed to momelotinib overall (SIMPLIFY-2)(8)

n (%)	Overall exposed to momelotinib	
	Hb <10 g/dL (n=96)	Hb ≥10 g/dL (n=48)
Any TEAE	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]
Vitamin B1 deficiency	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Hyperhidrosis	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Leucocytosis	[redacted]	[redacted]

Data not reported occurred in less in than 10% of patients in respective treatment arm.
Abbreviations: Hb = haemoglobin; NR = not reported; TEAE = treatment-emergent adverse event

Table 32. Grade 3 or 4 TEAEs in ≥5% of patients with Hb <10 g/dL and patients with Hb ≥10 g/dL who were exposed to momelotinib overall (SIMPLIFY-2)(8)

n (%)	Overall exposed to momelotinib	
	Hb <10 g/dL (n=96)	Hb ≥10 g/dL (n=48)
Grade 3 or 4 TEAE	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]

n (%)	Overall exposed to momelotinib	
	Hb <10 g/dL (n=96)	Hb ≥10 g/dL (n=48)
Pneumonia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; NR = not reported; TEAE = treatment-emergent adverse event

SIMPLIFY-2 AEs observed in patients with/without thrombocytopenia

In the overall exposed to momelotinib group, the safety profile was similar across patients with baseline platelets <100 x10^3/uL, 100-200 x10^3uL inclusive and >200 x10^3uL (Table 33).(8) Table 34 presents Grade 3 or 4 TEAEs reported in ≥5% of patients with baseline platelets <100 x10^3uL, 100-200 x10^3uL inclusive and >200 x10^3uL who were exposed to momelotinib overall.

Table 33. TEAEs reported in ≥10% of patients with baseline platelets <100 x10^3uL, 100-200 x10^3uL inclusive and >200 x10^3uL who were exposed to momelotinib overall (SIMPLIFY-2)(8)

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=66)	Platelet count 100-200 (inclusive) x10^3/uL (n=47)	Platelet count >200 x10^3/uL (n=31)
Any TEAE	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]
Night sweats	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=66)	Platelet count 100-200 (inclusive) x10^3/uL (n=47)	Platelet count >200 x10^3/uL (n=31)
Bronchitis	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Vitamin B1 deficiency	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]

Data not reported occurred in less in than 10% of patients in respective treatment arm.
Abbreviations: Hb = haemoglobin; NR = not reported; TEAE = treatment-emergent adverse event

Table 34. Grade 3 or 4 TEAEs reported in ≥5% patients with baseline platelets <100 x10^3/uL, 100-200 x10^3uL inclusive and >200 x10^3uL who were exposed to momelotinib overall (SIMPLIFY-2)(8)

n (%)	Overall exposed to momelotinib		
	Platelet count <100 x10^3/uL (n=66)	Platelet count 100-200 (inclusive) x10^3/uL (n=47)	Platelet count >200 x10^3/uL (n=31)
Grade 3 or 4 TEAE	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Diarrhoae	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Dyspnoa	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]

Data not reported in the CSR
Abbreviations: Hb = haemoglobin; NR = not reported; TEAE = treatment-emergent adverse event

A12. Some of the AE data reported in the CS do not appear to align with some of the AE data reported in the SmPC. For example, in the Summary of Product Characteristics (SmPC) it is reported that, "The most common severe adverse reactions (≥ Grade 3) were thrombocytopenia (10.7%) and infections (10.5%)" whereas in the CS (Table 43) the frequency of thrombocytopenia is reported as 16.4% and the frequency of infections is not reported. Similarly, in the SmPC it is reported that, "In the three randomised clinical studies, 8.7% (39/448) of patients treated with [redacted] experienced peripheral neuropathy" whereas in the CS (Table 43) the frequency is 14.8%. Please clarify why the frequencies differ.

Adverse event data in Section B.2.11 of the CS are based on the published pooled safety analysis set of patients including patients from SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM and those continuing treatment in the extended access protocol.(13) This includes patients randomised to receive momelotinib at baseline as well as those randomised to the comparator arm who later switched to momelotinib treatment. The number of patients included in the pooled safety analysis is 725.(13) These data represent the most complete safety analysis with the longest available follow-up.

Safety data in the SmPC includes only those patients from SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM who were randomised to the momelotinib treatment phase arm and excludes patients who crossed over to open-label momelotinib after Week 24. The number of patients randomised to momelotinib in the trial programs was 448. It is a standard approach for product labelling to match the duration of the safety analysis to the primary efficacy endpoint duration, in this case 24 weeks. However, as stated above, GSK believe that the adverse event data of 725 patients presented in the CS represents the most complete safety analysis relevant to the decision problem.

Quality assessment of trials

A12. Please explain why the completion rate for the SIMPLIFY-2 trial was assessed as 'unclear' for comparability (CS, Appendix D.1.3, Table 8) and why the SIMPLIFY-2 trial was assessed as having less internal validity than the SIMPLIFY-1 trial (CS, Appendix D.1.3, Table 7).

In SIMPLIFY-2, there were reported differences across the best available therapy (BAT) and momelotinib arms in the proportion of patients discontinuing treatment due to adverse events (0/52, 0% in BAT vs 14/104, 14% in momelotinib).(15) The trial investigators noted that discontinuations were “inconsistently reported” in the BAT arm “because changes in therapy or intentional no therapy were permissible options for this treatment group.”(15) As such, given the uncertainty in the ‘true’ rate of discontinuation in the BAT group, the comparability of completion rates was labelled as ‘unclear’ for this trial. Overall, despite this ‘unclear’ assessment for comparability, the risk of attrition bias was assessed as ‘low’ with respect to the reported outcomes, primary analyses of which were based on all or nearly all randomized patients, with non-responder imputation being used for outcomes with missing data.

The SIMPLIFY-2 trial was assessed as having less internal validity than the SIMPLIFY-1 trial because the SIMPLIFY-2 trial was an open-label trial whereas the SIMPLIFY-1 trial included a double-blind treatment phase (up to Week 24).(7, 8) It was thought that lack of blinding could lower the internal validity of the trial, with respect to patient reporting of certain outcomes (e.g., total symptom score).

SIMPLIFY-1 trial and SIMPLIFY-2 trial subgroups

A13. Please provide the following baseline characteristics: mean age, years (standard deviation), male sex, n (%) and MF subtype, n (%) for the int-2/HR with Hb<10g/dL and int-2-HR with Hb<12g/dL subgroups. These data have been provided for the intention-to-treat (ITT) population (CS, Table 9 and Table 10).

The baseline characteristics for the SIMPLIFY-1, int-2/HR with Hb <10 g/dL and int-2/HR with Hb <12 g/dL subgroups are presented in Table 35 and Table 36 (respectively).

The baseline characteristics for the SIMPLIFY-2, int-2/HR with Hb <10 g/dL and int-2/HR with Hb <12 g/dL subgroups are presented in Table 37 and Table 38 (respectively).

Baseline characteristics for each subgroup were broadly consistent with the ITT population for each trial.

Table 35. Baseline characteristics for int-2/HR and Hb <10 g/dL subgroup (SIMPLIFY-1)(10)

Characteristic	Momelotinib (n=84)	Ruxolitinib (n=90)
Mean age, years (SD)	[redacted]	[redacted]
Male sex, n (%)	[redacted]	[redacted]
MF subtype, n (%)		
PMF	[redacted]	[redacted]
Post-PV	[redacted]	[redacted]
Post-ET	[redacted]	[redacted]

Abbreviations: ET = essential thrombocythemia; Hb = haemoglobin; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation

Table 36. Baseline characteristics for int-2/HR and Hb <12 g/dL subgroup (SIMPLIFY-1)(10)

Characteristic	Momelotinib (n=137)	Ruxolitinib (n=143)
Mean age, years (SD)	[redacted]	[redacted]
Male sex, n (%)	[redacted]	[redacted]
MF subtype, n (%)		
PMF	[redacted]	[redacted]
Post-PV	[redacted]	[redacted]
Post-ET	[redacted]	[redacted]

Abbreviations: ET = essential thrombocythemia; Hb = haemoglobin; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation

Table 37. Baseline characteristics for int-2/HR and Hb <10 g/dL subgroup (SIMPLIFY-2)(12)

Characteristic	Momelotinib (n=61)	BAT (n=32)
Mean age, years (SD)	[redacted]	[redacted]
Male sex, n (%)	[redacted]	[redacted]
MF subtype, n (%)		
PMF	[redacted]	[redacted]
Post-PV	[redacted]	[redacted]
Post-ET	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ET = essential thrombocythemia; Hb = haemoglobin; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation

Table 38. Baseline characteristics for int-2/HR and Hb <12 g/dL subgroup (SIMPLIFY-2)(12)

Characteristic	Momelotinib (n=61)	BAT (n=32)
Mean age, years (SD)	[redacted]	[redacted]
Male sex, n (%)	[redacted]	[redacted]
MF subtype, n (%)		
PMF	[redacted]	[redacted]
Post-PV	[redacted]	[redacted]
Post-ET	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ET = essential thrombocythemia; Hb = haemoglobin; MF = myelofibrosis; PMF = primary myelofibrosis; PV = polycythemia vera; SD = standard deviation

Section B: Clarification on cost effectiveness data

Cost comparison analysis

B1. Priority question. For the cost comparison analysis (JAKi-naïve population), please provide subgroup results for the int-2/HR population with Hb <10g/dL. In addition, please justify why ITT data from the SIMPLIFY-1 trial were used in the company base case analysis rather than data from the population that is the focus of this appraisal.

List price and PAS price analyses with parameter values specific to the int-2/HR population with Hb <10g/dL are provided below in Table 39 and Table 40. Results were broadly similar to the base case analyses in the CS, where momelotinib increased total costs by [redacted] per patient over 10 years compared to ruxolitinib in the list price analysis, but resulted in [redacted] when the PAS discount of momelotinib was considered. With subgroup-specific parameter values for the int-2/HR population with Hb <10g/dL, momelotinib results in incremental costs of [redacted] over the 10-year horizon at list price, and a [redacted] when the confidential PAS discount is considered.

Table 39. Int-2/HR with Hb <10g/dL cost-comparison results [List price]

Technology	Drug acquisition cost	Subsequent medicine cost	ICT cost	RBC transfusion cost	AE costs	Total costs	Incremental costs
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruxolitinib	£39,361	£221,674	£5,157	£59,389	£2,120	£327,702	-

Abbreviations: AE = adverse event; ICT = iron chelation therapy; RBC = red blood cell

Table 40. Int-2/HR with Hb <10g/dL cost-comparison results [PAS price]

Technology	Drug acquisition cost	Subsequent medicine cost	ICT cost	RBC transfusion cost	AE costs	Total costs	Incremental costs
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruxolitinib	£39,361	£221,674	£5,157	£59,389	£2,120	£327,702	-

Abbreviations: AE = adverse event; ICT = iron chelation therapy; PAS = patient access scheme; RBC = red blood cell

Like in the base-case analyses from the original company submission, momelotinib results in cost-savings from a reduction in RBC transfusions. The transfusion rates for the Int-2/HR with Hb <10g/dL population are outlined in Table 41.

Table 41. Rates of RBC transfusions by subgroup

	Int-2/HR with Hb <10g/dL		Int-2/HR with Hb <12g/dL	
	Momelotinib	Ruxolitinib	Momelotinib	Ruxolitinib
RBC transfusion rate in RT phase				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) units per month	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusion rate in RT phase, adjusted for strata				
Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

Abbreviations: CI = confidence interval; Hb = haemoglobin; N RBC = red blood cell; RT = randomised treatment; SD = standard deviation

For the int-2/HR with Hb <10g/dL subgroup analyses, population specific RBC transfusion units and TTD data were applied from the SIMPLIFY-1 trial. In the CS base-case parameter values from the ITT population were used to avoid breakage of randomisation and to minimise the introduction of bias. This is appropriate if differences in data inputs are not expected to vary significantly between subgroups. Furthermore, use of the data inputs from the full ITT population maximises the available sample size and minimises any parameter uncertainty.

Cost utility analysis

B2. Priority question. Please provide SIMPLIFY-2 trial momelotinib data for each patient showing the time momelotinib treatment stopped, the time a patient became transfusion-requiring (TR) and/or transfusion-dependent (TD), and the time a patient died.

GSK are unable to share the patient level data from SIMPLIFY-2. Further discussion on the impact of momelotinib discontinuation in relation to transition probabilities, survival and quality of life, as well as the relationship between transfusion status and survival, is provided in response to question B3.

B3. Priority question. Please justify why, in the JAKi-experienced model, stopping treatment with momelotinib after 24 weeks has no impact on transfusion probabilities, survival or health-related quality of life.

GSK's view, expressed in the model and elsewhere in the submission, is that momelotinib has a material impact on transfusion burden (applied through transition probabilities), survival and health-related quality of life. Therefore, it appears to be contradictory that there should be no impact of stopping treatment with momelotinib on these outcomes after 24 weeks. In fact, GSK's approach is the most conservative response to a data under-specification problem, and likely results in a significant overestimation of the performance of BAT in clinical practice. GSK notes that the EAG are asking this question principally because they doubt that a relationship between TI and OS exists to the level claimed in the submission, and therefore addresses the relationship directly following a response to the question.

GSK's approach is conservative

As a simplifying modelling assumption, the impact of being on/off treatment on transfusion is not explicitly modelled. This is because the relationship between treatment status and transfusion status is complex, with no realistic way to quantify the interaction. For example, treatment discontinuation may be correlated with loss of transfusion independence, but clinicians have confirmed that this is not the only reason people might discontinue treatment and so the correlation will not be perfect or straightforward.

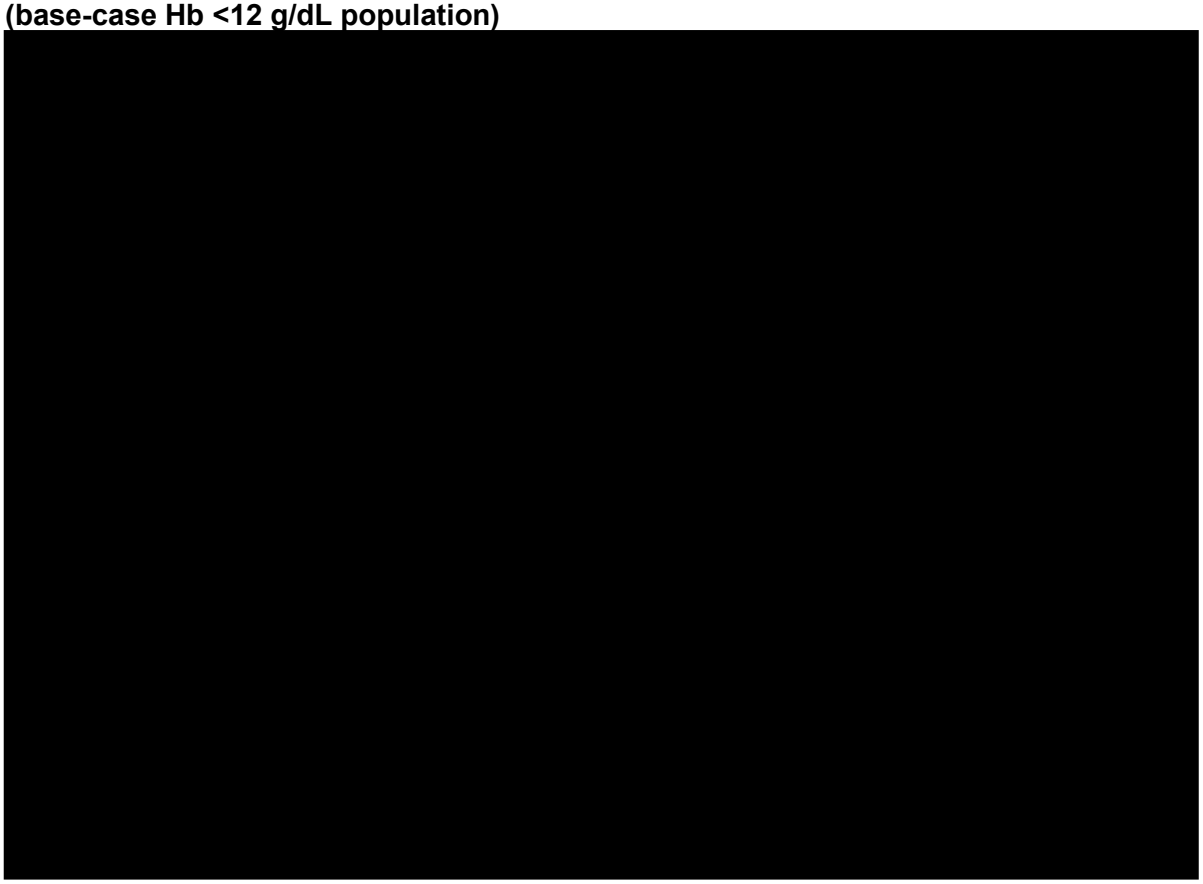
In extrapolating this treatment effect, and to maintain clinical plausibility with regard to discontinuation over time, a sustained TI-response beyond 24 weeks is *not* applied to either the momelotinib or BAT arm. Instead, following week 24 in the base-case, transition probabilities are restricted to prevent transitions to 'healthier' health states, contrary to what was observed in the initial 24 weeks in the case of

momelotinib, (see Table 122, Section B.3.4 (p255) of the CS for TI change-from-baseline for momelotinib and BAT) when the majority of patients are still on treatment.

Furthermore, as data was not available for the comparator arm after 24 weeks due to the cross-over from BAT to momelotinib in the SIMPLIFY-2 trial, GSK believe the patients in the BAT arm patients benefit from the application of a treatment effect partially derived from momelotinib-arm data. As noted in Section B.3.3.4.2 (p164) of the CS, a common transition probability matrix, derived from pooled momelotinib and BAT cycle 6 (week 20 to week 24) transition probabilities, is applied to both BAT and momelotinib patients following Week 24. This assumption applies to both MMB and BAT arm due to lack of data availability for the comparator arm after 24 weeks. Therefore, the BAT arm benefits from any persistent effect of momelotinib despite not incurring any cost for this benefit. The existence of this persistent effect given the myelosuppressive characteristics of ruxolitinib, as evidenced by the reduction in TI the BAT arm of SIMPLIFY-2 and the ruxolitinib arm of SIMPLIFY-1, which forms an integral part of BAT (ruxolitinib = 88.5%), is considered a conservative set of assumptions in the absence of more robust evidence.(8, 15)

If the assumption was unreasonable, the predicted time-in-state curves for momelotinib would diverge sharply from those actually observed in the trial (and later follow-up). Figure 3 below illustrates the time-to-loss of TI-response from Week 24 in SIMPLIFY-2 (grey KM curve), and the proportion of Week 24 TI responders, alive and remaining TI, as predicted by the model (red curve overlaid). For this time-to-event analysis, an event is defined as a Hb <8 g/dL, or RBC transfusion, or death, and the chart includes TI-responders from momelotinib (n=29) at Week 24. An analogous time-to-event analysis using all TI-responders being treated with momelotinib, including those crossing over from BAT (n=5) at Week 24, produces a very similar KM figure.(16) Overlayed in red is the proportion of momelotinib arm Week 24 TI responders, alive and remaining TI, following Week 24, as predicted by the model.

Figure 3. Time to loss of TI response from 24 weeks or death from SIMPLIFY-2 compared to momelotinib TI health state membership from 24 weeks in the CEM (base-case Hb <12 g/dL population)



As shown in Figure 3, momelotinib TI health state membership in the model aligns closely with available longer-term data from the SIMPLIFY-2 trial, although the red curve *underpredicts* the observed data in the trial suggesting that the model predictions for momelotinib are conservative. This is is evidence that the model is conservative with respect to the persistence of transfusion status.

Relevance to overall survival estimates

GSK notes that the EAG are asking this question principally because they doubt that a relationship between TI and OS exists to the level claimed in the submission. The EAG note that Verstovsek et el. 2017, a pooled analysis of the COMFORT-1 and COMFORT-2 trials of ruxolitinib in MF patients, indicated that transfusion status at 24 weeks did not have a bearing on OS in patients receiving ruxolitinib.(17)

However, there are a number of key limitations associated with this conclusion. Crucially, it is not based on results for the ITT populations in the pooled COMFORT

trials. Instead, the reported analyses of transfusion status (TI vs. no TI; and TD vs. no TD) were conducted only among subgroups first stratified by anaemia status at baseline (anaemia and no anaemia).(17) Consequently, these involve comparisons between subgroups of subgroups (baseline anaemia status and Week 24 transfusion status), and therefore it is unclear whether the study was sufficiently powered to detect potential differences in OS according to transfusion status in either of the anaemia-status subgroups.

In addition, visual inspection of the KM curves for OS vs. transfusion-dependence status (in Figure 2, of the study publication) suggests trends towards a relationship between these variables in both baseline-anaemia-status subgroups treated with ruxolitinib (i.e., anaemia, and no anaemia), although these were reportedly not statistically significant.(17) This raises the possibility that ITT results (i.e., for all patients randomised to ruxolitinib across the COMFORT trials, as opposed to subgroups stratified by baseline anaemia status) might have detected a significance difference in OS according to transfusion-dependence status. The absence of such analysis would appear to preclude a definitive conclusion on whether transfusion-dependence status affects OS generally in patients treated with ruxolitinib. Moreover, the conclusion is contradicted by the more recent Response to Ruxolitinib at 6 Month (RR6) model.(18). This is an observational study assessing outcomes in patients in the 6 months after starting ruxolitinib, and concluded that transfusion requirement in the first 6 months of ruxolitinib treatment predicts overall survival in MF.

As described in Section M.1.5 (p158) of the CS appendices, GSK conducted a targeted literature review to further explore the real-world evidence reporting on the relationship between transfusion status and OS.(19) The findings of this review have suggested that TD is associated with shorter OS, and TI with longer OS – results seen consistently despite the extensive heterogeneity in the design, patient populations, treatment characteristics and definitions of transfusion-dependence status across studies that have explored this inter-relationship.(19)

Quality of life

In terms of quality of life, as stated in Section B.3.3.5.6 (p188) of the CS, although patients on momelotinib in SIMPLIFY-2 had numerically higher utility values

compared to BAT for the TI and TD health states, differences were not statistically significant once transfusion status (TI, TR and TD) was controlled for and, therefore, treatment agnostic health state utility values were applied in the base case analysis. However, scenario analyses were performed in which treatment specific utilities were applied; Scenario 15 explored the impact of also applying BAT-specific health state utility values to reflect the potential for patients having lower overall quality of life upon discontinuing momelotinib. Momelotinib remained dominant in Scenario 15 for both list and PAS price analyses due to lower incremental total costs and higher incremental QALYs than BAT. Furthermore, incremental QALY gains observed in Scenario 15 (0.359) were larger than those observed in the base case analysis (0.346), suggesting that the base case analysis was relatively conservative in relation to QALY gains for momelotinib.

B4. Priority question. Please provide an economic analysis for JAKi-experienced patients where transfusion status is only determined by transfusions received by patients in the SIMPLIFY-2 trial and not by Hb status, i.e.,

- **TI: an absence of RBC transfusions in the three prior model cycles (12 weeks)**
- **TD: at least four units of RBC transfusions in the two prior model cycles (8 weeks)**
- **TR: not meeting the TI or TD criteria.**

This will require a re-analysis of survival by transfusion status at 24 weeks for patients who are TI or non-TI (TR and TD).

Base-case results with alternative transfusion definition

This section describes cost-effectiveness analysis results where the transfusion status is only determined by transfusions received by patients in the SIMPLIFY-2 trial and not by Hb status. Results based on the alternative health state definitions are presented below. Transition probabilities and OS curves after 24 weeks applied for

this analysis are presented in the B4 Appendix. OS curves are the same as for the revised company base-case presented below.

Revising the TI definition did not alter the number of patients who are TI (and non-TI) at Week 24, indicating that all patients in the relevant subgroups who had Hb <8 g/dL in the prior 12 weeks also received an RBCT. However, transition probabilities were changed as a result of the TI definition revision, reflecting that while most patients who had Hb <8 g/dL received RBCTs, there is not a perfect overlap.

The revised company base-case presented and described at the end of this section are slightly different to the results presented in the original CS. The reason for this is that some input parameters related to survival erroneously included intermediate-1 risk patients, rather than restriction to intermediate-2 or high-risk Hb<12 subgroup as intended. Correcting this error slightly lowers overall incremental QALYs, but does not change the conclusion that momelotinib dominates BAT.

This notwithstanding, the proposed analysis suggested by the EAG in this question has very little material impact on the decision problem. We first present the error-corrected results of the EAG analysis, and then for comparison, the error-corrected base case. In both cases, cost and QALYs are highly comparable. Despite this, GSK believe that the approach to the economic analysis in the CS is preferable to the requested alternative approach as:

- The TI definition used in the CS captures all patients who are free from transfusion and have not experienced episodes of severe anaemia, as indicated by Hb <8 g/dL, that may indicate a transfusion.
    - It is the most clinically relevant definition of transfusion independent and is supported by the 2020 Pan-London Haemoto-Oncology Clinical Guidelines for Myeloproliferative Neoplasms which advises that although at an individual level Hb levels need to be individualised, in general a threshold of 8 g/dL is appropriate for indication of an RBCT to treat anaemia in MF.(20)

- As shown by the reclassification of TI-responders for the base-case population, there is a significant overlap between patients with a Hb <8 g/dL in the previous 12 weeks and receiving an RBCT.

- The TI definition is the most appropriate definition for predicting survival, which is supported by the SIMPLIFY-2 trial as well as the prognostic model DIPSS+ which includes transfusion need and Hb <10 g/dL as independent prognostic variables(21), and the MIPPSS70+ v2.0 which includes Hb <8 g/dL and Hb <10 g/dL as independent prognostic variables.(22)
- Analysis of EQ-5D in the MMB trials shows that the existing health state definitions robustly capture quality of life in for this patient population.

Base-case incremental cost-effectiveness analysis results (EAG Scenario)

Total costs, LYs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT for the JAKi-experienced model population are presented in Table 42. Momelotinib decreased total costs against BAT by [redacted]; it also produced an increase in both total life years (0.109) and QALYs (0.111). BAT was therefore dominated by momelotinib.

The incremental net monetary benefit was [redacted] and [redacted] at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as shown in Table 43.

Results based on applying a PAS price discount of [redacted] are provided in Table 44. Incremental total cost savings for momelotinib were reduced further to [redacted] and momelotinib therefore remained dominant over BAT as in the list price results. The incremental net monetary benefit values increased to [redacted] and [redacted] for £20,000 and £30,000 per QALY thresholds (Table 45), respectively, after application of the PAS discount.

Table 42. Base-case results for momelotinib vs BAT in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.096	1.912	-	-	-	-	-
Momelotinib	[redacted]	3.204	2.023	-[redacted]	0.109	0.111	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; QALY = quality-adjusted life year

Table 43. Net monetary benefit in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.912	-	-	-	-
Momelotinib	[redacted]	2.023	-[redacted]	0.111	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; QALY = quality-adjusted life year

Table 44. Base-case results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.096	1.912	-	-	-	-	-
Momelotinib	[redacted]	3.204	2.023	[redacted]	0.109	0.111	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 45. Net monetary benefit in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.912	-	-	-	-
Momelotinib	[redacted]	2.023	[redacted]	0.111	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; PAS = patient access scheme; QALY = quality-adjusted life year

Exploring uncertainty - with alternative transfusion definition

Probabilistic sensitivity analysis

The probabilistic mean values for total costs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT generated through the PSA are presented in Table 46. Momelotinib generated a probabilistic average of 0.147 incremental QALYs gained and [redacted] lower incremental costs over a lifetime horizon compared with BAT, resulting in momelotinib dominating BAT (with higher total mean QALYs and lower total mean costs). Probabilistic mean incremental QALYs were slightly higher than the deterministic model incremental QALYs (0.147 vs 0.111) with slightly smaller probabilistic mean total cost savings compared to the deterministic based case (lower total costs for momelotinib of [redacted] vs [redacted]).

The corresponding incremental cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are presented in Figure 4 and Figure 5, respectively. At a willingness to pay (WTP) threshold of £0, £20,000 and £30,000 per QALY, momelotinib has a [redacted].

Table 46. PSA results for momelotinib vs BAT in JAKi-experienced patients [List price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean Incremental Costs (£) versus BAT	Mean Incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	1.865	-	-	
Momelotinib	[redacted]	2.012	[redacted]	0.147	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 4. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 5. Momelotinib versus BAT CEAC – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor

PSA results following application of the PAS price discount are presented in Table 47. Probabilistic mean incremental total QALYs for momelotinib were 0.153 and probabilistic mean incremental total costs were reduced with momelotinib by [redacted]. The corresponding ICEP and CEAC are presented in Figure 6 and Figure 7, respectively.

[redacted]

Table 47. PSA results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean incremental costs (£) versus BAT	Mean incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	1.854	-	-	
Momelotinib	[redacted]	2.008	[redacted]	0.153	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year.

Figure 6. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [PAS price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 7. Momelotinib versus BAT CEAC – base-case JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Deterministic sensitivity analysis

The parameters in the model with single input values were varied individually in deterministic sensitivity analysis (DSA). Upper and lower values were based on the confidence intervals or estimated confidence intervals based on other uncertainty data. In the absence of appropriate uncertainty data to inform the confidence intervals, the upper and lower values for the DSA were derived from assuming the SE values to be 10% of the mean base-case value, as for the PSA. Each parameter was set to the upper and lower bounds to test the impact of each individual parameter on the results.

A DSA tornado diagram presenting the top 20 most sensitive parameters for the momelotinib versus BAT cost-effectiveness results for the JAKi-experienced model population in descending order of sensitivity is shown in Figure 8. As the base-case results indicated that momelotinib was dominant over BAT, results are presented in terms of NMB at a WTP threshold of £30,000 per QALY.

The key drivers of cost-effectiveness were OS parameters (for both the non-TI and TI extrapolations after 24 weeks), the overall proportion on ruxolitinib with the BAT comparator, and utilities for the TD health state for both BAT and momelotinib. Some slight sensitivity was also observed around the momelotinib TTD model parameters, proportion of BAT patients on a low 5mg dose of ruxolitinib and TI utility values, with all other inputs generating relatively small variations in the incremental NMB results.

The 10 most impactful set of tabulated results from the sensitivity analysis (in terms of NMB) are presented in Table 48. Across all parameter variations, only the upper bound variation of the non-TI OS Weibull model parameters and lower bound variation in momelotinib Gompertz model parameters resulted in incremental NMB values below £0 at a £30,000 per QALY threshold.

Figure 8. Base-case DSA tornado diagram for momelotinib vs BAT – JAKi-experienced model [List price]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; OS = overall survival; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 48. Tabulated DSA results (top 10) for momelotinib versus BAT – JAKi-experienced model [List price]

Variable	LB NMB value	UB NMB value	Difference
JAKi exp - MMB and BAT OS - TD, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi exp - MMB TTD - Overall cohort, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on RUX (%)	[redacted]	[redacted]	[redacted]
JAKi exp - MMB and BAT OS - TI, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi experienced MMB utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of RUX on 5mg (%)	[redacted]	[redacted]	[redacted]
Mean RBC transfusion in unit per month - TD - Int2/high Hb <12	[redacted]	[redacted]	[redacted]
RBCT resource use per cycle - JAKi-experienced - MMB - TD	[redacted]	[redacted]	[redacted]
Resource use cost - RBCT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; TD = transfusion-dependent; TI = transfusion-independent; TTD = time to treatment discontinuation; UB = upper bound

DSA results following application of the PAS discount are available in Figure 9 and Table 49. Similar results were observed as for the results without the PAS discount in terms of which parameters produced the most variation around the base-case incremental NMB estimate, albeit with incremental NMB values greater than [redacted] in all cases and therefore indicating momelotinib to be cost-effective against BAT for all parameter variations.

Figure 9. Base-case NMB tornado diagram – JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; NMB = net monetary benefit; PAS = patient access scheme; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 49. Tabulated DSA results (top 10) for momelotinib versus BAT (NMB) – JAKi-experienced model [PAS price]

Variable	LB value	UB value	Difference
JAKi exp - MMB and BAT OS - TD, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on RUX (%)	[redacted]	[redacted]	[redacted]
JAKi exp - MMB and BAT OS - TI, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi exp - MMB TTD - Overall cohort, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi experienced MMB utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of RUX on 5mg (%)	[redacted]	[redacted]	[redacted]
Mean RBC transfusion in unit per month - TD - Int2/high Hb <12	[redacted]	[redacted]	[redacted]
RBCT resource use per cycle - JAKi-experienced - MMB - TD	[redacted]	[redacted]	[redacted]
Resource use cost - RBCT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; PAS = patient access scheme; TD = transfusion-dependent; TI = transfusion-independent; TTD = time to treatment discontinuation; UB = upper bound

Scenario analysis

Scenarios exploring alternative long-term extrapolations and data source of survival parameters, cure assumptions, utilities and, along with shorter model time horizons and lower discount rates, are summarised in Table 50.

Scenario analysis results are most sensitive to a shorter time horizon (5-year), transition probability extrapolation (applying treatment specific transition probabilities) and use of subsequent ruxolitinib (following discontinuation of momelotinib) (scenarios 1, 7 and 11), where they generated the greatest NMB decreases of [redacted], [redacted] and [redacted] compared to BAT and for which momelotinib was no longer dominant over BAT. The ICERs in these scenarios were [redacted] when using a shorter time horizon of 5 years, [redacted] when applying treatment specific transition probabilities to extrapolate transition probabilities after week 24, and [redacted] per QALY when assuming 39% of patients on ruxolitinib after discontinuing momelotinib as a result of increasing the costs of subsequent treatment for momelotinib.

Applying a 10-year time horizon also decreases the NMB by [redacted]. NMB is increased by [redacted] when using a lower discount rate (1.5%) for both cost and health outcomes in the model. Cost assumptions associated with transfusion (applying KOL suggested RBCT unit data) increased the NMB by [redacted].

The incremental NMB results were also sensitive to variations in assumptions around transition probability extrapolations for determining transfusion health state distribution over time, with both costs and QALYs impacted as a result of increased resource use costs and lower health state utilities for TR and TD compared to TI. Applying a less conservative assumption of no health state movement after 24 weeks increased the NMB by [redacted] compared to the base-case analysis. Other transition probability scenarios had a more modest impact on the results, generating [redacted] variations in the NMB.

Application of alternative model for OS had a modest impact on the results, with use of the Generalised Gamma model for TI OS (reduction of [redacted]).

As anticipated, given the numerically higher utility values observed for momelotinib-specific TI and TD health state utilities compared to BAT, application of treatment specific utilities instead of treatment independent utilities increased the cost-effectiveness of momelotinib compared to BAT, with an increase of [redacted] in the NMB.

Most of other scenario analyses had minimal impacts on the NMB values, with [redacted]% variation from the base-case NMB estimate.

Table 50. Scenario analysis results for momelotinib versus BAT – JAKi-experienced model [List price]

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
-	**Base-case**	[redacted]	0.111	[redacted]	N/A	Dominant
1	5-year time horizon	[redacted]	0.101	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	0.105	[redacted]	[redacted]	Dominant
3	Discount rate (cost and health outcomes) of 1.5%	[redacted]	0.117	[redacted]	[redacted]	Dominant
4	TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.117	[redacted]	[redacted]	Dominant
5	TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.172	[redacted]	[redacted]	Dominant
6	TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.109	[redacted]	[redacted]	Dominant
7	TP extrapolation: Treatment specific transition probabilities	[redacted]	0.046	[redacted]	[redacted]	[redacted]
8	TI OS: gen gamma	[redacted]	0.108	[redacted]	[redacted]	Dominant
9	Momelotinib TTDD: exponential	[redacted]	0.111	[redacted]	[redacted]	Dominant
10	Apply KOL RBC transfusion unit data	[redacted]	0.111	[redacted]	[redacted]	Dominant
11	Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.111	[redacted]	[redacted]	[redacted]
12	Exclude terminal care costs	[redacted]	0.111	[redacted]	[redacted]	Dominant
13	Treatment specific HSUVs	[redacted]	0.160	[redacted]	[redacted]	Dominant
14	Scenario 14 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.129	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
15	Higher anaemia AE cost	[redacted]	0.111	[redacted]	[redacted]	Dominant
16	Alternative RBC transfusion unit costs (Agrawal 2006)	[redacted]	0.111	[redacted]	[redacted]	Dominant
17	Exclude ICT costs	[redacted]	0.111	[redacted]	[redacted]	Dominant
18	Reduce deferasirox (ICT) dose to 14 mg/kg/day	[redacted]	0.111	[redacted]	[redacted]	Dominant

Abbreviations: AE = adverse event; BAT = best available therapy; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; JAKi = Janus kinase inhibitor; KOL = key opinion leader; N/A = not applicable; NMB = net monetary benefit; OS = overall survival; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TP = transition probability; TTDD = time to treatment discontinuation or death

Table 51 presents the scenario analysis including momelotinib PAS price. The directional impact on the NMB results was similar to the list price scenarios, albeit with the magnitude of the proportional change from the base-case NMB reduced as a result of lowering momelotinib drug acquisitions costs. Following application of the PAS discount, momelotinib dominated BAT across all scenarios.

Table 51. Scenario analysis results for momelotinib versus BAT – JAKi-experienced model [PAS price]

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER incremental (£/QALY)
-	**Base-case**	[redacted]	0.111	[redacted]	N/A	Dominant
1	5-year time horizon	[redacted]	0.101	[redacted]	[redacted]	Dominant
2	10-year time horizon	[redacted]	0.105	[redacted]	[redacted]	Dominant
3	Discount rate (cost and health outcomes) of 1.5%	[redacted]	0.117	[redacted]	[redacted]	Dominant
4	TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.117	[redacted]	[redacted]	Dominant
5	TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.172	[redacted]	[redacted]	Dominant
6	TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.109	[redacted]	[redacted]	Dominant
7	TP extrapolation: Treatment specific transition probabilities	[redacted]	0.046	[redacted]	[redacted]	Dominant
8	TI OS: gen gamma	[redacted]	0.108	[redacted]	[redacted]	Dominant
9	Momelotinib TTDD: exponential	[redacted]	0.111	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER incremental (£/QALY)
10	Apply KOL RBC transfusion unit data	[redacted]	0.111	[redacted]	[redacted]	Dominant
11	Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.111	[redacted]	[redacted]	Dominant
12	Exclude terminal care costs	[redacted]	0.111	[redacted]	[redacted]	Dominant
13	Treatment specific HSUVs	[redacted]	0.160	[redacted]	[redacted]	Dominant
14	Scenario 14 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.129	[redacted]	[redacted]	Dominant
15	Higher anaemia AE cost	[redacted]	0.111	[redacted]	[redacted]	Dominant
16	Alternative RBC transfusion unit costs (Agrawal 2006)	[redacted]	0.111	[redacted]	[redacted]	Dominant
17	Exclude ICT costs	[redacted]	0.111	[redacted]	[redacted]	Dominant
18	Reduce deferasirox (ICT) dose to 14 mg/kg/day	[redacted]	0.111	[redacted]	[redacted]	Dominant

Abbreviations: AE = adverse event; BAT = best available therapy; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; JAKi = Janus kinase inhibitor; KOL = key opinion leader; N/A = not applicable; NMB = net monetary benefit; OS = overall survival; PAS = patient access scheme; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TP = transition probability; TTDD = time to treatment discontinuation or death

Revised company base case results

Base-case results with revised OS curves

Following submission of the original CS, GSK have identified that patients with intermediate-1 MF were incorrectly included in the KM curves used to derived TI and Non-TI OS survival extrapolations after 24 weeks in the cost-effectiveness model. As such, the following section provides updated company base-case results using the company preferred health state definitions included in the original submission with revised OS extrapolations removing intermediate-1 patients which are described in the B4 Appendix. As a result of removing intermediate-1 disease patients from the OS curves, predicted total costs, life years and QALYs for both comparators are now lower than in the original submission (for example, total discounted life years of 3.207 and 3.077 compared to 3.819 and 3.355 for momelotinib and BAT, respectively).

The patients classified as TI and Non-TI at the end of the 24-week randomised phase of the SIMPLIFY-2 trial are the same for the company preferred health state definitions as for the EAG requested analysis with alternative health state definitions. Therefore, the differences between the revised company base-case and EAG scenario results are determined by differences in health state transition probabilities used for the first 24 weeks of the model.

Revised base-case incremental cost-effectiveness analysis results

Total costs, LYs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT for the JAKi-experienced model population are presented in Table 42. Momelotinib decreased total costs against BAT by [redacted]; it also produced an increase in both total life years (0.130) and QALYs (0.145). BAT was therefore dominated by momelotinib.

The incremental net monetary benefit was [redacted] and [redacted] at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as shown in Table 43.

Results based on applying a PAS price discount of [redacted] are provided in Table 44. Incremental total cost savings for momelotinib were reduced further to [redacted] and momelotinib therefore remained dominant over BAT as in the list price results. The incremental net monetary benefit values increased to [redacted] and [redacted] for £20,000 and £30,000 per QALY thresholds (Table 45), respectively, after application of the PAS discount.

Table 52. Base-case results for momelotinib vs BAT in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.077	1.898	-	-	-	-	-
Momelotinib	[redacted]	3.207	2.043	[redacted]	0.130	0.145	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; QALY = quality-adjusted life year

Table 53. Net monetary benefit in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.898	-	-	-	-
Momelotinib	[redacted]	2.043	[redacted]	0.145	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; QALY = quality-adjusted life year

Table 54. Base-case results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.077	1.898	-	-	-	-	-
Momelotinib	[redacted]	3.207	2.043	[redacted]	0.130	0.145	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 55. Net monetary benefit in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.898	-	-	-	-
Momelotinib	[redacted]	2.043	[redacted]	0.145	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; PAS = patient access scheme; QALY = quality-adjusted life year

Exploring uncertainty - revised company base-case

Probabilistic sensitivity analysis

The probabilistic mean values for total costs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT generated through the PSA are presented in Table 46. Momelotinib generated a probabilistic average of 0.147 incremental QALYs gained and [redacted] lower incremental costs over a lifetime horizon compared with BAT, resulting in momelotinib dominating BAT (with higher total mean QALYs and lower total mean costs). Probabilistic mean incremental QALYs were slightly higher than the deterministic model incremental QALYs (0.197 vs 0.145) with slightly smaller probabilistic mean total cost savings compared to the deterministic based case (lower total costs for momelotinib of [redacted] vs [redacted]).

The corresponding incremental cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are presented in Figure 4 and Figure 5, respectively. At a willingness to pay (WTP) threshold of £0, £20,000 and £30,000 per QALY, momelotinib has a [redacted].

Table 56. PSA results for momelotinib vs BAT in JAKi-experienced patients [List price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean Incremental Costs (£) versus BAT	Mean Incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	1.841	-	-	
Momelotinib	[redacted]	2.038	[redacted]	0.197	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 10. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 11. Momelotinib versus BAT CEAC – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor

PSA results following application of the PAS price discount are presented in Table 47. Probabilistic mean incremental total QALYs for momelotinib were 0.187 and probabilistic mean incremental total costs were reduced with momelotinib by [redacted]. The corresponding ICEP and CEAC are presented in Figure 6 and Figure 7, respectively.

[redacted]

Table 57. PSA results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean incremental costs (£) versus BAT	Mean incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	1.831	-	-	
Momelotinib	[redacted]	2.018	[redacted]	0.187	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year.

Figure 12. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [PAS price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 13. Momelotinib versus BAT CEAC – base-case JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Deterministic sensitivity analysis

The parameters in the model with single input values were varied individually in deterministic sensitivity analysis (DSA). Upper and lower values were based on the confidence intervals or estimated confidence intervals based on other uncertainty data. In the absence of appropriate uncertainty data to inform the confidence intervals, the upper and lower values for the DSA were derived from assuming the SE values to be 10% of the mean base-case value, as for the PSA. Each parameter was set to the upper and lower bounds to test the impact of each individual parameter on the results.

A DSA tornado diagram presenting the top 20 most sensitive parameters for the momelotinib versus BAT cost-effectiveness results for the JAKi-experienced model population in descending order of sensitivity is shown in Figure 8. As the base-case results indicated that momelotinib was dominant over BAT, results are presented in terms of NMB at a WTP threshold of £30,000 per QALY.

The key drivers of cost-effectiveness were the Non-TI OS parameters, momelotinib TTDD parameters and the overall proportion on ruxolitinib with the BAT comparator. Some slight sensitivity was also observed around the TD utility values, TI OS parameters, and proportion of BAT patients on a low 5mg dose of ruxolitinib, with all other inputs generating relatively small variations in the incremental NMB results.

The 10 most impactful set of tabulated results from the sensitivity analysis (in terms of NMB) are presented in Table 48. Across all parameter variations, only the upper bound variation of the non-TI OS Weibull model parameters and lower bound variation in momelotinib Gompertz TTDD model parameters resulted in incremental NMB values below £0 at a £30,000 per QALY threshold.

Figure 14. Base-case DSA tornado diagram for momelotinib vs BAT – JAKi-experienced model [List price]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; OS = overall survival; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 58. Tabulated DSA results (top 10) for momelotinib versus BAT – JAKi-experienced model [List price]

Variable	LB NMB value	UB NMB value	Difference
JAKi exp - MMB and BAT OS - TD, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi exp - MMB TTD - Overall cohort, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on RUX (%)	[redacted]	[redacted]	[redacted]
JAKi experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi exp - MMB and BAT OS - TI, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi experienced MMB utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of RUX on 5mg (%)	[redacted]	[redacted]	[redacted]
Mean RBC transfusion in unit per month - TD - Int2/high Hb <12	[redacted]	[redacted]	[redacted]
RBCT resource use per cycle - JAKi-experienced - MMB - TD	[redacted]	[redacted]	[redacted]
Resource use cost - RBCT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; TD = transfusion-dependent; TI = transfusion-independent; TTD = time to treatment discontinuation; UB = upper bound

DSA results following application of the PAS discount are available in Figure 9 and Table 49. Similar results were observed as for the results without the PAS discount in terms of which parameters produced the most variation around the base-case incremental NMB estimate, albeit with incremental NMB values greater than [redacted] in all cases and therefore indicating momelotinib to be cost-effective against BAT for all parameter variations.

Figure 15. Base-case NMB tornado diagram – JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; NMB = net monetary benefit; PAS = patient access scheme; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 59. Tabulated DSA results (top 10) for momelotinib versus BAT (NMB) – JAKi-experienced model [PAS price]

Variable	LB value	UB value	Difference
JAKi exp - MMB and BAT OS - TD, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on RUX (%)	[redacted]	[redacted]	[redacted]
JAKi exp - MMB TTD - Overall cohort, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi exp - MMB and BAT OS - TI, int2/highrisk&Hgb<12	[redacted]	[redacted]	[redacted]
JAKi experienced MMB utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of RUX on 5mg (%)	[redacted]	[redacted]	[redacted]
Mean RBC transfusion in unit per month - TD - Int2/high Hb <12	[redacted]	[redacted]	[redacted]
RBCT resource use per cycle - JAKi-experienced - MMB - TD	[redacted]	[redacted]	[redacted]
Resource use cost - RBCT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; PAS = patient 7discontinuation; UB = upper bound

Section C: Textual clarification and additional points

C1. Table 13 and Table 14 (CS, Appendix E) text and table headings are inconsistent. Please clarify which table provides LFS results and which table provides OS results for the SIMPLIFY-1 trial int-2/HR anaemic populations.

The text headings are correct, the table headings are incorrect. Table 13 (CS Appendix E) reports LFS and Table 14 (CS Appendix E) reports OS for the SIMPLIFY-1 int-2/HR anaemic populations.

Table 60 is the correct table for LFS which should be presented in Appendix E.1.1.4.1. Note the 'proportion difference (95% CI)' has been changed to 'stratified hazard ratio (95% CI)' in response to question C2.

Table 60. Median LFS in int-2/HR anaemic populations (SIMPLIFY-1)(7)

	Momelotinib	Ruxolitinib
Int-2/HR and Hb <10 g/dL		
Median Kaplan-Meir estimate of LFS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	

Int-2/HR and Hb <12 g/dL		
Median Kaplan-Meir estimate of LFS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	

Abbreviations: CI = confidence interval; Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; LFS = leukaemia free survival; NR = not reported

Table 61 is the correct table for OS which should be presented in Appendix E.1.1.4.2. Note the 'proportion difference (95% CI)' has been changed to 'stratified hazard ratio (95% CI)' to align with question C2.

Table 61. Median OS in int-2/HR anaemic populations (SIMPLIFY-1)(7)

	Momelotinib	**Ruxolitinib**
Int-2/HR and Hb <10 g/dL		
Median Kaplan-Meir estimate of OS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	
Int-2/HR and Hb <12 g/dL		
Median Kaplan-Meir estimate of OS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	

Abbreviations: CI = confidence interval; Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; NR = not reported; OS = overall survival

C2. In the CS, Appendix E, Table 13, Table 14, Table 19 and Table 20, please clarify whether the results reported as 'Proportion difference (95% CI)' are correctly labelled or whether these should be labelled as 'Hazard ratio (95% CI)'.

Company submission Appendix E Table 13 and Table 14 should be changed from 'proportion difference (95% CI)' to 'stratified hazard ratio (95% CI)'. Please see Table 60 and Table 61 (C.3) for the correct tables.

Company submission Appendix E Table 19 should be changed from 'proportion difference (95% CI)' to 'stratified hazard ratio (95% CI)'. Please see Table 62 for the corrected table.

Table 62. Median LFS in int-2/HR anaemic populations (SIMPLIFY-2)(8)

	Momelotinib	**Ruxolitinib**
Int-2/HR and Hb <10 g/dL		
Median Kaplan-Meir estimate of LFS (months)	[redacted]	[redacted]

95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	
Int-2/HR and Hb <12 g/dL		
Median Kaplan-Meir estimate of LFS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	

Abbreviations: CI = confidence interval; Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; LFS = leukaemia-free survival; NR = not reported

Company submission Appendix E Table 20 should be changed from 'proportion difference (95% CI)' to 'stratified hazard ratio (95% CI)'. Please see Table 63 for the corrected table.

Table 63. Median OS in int-2/HR anaemic populations (SIMPLIFY-2)(8)

	Momelotinib	**Ruxolitinib**
Int-2/HR and Hb <10 g/dL		
Median Kaplan-Meir estimate of OS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	
Int-2/HR and Hb <12 g/dL		
Median Kaplan-Meir estimate of OS (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Stratified hazard ratio (95% CI)	[redacted]	

Abbreviations: CI = confidence interval; Hb = haemoglobin; Int-2/HR = intermediate 2/high-risk; NR = not reported; OS = overall survival

C3. The External Assessment Group has received CSRs plus supplementary CSR tables for the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials and has also received statistical analysis plans (SAPs) for the SIMPLIFY-1 and SIMPLIFY-2 trials. However, the file which is labelled as the MOMENTUM SAP is a duplicate copy of the SIMPLIFY-2 SAP. Please provide the MOMENTUM trial SAP. Please also provide the protocols for all three of the momelotinib trials.

The MOMENTUM SAP and SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM protocols have been added to the submission reference pack.

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B.1 Health state transition probabilities (alternative health state definitions)

The transition probability matrices for momelotinib and BAT for the first 24 weeks in the model (base-case Hb <12 g/dL population), applied in the requested clarification question B4 analysis using alternative transfusion status health state definitions, are presented in Table 1 to Table 5.

Table 1. Transition probability matrix for baseline to cycle 1 (Week 0-4), and cycle 1 to cycle 2 (Week 4-8), alternative health state definitions

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	100%	0%	0%	100%	0%	0%
TR	0%	100%	0%	0%	100%	0%
TD	0%	0%	100%	0%	0%	100%

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 2. Transition probability matrix for cycle 2 to cycle 3 (Week 8-12), alternative health state definitions

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note that figures may not sum to 100% due to rounding.
Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 3. Transition probability matrix for cycle 3 to cycle 4 (Week 12-16), alternative health state definitions

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 4. Transition probability matrix for cycle 4 to cycle 5 (Week 16-20), alternative health state definitions

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 5. Transition probability matrix for cycle 5 to cycle 6 (Week 20-24), alternative health state definitions

	Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring

Table 6 presents the transition probability matrices for momelotinib and BAT used to extrapolate transfusion health state membership beyond 24 weeks, derived from the transition probability matrix in Table 5 but conservatively assuming no backwards movement, and based on the alternative health state definitions from clafirication question B4. Pooled data were applied in the base-case analysis, with treatment specific estimates applied in scenario analyses. Additional transition probability extrapolation matrices explored in scenario analyses are presented in Table 7, Table 8 and Table 9.

Table 6. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) –probabilities using cycle 6 transition probabilities and assuming no improvement in transfusion status, alternative health state definitions

	Pooled momelotinib + BAT (base-case)			Momelotinib			BAT		
From/to health state	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: extrapolate based on cycle 6 transition probabilities but assuming no movement to better health states
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

Table 7. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – average of cycle 4-6 transition probabilities scenario analysis, alternative health state definitions

	Pooled Momelotinib + BAT		
From/to health state	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

Note: extrapolate based on average of cycle 4-6 probabilities. Figures may not sum to 100% due to rounding.
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

Table 8. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – no change in transfusion status after Week 24 scenario analysis, alternative health state definitions

	Pooled Momelotinib + BAT		
From/to health state	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

Note: extrapolate assumed no movement to better health states
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

Table 9. Extrapolated transition probability matrix for cycle 7+ (Week 24+) (base-case Hb <12 g/dL population) – cap probability of improvement in transfusion status by probability of worsening transfusion status scenario analysis, alternative health state definitions

	Pooled Momelotinib + BAT		
From/to health state	**TI**	**TR**	**TD**
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

Note: extrapolate based on cycle 6 transition probabilities but assuming no movement to better health states
Abbreviations: BAT = best available therapy; Hb = haemoglobin; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring.

B.2 Revised TI and Non-TI OS extrapolations

B.2.1 Survival – revised base-case Hb <12 g/dL population

TI and non-TI OS KM curves and associated number at risk based on the alternative health state definitions are presented in Figure 1.

Figure 1. TI and non-TI OS KM curves from Week 24 and number at risk, SIMPLIFY-2 momelotinib only (revised base-case Hb <12 g/dL population)

Abbreviations: CI = confidence interval; Hb = haemoglobin; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; TI = transfusion-independent

Prior to the fitting of parametric models based on alternative transfusion status health state definitions for the revised base-case Hb <12 g/dL population, log-cumulative hazard plot and Schoenfeld residual plots were generated to assess whether the PH assumption holds (Figure 2 and Figure 3, respectively).

Figure 2. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 3. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Given that the log-cumulative hazard plots for TI and non-TI cohorts are non-parallel, the p-value from the Schoenfeld residuals test (<0.05) suggests a PH assumption is not plausible, and the fitted residuals line on the Schoenfeld residuals plot is clearly non-parallel to the 0 line, the PH assumption was assumed to be unsuitable, with independent parametric fits explored.

B.2.1.1 Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 10 for each pure momelotinib arm parametric model for the revised base-case Hb <12 g/dL population, for those who are TI at Week 24. The log-logistic model produced the best statistical fit with the lowest AIC and BIC.

Table 10. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	3	[redacted]	3
Gompertz	[redacted]	5	[redacted]	4
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	2	[redacted]	2
Generalised gamma	[redacted]	4	[redacted]	5

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independence

AIC and BIC relative fit classifications for the revised base-case TI models are shown below in Table 11. All other parametric models were within 4 AIC points and 10 BIC points of the log-logistic, with the exception of the exponential model with a different of 4-7 AIC points indicating a reasonable instead of good relative statistical fit.

Table 11. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	-	[redacted]	-
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independence

Figure 4 and Table 12 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Gompertz) to [redacted] (exponential) at 5 years and [redacted] (Gompertz) to [redacted] (exponential) at 10 years across parametric models.

Figure 4. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, TI, from Week 24 (revised base-case Hb<12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 12. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (revised base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In terms of visual fit to the observed data, most curves had a reasonable fit the KM curve except for the exponential model which appeared to underpredict the KM curve for the first 2 years.

Furthermore, additional considerations in the selection of the most appropriate curve for those who were TI at 24 weeks were:

1. Internal consistency:

a) TI patients are expected to have greater or comparable long-term survival to non-TI patients. Therefore, Weibull and Gompertz models are not considered plausible, since they produced 10-year survival estimates ([redacted] and [redacted], respectively) which were lower than all parametric models for the non-TI parametric extrapolations (Table 15). In addition, the log-logistic model was excluded from consideration as it crossed the most plausible non-TI parametric model (Weibull) at 232 weeks in the model.

b) It is assumed that landmark survival of the revised base-case Hb <12 g/dL population at 5 and 10 years is expected to be less than or equal to the ITT group and greater than the corresponding revised Hb <10 g/dL population. The log-normal ([redacted]) and generalised gamma ([redacted]) Hb <12 g/dL subgroup TI OS models may be suitable on the basis that they produce 10-year survival estimates lower than all of the more plausible TI OS candidates for the ITT population ([redacted] [log-logistic] to [redacted] [exponential]), while the Hb <12 g/dL exponential model produced a slightly higher 10-year survival estimate ([redacted]) than the ITT population log-logistic model ([redacted]) but lower than other plausible candidate models ([redacted] to [redacted]). In conclusion, comparing against ITT and in-2/high risk and Hb<10 TI curves indicate the log-normal and generalised gamma may be suitable model choices, although exponential could not be excluded.

2. Clinical expectation for TI survival:

a) At a clinical-HEOR advisory board, clinicians were shown two blinded parametric survival curves reporting estimated survival based on transfusion status for the full SIMPLIFY-2 population from Week 24. Parametric model 1 reported 5- and 10-year TI survival to be [redacted] and [redacted], respectively, while parametric model 2 reported 5- and 10-year survival to be [redacted] and [redacted], respectively. Clinicians choose parametric model 1 as a reasonable model choice while the alternative model was not considered likely given that more patients are expected to be alive 10 years. While this advice related to the ITT population

rather than the revised base-case Hb <12 g/dL population, survival estimates are expected to be less than or equal to the ITT population for this subgroup.

b) Given that the revised HB <12 g/dL subgroup, which excludes intermediate-1 risk patients, are anticipated to have survival less than or equal lower to the ITT population, this further indicates the that the exponential, log-normal and generalised gamma models all produce plausible long-term extrapolations in relation to ITT population expectations.

The log-normal and generalised gamma models both produced relatively good statistical and visual fits to the observed KM data, and 10-year survival estimates which were not contradicted by TI or non-TI extrapolations for other population groups. The log-normal model was selected based on slightly better statistical fit, in the absence of other clear criteria to differentiate between parametric models. Generalised gamma was then explored via scenario analysis.

While the exponential model also produced theoretically plausible extrapolations when compared to the non-TI curves for the Hb <12 g/dL base case population and ITT population TI OS curves, this model was considered less appropriate given its relatively poor visual fit to the observed data.

B.2.1.2 Survival extrapolation for Non-TI patients

AIC and BIC statistics are shown in Table 13 for each pure momelotinib arm parametric model for the revised base-case Hb <12 g/dL population according to the alternative transfusion health state definitions for patients who were non-TI at 24 weeks. The exponential model produced the best statistical fit with the lowest AIC and BIC.

Table 13. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	6	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

AIC and BIC relative fit classifications for the revised base-case Hb <12 g/dL population TI models are shown in Table 14. Compared to the exponential model, all models produced good relative fits based on AIC (<4-point difference) and reasonable relative statistical fits according to BIC (<10-point difference).

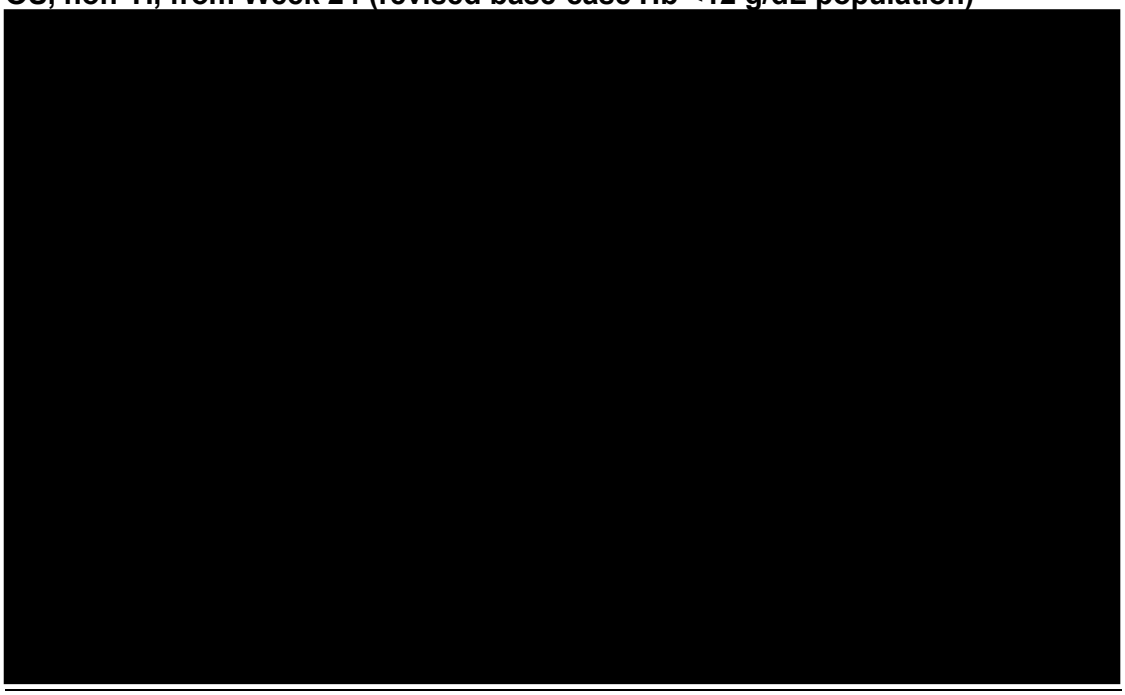
Table 14. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	-	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 5 and Table 15 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Weibull) and [redacted] (Gompertz) at 5 years, and [redacted] (Weibull) to [redacted] (Gompertz) at 10 years, across parametric models.

Figure 5. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)



Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 15. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential				
Weibull				
Gompertz				
Log-logistic				
Log-normal				
Generalised gamma				

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In line with the statistical fit results, all parametric models appeared to produce reasonable visual fits to the KM curve.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have greater OS than patients who are TR or TD (i.e., non-TI), and that they would expect few patients in the TD health state to be alive after 10 years.(32) In addition, clinical experts noted that patients who are TI would have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations between TI and TR/TD patients.

While not explicit in terms of specific survival expectations at 10 years for TI and non-TI groups, this suggested that the exponential and Weibull models produced more clinically plausible extrapolations for the revised base-case Hb <12 g/dL

population non-TI cohorts (assuming similar or slightly lower survival expectations compared to the ITT population) than other parametric models. The remaining parametric models (Gompertz, log-logistic, log-normal, generalised gamma) each produce 10-year survival estimates ([redacted] to [redacted]) greater than all parametric models for the Hb <12 g/dL TI group ([redacted] to [redacted]).

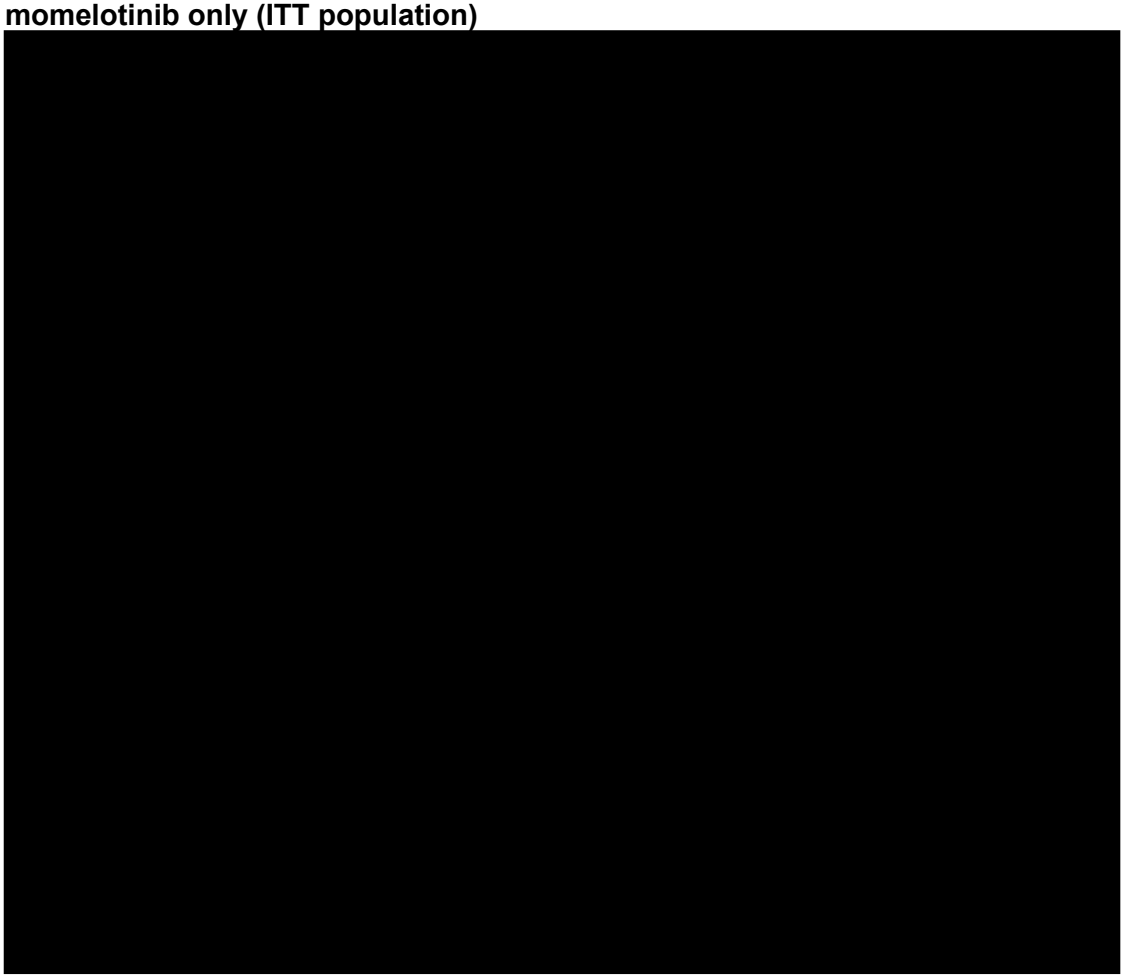
Between the exponential and Weibull models, the Weibull model was considered more clinically plausible as it remained consistently below two of three of the more plausible TI OS extrapolations (log-normal and generalized gamma; crosses log-logistic at 232 weeks), while the exponential model crossed over with all three of the more plausible TI OS models (log-logistic at 224 weeks, log-normal at 328 weeks, generalised gamma at 308 weeks). Therefore, the Weibull model was applied in the base case analysis.

B.2.2 Survival – ITT population

Overall survival data are presented below for the SIMPLIFY-2 ITT population which was used to help validate parametric model selection for both population groups considered in the appraisal. ITT population curves remain unchanged compared to those presented in the original submission regardless of the health state definition chose, but the original review of these curves is provided below for completeness with some updated discussion in regards to comparisons to other population subgroups.

TI and non-TI OS KM curves and associated numbers at risk for the ITT population curves are presented in Figure 6.

Figure 6. TI and non-TI OS KM curves from Week 24 and number at risk, SIMPLIFY-2 momelotinib only (ITT population)



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meir; OS = overall survival; TI = transfusion independent

Prior to the fitting of parametric models, a log-cumulative hazard plot and Schoenfeld residuals plot were produced to assess whether the PH assumption may hold (Figure 7 and Figure 8, respectively).

Figure 7. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (ITT population)

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

Figure 8. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (ITT population)

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

As the log-cumulative hazard plots for TI and non-TI cohorts appear to converge over time, and given the p value (<0.05) and fitted residuals line (non-parallel to 0) from the Schoenfeld residuals plot, the PH assumption was assumed to be

inappropriate. As such, independent parametric fits were considered more appropriate for TI and non-TI cohorts for the ITT population.

B.2.2.1 Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 16 for each pure momelotinib arm parametric model for the ITT population, for those who are transfusion independent (TI). The log-normal model produced the best statistical fit with the lowest AIC and BIC.

Table 16. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (ITT population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	6	[redacted]	4
Weibull	[redacted]	3	[redacted]	3
Gompertz	[redacted]	5	[redacted]	6
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	1	[redacted]	1
Generalised gamma	[redacted]	4	[redacted]	5

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

AIC and BIC relative fit classifications for the ITT TI models are shown below in Table 17. Compared to the log-normal model, all models produced good relative fits based on AIC (<4 point difference) except the exponential model which provided a reasonable relative statistical fit (4-7 point difference). All models were within 10 BIC points of the log-normal, indicating a reasonable relative statistical fit according to BIC.

Table 17. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (ITT population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	-	[redacted]	-
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ITT = intention-to-treat; OS = overall survival; TI = transfusion independent

Figure 9 and Table 18 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted]% (Gompertz) to [redacted]% (exponential) at 5 years and [redacted]% (Gompertz) to [redacted]% (exponential) at 10 years across parametric models.

Figure 9. Kaplan-Meier and parametric distributions for momelotinib SIMPLIFY-2 OS, TI, from Week 24 (ITT population)

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

Table 18. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (ITT population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

Similar to the statistical fit results, most models produced reasonably accurate visual fits to the KM curve, excluding exponential which substantially underpredicted most of the first half of the KM curve. All models produced relatively inconclusive fits to the tail of the KM curve, given the elongated flat section at the tail where there were relatively low numbers of patients at risk.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have an greater OS compared to patients who are TR or TD (i.e. non-TI).(127) As both Weibull and Gompertz models for the ITT TI cohort produced 10-year survival estimates lower than all ITT non-TI parametric models, these extrapolations were considered clinically implausible.

In addition, clinicians indicated that while they would expect hardly any patients in the TD health state to be alive after 10 years, they would expect some TI patients to be alive. While not fully conclusive in terms of a specific proportion of individuals

alive at 10 years, this suggested that the exponential and Weibull models produced the more clinically plausible extrapolations for the ITT non-TI cohort, and further indicated that the Weibull and Gompertz models were implausible for the ITT TI cohort. Assuming that the exponential and Weibull models are more appropriate for the ITT non-TI cohort, this therefore suggests that the remaining ITT TI parametric models (exponential, log-logistic, log-normal, generalised gamma) all produced reasonable long-term OS predictions in relation to available clinical expert feedback.

Overall, log-logistic, log-normal and generalised gamma were all considered reasonable survival model candidates for the ITT population TI group with similar statistical and visual fits to the observed data and plausible long-term extrapolations in relation to clinical expert feedback and the more plausible TI OS extrapolations for other subgroups. The log-normal model was considered the best overall candidate on the basis of small improvements in statistical fit compared to the log-logistic and generalised gamma models

While the exponential also produced a clinically plausible long-term extrapolation, it produced a relatively poor visual fit to the observed KM data, and only a "reasonable" relative statistic fit for AIC based on modified Burnham/Anderson criteria.

B.2.2.2 Survival extrapolation for Non-TI patients

AIC and BIC statistics are shown in Table 19 for each pure momelotinib arm parametric model for the ITT population for patients who were non-TI at 24 weeks. The exponential model produced the best statistical fit with the lowest AIC and BIC.

Table 19. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (ITT population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	6	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

AIC and BIC relative fit classifications for the ITT population non-TI models are shown in Table 20. Compared to the exponential model, all models produced good

relative fits based on AIC (<4-point difference) and reasonable relative statistical fits according to BIC (<10-point difference).

Table 20. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (ITT population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	-	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 10Figure 5 and Table 21Table 15 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Weibull) and [redacted] (log-normal) at 5 years, and [redacted] (Weibull) to [redacted] (log-normal) at 10 years, across parametric models.

Figure 10. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (ITT population)

[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 21. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (ITT population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In line with the statistical fit results, all parametric models appeared to produce reasonable visual fits to the KM curve.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have greater OS than patients who are TR or TD (i.e., non-TI), and that they would expect few patients in the TD health state to be alive after 10 years.(32) In addition, clinical experts noted that patients who are TI would have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations between TI and TR/TD patients.

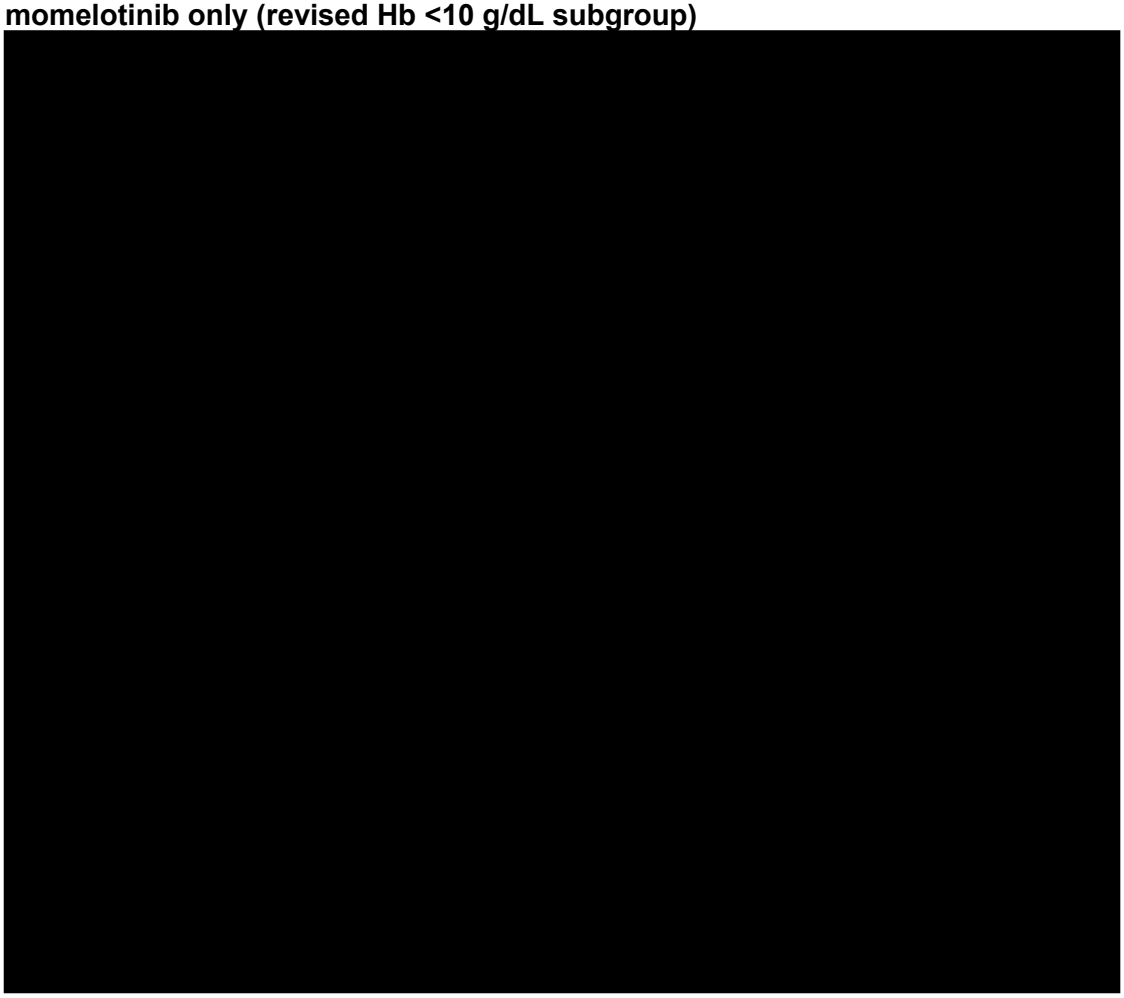
While not explicit in terms of specific survival expectations at 10 years for TI and non-TI groups, this suggested that the exponential and Weibull models produced more clinically plausible extrapolations for the ITT population non-TI cohort than other parametric models, with the remaining parametric models (Gompertz, log-logistic, log-normal, generalised gamma) all producing 10-year survival estimates ([redacted] to [redacted]) similar to or potentially greater than the most plausible parametric models (log-logistic, log-normal, generalised gamma) for the ITT TI group ([redacted] to [redacted]).

Based on the criteria above, the exponential model was considered the best overall parametric model fit for the ITT population, with a marginal improvement over the Weibull model in terms of statistical fit (lower AIC/BIC).

B.2.3 Survival – revised Hb <10 g/dL subgroup population

TI and non-TI OS KM curves and associated numbers at risk for the Hb <10 g/dL population based on the alternative transfusion dependence health state definitions are presented in Figure 11.

Figure 11. TI and non-TI OS KM curves from week 24 and number at risk, SIMPLIFY-2, momelotinib only (revised Hb <10 g/dL subgroup)



Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival; TI = transfusion independent

Prior to the fitting of parametric models for the intermediate-2/high risk (int-2/HR) and Hb <10 g/dL subgroup, log-cumulative hazard and Schoenfeld residual plots were generated to assess whether the PH assumption may hold (Figure 12 and Figure 13, respectively).

Figure 12. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (revised Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival; TI = transfusion independent

Figure 13. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival; TI = transfusion independent

As the log-cumulative hazard plots for TI and non-TI cohorts appear to converge over time and cross towards the end of follow-up, and given the p value (<0.05) and

fitted residuals line (non-parallel to 0) from the Schoenfeld residuals plot, the PH assumption was assumed to be inappropriate. Therefore, independent parametric fits were also explored for TI and non-TI cohorts for the int-2/HR and Hb <10 g/dL subgroup population applying alternative health state definitions.

B.2.3.1 Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 22 for each pure momelotinib arm parametric model for the int-2/HR and Hb <10 g/dL subgroup, for those who are TI. The log-logistic model produced the best statistical fit with the lowest AIC and BIC.

Table 22. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (Hb <10 g/dL subgroup)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	2	[redacted]	2
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	5	[redacted]	5

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

AIC and BIC relative fit classifications for the int-2/HR and Hb <10 g/dL TI models are shown below in Table 23. Compared to the log-logistic model, all models produced good relative fits based on AIC (<4-point difference) excluding the exponential model which provided a reasonable relative statistical fit (4-7 point difference). All models were within 10 BIC points of the log-logistic.

Table 23. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (Hb <10 g/dL subgroup)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	-	[redacted]	-
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Figure 14 and Table 24 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted]% (Gompertz) to [redacted]% (exponential) at 5 years and [redacted]% (Weibull and Gompertz) to [redacted]% (exponential) at 10 years across the different parametric models.

Figure 14. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, TI, from Week 24 (Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Table 24. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (Hb <10 g/dL subgroup)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

In line with the statistical fit results and similar to the ITT population results, most models produced reasonable visual fits to the KM curve excluding the exponential model, which substantially underestimated the KM curve up to approximately two and a half years before potentially overpredicting the tail.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have an greater OS compared to patients who are TR or TD (i.e. non-TI), and that they would expect hardly any patients in the TD health state to be alive after 10 years.(127) In addition, clinical experts noted that patients who are TI would certainly have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations among TI and TR or TD patients.

While these comments were provided by the clinical experts in relation to survival expectations for the ITT population rather than the int-2/HR and Hb <10 g/dL population who are expected to have a worse prognosis (and therefore lower survival expectations), it was assumed that TI patients at 24 weeks would expect to have some increase in long-term survival over non-TI patients also in the int-2/HR and Hb <10 g/dL population subgroup, and that the survival over time in the int-2/HR and Hb <10 g/dL subgroup TI cohort would be less than or equal than the preferred int-2/HR and Hb <12 g/dL population TI parametric model (log-normal).

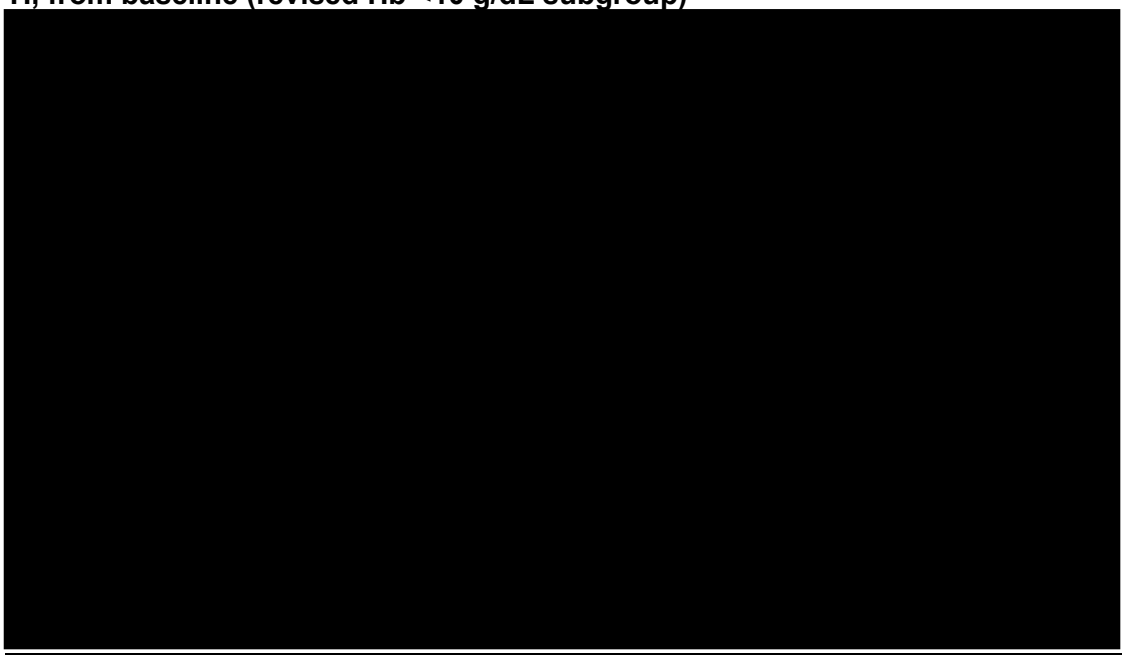
The exponential model was therefore excluded from consideration for the int-2/HR and Hb <10 g/dL population TI cohort given that it produced a higher long-term survival at 10 years ([redacted]%) than the preferred log-normal model for the int-2/HR and Hb <12 g/dL population TI cohort ([redacted]%).

However, all other TI parametric models for the int-2/HR and Hb <10 g/dL population crossed over with the non-TI parametric models for the int-2/HR and Hb <10 g/dL population, including the preferred Weibull model which was the most pessimistic extrapolation for the non-TI cohort. The Weibull, Gompertz and generalised gamma TI models produced lower OS than the Weibull non-TI model at approximately 156, 160 and 152 weeks respectively, and remained lower than the Weibull non-TI model for the full duration of the model time horizon. The log-logistic and log-normal TI models both produced lower OS than the Weibull non-TI model at approximately 152 weeks, before crossing over with the Weibull non-TI model models again and producing higher OS from approximately 516 and 560 weeks, respectively.

In order to prevent crossing of the TI and non-TI curves, which appeared implausible in relation to clinical expert feedback, mechanics were included in the model to set

per cycle mortality probabilities for the TI equal to non-TI per cycle mortality probabilities from a user-specified time point or cap the TI OS curve with the non-TI OS curve. Weibull, Gompertz and generalised gamma models were excluded from consideration given their particularly pessimistic long-term extrapolations and sharper crossings with the Weibull non-TI model. Among the log-logistic and log-normal models, which both produced more plausible and optimistic extrapolations, the log-logistic TI model was preferred on the basis of slightly improved statistical fit to the observed data and given its shorter duration of crossover with the non-TI Weibull model compared to the TI log-normal model. The log-logistic TI OS curve capped with the Weibull non-TI OS curve at the point of crossing was considered the most suitable approach to modelling TI OS for the revised Hb <10 g/dL subgroup. Final revised OS curves, appended to the OS KM curves from SIMPLIFY-2 applied to both treatment arms in the first 24 weeks, are shown in Figure 15.

Figure 15. Final revised OS curves for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from baseline (revised Hb <10 g/dL subgroup)



Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

B.2.3.2 Survival extrapolation for Non-TI patients

AIC and BIC statistics are shown in Table 25 for each pure momelotinib arm parametric model for the int-2/HR and Hb <10 g/dL subgroup, for those who are non-TI. The log-normal model produced the best statistical fit according to AIC, while the exponential model produced the best statistical fit according to BIC.

Table 25. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (Hb <10 g/dL subgroup)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	3	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	6	[redacted]	6
Log-logistic	[redacted]	4	[redacted]	3
Log-normal	[redacted]	1	[redacted]	2
Generalised gamma	[redacted]	2	[redacted]	4

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

AIC and BIC relative fit classifications for the int-2/HR and Hb <10 g/dL non-TI models are shown below in Table 26. In terms of AIC, all other models produced good relative fits (<4 AIC point difference) compared to the log-normal. All alternative models were reasonable relative fits according to BIC compared to the exponential.

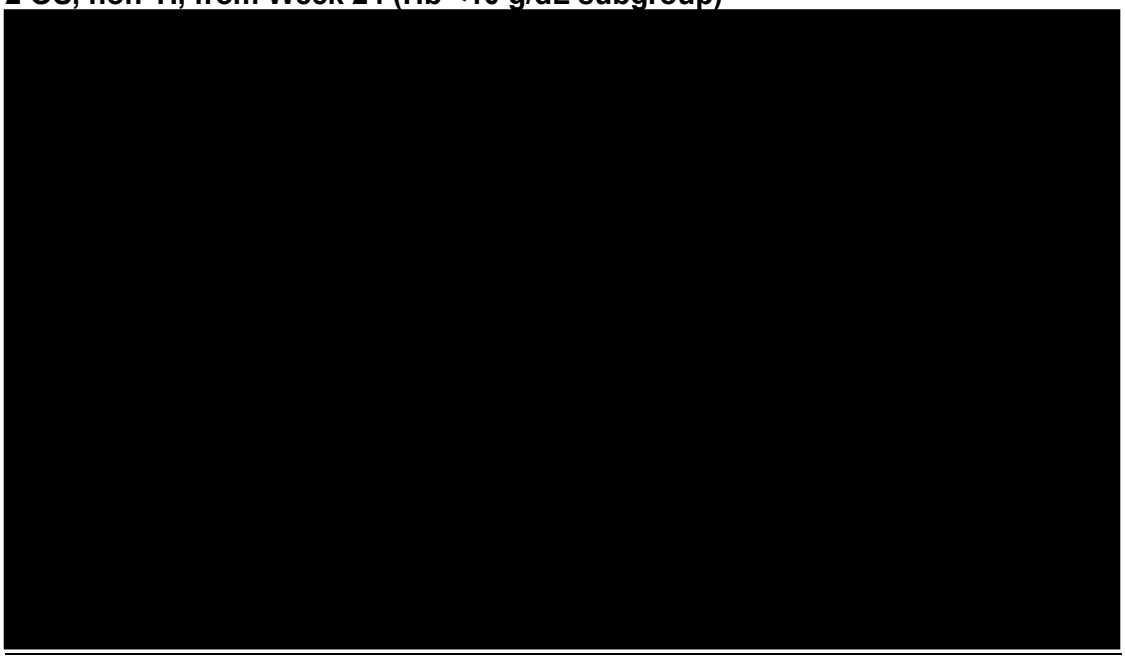
Table 26. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (Hb <10 g/dL subgroup)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Good	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	-	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Figure 16 and Table 27 show survival estimates for each distribution over time up to 10 years for the int-2/HR and Hb <10 g/dL non-TI cohort. Survival estimates ranged from [redacted]% (Weibull) to [redacted]% (generalised gamma) at 5 years and [redacted]% (Weibull) to [redacted]% (generalised gamma) at 10 years across the different parametric models.

Figure 16. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (Hb <10 g/dL subgroup)



Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Table 27. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (Hb <10 g/dL subgroup)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

While the generalized gamma model generated the best statistical fit to the data, the visual fit was implausible and likely a result of the model parameters failing to properly converge, and as such was excluded from consideration. Exponential, Weibull and Gompertz models slightly underpredicted the KM curve for the first 20 weeks and slightly overpredicted the KM curve between approximately 50 and 110 weeks, before underpredicting the tail. Log-logistic and log-normal models both produced fairly good visual fits to the majority of the KM curves, although appeared to more substantially underpredict the tail compared to the other models. However, interpretations of fit to the tail should be interpreted with caution given the elongated flat sections at the end of the KM curve where there are few patients at risk.

Given clinical expert feedback that they would expect hardly any patients in the TD health state to be alive after 10 years for the ITT population, and that the int-2/HR and Hb <10 g/dL is expected to have worse survival outcomes than the ITT and int-

2/HR and Hb <12 g/dL populations(127), the Weibull model was preferred for the revised Hb <10 g/dL subgroup given that all other non-TI parametric models for the Hb <10 g/dL population produced higher long-term survival than the preferred non-TI model (Weibull) for the revised base-case Hb <12 g/dL population.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Results Addendum

September 2023

File name	Version	Contains confidential information	Date
ID6141 momelotinib results addendum.docx	V1.0	Yes	22/9/2023

1. Description of error identified

Following submission of the original company submission (CS), GSK identified a minor error with the Kaplan-Meier (KM) survival curves uses in the original base-case cost-effectiveness modelling approach. The impact of this error is to slightly increase the survival estimates for both intervention and comparator arms of the modelling results. Overall, however, it does not alter the conclusion that momelotinib is highly likely to be both cost-saving and health-enhancing compared to BAT in a JAKi-experienced population.

The error is specifically that patients with intermediate-1 risk MF were incorrectly included in the KM curves used to derive transfusion independent (TI) and non-TI overall survival (OS) extrapolations after 24 weeks in the cost-effectiveness model. These patients were included within the momelotinib trial program but due to reimbursement restrictions in England and Wales, a JAKi-experienced population would not include this lower risk subgroup. Consequently, we regard this as an error, and as such the following addendum provides updated company base-case results with revised OS extrapolations.

As a result of removing intermediate-1 risk patients from the OS curves described in Section 2 and in relevant appendices, predicted total costs, life years and QALYs for both comparators are now lower than in the original submission (for example, total discounted life years of 3.207 and 3.077 compared to 3.819 and 3.355 for momelotinib and BAT, respectively). Momelotinib is still associated with an incremental QALY gain of 0.145, a reduction from 0.346 QALYs in the original CS. The cost savings in the updated analyses at list and PAS price [redacted] are of a similar magnitude to what was presented in the original CS, [redacted]. The cost-effectiveness results are consistent with the original CS; momelotinib dominates BAT with a Net Monetary Benefit (NMB) of [redacted] at a willingness-to-pay threshold of £20,000 per QALY. This represents a small NMB reduction from what was presented in the original CS, [redacted], at list and PAS price respectively. A

comparable trend is observed at a willingness-to-pay threshold of £30,000 per QALY.

The results of the revised scenario analyses are consistent with the original CS, with momelotinib continuing to dominate BAT in all scenarios when the PAS offering is considered. Similarly, probabilistic cost-effectiveness results continue to be consistent with deterministic. As such, and consistent with the original CS, the revised economic analysis supports the conclusion that use of momelotinib of a JAKi-experienced population would represent good value-for-money to the NHS.

2. Revised TI and non-TI OS extrapolations

Survival – revised base-case Hb <12 g/dL population

TI and non-TI OS KM curves and associated number at risk for the revised base-case intermediate-2 or high-risk (int-2/HR) and Hb <12 g/dL population are presented in Figure 1.

Figure 1. TI and non-TI OS KM curves from Week 24 and number at risk, SIMPLIFY-2 momelotinib only (revised base-case Hb <12 g/dL population)

Abbreviations: CI = confidence interval; Hb = haemoglobin; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; TI = transfusion-independent

Prior to the fitting of parametric models based on alternative transfusion status health state definitions for the revised base-case Hb <12 g/dL population, log-cumulative hazard plot and Schoenfeld residual plots were generated to assess whether the PH assumption holds (Figure 2 and Figure 3, respectively).

Figure 2. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 3. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Given that the log-cumulative hazard plots for TI and non-TI cohorts are non-parallel, the p-value from the Schoenfeld residuals test (<0.05) suggests a PH assumption is not plausible, and the fitted residuals line on the Schoenfeld residuals plot is clearly non-parallel to the 0 line, the PH assumption was assumed to be unsuitable, with independent parametric fits explored.

Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 1 for each pure momelotinib arm parametric model for the revised base-case Hb <12 g/dL population, for those who are TI at Week 24. The log-logistic model produced the best statistical fit with the lowest AIC and BIC.

Table 1. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	3	[redacted]	3
Gompertz	[redacted]	5	[redacted]	4
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	2	[redacted]	2
Generalised gamma	[redacted]	4	[redacted]	5

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independence

AIC and BIC relative fit classifications for the revised base-case TI models are shown below in Table 2. All other parametric models were within 4 AIC points and 10 BIC points of the log-logistic, with the exception of the exponential model with a different of 4-7 AIC points indicating a reasonable instead of good relative statistical fit.

Table 2. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	-	[redacted]	-
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independence

Figure 4 and Table 3 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Gompertz) to [redacted] (exponential) at 5 years and [redacted] (Gompertz) to [redacted] (exponential) at 10 years across parametric models.

Figure 4. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, TI, from Week 24 (revised base-case Hb<12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 3. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (revised base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In terms of visual fit to the observed data, most curves had a reasonable fit the KM curve except for the exponential model which appeared to underpredict the KM curve for the first 2 years.

Furthermore, additional considerations in the selection of the most appropriate curve for those who were TI at 24 weeks were:

1. Internal consistency:

    a) TI patients are expected to have greater or comparable long-term survival to non-TI patients. Therefore, Weibull and Gompertz models are not considered plausible, since they produced 10-year survival

estimates ([redacted] and [redacted], respectively) which were lower than all parametric models for the non-TI parametric extrapolations (Table 6). In addition, the log-logistic model was excluded from consideration as it crossed the most plausible non-TI parametric model (Weibull) at 232 weeks in the model.

b) It is assumed that landmark survival of the revised base-case Hb <12 g/dL population at 5 and 10 years is expected to be less than or equal to the ITT group (see Appendix 1) and greater than the corresponding revised Hb <10 g/dL population (see Appendix 2). The log-normal ([redacted]) and generalised gamma ([redacted]) Hb <12 g/dL subgroup TI OS models may be suitable on the basis that they produce 10-year survival estimates lower than all of the more plausible TI OS candidates for the ITT population ([redacted] [log-logistic] to [redacted] [exponential]), while the Hb <12 g/dL exponential model produced a slightly higher 10-year survival estimate ([redacted]) than the ITT population log-logistic model ([redacted]) but lower than other plausible candidate models ([redacted] to [redacted]). In conclusion, comparing against ITT and int-2/high risk and Hb<10 TI curves indicate the log-normal and generalised gamma may be suitable model choices, although exponential could not be excluded.

2. Clinical expectation for TI survival:

a) At a clinical-HEOR advisory board, clinicians were shown two blinded parametric survival curves reporting estimated survival based on transfusion status for the full SIMPLIFY-2 population from Week 24. Parametric model 1 reported 5- and 10-year TI survival to be [redacted] and [redacted], respectively, while parametric model 2 reported 5- and 10-year survival to be [redacted] and [redacted], respectively. Clinicians choose parametric model 1 as a reasonable model choice while the alternative model was not considered likely given that more patients are expected to be alive 10 years. While this advice related to the ITT population

rather than the revised base-case Hb <12 g/dL population, survival estimates are expected to be less than or equal to the ITT population for this subgroup.

b) Given that the revised base-case Hb <12 g/dL subgroup, which excludes intermediate-1 risk patients, are anticipated to have survival less than or equal lower to the ITT population, this further indicates the that the exponential, log-normal and generalised gamma models all produce plausible long-term extrapolations in relation to ITT population expectations.

The log-normal and generalised gamma models both produced relatively good statistical and visual fits to the observed KM data, and 10-year survival estimates which were not contradicted by TI or non-TI extrapolations for other population groups. The log-normal model was selected based on slightly better statistical fit, in the absence of other clear criteria to differentiate between parametric models. Generalised gamma was then explored via scenario analysis.

While the exponential model also produced theoretically plausible extrapolations when compared to the non-TI curves for the Hb <12 g/dL base case population and ITT population TI OS curves, this model was considered less appropriate given its relatively poor visual fit to the observed data.

Survival extrapolation for non-TI patients

AIC and BIC statistics are shown in Table 4 for each pure momelotinib arm parametric model for the revised base-case Hb <12 g/dL population who were non-TI at 24 weeks. The exponential model produced the best statistical fit with the lowest AIC and BIC.

Table 4. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	6	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

AIC and BIC relative fit classifications for the revised base-case Hb <12 g/dL population non-TI models are shown in Table 5. Compared to the exponential model, all models produced good relative fits based on AIC (<4-point difference) and reasonable relative statistical fits according to BIC (<10-point difference).

Table 5. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	-	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 5 and Table 6 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Weibull) and [redacted] (Gompertz) at 5 years, and [redacted] (Weibull) to [redacted] (Gompertz) at 10 years, across parametric models.

Figure 5. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 6. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (revised base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential				
Weibull				
Gompertz				
Log-logistic				
Log-normal				
Generalised gamma				

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In line with the statistical fit results, all parametric models appeared to produce reasonable visual fits to the KM curve.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have greater OS than patients who are transfusion requiring (TR) or transfusion dependent (TD) (i.e., non-TI), and that they would expect few patients in the TD health state to be alive after 10 years.(32) In addition, clinical experts noted that patients who are TI would have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations between TI and TR/TD patients.

While not explicit in terms of specific survival expectations at 10 years for TI and non-TI groups, this suggested that the exponential and Weibull models produced more clinically plausible extrapolations for the revised base-case Hb <12 g/dL population non-TI cohorts (assuming similar or slightly lower survival expectations compared to the ITT population) than other parametric models. The remaining parametric models (Gompertz, log-logistic, log-normal, 13eneralized gamma) each produce 10-year survival estimates ([redacted] to [redacted]) greater than all parametric models for the Hb <12 g/dL TI group ([redacted] to [redacted]).

Between the exponential and Weibull models, the Weibull model was considered more clinically plausible as it remained consistently below two of three of the more plausible TI OS extrapolations (log-normal and generalized gamma; crosses log-logistic at 232 weeks), while the exponential model crossed over with all three of the more plausible TI OS models (log-logistic at 224 weeks, log-normal at 328 weeks, generalized gamma at 308 weeks). Therefore, the Weibull model was applied in the base case analysis.

3. Revised company base case results (<12 g/dL)

Base-case results with revised OS curves

Revised base-case incremental cost-effectiveness analysis results

Total costs, Lys, QALYs, and incremental cost per QALY gained for momelotinib versus BAT for the JAKi-experienced model population are presented in Table 7. Momelotinib decreased total costs against BAT by [redacted]; it also produced an increase in both total life years (0.130) and QALYs (0.145). BAT was therefore dominated by momelotinib.

The incremental net monetary benefit was [redacted] and [redacted] at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as shown in Table 8.

Results based on applying a [redacted] are provided in Table 9. Incremental total cost savings for momelotinib were reduced further to [redacted] and momelotinib therefore remained dominant over BAT as in the list price results. The incremental net monetary benefit values increased to [redacted] and [redacted] for £20,000 and £30,000 per QALY thresholds (Table 10), respectively, after application of the PAS discount.

Table 7. Base-case results for momelotinib vs BAT in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.077	1.898	-	-	-	-	-
Momelotinib	[redacted]	3.207	2.043	[redacted]	0.130	0.145	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; QALY = quality-adjusted life year

Table 8. Net monetary benefit in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.898	-	-	-	-
Momelotinib	[redacted]	2.043	[redacted]	0.145	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; QALY = quality-adjusted life year

Table 9. Base-case results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	3.077	1.898	-	-	-	-	-
Momelotinib	[redacted]	3.207	2.043	[redacted]	0.130	0.145	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 10. Net monetary benefit in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.898	-	-	-	-
Momelotinib	[redacted]	2.043	[redacted]	0.145	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; PAS = patient access scheme; QALY = quality-adjusted life year

Exploring uncertainty – revised company base-case

Probabilistic sensitivity analysis

The probabilistic mean values for total costs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT generated through the PSA are presented in Table 11. Momelotinib generated a probabilistic average of 0.147 incremental QALYs gained and [redacted] lower incremental costs over a lifetime horizon compared with BAT, resulting in momelotinib dominating BAT (with higher total mean QALYs and lower total mean costs). Probabilistic mean incremental QALYs were slightly higher than the deterministic model incremental QALYs (0.197 vs 0.145) with slightly smaller probabilistic mean total cost savings compared to the deterministic based case (lower total costs for momelotinib of [redacted] vs [redacted]).

The corresponding incremental cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are presented in Figure 6 and Figure 7, respectively. At a willingness to pay (WTP) threshold of £0, £20,000 and £30,000 per QALY, momelotinib has a [redacted].

Table 11. PSA results for momelotinib vs BAT in JAKi-experienced patients [List price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean Incremental Costs (£) versus BAT	Mean Incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	1.841	-	-	
Momelotinib	[redacted]	2.038	[redacted]	0.197	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 6. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years.

Figure 7. Momelotinib versus BAT CEAC – base-case JAKi-experienced patients [List price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor

PSA results following application of the PAS price discount are presented in Table 12. Probabilistic mean incremental total QALYs for momelotinib were 0.187 and probabilistic mean incremental total costs were reduced with momelotinib by [redacted]. The corresponding ICEP and CEAC are presented in Figure 8 and Figure 9, respectively. [redacted]

Table 12. PSA results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Intervention	Mean Total costs (£)	Mean Total QALYs	Mean incremental costs (£) versus BAT	Mean incremental QALYs versus BAT	PSA ICER versus baseline (£/QALY)
BAT	[redacted]	1.831	-	-	
Momelotinib	[redacted]	2.018	[redacted]	0.187	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year.

Figure 8. Momelotinib versus BAT incremental cost-effectiveness plane – base-case JAKi-experienced patients [PAS price]

Abbreviations: BAT = best available therapy; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 9. Momelotinib versus BAT CEAC – base-case JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; CEAC = cost-effectiveness acceptability curve; JAKi = Janus kinase inhibitor; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Deterministic sensitivity analysis

The parameters in the model with single input values were varied individually in deterministic sensitivity analysis (DSA). Upper and lower values were based on the confidence intervals or estimated confidence intervals based on other uncertainty data. In the absence of appropriate uncertainty data to inform the confidence intervals, the upper and lower values for the DSA were derived from assuming the SE values to be 10% of the mean base-case value, as for the PSA. Each parameter was set to the upper and lower bounds to test the impact of each individual parameter on the results.

A DSA tornado diagram presenting the top 20 most sensitive parameters for the momelotinib versus BAT cost-effectiveness results for the JAKi-experienced model population in descending order of sensitivity is shown in Figure 10. As the base-case results indicated that momelotinib was dominant over BAT, results are presented in terms of NMB at a WTP threshold of £30,000 per QALY.

The key drivers of cost-effectiveness were the non-TI OS parameters, momelotinib time-to-treatment-discontinuation-or-death (TTDD) parameters and the overall proportion on ruxolitinib with the BAT comparator. Some slight sensitivity was also observed around the TD utility values, TI OS parameters, and proportion of BAT patients on a low 5mg dose of ruxolitinib, with all other inputs generating relatively small variations in the incremental NMB results.

The 10 most impactful set of tabulated results from the sensitivity analysis (in terms of NMB) are presented in Table 13. Across all parameter variations, only the upper bound variation of the non-TI OS Weibull model parameters and lower bound variation in momelotinib Gompertz TTDD model parameters resulted in incremental NMB values below £0 at a £30,000 per QALY threshold.

Figure 10. Base-case DSA tornado diagram for momelotinib vs BAT – JAKi-experienced model [List price]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; OS = overall survival; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 13. Tabulated DSA results (top 10) for momelotinib versus BAT – JAKi-experienced model [List price]

Variable	LB NMB value	UB NMB value	Difference
JAKi exp – MMB and BAT OS – TD, int2/HR &Hb<12	[redacted]	[redacted]	[redacted]
JAKi exp – MMB TTD – Overall cohort, int2/HR & Hb<12	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on RUX (%)	[redacted]	[redacted]	[redacted]
JAKi experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi exp – MMB and BAT OS – TI, int2/HR &Hb<12	[redacted]	[redacted]	[redacted]
JAKi experienced MMB utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of RUX on 5mg (%)	[redacted]	[redacted]	[redacted]
Mean RBC transfusion in unit per month – TD – Int2/HR Hb <12	[redacted]	[redacted]	[redacted]
RBCT resource use per cycle – JAKi-experienced – MMB – TD	[redacted]	[redacted]	[redacted]
Resource use cost – RBCT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; TD = transfusion-dependent; TI = transfusion-independent; TTD = time to treatment discontinuation; UB = upper bound

DSA results following application of the PAS discount are available in Figure 11 and Table 14. Similar results were observed as for the results without the PAS discount in terms of which parameters produced the most variation around the base-case incremental NMB estimate, albeit with incremental NMB values greater than [redacted] in all cases and therefore indicating momelotinib to be cost-effective against BAT for all parameter variations.

Figure 11. Base-case NMB tornado diagram – JAKi-experienced model [PAS price]

Abbreviations: BAT = best available therapy; Hb = haemoglobin; int = intermediate; JAKi = Janus kinase inhibitor; NMB = net monetary benefit; PAS = patient access scheme; RBC = red blood cell; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TR = transfusion-requiring; TTD = time to treatment discontinuation

Table 14. Tabulated DSA results (top 10) for momelotinib versus BAT (NMB) – JAKi-experienced model [PAS price]

Variable	LB value	UB value	Difference
JAKi exp – MMB and BAT OS – TD, int2/HR &Hb<12	[redacted]	[redacted]	[redacted]
BAT 2L overall proportion on RUX (%)	[redacted]	[redacted]	[redacted]
JAKi exp – MMB TTD – Overall cohort, int2/HR &Hb<12	[redacted]	[redacted]	[redacted]
JAKi experienced BAT utility: TD	[redacted]	[redacted]	[redacted]
JAKi exp – MMB and BAT OS – TI, int2/HR &Hb<12	[redacted]	[redacted]	[redacted]
JAKi experienced MMB utility: TD	[redacted]	[redacted]	[redacted]
BAT 2L proportion of RUX on 5mg (%)	[redacted]	[redacted]	[redacted]
Mean RBC transfusion in unit per month – TD – Int2/HR Hb <12	[redacted]	[redacted]	[redacted]
RBCT resource use per cycle – JAKi-experienced – MMB – TD	[redacted]	[redacted]	[redacted]
Resource use cost – RBCT	[redacted]	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; DSA = deterministic sensitivity analysis; Hb = haemoglobin; JAKi = Janus kinase inhibitor; LB = lower bound; NMB = net monetary benefit; OS = overall survival; PAS = patient 7discontinuation; UB = upper bound

Scenario analysis

Scenarios exploring alternative long-term extrapolations and data source of survival parameters, utilities and, along with shorter model time horizons and lower discount rates, are summarised in Table 15.

Scenario analysis results are most sensitive to a shorter time horizon (5-year) and use of subsequent ruxolitinib (following discontinuation of momelotinib) (scenarios 1 and 11), where they generated the greatest NMB decreases of [redacted] and [redacted] compared to BAT and momelotinib was no longer dominant over BAT for scenarios 1 and 11. The ICERs in these scenarios were [redacted] when using a shorter time horizon of 5 years and [redacted] per QALY when assuming 39% of patients on ruxolitinib after discontinuing momelotinib as a result of increasing the costs of subsequent treatment for momelotinib.

NMB is decreased by [redacted] when applying treatment specific transition probabilities. Applying a 10-year time horizon also decreases the NMB by [redacted]. NMB is increased by [redacted] when using a lower discount rate (1.5%) for both cost and health outcomes in the model. Cost assumptions associated with transfusion (applying KOL suggested RBCT unit data) increased the NMB by [redacted].

The incremental NMB results were also sensitive to variations in assumptions around transition probability extrapolations for determining transfusion health state distribution over time, with both costs and QALYs impacted as a result of increased resource use costs and lower health state utilities for TR and TD compared to TI. Applying a less conservative assumption of no health state movement after 24 weeks increased the NMB by [redacted] compared to the base-case analysis. Other transition probability scenarios had a more modest impact on the results, generating a reduction varying from [redacted] in the NMB.

As anticipated, given the numerically higher utility values observed for momelotinib-specific TI and TD health state utilities compared to BAT, application of treatment specific utilities instead of treatment independent utilities increased the cost-effectiveness of momelotinib compared to BAT, with an increase of [redacted] in the NMB.

Most of other scenario analyses had minimal impacts on the NMB values, with [redacted]% variation from the base-case NMB estimate.

Furthermore, results of a scenario whereby there is no survival benefit for momelotinib is presented in scenario 19. The assumption of equal survival for both treatment arms also had a moderate impact on the results. Assumption of equal survival regardless of transfusion status at 24 weeks reduced the incremental QALY gains for momelotinib to 0.065 from 0.145; however, incremental cost savings were also increased from [redacted] to [redacted], resulting in a [redacted]% higher NMB value compared to the base-case analysis.

Table 15. Scenario analysis results for momelotinib versus BAT – JAKi-experienced model [List price]

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
-	**Base-case**	[redacted]	0.145	[redacted]	N/A	Dominant
1	5-year time horizon	[redacted]	0.132	[redacted]	[redacted]	[redacted]
2	10-year time horizon	[redacted]	0.138	[redacted]	[redacted]	Dominant
3	Discount rate (cost and health outcomes) of	[redacted]	0.153	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
	1.5%					
4	TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.142	[redacted]	[redacted]	Dominant
5	TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.203	[redacted]	[redacted]	Dominant
6	TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.145	[redacted]	[redacted]	Dominant
7	TP extrapolation: Treatment specific transition probabilities	[redacted]	0.112	[redacted]	[redacted]	Dominant
8	TI OS: gen gamma	[redacted]	0.142	[redacted]	[redacted]	Dominant
9	Momelotinib TTDD: exponential	[redacted]	0.145	[redacted]	[redacted]	Dominant
10	Apply KOL RBC transfusion unit data	[redacted]	0.145	[redacted]	[redacted]	Dominant
11	Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.145	[redacted]	[redacted]	[redacted]
12	Exclude terminal care costs	[redacted]	0.145	[redacted]	[redacted]	Dominant
13	Treatment specific HSUVs	[redacted]	0.201	[redacted]	[redacted]	Dominant
14	Scenario 13 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.164	[redacted]	[redacted]	Dominant
15	Higher anaemia AE cost	[redacted]	0.145	[redacted]	[redacted]	Dominant
16	Alternative RBC transfusion unit costs (Agrawal 2006)	[redacted]	0.145	[redacted]	[redacted]	Dominant
17	Exclude ICT costs	[redacted]	0.145	[redacted]	[redacted]	Dominant
18	Reduce deferasirox (ICT) dose to 14 mg/kg/day	[redacted]	0.145	[redacted]	[redacted]	Dominant
19	Assume equal OS after 24 weeks using	[redacted]	0.065	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER (£/QALY)
	pooled SIMPLIFY-2 data†					

Abbreviations: AE = adverse event; BAT = best available therapy; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; JAKi = Janus kinase inhibitor; KOL = key opinion leader; N/A = not applicable; NMB = net monetary benefit; OS = overall survival; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TP = transition probability; TTDD = time to treatment discontinuation or death

†Pooled survival for MMB and BAT arms of SIMPLIFY-2 fitted to gompertz model. See Appendix 3 for details of model selection

Table 15 presents the scenario analysis including momelotinib PAS price. The directional impact on the NMB results was similar to the list price scenarios, albeit with the magnitude of the proportional change from the base-case NMB reduced as a result of lowering momelotinib drug acquisitions costs. Following application of the PAS discount, momelotinib dominated BAT across all scenarios.

Table 16. Scenario analysis results for momelotinib versus BAT – JAKi-experienced model [PAS price]

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER incremental (£/QALY)
-	**Base-case**	[redacted]	0.145	[redacted]	N/A	Dominant
1	5-year time horizon	[redacted]	0.132	[redacted]	[redacted]	Dominant
2	10-year time horizon	[redacted]	0.138	[redacted]	[redacted]	Dominant
3	Discount rate (cost and health outcomes) of 1.5%	[redacted]	0.153	[redacted]	[redacted]	Dominant
4	TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.142	[redacted]	[redacted]	Dominant
5	TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.203	[redacted]	[redacted]	Dominant
6	TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.145	[redacted]	[redacted]	Dominant
7	TP extrapolation: Treatment specific transition probabilities	[redacted]	0.112	[redacted]	[redacted]	Dominant
8	TI OS: gen gamma	[redacted]	0.142	[redacted]	[redacted]	Dominant
9	Momelotinib TTDD: exponential	[redacted]	0.145	[redacted]	[redacted]	Dominant
10	Apply KOL RBC transfusion unit data	[redacted]	0.145	[redacted]	[redacted]	Dominant

Scenario #	Scenario	Incremental costs (£)	Incremental QALYs	NMB (£) at £30,000	% change compared to base-case NMB	ICER incremental (£/QALY)
11	Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.145	[redacted]	[redacted]	Dominant
12	Exclude terminal care costs	[redacted]	0.145	[redacted]	[redacted]	Dominant
13	Treatment specific HSUVs	[redacted]	0.201	[redacted]	[redacted]	Dominant
14	Scenario 13 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.164	[redacted]	[redacted]	Dominant
15	Higher anaemia AE cost	[redacted]	0.145	[redacted]	[redacted]	Dominant
16	Alternative RBC transfusion unit costs (Agrawal 2006)	[redacted]	0.145	[redacted]	[redacted]	Dominant
17	Exclude ICT costs	[redacted]	0.145	[redacted]	[redacted]	Dominant
18	Reduce deferasirox (ICT) dose to 14 mg/kg/day	[redacted]	0.145	[redacted]	[redacted]	Dominant
19	Assume equal OS after 24 weeks using pooled SIMPLIFY-2 data†	[redacted]	0.065	[redacted]	[redacted]	Dominant

Abbreviations: AE = adverse event; BAT = best available therapy; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; JAKi = Janus kinase inhibitor; KOL = key opinion leader; N/A = not applicable; NMB = net monetary benefit; OS = overall survival; PAS = patient access scheme; QALY = quality-adjusted life year; RBC = red blood cell; TD = transfusion-dependent; TI = transfusion-independent; TP = transition probability; TTDD = time to treatment discontinuation or death
†Pooled survival for MMB and BAT arms of SIMPLIFY-2 fitted to gompertz model. See Appendix 3 for details of model selection

Subgroup analysis: revised company results for int-2/HR and <10 g/dL population

Total costs, LYs, QALYs, and incremental cost per QALY gained for momelotinib versus BAT for the JAKi-experienced model population are presented in Table 17. Momelotinib decreased total costs against BAT by [redacted]; it also produced an increase in both total life years (0.048) and QALYs (0.077). BAT was therefore dominated by momelotinib.

The incremental net monetary benefit was [redacted] and [redacted] at £20,000 and £30,000 per QALY willingness to pay thresholds, respectively, as shown in Table 18.

Results based on applying a PAS price discount of [redacted] are provided in Table 19. Incremental total cost savings for momelotinib were reduced further to [redacted] and

momelotinib therefore remained dominant over BAT as in the list price results. The incremental net monetary benefit values increased to [redacted] and [redacted] for £20,000 and £30,000 per QALY thresholds (Table 20), respectively, after application of the PAS discount.

Table 17. Base-case results for momelotinib vs BAT in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	2.791	1.723	-	-	-	-	-
Momelotinib	[redacted]	2.839	1.800	[redacted]	0.048	0.077	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; QALY = quality-adjusted life year

Table 18. Net monetary benefit in JAKi-experienced patients [List price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.723	-	-	-	-
Momelotinib	[redacted]	1.800	[redacted]	0.077	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; QALY = quality-adjusted life year

Table 19. Base-case results for momelotinib vs BAT in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BAT	[redacted]	2.791	1.723	-	-	-	-	-
Momelotinib	[redacted]	2.839	1.800	[redacted]	0.048	0.077	Dominant	Dominant

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Table 20. Net monetary benefit in JAKi-experienced patients [PAS price]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
BAT	[redacted]	1.723	-	-	-	-
Momelotinib	[redacted]	1.800	[redacted]	0.077	[redacted]	[redacted]

Abbreviations: BAT = best available therapy; ICER = incremental cost-effectiveness ratio; JAKi = Janus kinase inhibitor; LYG = life years gained; NMB = net monetary benefit; PAS = patient access scheme; QALY = quality-adjusted life year

Appendices

Appendix 1

Overall survival stratified by TI and non-TI from Week 24 (ITT population)

Overall survival data are presented below for the full SIMPLIFY-2 ITT population which was used to help validate parametric model selection for both population groups considered in the appraisal. ITT population curves remain unchanged compared to those presented in the original submission regardless of the health state definition chose, but the original review of these curves is provided below for completeness with some updated discussion with regards to comparisons to other population subgroups.

TI and non-TI OS KM curves and associated numbers at risk for the ITT population curves are presented in Figure 12.

Figure 12. TI and non-TI OS KM curves from Week 24 and number at risk, SIMPLIFY-2 momelotinib only (ITT population)

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meir; OS = overall survival; TI = transfusion independent

Prior to the fitting of parametric models, a log-cumulative hazard plot and Schoenfeld residuals plot were produced to assess whether the PH assumption may hold (Figure 13 and Figure 14, respectively).

Figure 13. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (ITT population)

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

Figure 14. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (ITT population)

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

As the log-cumulative hazard plots for TI and non-TI cohorts appear to converge over time, and given the p value (<0.05) and fitted residuals line (non-parallel to 0)

from the Schoenfeld residuals plot, the PH assumption was assumed to be inappropriate. As such, independent parametric fits were considered more appropriate for TI and non-TI cohorts for the ITT population.

Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 21 for each pure momelotinib arm parametric model for the ITT population, for those who are transfusion independent (TI). The log-normal model produced the best statistical fit with the lowest AIC and BIC.

Table 21. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (ITT population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	6	[redacted]	4
Weibull	[redacted]	3	[redacted]	3
Gompertz	[redacted]	5	[redacted]	6
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	1	[redacted]	1
Generalised gamma	[redacted]	4	[redacted]	5

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

AIC and BIC relative fit classifications for the ITT TI models are shown below in Table 22. Compared to the log-normal model, all models produced good relative fits based on AIC (<4 point difference) except the exponential model which provided a reasonable relative statistical fit (4-7 point difference). All models were within 10 BIC points of the log-normal, indicating a reasonable relative statistical fit according to BIC.

Table 22. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (ITT population)

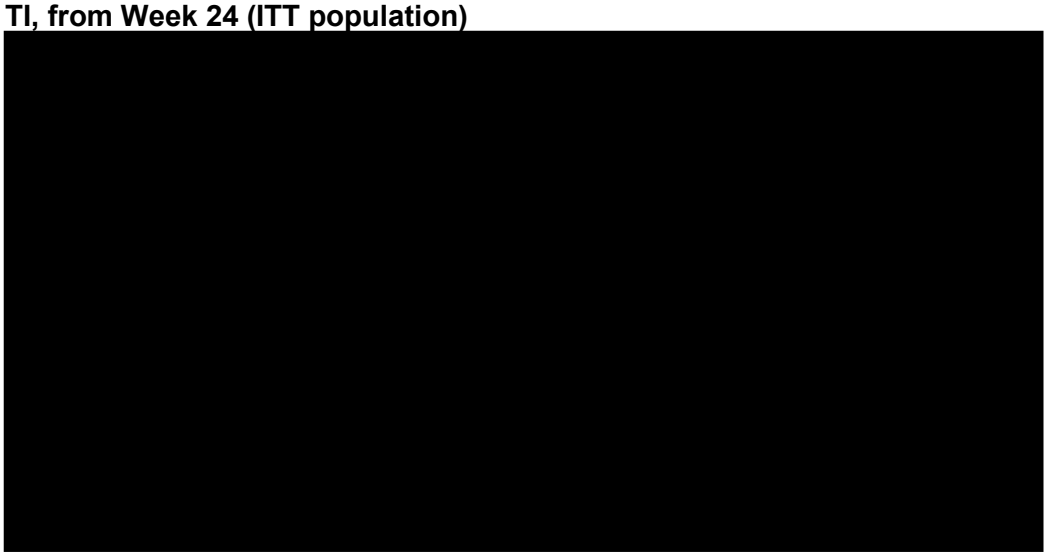
Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	-	[redacted]	-
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ITT = intention-to-treat; OS = overall survival; TI = transfusion independent

Figure 15 and Table 23 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted]% (Gompertz) to [redacted]%

(exponential) at 5 years and [redacted]% (Gompertz) to [redacted]% (exponential) at 10 years across parametric models.

Figure 15. Kaplan-Meier and parametric distributions for momelotinib SIMPLIFY-2 OS, TI, from Week 24 (ITT population)



Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

Table 23. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (ITT population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT = intent-to-treat; OS = overall survival; TI = transfusion independent

Similar to the statistical fit results, most models produced reasonably accurate visual fits to the KM curve, excluding exponential which substantially underpredicted most of the first half of the KM curve. All models produced relatively inconclusive fits to the tail of the KM curve, given the elongated flat section at the tail where there were relatively low numbers of patients at risk.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have an greater OS compared to patients who are TR or TD (i.e. non-TI).(127) As both Weibull and Gompertz models for the ITT TI cohort produced 10-year survival estimates lower than all ITT non-TI parametric models, these extrapolations were considered clinically implausible.

In addition, clinicians indicated that while they would expect hardly any patients in the TD health state to be alive after 10 years, they would expect some TI patients to be alive. While not fully conclusive in terms of a specific proportion of individuals alive at 10 years, this suggested that the exponential and Weibull models produced the more clinically plausible extrapolations for the ITT non-TI cohort, and further indicated that the Weibull and Gompertz models were implausible for the ITT TI cohort. Assuming that the exponential and Weibull models are more appropriate for the ITT non-TI cohort, this therefore suggests that the remaining ITT TI parametric models (exponential, log-logistic, log-normal, generalised gamma) all produced reasonable long-term OS predictions in relation to available clinical expert feedback.

Overall, log-logistic, log-normal and generalised gamma were all considered reasonable survival model candidates for the ITT population TI group with similar statistical and visual fits to the observed data and plausible long-term extrapolations in relation to clinical expert feedback and the more plausible TI OS extrapolations for other subgroups. The log-normal model was considered the best overall candidate on the basis of small improvements in statistical fit compared to the log-logistic and generalised gamma models

While the exponential also produced a clinically plausible long-term extrapolation, it produced a relatively poor visual fit to the observed KM data, and only a “reasonable” relative statistic fit for AIC based on modified Burnham/Anderson criteria.

Survival extrapolation for Non-TI patients

AIC and BIC statistics are shown in Table 24 for each pure momelotinib arm parametric model for the ITT population for patients who were non-TI at 24 weeks. The exponential model produced the best statistical fit with the lowest AIC and BIC.

Table 24. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (ITT population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	2	[redacted]	2
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	6	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

AIC and BIC relative fit classifications for the ITT population non-TI models are shown in Table 25. Compared to the exponential model, all models produced good relative fits based on AIC (<4-point difference) and reasonable relative statistical fits according to BIC (<10-point difference).

Table 25. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (ITT population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	-	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Figure 16, Figure 5 and Table 26, Table 6 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted] (Weibull) and [redacted] (log-normal) at 5 years, and [redacted] (Weibull) to [redacted] (log-normal) at 10 years, across parametric models.

Figure 16. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (ITT population)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

Table 26. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (ITT population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential				
Weibull				
Gompertz				
Log-logistic				
Log-normal				
Generalised gamma				

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion-independent

In line with the statistical fit results, all parametric models appeared to produce reasonable visual fits to the KM curve.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have greater OS than patients who are TR or TD (i.e., non-TI), and that they would expect few patients in the TD health state to be alive after 10 years.(32) In addition, clinical experts noted that patients who are TI would have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations between TI and TR/TD patients.

While not explicit in terms of specific survival expectations at 10 years for TI and non-TI groups, this suggested that the exponential and Weibull models produced more clinically plausible extrapolations for the ITT population non-TI cohort than

other parametric models, with the remaining parametric models (Gompertz, log-logistic, log-normal, generalised gamma) all producing 10-year survival estimates ([redacted] to [redacted]) similar to or potentially greater than the most plausible parametric models (log-logistic, log-normal, generalised gamma) for the ITT TI group ([redacted] to [redacted]).

Based on the criteria above, the exponential model was considered the best overall parametric model fit for the ITT population, with a marginal improvement over the Weibull model in terms of statistical fit (lower AIC/BIC).

Appendix 2

Overall survival stratified by TI and non-TI from Week 24 (Int-2/HR and Hb <10 g/dL subgroup population)

TI and non-TI OS KM curves and associated numbers at risk for the int-2/HR and Hb <10 g/dL population based on the alternative transfusion dependence health state definitions are presented in Figure 17.

Figure 17. TI and non-TI OS KM curves from week 24 and number at risk, SIMPLIFY-2, momelotinib only (revised Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival; TI = transfusion independent

Prior to the fitting of parametric models for the int-2/HR and Hb <10 g/dL subgroup, log-cumulative hazard and Schoenfeld residual plots were generated to assess whether the PH assumption may hold (Figure 18 and Figure 19, respectively).

Figure 18. Log-cumulative hazard plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival; TI = transfusion independent

Figure 19. Schoenfeld residuals plot for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival; TI = transfusion independent

As the log-cumulative hazard plots for TI and non-TI cohorts appear to converge over time and cross towards the end of follow-up, and given the p value (<0.05) and fitted residuals line (non-parallel to 0) from the Schoenfeld residuals plot, the PH assumption was assumed to be inappropriate. Therefore, independent parametric fits were also explored for TI and non-TI cohorts for the int-2/HR and Hb <10 g/dL subgroup.

Survival extrapolation for TI patients

AIC and BIC statistics are shown in Table 27 for each pure momelotinib arm parametric model for the int-2/HR and Hb <10 g/dL subgroup, for those who are TI. The log-logistic model produced the best statistical fit with the lowest AIC and BIC.

Table 27. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	2	[redacted]	2
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	1	[redacted]	1
Log-normal	[redacted]	3	[redacted]	3
Generalised gamma	[redacted]	5	[redacted]	5

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

AIC and BIC relative fit classifications for the int-2/HR and Hb <10 g/dL TI models are shown below in Table 28. Compared to the log-logistic model, all models produced good relative fits based on AIC (<4-point difference) excluding the exponential model which provided a reasonable relative statistical fit (4-7 point difference). All models were within 10 BIC points of the log-logistic.

Table 28. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Reasonable	[redacted]	Reasonable
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	-	[redacted]	-
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Figure 20 and Table 29 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted]% (Gompertz) to [redacted]% (exponential) at 5 years and [redacted]% (Weibull and Gompertz) to [redacted]% (exponential) at 10 years across the different parametric models.

Figure 20. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Table 29. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

In line with the statistical fit results and similar to the ITT population results, most models produced reasonable visual fits to the KM curve excluding the exponential model, which substantially underestimated the KM curve up to approximately two and a half years before potentially overpredicting the tail.

Clinical experts consulted as part of an advisory board meeting in May 2023 agreed that patients who are TI are expected to have an greater OS compared to patients who are TR or TD (i.e. non-TI), and that they would expect hardly any patients in the TD health state to be alive after 10 years.(127) In addition, clinical experts noted that patients who are TI would certainly have increased survival expectations compared to TD and TR patients, with one clinician noting that they may expect more diversion in the survival expectations among TI and TR or TD patients.

While these comments were provided by the clinical experts in relation to survival expectations for the ITT population rather than the int-2/HR and Hb <10 g/dL population who are expected to have a worse prognosis (and therefore lower survival expectations), it was assumed that TI patients at 24 weeks would expect to have some increase in long-term survival over non-TI patients also in the int-2/HR and Hb <10 g/dL population subgroup, and that the survival over time in the int-2/HR and Hb <10 g/dL subgroup TI cohort would be less than or equal than the preferred int-2/HR and Hb <12 g/dL population TI parametric model (log-normal).

The exponential model was therefore excluded from consideration for the int-2/HR and Hb <10 g/dL population TI cohort given that it produced a higher long-term survival at 10 years ([redacted]%) than the preferred log-normal model for the int-2/HR and Hb <12 g/dL population TI cohort ([redacted]%).

However, all other TI parametric models for the int-2/HR and Hb <10 g/dL population crossed over with the non-TI parametric models for the int-2/HR and Hb <10 g/dL population, including the preferred Weibull model which was the most pessimistic extrapolation for the non-TI cohort. The Weibull, Gompertz and generalised gamma TI models produced lower OS than the Weibull non-TI model at approximately 156, 160 and 152 weeks respectively, and remained lower than the Weibull non-TI model for the full duration of the model time horizon. The log-logistic and log-normal TI models both produced lower OS than the Weibull non-TI model at approximately 152 weeks, before crossing over with the Weibull non-TI model models again and producing higher OS from approximately 516 and 560 weeks, respectively.

In order to prevent crossing of the TI and non-TI curves, which appeared implausible in relation to clinical expert feedback, mechanics were included in the model to set per cycle mortality probabilities for the TI equal to non-TI per cycle mortality probabilities from a user-specified time point or cap the TI OS curve with the non-TI OS curve. Weibull, Gompertz and generalised gamma models were excluded from consideration given their particularly pessimistic long-term extrapolations and sharper crossings with the Weibull non-TI model. Among the log-logistic and log-normal models, which both produced more plausible and optimistic extrapolations, the log-logistic TI model was preferred on the basis of slightly improved statistical fit to the observed data and given its shorter duration of crossover with the non-TI Weibull model compared to the TI log-normal model. The log-logistic TI OS curve capped with the Weibull non-TI OS curve at the point of crossing was considered the most suitable approach to modelling TI OS for the revised int-2/HR and Hb <10 g/dL subgroup. Final revised OS curves, appended to the OS KM curves from SIMPLIFY-2 applied to both treatment arms in the first 24 weeks, are shown in Figure 21.

Figure 21. Final revised OS curves for pure momelotinib SIMPLIFY-2 OS, TI and non-TI, from baseline (int-2/HR and Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Survival extrapolation for Non-TI patients

AIC and BIC statistics are shown in Table 30 for each pure momelotinib arm parametric model for the int-2/HR and Hb <10 g/dL subgroup, for those who are non-TI. The log-normal model produced the best statistical fit according to AIC, while the exponential model produced the best statistical fit according to BIC.

Table 30. Goodness of fit statistics for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	3	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	6	[redacted]	6
Log-logistic	[redacted]	4	[redacted]	3
Log-normal	[redacted]	1	[redacted]	2
Generalised gamma	[redacted]	2	[redacted]	4

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

AIC and BIC relative fit classifications for the int-2/HR and Hb <10 g/dL non-TI models are shown below in Table 31. In terms of AIC, all other models produced good relative fits (<4 AIC point difference) compared to the log-normal. All models were reasonable relative fits according to BIC compared to the exponential.

Table 31. Relative goodness of fit classifications for the pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Good	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	-	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Figure 22 and Table 32 show survival estimates for each distribution over time up to 10 years for the int-2/HR and Hb <10 g/dL non-TI cohort. Survival estimates ranged from [redacted]% (Weibull) to [redacted]% (generalised gamma) at 5 years and [redacted]% (Weibull) to [redacted]% (generalised gamma) at 10 years across the different parametric models.

Figure 22. Kaplan-Meier and parametric distributions for pure momelotinib SIMPLIFY-2 OS, non-TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

Table 32. Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, non-TI, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival; TI = transfusion independent

While the generalized gamma model generated the best statistical fit to the data, the visual fit was implausible and likely a result of the model parameters failing to properly converge, and as such was excluded from consideration. Exponential, Weibull and Gompertz models slightly underpredicted the KM curve for the first 20 weeks and slightly overpredicted the KM curve between approximately 50 and 110 weeks, before underpredicting the tail. Log-logistic and log-normal models both produced fairly good visual fits to the majority of the KM curves, although appeared to more substantially underpredict the tail compared to the other models. However, interpretations of fit to the tail should be interpreted with caution given the elongated flat sections at the end of the KM curve where there are few patients at risk.

Given clinical expert feedback that they would expect hardly any patients in the TD health state to be alive after 10 years for the ITT population, and that the int-2/HR and Hb <10 g/dL is expected to have worse survival outcomes than the ITT and int-2/HR and Hb <12 g/dL populations(127), the Weibull model was preferred for the revised Hb <10 g/dL subgroup given that all other non-TI parametric models for the Hb <10 g/dL population produced higher long-term survival than the preferred non-TI model (Weibull) for the revised base-case Hb <12 g/dL population.

Appendix 3

Overall Cohort OS extrapolations

GSK have included an additional scenario analysis for the base-case Hb <12 g/dL population where survival is conservatively assumed to be equal for both momelotinib and BAT using pooled OS data for both treatment arms from SIMPLIFY-2 after 24 weeks (i.e. after patients in the BAT treatment arm of the trial switch to momelotinib), with differences between comparators in the model then driven only by health state membership over time. The following sections describe the overall cohort OS data and the rationale for parametric curve selection for this scenario analysis, with overall cohort OS data also presented for the <10 g/dL subgroup for completeness.

Base-case Hb <12 g/dL population

The overall cohort OS KM curve and associated numbers at risk for the base-case Hb <12 g/dL population are presented in Figure 23.

Figure 23. Overall cohort OS KM curve from week 24 and number at risk, SIMPLIFY-2, pooled momelotinib and BAT (base-case Hb <12 g/dL population)

Note that the 'ITT patients' labelling on the plot and table refers to the 'overall cohort'
Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival

AIC and BIC statistics are shown in Table 33 for each overall cohort OS parametric model for the base-case int-2/HR and Hb <12 g/dL population. The exponential model produced the best statistical fit with the lowest AIC and BIC.

Table 33. Goodness of fit statistics for the overall cohort SIMPLIFY-2 OS parametric distributions, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	2	[redacted]	2
Gompertz	[redacted]	3	[redacted]	3
Log-logistic	[redacted]	4	[redacted]	4
Log-normal	[redacted]	6	[redacted]	5
Generalised gamma	[redacted]	5	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival

AIC and BIC relative fit classifications for the base-case int-2/HR and Hb <12 g/dL overall cohort OS models are shown below in Table 34. Compared to the exponential model, all models produced good relative fits based on AIC (<4-point difference) except for the log-normal model which produced a reasonable relative statistical fit (4-7 point difference). All models were within 10 BIC points of the exponential.

Table 34. Relative goodness of fit classifications for overall cohort SIMPLIFY-2 OS parametric distributions, from Week 24 (base-case Hb <12 g/dL population)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	-	[redacted]	-
Weibull	[redacted]	Good	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Reasonable	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival

Figure 24 and Table 35 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted]% (Gompertz) to [redacted]% (log-normal) at 5 years and [redacted]% (Gompertz) to [redacted]% (log-normal) at 10 years across parametric models.

Figure 24. Kaplan-Meier and parametric distributions for overall cohort SIMPLIFY-2 OS, from Week 24 (base-case Hb <12 g/dL population)

Abbreviations: Hb = haemoglobin; OS = overall survival

Table 35. Landmark survival rates for overall cohort SIMPLIFY-2 OS, from Week 24 (base-case Hb <12 g/dL population)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival

Similar to the statistical fit results, most models produced good visual fits to the observed KM curve except for the log-normal model, which slightly underestimated the KM curve up to approximately two years before likely overfitting the flat section at the tail of the KM curve.

For the revised company base-case analysis for the Hb <12 g/dL population, the log-normal model was selected to model patients who were TI at 24 weeks, with the Weibull model chosen for non-TI patients at 24 weeks. These models generated 5-year OS of [redacted]% and [redacted]%, and relatively similar long-term survival expectations at 10 years with [redacted]% and [redacted]%, respectively. Assuming that overall cohort OS should produce similar long-term survival expectations, this suggests that the exponential ([redacted]% and [redacted]%), log-logistic ([redacted]% and [redacted]%) and log-normal ([redacted]% and [redacted]%) overpredict long-term survival.

All three of the remaining models produced higher long-term survival at 5 and 10 years than the preferred Weibull overall cohort OS curve for the corresponding Hb <10 g/dL subgroup population ([redacted]% and [redacted]%). The Gompertz model produced the closest 5-year prediction ([redacted]%) to 5-year OS estimates for TI and non-TI OS models with the generalised gamma ([redacted]%) and Weibull ([redacted]%) slightly overpredicting survival. However, the generalised gamma produced the closest 10-year predictions to the revised TI and non-TI curves for the revised base-case Hb <12 g/dL population with [redacted]% closely followed by Weibull at [redacted]%, with the Gompertz model ([redacted]%) slightly underpredicting survival at 10 years compared to the preferred TI and non-TI OS models.

Given the relatively small differences in statistical and visual fit to the observed data between these models, and limited differentiation in terms of internal validity compared to the chosen TI and non-TI OS models applied for the revised base-case analysis, the Gompertz was chosen for the overall OS cohort scenario analysis as the most conservative long-term extrapolation.

Intermediate-2 and high-risk with Hb <10 g/dL subgroup population

The overall cohort OS KM curve and associated numbers at risk for the int-2/HR and Hb <10 g/dL subgroup population are presented in Figure 25.

Figure 25. Overall cohort OS KM curve from week 24 and number at risk, SIMPLIFY-2, pooled momelotinib and BAT (int-2/HR and Hb <10 g/dL subgroup)

Note that the 'ITT patients' labelling on the plot and table refers to the 'overall cohort'
Abbreviations: Hb = haemoglobin; KM = Kaplan-Meier; OS = overall survival

AIC and BIC statistics are shown in Table 36 for each overall cohort OS parametric model for the base-case int-2/HR and Hb <12 g/dL population. The Weibull model produced the lowest AIC, with the exponential producing the lowest BIC.

Table 36. Goodness of fit statistics for the overall cohort SIMPLIFY-2 OS parametric distributions, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Curve	AIC	AIC ranking	BIC	BIC ranking
Exponential	[redacted]	4	[redacted]	1
Weibull	[redacted]	1	[redacted]	2
Gompertz	[redacted]	3	[redacted]	4
Log-logistic	[redacted]	2	[redacted]	3
Log-normal	[redacted]	6	[redacted]	5
Generalised gamma	[redacted]	5	[redacted]	6

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival

AIC and BIC relative fit classifications for the int-2/HR and Hb <10 g/dL overall cohort OS models are shown below in Table 37. AIC and BIC differences were relatively uninformative with all models generating good (<4-point difference) and reasonable (<10-point difference) relative fits in terms of AIC and BIC, respectively.

Table 37. Relative goodness of fit classifications for overall cohort SIMPLIFY-2 OS parametric distributions, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Curve	AIC Difference	AIC Relative Fit Classification	BIC Difference	BIC Relative Fit Classification
Exponential	[redacted]	Good	[redacted]	-
Weibull	[redacted]	-	[redacted]	Reasonable
Gompertz	[redacted]	Good	[redacted]	Reasonable
Log-logistic	[redacted]	Good	[redacted]	Reasonable
Log-normal	[redacted]	Good	[redacted]	Reasonable
Generalised gamma	[redacted]	Good	[redacted]	Reasonable

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Hb = haemoglobin; OS = overall survival

Figure 26 and Table 38 show survival estimates for each distribution over time up to 10 years, with survival estimates ranging between [redacted]% (Gompertz) to [redacted]% (log-normal) at 5 years and [redacted]% (Gompertz) to [redacted]% (log-normal) at 10 years across parametric models.

Figure 26. Kaplan-Meier and parametric distributions for overall cohort SIMPLIFY-2 OS, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Abbreviations: Hb = haemoglobin; OS = overall survival

Table 38. Landmark survival rates for overall cohort SIMPLIFY-2 OS, from Week 24 (int-2/HR and Hb <10 g/dL subgroup)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Hb = haemoglobin; OS = overall survival

Similar to the statistical fit results, most models produced relatively good visual fits to the observed KM curve albeit with the exponential appearing to underpredict the KM curve in the first two years before likely overfitting the flat section at the tail of the KM curve along with the log-logistic and lognormal.

In addition, these three models (exponential, log-logistic and lognormal) produce 10-year survival estimates which are inconsistent with survival expectation for this higher-risk population ([redacted]%, [redacted]% and [redacted]%). The Gompertz OS curve is also not considered plausible due to under-prediction of 10-year survival ([redacted]%). This is inconsistent with clinician's view that they would expect a small proportion of non-TI

JAKi-experienced patients, a subpopulation with poorer prognosis, to be alive at 10-years.

Between the Weibull and generalised gamma, the Weibull was considered the most appropriate fit given it produced slightly better statistical fits and slightly closer OS predictions to the non-TI Weibull model compared to the generalised gamma.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	MPN Voice and Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	MPN Voice is the patient support organisation for people with Myeloproliferative Neoplasms (MPNs) in the UK. MPN Voice's mission is to provide clear and accurate information and emotional support to everyone who has been diagnosed with a myeloproliferative neoplasm and their families/friends. MPN Voice has members across the UK and in many other countries throughout the world. MPN Voice offers a website (http://www.mpnvoice.org.uk), patients' forums around the UK during the year, and a Peer Support programme to allow people with MPNs to contact others in similar circumstances. MPN Voice also has an online forum at HealthUnlocked which is a supportive and informative online forum where patients and carers can ask questions about anything related to MPNs, and get replies from people who really understand the challenges of living with a MPN. In addition, MPN Voice produces information leaflets and a newsletter for people with MPNs so that patients are better informed and have more confidence dealing with the management of their condition. MPN Voice also raises money to fund research towards a cure and advocacy for patients. MPN Voice's work is primarily funded by donations from the public, through a wide range of fundraising activities. MPN Voice also accepts financial support from pharmaceutical companies for specific activities (see below)

	Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected by leukaemia, MDS or MPNs receives the best possible diagnosis, information, advice, treatment and support. Approximately 80% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 20% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf. pdf
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**MPN Voice:** Novartis UK: Sept 2022: £525 honorarium Novartis Ireland: Dec 2022: £12,827 support for face-to-face forum in Ireland. Novartis Ireland: Apr 2023: £14,689 support for face-to-face forum in Ireland. GSK have committed to a grant of £30,000 for general support for MPN Voice activities, but the grant has not yet been received. **Leukaemia Care** Novartis: £25,000 core funding, £25,000 for videos, podcasts and webinars and £487 honorarium
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	MPN Voice: No LC: No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Data supporting this submission has been gathered from a range of sources: MPN Voice is a founding member of MPN Advocates Network (MPNAN), a global coalition of MPN Patient groups. In 2019 MPNAN began the largest survey of MPN patient needs to date, with over 1700 responses at the time of writing. 302 responses have been received from myelofibrosis patients. Evidence has also been taken from two MPN Landmark studies, the original US-based one in 2016 and a subsequent international study. The 2016 study had 816 respondents, of which 2017 were Myelofibrosis patients. The international study had 174 responses from myelofibrosis patients, 45 from the UK, and provides information on patient reported quality of life and productivity. (Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5569657/) This submission is also informed by a patient experience survey of 34 adults diagnosed with myelofibrosis, carried out by Leukaemia Care in 2016. This was part of a wider survey of over 2500 blood cancer patients. Further, we have recently (July-August 2023) conducted a targeted survey of MF patients and their family and carers in the UK, to gain information about their real-life experience of living with MF and its symptoms, plus the impact, both positive and negative, of the drugs with which they have been treated. Responses were received from 197 MF patients, including 7 treated with Momelotinib, and 57 family and carers. Lastly, we have carried out telephone interviews with 4 MF patients already treated with Momelotinib, to understand more about their experience of this drug and any other drugs with which they may have previously been treated.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myelofibrosis (MF) is a rare form of blood cancer, known as a myeloproliferative neoplasm (MPN), that causes the overproduction of fibroblasts in the bone marrow. There are fewer than 1-2 people per 100,000 diagnosed every year in the UK. Most patients will be over the age of 50 years old at diagnosis, with the average age in the Landmark study being 59.6 years old. There are two types of myelofibrosis, primary and secondary. In primary MF the disorder has arisen by itself and secondary MF is a progression from another MPN. Around 50-60% of MF patients will have a mutation in the JAK2 protein. The international MPN Landmark study performed a systematic analysis of the burden of MPN illnesses. Quoting from the peer-reviewed report of the study, "*MPNs are associated with a substantial disease burden, often leading to a reduced quality of life (QOL) for many patients. Symptoms may include fatigue, pruritus, night sweats, microvascular symptoms, splenomegaly, and splenomegaly associated symptoms (e.g., abdominal pain, early satiety), with fatigue being one of the most severe symptoms. Among patients with MF, PV, or ET, patients with MF generally have the highest symptom burden and the lowest QOL*." MF patients reported to the 2016 Landmark researchers a range of symptoms. The following are illustrations of the numbers of patients for whom the symptoms have a significant impact: • Fatigue 80% of patients • Depression or sad mood 75% • Abdominal discomfort 53% • Night sweats 51% Respondents to our latest 2023 survey of MF patients reported the following symptoms most frequently: • Fatigue 91% of patients • Weakness 45% • Bruising or bleeding 40% • Abdominal discomfort 34% • Bone pain 34% • Excessive sweating 30%

	Apart from the actual symptoms, MF affects many other aspects of patients' lives. The MF patients in the UK who responded to the MPNAN survey scored 4.2/10 in terms of financial impact (0 being the most significant impact). Over 30% of these patients reported significant financial difficulties. 66% of patients responding to the latest survey reported that MF impacted their ability to carry out everyday tasks and activities. 65% reported that MF impacted their ability to work, with the same percentage reporting a significant impact on their own social life and that of their carers. The impact of the disease is also felt by the people who care for MF patients. This impact is felt in a variety of ways, from the psychological and emotional burden of caring for someone with an incurable, debilitating disease, to the practical and financial effect. On average respondents to the MPNAN survey who specifically identified as carers of MF patients scored 6.7/10 for the impact on their ability to work (10 meaning they couldn't work at all), and over 30% reported that they were unable to work at all because of their role as carers. From the latest survey 58% of carers reported having to support the patient with everyday tasks and activities, with a significant impact on their own day to day life and on their relationship with the patient. 32% of carers reported that providing this support had significantly impacted their own ability to work. A patient who we spoke to recently told us about the debilitating symptoms that MF caused – he suffered badly from fatigue, severe itching of his skin and weight loss. He had been treated with ruxolitinib for several years, but gradually, the symptoms returned. The ruxolitinib treatment had problematic side effect of skin lesions requiring frequent removal procedures. Additionally, he became severely anaemic and needed 2-3 blood transfusions each week to maintain his red cell count. He described the huge impact that this had on his life, with the need to

	travel to Guys hospital (a 2-3 hr round trip) multiple times each week. He was also very concerned about the cost of the transfusion regime to the NHS. Some of the comments from patients responding to the latest survey included: 'I get tired easily and have had to retire on ill health grounds from working as GP due to fatigue/struggling cognitively.' 'I become totally out of energy in 10 seconds, I just need a rest there and then. I am really feeling tired just by thinking of a task I need to do' 'My husband has had to take over shopping and cooking. Not walking too far, have applied for a blue badge' 'Extreme fatigue and bone pain make it impossible on some days to stand and cook, walk dog, play with kids, socialise' 'I am no longer able to work. The fatigue has not changed only gets worse. Infections are pretty frequent, and transfusions are now a big part of maintaining haemoglobin. I need shopping, cooking, cleaning and driving all done for me' 'I have not been able to work for years due to level of fatigue and or chronic skeletal pain' 'Was working full time in demanding job but have taken early retirement due to constant fatigue and recurring infections' 'I have a shorter active day because of fatigue and also, I miss sleep due to night sweats. Also, I have inertia and loss of concentration some days which makes it difficult to do things'

	The disease significantly impacts the economic productivity of patients and their carers. The 2016 Landmark survey reported that 59% of MF patients had reduced work hours owing to the disease. About their ability to work, the patients we spoke to recently said: “I had to retire early from teaching. It was very difficult, but I simply could not do it any longer due to severe fatigue, pain, and the constant doctor/lab visits” “[I am] trying to continue to work full time to support [my] young family, but [I am] really struggling to do so”

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Following diagnosis, some patients who aren't experiencing symptoms will be put on 'Watch and Wait' where the MF is monitored over time. In the Leukaemia Care (LC) survey, 29% of patients were placed on Watch and Wait and this caused some level of concern or worry for many patients. Overall, 62% of MF patients felt to some extent more depressed or anxious following diagnosis, including those who had started treatment or were still on Watch and Wait, demonstrating the significant emotional impact that a diagnosis has on the patient. Other MF patients will be given treatments to manage MF and the side effects, as the only curative option is stem cell transplant. With this being an intensive treatment option, it is not often advised. Just 9% of patients in the Leukaemia Care survey had received a stem cell transplant. LC asked about the side effects of their current treatments, the majority of patients experienced side effects (94%) with the most common being: fatigue (68%), sleeping problems (41%), bruising (41%), sore mouth (38%), anaemia (35%), loss of concentration/memory (32%), and breathing difficulties (32%). The side effects had an impact on 82% of patients (54% small impact, 25% large impact, 4% intolerable). Comments from patients being treated with drugs other than Momelotinib generally underline their concerns about both side-effects and the limited effectiveness of these drugs, especially over time. They hope that another treatment may become available that offers longer-term efficacy and less debilitating side-effects. LC also gained anonymous evidence from three patients about their treatment with ruxolitinib (the primary treatment currently available to UK patients). The degree to which the treatment impacted on their symptoms was very different, with one patient saying symptoms had gotten worse, and the others stating symptoms had partially or significantly improved. One patient stated that they failed to respond to ruxolitinib after 2-3 years and their spleen enlarged. This was their most recent treatment for MF, demonstrating the lack of options for patients. The experiences of the patient we spoke to illustrate the shortcomings of ruxolitinib. He suffered from some of ruxolitinib's unpleasant and potentially dangerous side effects (skin lesions) but also found that its effectiveness does not last. This patient experienced a return of his MF symptoms after 7 years of treatment with ruxolitinib.

8. Is there an unmet need for patients with this condition?	Most therapies for MF focus on controlling the symptoms of the disease and these therapies are not effective for all MF patients; many patients do not tolerate their side effects well. Ruxolitinib treatment is effective for some patients, but response if frequently inadequate. Furthermore, the median duration of response to ruxolitinib is 3 years and we are seeing increasing numbers of patients with progressive disease after previous response to ruxolitinib. To quote from the Dec 2019 paper *Beyond Ruxolitinib: Fedratinib and Other Emergent Treatment Options for Myelofibrosis*, "…patients who discontinue ruxolitinib have dismal outcomes, making this situation an area of significant unmet need" This patient group (those who need to discontinue ruxolitinib treatment) represents an area of major unmet medical need as currently there are no approved therapies for this patient group in the UK. The lack of other effective treatments for patients who are unresponsive to or intolerant of ruxolitinib and other drugs is a concern for many of the patients who responded to our latest survey. Comments in this area included: 'I'm only 53 and worry that the Jakafi will lose effectiveness over time. I feel an additional treatment option is important' 'Have tried all anti cancer drugs and now was most excited to think that Momelotinib might help me' 'Although the medication has had a positive effect on my blood results, it has had a negative effect on my energy levels, fatigue being my biggest concern' 'I have been watching the momelotinib up and coming for well over a year now. It is the drug that I would like to switch to since it has the ability to help MF patients with anaemia' 'After 18 months on Ruxolitinib 5mg x 2. Symptoms have got worse, weight loss & loss of appetite, bruises & night sweats' 'Anxiety of what happens when medication is no longer effective'

	‘Not taking Momelotinib currently but need to because it is the only medication that would improve symptoms and quality of life without worsening my anaemia.’ ‘I really hope NICE will give Momelotinib the green light. For patients like me who are resistant to the existing Jak2 inhibitors this is the only hope we have. Thank you’ ‘I have been taking 20mg of Rux for 6 years now (2 x 10mg) a day. This was increased to 25mg a day because my spleen has started growing back. The increase in dosage has helped reduce it but I worry a lot about it ultimately losing its effect’ ‘My concern is that for 50 percent of patients ruxolitinib stops working after two to three years - there isn't yet a viable follow on medication.’ One of the patients we spoke to is a perfect example of this scenario – his ruxolitinib treatment that had been initially effective, but started to lose its effect on his blood counts and symptoms and he needed a therapy that would re-establish control over his disease. As well as the need for an effective treatment for patients where ruxolitinib is no longer effective, there is also a specific unmet need for patients with anaemia. Another one of the patients we spoke to exemplifies this particular problem; without a drug that improves anaemia, the only treatment available was frequent transfusions. He needed a transfusion more than once a week and each one involved several hours in hospital. The disruption, as well as the discomfort and significant financial impact was having a huge impact on the patient’s life.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In our recent survey, 60% of the patients being treated with Momelotinib reported an improvement in their MF symptoms and the side-effects of other medication, including reductions in anaemia, fatigue and bone pain, even though some had only recently begun treatment. To quote one patient: 'Ruxolitinib was good but the anaemia was awful. The low energy affected my daily life, my physical activities and mental state, my well-being suffered. Momelotinib, whilst still very early days, seems to have improved my anaemia. Another patient we spoke to told us that momelotinib worked immediately to improve both the symptoms of MF and his anaemia. He said that the night sweats and itching were quickly relieved, and his fatigue is also greatly reduced. He said that he now feels able to resume daily exercise. He has not had any more skin lesions or mouth ulcers since starting the new drug and stopping the ruxolitinib treatment. Another advantage he told us about was that he only needed to take the tablets once a day – he noted the convenience of this and recognised that it helped him adhere to the treatment regime. However, by far the main benefit this patient appreciates is the fact that, because his anaemia has improved, he no longer needs to have blood transfusions – he described momelotinib as 'brilliant' and is very grateful for having been given the opportunity to be treated with it.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Respondents to the recent survey reported some issues with nausea and gastro-intestinal issues after taking Momelotinib. The patient we spoke to said that the initial side effects of momelotib were nausea (which is now being effectively controlled with an anti-emetic) and some low blood pressure and tiredness. These effects have lessened after a few weeks of treatment.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Myelofibrosis is a debilitating disease that has a significant impact on patients' quality of life • The impact of the disease is felt by patients' carers as well as by the patients themselves and has significant social and economic effects • The only cure for MF is a stem cell transplant, which is not an option for most patients. Many patients do not tolerate existing therapies and therefore need other options • The only targeted therapies for MF are ruxolitinib and fedratinib which, if they work, are only effective for a few years. Patients need an option for subsequent treatment • Momelotinib has an improved side-effect profile and a convenient delivery method and reduces the need for blood transfusions for anaemic patients. It should be made available as an option for all MF patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

1. Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating myelofibrosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Tim Somervaille
2. Name of organisation	The Christie NHS Foundation Trust
3. Job title or position	Professor of Haematological Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with myelofibrosis? ☐ A specialist in the clinical evidence base for myelofibrosis or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for myelofibrosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are multiple goals of treatment in myelofibrosis which depend on the age and disease status of the patient. Myelofibrosis is a very heterogeneous disease. The range of desired outcomes can include the goal of cure where you have a younger fitter patient with high risk disease and you might consider offering them

	allogeneic transplantation. Much more frequently the goal of therapy is to improve quality of life and to reduce the impact of the disease associated symptoms on the individual patient. Some patients have anaemia as their main issue and historically we have tried to mitigate that with erythropoietic injections, drugs such as danazol, or blood transfusions. Other patients have issues relating to sweats, weight loss, itching and/or a bulky uncomfortable spleen, and these patients typically do very well with JAK2 inhibitors such as ruxolitinib or fedratinib. There is a widespread feeling that drugs such as ruxolitinib prolong survival in patient who are unwell with symptoms from their disease, and who have a good symptomatic and spleen response.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This again varies from patient to patient, depending on their disease status, but would include: Symptom improvement: reduction in symptoms like fatigue, night sweats, weight loss, and bone pain (as measured by a scale such as MPN-SAF). Splenomegaly reduction: decrease in spleen size, often measured through physical examination or imaging studies. Anaemia management: improvement in anemia, evidenced by increased hemoglobin levels and a reduced need for blood transfusions. Blood counts normalization: improvement or normalization of blood counts, including platelets and white blood cells, which are often affected by myelofibrosis. Other items might include reduced marrow fibrosis or reduced variant allele frequency, and improved survival.
10. In your view, is there an unmet need for patients and healthcare professionals in myelofibrosis?	Yes, absolutely.

11. How is myelofibrosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	MF is managed in the UK as per our recently updated guideline on ***diagnosis*** shown here: https://pubmed.ncbi.nlm.nih.gov/37932932/ and ***treatment*** (this is accepted for publication in the British Journal of Haematology and is currently in press). A PDF version of this accepted manuscript is sent with this form. The pathway of care is generally well defined. MF patients with symptoms and/or an enlarged spleen generally benefit in terms of symptom response and spleen volume reduction with a JAK2 inhibitor such as ruxolitinib. The availability of momelotinib as an alternative to ruxolitinib in first line treatment of myelofibrosis will make a substantial difference for patients with myelofibrosis. For example, momelotinib would provide an alternative for patients who might not respond well to or cannot tolerate ruxolitinib. In anaemia management, one of the distinctive advantages of momelotinib is its ability to manage anaemia, a common and challenging complication of myelofibrosis. This could be particularly beneficial for patients who suffer from significant anaemia and may reduce the need for regular blood transfusions. It will also permit a better personalized treatment approach, e.g. allowing the physician to tailor therapy to individual patient needs, especially considering factors like symptom profile, disease severity and side effect tolerance. There may be an impact on resource: the management of myelofibrosis patients, particularly those with anaemia, can be resource-intensive (e.g., frequent blood transfusions). Momelotinib might reduce this burden by better controlling anaemia.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Momelotinib and ruxolitinib are both JAK inhibitors used in the treatment of myelofibrosis (which is delivered in specialist cancer care centres), but they have some key differences: Ruxolitinib primarily inhibits JAK1 and JAK2 enzymes. JAK2 mutations are common in myelofibrosis and contribute to disease pathology, making JAK2 inhibition a central strategy in treating myelofibrosis. Momelotinib inhibits JAK1, JAK2 and also ACVR1/ALK2, another kinase involved in inflammation and fibrosis. This broader inhibition profile may offer different clinical benefits including an effect on anaemia. Ruxolitinib often worsens anaemia, a common side effect, even precipitating a transfusion requirement. Momelotinib has a unique benefit in improving anaemia in some patients. It is thought that its inhibition of ACVR1/ALK2 contributes to this effect, making it potentially more favourable for patients with significant anaemia. Both drugs are effective in reducing spleen size and alleviating symptoms associated with myelofibrosis, although for symptoms ruxolitinib is likely superior to momelotinib. Common side effects of ruxolitinib include anaemia, thrombocytopenia and increased risk of infections. Side effects of momelotinib include dizziness, nausea and in some patients peripheral neuropathy has been reported. There will be little extra investment required to introduce the technology given it is just another oral medication.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I do expect the technology to provide clinically meaningful benefits compared with current care. The comments I have made above are pertinent to this. Regarding length of life it is not clear currently whether or not momelotinib would be superior to ruxolitinib although my instincts are that they would deliver similar benefit. Where momelotinib may be superior is in anaemia response as mentioned above and there will most certainly be a subgroup of myelofibrosis patient to

	have a superior quality of life through not requiring blood transfusions or erythropoietic stimulating agents to assist with their baseline disease-related anaemia, or ruxolitinib-induced anaemia.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	See comments above. I would expect momelotinib to be superior to ruxolitinib for patients who have significant anaemia with myelofibrosis.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	I would anticipate no significant differences in delivering momelotinib by comparison with ruxolitinib.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I think these should be similar to those mandated for ruxolitinib.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	As mentioned above for some patients there will be a reduced requirement to attend hospital for blood transfusions.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The introduction of momelotinib would be an important addition to the repertoire of therapies physicians treating myelofibrosis have access to in the United Kingdom for the reasons mentioned above.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no substantial considerations in this regard. One has to keep an eye out for the rare patient that might develop neuropathy and that might prompt reevaluation of the choice of JAK2 inhibitor. Some patients need to persevere with treatment over the first few weeks but often initial adverse effects such as nausea and dizziness subside with time or can be effectively dealt with by adding in concomitant antiemetics and other medications.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The key trials are SIMPLIFY1, SIMPLIFY2 and MOMENTUM. A proportion of patients were enrolled from the UK. As with all clinical trials a number of less fit patients might have been excluded but I do not think that that practically affects their conclusions in any significant way. The most important outcomes of the trials was that momelotinib is equally effective as ruxolitinib in reducing spleen volume although perhaps not as effective in improving symptoms. By comparison with danazol momelotinib is significantly superior in improving anaemia responses and in inducing symptom responses. There are no adverse effects not apparent from the clinical trials as far as I am aware.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [TA386] or NICE technology appraisal guidance fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis [TA756]?	There is plentiful new data and of course clinical experience around the use of ruxolitinib and fedratinib in the treatment of patients with myelofibrosis which will be available through a standard literature search. However it remains the case that the core principles elaborated in the original trials for these agents remain the same: that JAK2 inhibitors are generally effective medications in inducing disease responses with spleen volume reduction and improvement of symptoms and that these treatment related outcomes improve quality of life for patients and likely improved survival.
23. How do data on real-world experience compare with the trial data?	Similar in my view.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	None.

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

JAK2 inhibitors are effective treatments for patients with myelofibrosis who have significant disease-related symptoms
By comparison with ruxolitinib, momelotinib is equally effective in reducing spleen size but does not induce anaemia so much and may even induce anaemia responses.
Without doubt, there is a population of patients who have myelofibrosis-related anaemia who would be better off having momelotinib therapy as their first line JAK2 inhibitor because it is less likely to induce anaemia and a requirement for blood product support.
In my view it is essential that momelotinib is made available to patients with myelofibrosis in the up front setting and also in second/third line, to increase the choice of therapies available to physicians at all points along the care pathway.
Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

1. Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating myelofibrosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	DONAL MCLORNAN
2. Name of organisation	UNIVERSITY COLLEGE HOSPITAL LONDON
3. Job title or position	CONSULTANT HAEMATOLOGIST
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with myelofibrosis? ☒ A specialist in the clinical evidence base for myelofibrosis or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NIL
8. What is the main aim of treatment for myelofibrosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Current management approaches are based upon clinical phenotype, prognostic group, patient age and performance status with consideration of co-morbidities. Joint patient and clinician decision making is of key importance. The main aims are to reduce symptoms, including those related to anaemia, and splenomegaly,

	improve quality of life, improve cytopaenias, extend survival and reduce time spent at hospital(e.g requiring regular blood transfusions).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Clinically significant responses are dependent on disease phenotype. Although trials utilise a splenic volume reduction (SVR) >35% and a reduction in total symptom score (TSS) >50%, it is key to note that smaller reductions in spleen volume or TSS or stability can also improve patients quality of life. Specific endpoints of a reduction in transfusion requirements and ideally achievement of transfusion independence are key. We know that anaemia is an adverse prognostic marker in MF and amelioration of such is pivotal where required.
10. In your view, is there an unmet need for patients and healthcare professionals in myelofibrosis?	Despite advances in the therapeutic options for MF there remain many unmet needs.
11. How is myelofibrosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Please refer to the updated guidance on diagnosis/prognosis and also management. I am the lead author of these papers written with colleagues on a national basis. We discuss all aspects of management in these papers. 1.McLornan DP, Psaila B, Ewing J, Innes A, Arami S, Brady J, Butt NM, Cargo C, Cross NCP, Francis S, Frewin R, Garg M, Godfrey AL, Green A, Khan A, Knapper S, Lambert J, McGregor A, McMullin MF, Nangalia J, Neelakantan P, Woodley C, Mead A, Somervaille TCP, Harrison CN; BSH Committee. The management of myelofibrosis: A British Society for Haematology Guideline. Br J Haematol. 2023 Dec 1. doi: 10.1111/bjh.19186. Epub ahead of print. PMID: 38037886. 2. McLornan DP, Godfrey AL, Green A, Frewin R, Arami S, Brady J, Butt NM,m Cargo C, Ewing J, Francis S, Garg M, Harrison C, Innes A, Khan A, Knapper S, Lambert J, Mead A, McGregor A, Neelakantan P, Psaila B, Somervaille TCP, Woodley C, Nangalia J, Cross NCP, McMullin MF; BSH Committee. Diagnosis and evaluation of prognosis of myelofibrosis: A British Society for Haematology Guideline. Br J Haematol. 2023 Nov 6. doi: 10.1111/bjh.19164. Epub ahead of print. PMID: 37932932.

	The pathways of care differ nationally as per most blood cancers. However the above guidance is written by leading UK MPN experts and covers the largest centres and experience. Anaemia is one of the cardinal hallmarks of myelofibrosis (MF) alongside splenomegaly and MF-related symptoms. It is estimated that around 35–40% of MF patients will present with anaemia and most of the remainder will develop anaemia during their disease course. One study from a large tertiary centre of 1000 consecutive patients with MF suggested that over one third were red cell transfusion dependent at the time of referral. Treatment can be challenging, particularly for those patients who are rendered red cell transfusion dependent, paralleled with the limitations of disease-directed therapies where optimal dose density is not possible due to the presence of cytopenias. Moreover, anaemia is a key contributor to the significant symptom burden in MF and transfusion dependency leads to increased health care costs and can significantly impact ambulatory facility capacity. Moreover, there is a direct correlation between the degree of anaemia and red cell transfusion dependency and impaired quality of life (QoL), as highlighted by application of the Functional Assessment of Cancer Therapy (FACT) anaemia tool. The 'MPN-10' symptom assessment tool has been devised to help clinicians objectively assess MF-related symptom burdens, and anaemia can impact many of its parameters. Availability of MMB would be a game changer for the UK practice as it will permit access to a novel drug that targets the triad of anaemia, symptom burden and splenomegaly. The ability to use one agent to improve the above aspects alongside a proportion of patients becoming transfusion independent would be a major improvement in current patient pathways and lead to improved QOL and outcomes.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	MMB will be used in haematology units within current SACT frameworks for assessment and monitoring and will not be prescribed in primary practice. No additional investment is hence required and it would only be prescribed by prescribers trained in haemato-oncology practice. As regards healthcare resource use, an ability to decrease transfusions requirements will reduce cost

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	and travel related burden for patients, reduce ambulatory care costs and improve capacity across day units and reduce blood product usage. No additional investment would be required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Momelotinib (MMB) is a novel potent JAK1/JAK2 and ACVR1 inhibitor and the only JAK inhibitor to consistently address the three cardinal hallmarks of MF. Its mode of action by ACVR1 inhibition leads to decreased hepcidin production and can hence boost erythropoietic potential and lead to anaemia responses and achievement of transfusion independence in some. To date, three large phase III global trials have reported on MMB efficacy. SIMPLIFY-1 compared MMB to ruxolitinib in intermediate-II, high-risk or intermediate risk 1 (with a symptom burden) patients who were JAK inhibitor naïve. SIMPLIFY-2 compared MMB to BAT in a 2:1 fashion for those patients who had a suboptimal response to ruxolitinib or haematological toxicity. Of note, BAT was ruxolitinib in 89% of cases. Crossover to MMB was possible after a period of 24 weeks in both trials. Both trials highlighted the spleen and symptom benefits of MMB. Importantly, readouts from both trials highlighted the anaemia benefits of MMB: MMB led to higher transfusion independence response rates compared to ruxolitinib in SIMPLIFY-1 (67% versus 49%) and BAT in SIMPLIFY-2 (43% versus 21%). Retrospective analysis of SIMPLIFY-1 data highlighted that there was a >9 times odds that MMB-treated patients in the trial remained transfusion independent compared to those undergoing therapy with ruxolitinib (p 0.0001). Mature survival data from both trials has recently been analysed. Of key importance, gaining transfusion independence by week 24 in the MMB-treated cohort in SIMPLIFY-1 associated with improved OS in both univariate (HR=0.323; p<0.0001) and multivariate (HR=0.311; p<0.0001) analyses. This highlights the importance of addressing anaemia adequately and aiming for transfusion independence where applicable. More recently, the phase III MOMENTUM trial compared MMB to danazol in JAKi-exposed patients. MMB met the primary end point of superior total symptom score improvement and

	secondary end points of spleen and anaemia responses highlighting superiority over danazol.28 A trend towards improved OS was also seen by week 24. All three trials have hence demonstrated anaemia, spleen and symptoms responses and robust OS in both JAKi-naïve and previously ruxolitinib-treated patients. Low myelosuppressive potential, lack of cumulative toxicity and ability to maintain good dose density makes MMB a very appealing agent for MF patients with anaemia. I would expect MMB to increase health related QOL and also to improve survival in responding patients, especially in patients who have lost response or cannot gain adequate response to RUX.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	MMB can improve spleen and symptoms in all patients with MF, irrespective of anaemia. Clearly the anaemia directed mechanism that may lead to improvements in Hb and reduce/ negate transfusion requirements and the fact that it can be used in thrombocytopaenic patients means that its will of particular benefit in myelodepletive MF, where frequently adequate dose density of ruxolitinib or fedratinib is not possible.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Will be similar to current use of JAK inhibitors No additional concomitant therapies, clinical requirements or additional tests above standard of care would be required.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Like all JAK inhibitors -ongoing monitoring of spleen and symptom and anaemia response will be required. A lack of utility by 24 weeks with appropriate dosing would lead to alternative strategies being considered.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Improved symptom and spleen burden related and particular anaemia related QOL improvements. Less travel time and need for costly transfusions in responding patients. Increased ambulatory care capacity and less blood product usage. Need to include standard TSS assessment as well as FACT-An. There is

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	no difference in the administration – in fact it is once daily dosing rather than twice daily for ruxolitinib.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes this is step change in the management of MF, in particularly anaemia. It addresses the triad of spleen and symptom burdens and also anaemia. It has demonstrable activity in the JAK I niave and also JAK I exposed populations. Using one agents to address these issues is much more conise for the patient and clinician and avoids inadequate dose density of rux/ fedratinib (with suboptimal responses), and the need for adjunctive drugs such as danazol or recombinant erythropoietin.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common serious adverse reactions (≥2%) in the MOMENTUM study included bacterial infection (8%), viral infection (5%), hemorrhage (4%), acute kidney injury (3%), pneumonia (3%), pyrexia (3%), thrombosis (3%), syncope (2%), thrombocytopenia (2%), and renal and urinary tract infection (2%). These are not dissimilar to effects that can be seen with both ruxolitinib and fedratinbib (in fact the incidence of infection is higher with those two agents).
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes the three clinical trials listed again below are applicable to UK practice amnd the main endpoints of symptom, spleen and anaemia responses are appropriate. The emerging data on OS benefit is also pivotal. To date, three large phase III global trials have reported on MMB efficacy. SIMPLIFY-1 compared MMB to ruxolitinib in intermediate-II, high-risk or intermediate risk 1 (with a symptom burden) patients who were JAK inhibitor naïve. SIMPLIFY-2 compared MMB to BAT in a 2:1 fashion for those patients who had a suboptimal response to ruxolitinib or haematological toxicity. Of note, BAT was ruxolitinib in 89% of cases. Crossover to MMB was possible after a period of 24 weeks in both trials. Both trials highlighted the spleen and symptom benefits of MMB. Importantly, readouts from both trials highlighted the anaemia benefits of MMB: MMB led to higher transfusion independence response rates compared to ruxolitinib in

	SIMPLIFY-1 (67% versus 49%) and BAT in SIMPLIFY-2 (43% versus 21%). Retrospective analysis of SIMPLIFY-1 data highlighted that there was a >9 times odds that MMB-treated patients in the trial remained transfusion independent compared to those undergoing therapy with ruxolitinib (p 0.0001). Mature survival data from both trials has recently been analysed. Of key importance, gaining transfusion independence by week 24 in the MMB-treated cohort in SIMPLIFY-1 associated with improved OS in both univariate (HR=0.323; p<0.0001) and multivariate (HR=0.311; p<0.0001) analyses. This highlights the importance of addressing anaemia adequately and aiming for transfusion independence where applicable. More recently, the phase III MOMENTUM trial compared MMB to danazol in JAKi-exposed patients. MMB met the primary end point of superior total symptom score improvement and secondary end points of spleen and anaemia responses highlighting superiority over danazol.28 A trend towards improved OS was also seen by week 24. All three trials have hence demonstrated anaemia, spleen and symptoms responses and robust OS in both JAKi-naïve and previously ruxolitinib-treated patients. Low myelosuppressive potential, lack of cumulative toxicity and ability to maintain good dose density makes MMB a very appealing agent for MF patients with anaemia. No additional adverse events have come to light.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Only the updates just presented at the ASH 2023 meeting.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [TA386] or NICE technology appraisal guidance fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis [TA756]?	Not applicable.
23. How do data on real-world experience compare with the trial data?	The UK has an EAMs scheme open at present and the real world experience is currently being collated nationally.

	US data of the trials has recently been published with longer term follow up including those on the extended access program - one of the largest randomized trial databases for a JAK inhibitor to date in MF demonstrated a consistent safety profile of momelotinib without long-term or cumulative toxicity; doi: 10.1182/bloodadvances.2022009311
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Nil applicable to this technology that I am aware.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Anaemia is one of the cardinal hallmarks of myelofibrosis (MF) alongside splenomegaly and MF-related symptoms.
It is estimated that around 35–40% of MF patients will present with anaemia and most of the remainder will develop anaemia during their disease course
Momelotinib (MMB) is a novel potent JAK1/JAK2 and ACVR1 inhibitor and the only JAK inhibitor to consistently address the three cardinal hallmarks of MF. Its mode of action by ACVR1 inhibition leads to decreased hepcidin production and can hence boost erythropoietic potential and lead to anaemia responses and achievement of transfusion independence in some.
This is supported from data from 3 large phase III trials and also long term follow up.
MMB is a step change for improving management of the patient with cytopaenic MF and addressing anaemia alongside spleen and symptom burdens with low toxicity and good long term safety data.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with myelofibrosis or caring for a patient with myelofibrosis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Living with this condition or caring for a patient with myelofibrosis

Table 1 About you, myelofibrosis, current treatments and equality

1. Your name	Andy Tattersall
2. Are you (please tick all that apply)	☐ A patient with myelofibrosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with myelofibrosis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MPN Voice
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Through my voluntary work as an Advocacy Coordinator for MPN Voice, including reading studies and clinical trial reports relating to MF and gathering information from patients on their lived experience of having MF and of the existing therapies with which they have been treated

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference **(as there wasn't one!)** ☐ I have not completed part 2 of the statement
6. What is your experience of living with myelofibrosis? **If you are a carer (for someone with myelofibrosis) please share your experience of caring for them**	I have no personal experience of living with myelofibrosis but having been diagnosed with essential thrombocythaemia over 20 years ago, I am well aware of the symptoms of MF and its potential treatments, in view of the possibility that my ET may one day transform to MF
7a. What do you think of the current treatments and care available for myelofibrosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. While there are a small number of current treatments available on the NHS, a significant number of patients are, or become in time, either unresponsive to, or intolerant of them. Once these treatments have had to be discontinued the only currently remaining option is stem cell transplantation, for which many patients are ineligible due to age or other factors. Studies have shown that life expectancy for many MF patients declines rapidly once they are no longer receiving treatment. b. I believe that my views on these current treatments are similar to those of other people, including patients, their carers and clinicians
8. If there are disadvantages for patients of current NHS treatments for myelofibrosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I agree with the response given in the joint patient organisation submission from MPN Voice and Leukaemia Care
9a. If there are advantages of momelotinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	I agree with the response given in the joint patient organisation submission from MPN Voice and Leukaemia Care

9c. Does momelotinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of momelotinib over current treatments on the NHS please describe these. For example, are there any risks with momelotinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I agree with the response given in the joint patient organisation submission from MPN Voice and Leukaemia Care
11. Are there any groups of patients who might benefit more from momelotinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The lack of alternative treatments for MF in those patients who are unresponsive to or intolerant of the existing treatments is a particular issue for elderly patients and those with other illnesses. Both groups are less likely to be considered for stem cell transplantation than younger or fitter patients, due to the risks involved and the high burden of side effects following the procedure. The availability of momelotinib as another treatment would therefore particularly benefit these groups of patients.
12. Are there any potential equality issues that should be taken into account when considering myelofibrosis and momelotinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	As mentioned in point 11 above, there is a significant unmet need for additional treatments in elderly patients who, in many cases, are ineligible for stem cell transplantation as the only potential cure for their MF. In the absence of other alternative treatments, such as momelotinib, this cohort of elderly MF patients is therefore disadvantaged compared to younger patients, who are more likely to be considered for stem cell transplantation

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I agree with the joint patient group submission made by MPN Voice and Leukaemia Care
- There are a limited number of current treatments for myelofibrosis and a significant number of patients are, or become in time, intolerant of or unresponsive to them, with poor outcomes once treatment is ended
- The lack of other alternative treatments is a particular problem for elderly patients and/or those with other illnesses, who are unlikely to be eligible for stem cell transplantation, which is the only potential cure for MF
- Elderly patients are therefore disadvantaged by the lack of alternative treatments, compared to younger patients

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136076

Completed 12 October 2023
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CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

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James Mahon	Critical appraisal of the economic evidence
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Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
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Joanne McEntee	Critical appraisal of the company submission
Nauman Butt	Clinical advice and critical appraisal of the clinical evidence

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AE	Adverse event
AIC	Akaike information criterion
Allo-SCT	Allogeneic-stem cell transplantation
BAT	Best available therapy
BIC	Bayesian information criterion
BID	Twice daily
BSH	British Committee for Standards in Haematology
CDF	Cancer Drugs Fund
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CS	company submission
CSR	clinical study report
DIPSS	Dynamic International Prognostic Scoring System
EAG	External Assessment Group
EPO	Erythropoietin
EQ-5D	EuroQoL 5-Dimensions
ERG	Evidence review group
ESA	Erythropoiesis-stimulating agent
Hb	Haemoglobin
HR	Hazard ratio
HRQoL	Health-Related Quality of life
ICER	Incremental Cost Effectiveness Ratio
ICT	Iron chelation therapy
Int-1	Intermediate-1 risk
Int-2/HR	Intermediate-2/high risk
IPSS	International Prognostic Scoring System
ITT	Intent-to-treat
JAK	Janus Kinase
JAKi	Janus kinase inhibitor
LFS	Leukaemia-free survival
MCS	Mental health component score
MF	Myelofibrosis
MPN	Myeloproliferative Neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMSC	Nonmelanoma skin cancer
OS	Overall survival
PAS	Patient access scheme
PCS	Physical function component score
PGIC	Patient Global Impression Change
PSS	Personal social services
QALY	Quality-adjusted life year
QD	Once daily
RBC	Red blood cell

RCT	Randomised controlled trial
SD	Standard Deviation
SF-36	Short Form-36
SLR	Systematic literature review
SMC	Scottish medicine consortium
SmPC	Summary of Product Characteristics
TD	Transfusion-dependent
TEAE	Treatment-emergent adverse event
TI	Transfusion-independent
TR	Transfusion-requiring
TSS	Total symptom score
TTDD	Time to treatment discontinuation or death
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER per quality adjusted life year (QALY) gained. Section 1.3 to Section 1.6 explain the key issues identified by the EAG in more detail. Section 1.7 outlines the key cost effectiveness issues identified by the EAG.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

Issue	Summary of issue	Report sections
Issue 1	Anticipated licensed indication for momelotinib	2.4.1
Issue 2	JAKi-naïve population: ESAs as anaemia supportive measures	3.2.2 and 3.3
Issue 3	JAKi-experienced population: ESAs as anaemia supportive measures	3.2.3 and 3.5
Issue 4	JAKi-naïve population: appropriateness of a cost comparison analysis	6.2.1
Issue 5	JAKi-naïve and JAKi-experienced populations: ESA usage	6.2.3 and 6.3.6
Issue 6	JAKi-experienced population: company assumption that OS is linked to transfusion status	4.4.5, 6.3.3, 6.3.7 and 6.4.2
Issue 7	JAKi-experienced population: treatment with ruxolitinib as part of BAT after stopping treatment with momelotinib	6.3.3 and 6.3.7
Issue 8	SIMPLIFY-2 trial comparator	2.3.1 and 3.5.2

BAT=best available therapy; JAKi= Janus kinase inhibitor; OS=overall survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Anticipated licensed indication for momelotinib

Report section	2.4.1
Description of issue and why the EAG has identified it as important	The anticipated marketing authorisation for momelotinib [redacted] For the purposes of this submission, the company considers that moderate to severe anaemia means treatment requiring anaemia. The company uses an inclusive threshold of Hb<12g/dL to identify patients with moderate to severe anaemia. Clinical advice to the EAG is that results for patients with Hb<10g/dL should also be used to inform decision making. To allow comparison of momelotinib versus ruxolitinib (recommended by NICE for patients with Int-2/HR disease) the company has focused on patients with Int-2/HR disease. Clinical advice to the EAG is that patients with Int-2/HR disease are more likely to have moderate to severe anaemia than patients with Int-1 disease. The EAG acknowledges that these Hb level subgroups were not pre-specified and the trials were not powered to show differences between treatment with momelotinib versus ruxolitinib for these subgroups. There were imbalances in the baseline characteristics of the SIMPLIFY-1 and SIMPLIFY-2 trial subgroups; most of the imbalanced baseline characteristics tend to be biased towards better expected outcomes for patients treated with ruxolitinib/BAT.
What alternative approach has the EAG suggested?	The EAG report includes cost comparison analysis and cost utility analysis results for the Int-2/HR Hb<10g/dL subgroup.
What is the expected effect on the cost effectiveness estimates?	Cost comparison analysis: [redacted] Cost utility analysis: treatment with momelotinib dominates treatment with BAT (Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup).

What additional evidence or analyses might help to resolve this key issue?	None. Int-2/HR Hb<10g/dL subgroup cost effectiveness results have resolved the issue.

BAT=best available therapy; ET=essential thrombocythemia; Hb=haemoglobin; Int-1=intermediate-1 risk; Int-2/HR=intermediate-2 or high risk; MF=myelofibrosis; PMF=primary myelofibrosis; PV=polycythemia vera

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 JAKi-naïve population: ESAs as anaemia supportive measures

Report section	Section 3.2.2 and Section 3.3
Description of issue and why the EAG has identified it as important	Concomitant use of ESAs as anaemia supportive measures were prohibited during the 24-week randomised controlled period of the SIMPLIFY-1 trial for patients in both treatment arms (momelotinib and ruxolitinib). Clinical advice to the EAG is that patients with MF treated with ruxolitinib may also receive an ESA to control anaemia (but it is unknown if patients treated with momelotinib would also receive ESAs). SIMPLIFY-1 trial efficacy result, particularly RBC TI and RBC TD outcomes, may have differed had ESAs been permitted.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion to estimate the effect on RBC TI and RBC TD outcomes if ESAs had been available to SIMPLIFY-1 trial patients.

ESA=erythropoiesis-stimulating agent; JAKi=Janus kinase inhibitor; MF=myelofibrosis; RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent

Issue 3 JAKi-experienced population: ESAs as anaemia supportive measures

Report section	Section 3.2.3 and Section 3.5
Description of issue and why the EAG has identified it as important	The use of ESAs as concomitant anaemia supportive measures were prohibited in the SIMPLIFY-2 trial momelotinib arm and were not commonly used in the BAT arm (5.7%). Clinical advice to the EAG is that ESAs are often given alongside BAT (e.g., ruxolitinib) in NHS clinical practice. The SIMPLIFY-2 trial efficacy results may have differed, particularly in relation to the RBC TI and RBC TD outcomes, if levels of ESA usage had reflected NHS clinical practice.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion to estimate the effect on RBC TI and RBC TD outcomes if SIMPLIFY-2 trial patients had been treated with ESAs at a level that reflected ESA usage in NHS clinical practice.

BAT=best available therapy; ESA=erythropoiesis-stimulating agent; JAKi=Janus kinase inhibitor; RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 4 JAKi-naïve population: appropriateness of a cost comparison analysis

Report section	Section 6.2.1 and Table 42
Description of issue and why the EAG has identified it as important	Overall, SIMPLIFY-1 trial results were mixed; compared to treatment with ruxolitinib, momelotinib was: • statistically significantly non-inferior in terms of spleen response rate (primary outcome), although the non-inferiority margin was wide; however clinical advice to the EAG was that the results appeared similar (Section 3.3.1) • not statistically significantly non-inferior in terms of total symptom score; however, post-hoc analyses suggest there appeared to be little difference between treatment arms when assessing individual symptom scores and absolute change in TSS from baseline (Section 3.3.2) • nominally significantly superior in terms of RBC TI rate and RBC TD rate (Sections 3.3.3 and 3.3.4)
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice to help determine whether the benefits delivered by treatment with momelotinib and ruxolitinib are so clinically similar that any differences in patient outcomes can be ignored. If the differences can be ignored, then a cost comparison analysis is appropriate.

JAKi=Janus kinase inhibitor; EAG=External Assessment Group

Issue 5 JAKi-naïve and JAKi-experienced populations: ESA usage

Report section	Section 6.2.3, Section 6.3.6, Table 21 and Table 42
Description of issue and why the EAG has identified it as important	See Issue 2 and Issue 3. The EAG considers that these issues affect both clinical and cost effectiveness results.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion to estimate the effect on RBC TI and RBC TD outcomes if SIMPLIFY-1 trial and SIMPLIFY-2 trial patients had been treated with ESAs at levels that reflect ESA usage in NHS clinical practice. If the effects of NHS ESA usage on clinical effectiveness can be quantified, then these effects should be incorporated into the cost comparison and the cost utility analyses.

ESA=erythropoiesis-stimulating agent; JAKi=Janus kinase inhibitor; RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent

Issue 6 JAKi-experienced population: company assumption that OS is linked to transfusion status

Report section	Section 4.4.5, Section 6.3.3, Section 6.3.7, Section 6.4.2, Table 21 and Table 42
Description of issue and why the EAG has identified it as important	The company has modelled OS based on transfusion status. There is an absence of compelling evidence to support this approach.
What alternative approach has the EAG suggested?	The EAG has assumed that OS does not vary by transfusion status.
What is the expected effect on the cost-effectiveness estimates?	Momelotinib (still) dominates treatment with BAT.
What additional evidence or analyses might help to resolve this key issue?	None. EAG cost effectiveness results have resolved this issue.

BAT=best available therapy; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; OS=overall survival

Issue 7 JAKi-experienced population: treatment with ruxolitinib as part of BAT after stopping treatment with momelotinib

Report section	Section 6.3.3, Section 6.3.7, Table 48, Table 50 and Table 51
Description of issue and why the EAG has identified it as important	In the company model, it is assumed that patients who stop treatment with momelotinib will not receive ruxolitinib. However, clinical advice to the EAG and to the company was that if patients stopped treatment with momelotinib, it is likely that they would be retreated with ruxolitinib.
What alternative approach has the EAG suggested?	The EAG has amended the model so that 88.5% of patients who stop treatment with momelotinib are treated with ruxolitinib as part of BAT.
What is the expected effect on the cost-effectiveness estimates?	Momelotinib (still) dominates treatment with BAT.
What additional evidence or analyses might help to resolve this key issue?	None. EAG cost effectiveness results have resolved this issue.

Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; OS=overall survival

1.6 Other key issues: summary of the EAG's view

Issue 8: SIMPLIFY-2 trial comparator

Report section	Section 2.3.1 and Section 3.5.2
Description of issue and why the EAG has identified it as important	The open-label SIMPLIFY-2 trial compares treatment with momelotinib versus BAT for patients previously treated with ruxolitinib. In the BAT arm, 88.5% of patients continued to receive treatment with ruxolitinib. Clinical advice to the EAG is that clinicians are reluctant to stop treatment with ruxolitinib due to the absence of effective treatments and, instead, often reduce ruxolitinib doses. Treatment with dose-adjusted ruxolitinib doses may help to explain the poor SIMPLIFY-2 trial BAT arm results, specifically TSS.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	None

BAT=best alternative therapy; TSS=total symptom score

1.7 Summary of EAG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the EAG are described in Table B (cost comparison analysis) and Table C and Table D (cost utility analysis). Further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.2 and 6.3.

JAKi-naïve population: cost comparison analysis

Table B Cost comparison analysis (PAS price for momelotinib, list prices for all other drugs)

Analysis	Total costs		Incremental cost
	Momelotinib	Ruxolitinib	
Company's base case (ITT population)	[redacted]	£326,021	[redacted]
EAG corrected company base case (ITT population)	[redacted]	£376,846	[redacted]
EAG corrected company base case (Int-2/HR Hb<12g/dL subgroup)	[redacted]	£337,550	[redacted]
EAG corrected company base case (Int-2/HR Hb<10g/dL subgroup)	[redacted]	£339,529	[redacted]

Hb=haemoglobin; ITT=intention to treat; Int-2/HR=intermediate-2/high risk PAS=Patient Access Scheme

JAKi-experienced population: cost utility analysis

Table C JAKi-experienced Int-2/HR Hb<12g/dL population: probabilistic base case results with EAG revisions, momelotinib versus BAT (PAS price momelotinib, list prices all other treatments)

Analysis	Incremental		ICER per QALY gained
	Cost	QALYs	
Company base case*	[redacted]	0.196	Momelotinib dominates
EAG corrected company base case**	[redacted]	0.195	Momelotinib dominates
EAG preferred base case (R1+R2)	[redacted]	0.081	Momelotinib dominates

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; Int-2/HR=intermediate-2/high risk; PAS=Patient Access Scheme; QALY=quality adjusted life year
*Company corrected model submitted after clarification
**EAG revisions are applied to the EAG corrected company base case

Table D JAKi-experienced Int-2/HR Hb<10g/dL population: probabilistic base case results with EAG revisions, momelotinib versus BAT (PAS price momelotinib, list prices all other treatments)

Analysis	Incremental		ICER per QALY gained
	Cost	QALYs	
Company base case*	[redacted]	0.096	Momelotinib dominates
EAG corrected company base case**	[redacted]	0.097	Momelotinib dominates
EAG preferred base case (R1+R2)	[redacted]	0.051	Momelotinib dominates

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; Int-2/HR=intermediate-2/high risk; PAS=Patient Access Scheme; QALY=quality adjusted life year
*Company corrected model submitted after clarification
**EAG revisions are applied to the EAG corrected company base case

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on the use of momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (MF). In this External Assessment Group (EAG) report, references to the company submission (CS) refer to the company's Document B, which is the company's full evidence submission. A summary Document A, appendices and two economic models were also provided by the company and are referred to as the CS Summary, CS Appendices, Janus kinase inhibitor (JAKi)-naïve cost comparison model and JAKi-experienced cost utility model, respectively. The draft Summary of Product Characteristics (SmPC)[1] was included as an appendix to the CS (CS, Appendix C). Additional evidence referred to in this EAG report includes evidence provided by the company in response to the clarification letter.

2.2 Background

MF is a type of myeloproliferative neoplasm (MPN), a rare blood disorder that can cause progressive scarring of bone marrow (fibrosis).[2] MF can result in low levels of red blood cells (anaemia) and changes in levels of white blood cells and platelets.[2] As the bone marrow is affected, compensatory extramedullary haematopoiesis occurs (EMH). EMH occurs mainly in the spleen and can cause the spleen to enlarge up to 20-fold;[2] an enlarged spleen is also known as splenomegaly.

MF primarily affects older adults, with a median age at diagnosis of approximately 65 years.[3] Three key clinical manifestations of MF are anaemia, splenomegaly and constitutional symptoms.[4] A high proportion (≥80%)[3] of patients are symptomatic at diagnosis. The symptom burden of MF leads to impaired health-related quality of life (HRQoL).[5]

Patients with MF are stratified into risk categories using the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS) or Dynamic International Prognostic Scoring System Plus (DIPSS Plus). The DIPSS and/or DIPSS Plus are most commonly used in NHS clinical practice (CS, p19). As explained by the company, (CS, Table 4), the scoring of all three systems are dependent on the presence (or absence) of the following prognostic factors:

- age >65 years
- haemoglobin (Hb) <10g/dL
- white blood cell count >25x10^9/L
- peripheral blood blasts ≥1%
- presence of constitutional symptoms (e.g., fever, night sweats, pruritus, weight loss).

The DIPSS Plus also includes red blood cell (RBC) transfusion dependence (TD), karyotype, and platelet count <100×10^9/L.

IPSS is designed to be used at the time of diagnosis whereas DIPSS and DIPSS Plus can be applied at any time during the disease course.[6,7] As described in Section 2.3, some MF treatment options are only available for patients classified as having at least Int-2 risk disease, i.e., ≥2 prognostic factors (≥3 using DIPSS Plus). Life expectancy varies by risk status.[6,7] As shown in the CS, Table 4, patients classified as having Int-2 risk have a life expectancy of 2.9 to 4 years and those classified as high risk (HR) have a life expectancy of 1.3 to 2.3 years.[6,7]

In the CS, the company has "presented a case only for approving momelotinib in Int-2/HR patients" (CS, p20) and, more specifically, patients with moderate to severe anaemia (CS, Table 2). Grading of anaemia, according to the National Cancer Institute (NCI),[8] is as follows:

- mild: Hb 10.0g/dL to lower limit of normal
- moderate: Hb 8.0g/dL to 9.9g/dL
- severe: Hb 6.5g/dL to 7.9g/dL
- life-threatening: Hb <6.5g/dL.

Clinical advice to the EAG is in line with advice to the company (CS, p22) that, for patients with MF, the term moderate to severe anaemia has no accepted clinical definition. Clinical advice to the company and the EAG is that the definition of moderate to severe anaemia presented in the CS ("any clinically relevant anaemia severe enough to warrant treatment") reflects NHS clinical understanding.

2.3 Company's overview of current service provision

Apart from allogeneic-stem cell transplant (allo-SCT), which is not a suitable option for most patients, there are no curative treatment options for patients with MF.

2.3.1 Current treatment options for patients with MF

In NHS clinical practice, treatment options for patients with MF largely depend on disease severity, disease symptoms and prognostic risk; the focus of disease management is to delay progression and alleviate symptoms. The guidelines most commonly used by UK haematologists are the British Committee for Standards in Haematology (BSH) guidelines for the diagnosis and management of MF,[7] which were first published in 2012. A revision to the BSH guidelines[9] was published in 2014, after the European Medicines Agency (EMA) licensed ruxolitinib as a treatment for disease-related splenomegaly or symptoms in adult patients with MF.[10]

Best available therapy

In 2012, the BSH[7] considered medical treatment to be "the treatment of choice for most patients with symptomatic splenomegaly." A summary of best available therapy (BAT), as described in the 2012 BSH guidelines,[7] is provided in Table 1.

Table 1 Summary of BSH recommended best available therapy for patients with MF

Therapy	BSH recommendation
Medical treatment	
JAKi	First-line therapy where permitted Consideration should be given to use as second-line therapy as part of a clinical trial, or via patient access protocols until widely available
Hydroxycarbamide	Treatment for patients with splenomegaly who do not have cytopenia First-line choice treatment for myelosuppression
Thalidomide and prednisolone	Myelosuppressive treatment for patients with splenomegaly and cytopenia
Lenalidomide	Myelosuppressive treatment for patients with splenomegaly anaemia and platelet count >100x10^9/l
Anagrelide	Myelosuppressive treatment with caution in patients with established MF
IFN-α	Myelosuppressive treatment in early phase MF with more proliferative disease features
Anaemia supportive measures	
RBC transfusion	Anaemia supportive measure for patients with MF and symptomatic anaemia (iron chelation therapy is not routinely recommended)
EPO	Anaemia supportive measure for patients with MF and anaemia and endogenous erythropoietin <125u/l
Androgens (danazol)	Anaemia supportive measure for patients with MF and transfusion-dependent anaemia
Other treatment	
Splenectomy	Surgical intervention for patients with drug-refractory symptomatic splenomegaly or anaemia, symptomatic portal hypertension or severe catabolic symptoms
Radiotherapy	For patients with symptomatic splenomegaly and platelet count >50x10^9/l for whom splenectomy is not suitable

Source: BSH guidelines 2012[7]
allo-SCT=allogeneic-stem cell transplant; BSH=British Committee for Standards in Haematology; EPO=erythropoietin; MF=myelofibrosis; IFN-α=interferon-alpha; JAKi=Janus kinase inhibitors; MF=myelofibrosis; RBC=red blood cell

Janus kinase inhibitors

In the 2014 BSH guidelines revision,[9] ruxolitinib is the recommended first-line treatment for disease-related splenomegaly or symptoms in patients with MF. In March 2016, NICE recommended ruxolitinib (TA386)[11] as an option for treating disease-related splenomegaly or symptoms in patients with Int-2/HR disease. Ruxolitinib is the only JAKi routinely commissioned in NHS clinical practice (in England and Wales) for patients with MF. Fedratinib is available via the Cancer Drugs Fund (CDF) (TA756)[12] as an option for treating disease-related splenomegaly or symptoms of MF in patients previously treated with ruxolitinib. As it is only available via the CDF, NICE does not consider that treatment with fedratinib is established NHS clinical practice (in England and Wales) and, therefore, it is not a comparator in this appraisal.

Clinical advice to the EAG is that in NHS clinical practice, if a patient is being treated with ruxolitinib but that treatment becomes less effective, then the patient continues to be prescribed ruxolitinib as clinicians consider that the patient is continuing to receive some benefit from treatment. Clinical advice to the EAG is that the majority of ruxolitinib patients remain on treatment for at least 3 to 5 years. A small proportion of patients may be unresponsive to treatment or lose any benefit from treatment within 3 years. A few patients can remain on ruxolitinib treatment for ≥10 years. There is no standard ruxolitinib dose for patients with MF; patients can receive a maximum dose of 25mg twice daily (BID) and the dose can be reduced to the lowest dose of 5mg once daily (QD).[10]

Curative treatment: Allogeneic-stem cell transplant

Allo-SCT is only recommended in the BSH[7] for patients with Int-2/HR disease who are "deemed fit enough" and who have a human leukocyte antigens (HLA)-matched sibling or unrelated donor available. Allo-SCT has a high risk of transplant-related mortality (depending on the donor type; 18% to 35% at 100 days, 24% to 43% at 1-year and 35% to 50% at 5-years).[13] Clinical advice agrees that the reported allo-SCT rates of 5% in the REALISM UK real-world study[14] reflect NHS clinical practice. The company (CS, pp27-29), "… expects it to be rare that a patient who is eligible for allo-SCT would be offered any alternative treatment, including momelotinib, so allo-SCT is not a comparator in this appraisal." Clinical advice to the EAG agrees.

2.3.2 Treatment pathways for JAKi-naïve and JAKi-experienced patients

The company has presented the treatment pathways for JAKi-naïve and JAKi-experienced patients (who are ruxolitinib relapsed, refractory or intolerant) in the CS, Figure 3:

- **JAKi-naïve patients:** Alternative first-line treatments to ruxolitinib for patients with Int-2/HR disease are hydroxycarbamide and interferon-alpha. Clinical advice to the NICE Appraisal Committee for ruxolitinib (TA386)[11] was that hydroxycarbamide is less clinically effective than ruxolitinib. Clinical advice to the EAG is that hydroxycarbamide is used for patients with Int-2 risk disease but, more commonly, for patients with low and Int-1 risk disease. Interferon-alpha is only recommended as a myelosuppressive therapy for patients "with early phase disease with more proliferative disease features" and is not recommended for the reduction of splenomegaly. Clinical advice is that interferon-alpha is a possible treatment for patients with low and Int-1 risk disease. Clinical advice to the NICE Appraisal Committee for ruxolitinib (TA386)[11] was that thalidomide can be used in NHS clinical practice but that lenalidomide is rarely used. Clinical advice to the EAG agrees.
- **JAKi-experienced patients:** Ruxolitinib and dose-adjusted ruxolitinib are the only established NHS clinical practice treatment options for JAKi-experienced patients. Ruxolitinib can be used alone or in combination with hydroxycarbamide, interferon-alpha, other chemotherapies, radiation therapy and splenectomy. Clinical advice to the EAG is that most patients only receive these treatments as monotherapies in NHS clinical practice. Clinical advice to the EAG is that, typically, 80%-90% of JAKi-experienced NHS patients receive ruxolitinib monotherapy, with 5%-10% receiving

hydroxycarbamide or corticosteroids (e.g., prednisolone). Clinical advice to the EAG is that for patients who experience toxicity during ruxolitinib treatment, the ruxolitinib dose would be reduced; patients would not be re-treated with ruxolitinib following an extended break in treatment with ruxolitinib.

The retrospective REALISM UK real-world study[14] included details about the most commonly used NHS clinical management strategies for patients with MF (January 2018 to January 2019). The REALISM study[14] focused on information provided in 200 patient records from 15 UK centres (14 centres in England and 1 centre in Scotland). Nearly half (n=98/200) of the included patients were classified as Int-2/HR risk; risk classification was missing for 29 patients. 'Watch and wait' was the most common first choice management strategy for patients with Low and Int-1 risk disease (n=45/73, 61.6%) and for patients with Int-2/HR disease (n=47/98, 48.0%; Table 2). In the company's representation of the treatment pathway (CS, Figure 3), 'watch and wait' is only listed as a treatment option for patients with Low risk or Int-1 risk disease. Clinical advice to the EAG is that, in NHS practice, 'watch and wait' is more commonly used for patients with Low risk or Int-1 risk disease than for patients with Int-2/HR disease, especially now clinicians are familiar with using ruxolitinib.

The EAG notes that, in the REALISM study,[14] ruxolitinib was the second most common management strategy for patients with Int-2/HR disease (n=47/98, 48.0%; Table 2) and that one patient with Low-risk disease and nine patients with Int-1 risk disease received treatment with ruxolitinib; this is contrary to NICE guidance for England and Wales.[11] It is possible that most, if not all, of these lower risk patients were people treated in Scotland where ruxolitinib is permitted for NHS patients with any disease risk status.

Table 2 First choice management strategy for patients with Int-2/HR disease[a] in the UK REALISM study

Management strategy	Patients with Int-2/HR disease[a] (N=98)
Watch and wait, n (%)	47 (48.0)
Ruxolitinib, n (%)	23 (23.5)
Hydroxycarbamide, n (%)	21 (21.4)
Anagrelide, n (%)	2 (2.0)
Clinical trial - other JAKi, n (%)	2 (2.0)
Hydroxycarbamide + anagrelide, n (%)	2 (2.0)
IFN-α, n (%)	1 (1.0)

[a]Risk defined using IPSS
IFN-α=Interferon alpha; Int-2/HR=intermediate-2 or high risk; IPSS=International Prognostic Scoring System; JAKi=Janus kinase inhibitor; MF=myelofibrosis
Source: Mead 2022[14]

2.3.3 Anaemia supportive measures for patients with MF

As shown in Table 1 (and CS, Table 6), anaemia supportive measures are available for patients with MF because (as noted in Section 2.2) anaemia is a key clinical manifestation of

MF. Anaemia can also be a side effect of treatment for MF, for example, treatment with ruxolitinib (CS, p22 and p30). The BSH[7] states that iron chelation therapy is not routinely recommended for treating MF; clinical advice to the EAG is that <10% of patients with MF receive iron chelation.

In the REALISM UK study,[14] 88/200 (44.0%) patients were recorded as having anaemia at baseline; where Hb levels were recorded, 63/191 (33.0%) had Hb <10g/dL. According to a 2017 review of MF-related anaemia[15] "…Nearly one-quarter of patients with MF are RBC transfusion-dependent at time of diagnosis and nearly all patients with MF will eventually develop RBC transfusion-dependence". Clinical advice to the EAG is that nearly all patients with MF will develop some degree of anaemia as part of the condition or its treatment.

Anaemia supportive measures listed in the CS (CS, Figure 3), are erythropoiesis-stimulating agents (ESA) (e.g., erythropoietin [EPO]), RBC transfusions and danazol (an androgen). All three anaemia supportive measures are recommended by the BSH:[7,9]

- BSH 2012:[7] EPO for anaemic patients with low erythropoietin levels (<125u/l) was recommended. The guideline authors noted that patients with "relatively moderate anaemia" were most likely to respond to EPO. RBC transfusions were recommended for patients with symptomatic anaemia. Danazol was recommended as a therapeutic option to improve the Hb concentration of patients with MF and TD anaemia.
- BSH 2014:[9] It was noted that anaemia and thrombocytopenia are associated with ruxolitinib treatment, with "anaemia usually peaking by Weeks 12 to 16 and improving thereafter". It was recommended that anaemia may be ameliorated by lowering the dose of ruxolitinib or by concomitant use of ESA, and/or an androgen, such as danazol.

Clinical advice to the company (CS, p29) is that in NHS clinical practice, supportive measures for patients treated with ruxolitinib "mirror those used in the overall MF population and include ESAs (20% to 60% of patients), RBC transfusions (10% to 25% of patients) and other treatments such as corticosteroids, danazol and thalidomide (<10% of patients).[16]" Clinical advice to the EAG is that approximately a third to a half of patients treated with ruxolitinib require anaemia supportive measures which most commonly include EPO and RBC transfusions, as appropriate. As highlighted in Table 1, danazol is recommended by the BSH[7] as an option for patients who are RBC TD. However, the company highlighted (CS, Table 6) that there are supply issues with danazol in the UK; clinical advice to the EAG is that the limited availability of danazol means that it is not commonly used in NHS clinical practice.

2.3.4 Momelotinib

Momelotinib is a selective small-molecule inhibitor of wild-type JAK1 and JAK2 (JAK1/JAK2) and mutant JAK2V617F; JAK1/JAK2 are involved in haematopoiesis and immune system regulation signalling pathways.[17] Momelotinib and its major human circulating metabolite, M21, also inhibit activin A receptor type 1 (ACVR1) to reduce liver hepcidin expression which

results in increased iron availability in the blood serum and stimulates bone marrow erythropoiesis.[4] Momelotinib therefore can reduce symptoms of anaemia in contrast to ruxolitinib which typically worsens anaemia symptoms and is associated with treatment-related anaemia.[18]

Momelotinib is available as 100mg, 150mg and 200mg oral tablets (CS, Appendix C, Draft SmPC). The recommended starting (and maximum) dose is 200mg QD taken orally. The dose can be reduced by 50mg decrements to 150mg QD and to 100mg QD. If patients are unable to tolerate 100mg QD, then patients are recommended to discontinue treatment. Patients can restart treatment with momelotinib after dose interruptions and the dose can be increased up to 200mg QD, as clinically appropriate.

2.4 Critique of company's definition of the decision problem

The company has presented, separately, clinical and cost effectiveness evidence for patients with MF who are JAKi-naïve and patients with MF who are JAKi-experienced.

The primary sources of direct clinical effectiveness evidence presented by the company were the SIMPLIFY-1 trial[19] and SIMPLIFY-2 trial,[17] with supportive evidence from the MOMENTUM trial.[20] The key trial characteristics are presented in Table 3.

Table 3 Key characteristics of the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials

Trial	Study design	Statistical hypothesis for primary outcome	Intervention	Comparator	Population
SIMPLIFY-1	Phase III, multicentre, international, double-blind RCT	Non-inferiority[a]	Momelotinib (N=215)	Ruxolitinib (N=217)	JAKi-naïve patients with MF
SIMPLIFY-2	Phase III, multicentre, international, open-label RCT	Superiority[a]	Momelotinib (N=104)	BAT including ruxolitinib (N=52)	JAKi-experienced patients with MF (all patients previously treated with ruxolitinib)
MOMENTUM	Phase III, multicentre, international, double-blind, RCT	Non-inferiority and superiority[b]	Momelotinib (N=130)	Danazol (N=65)	JAKi-experienced patients with symptomatic MF and anaemia

[a]Statistical hypothesis tested for spleen response rate
[b]Statistical hypothesis tested for co-primary outcomes of red blood cell transfusion independence (non-inferiority) and total symptom score (superiority)
BAT=best available therapy; JAKi=Janus kinase inhibitor; MF=myelofibrosis; RCT=randomised controlled trial
Source: CS, pp34-35 and CS, Table 7

A summary of the decision problem outlined in the final scope[21] issued by NICE and addressed by the company is summarised in Table 4. More information regarding the key issues relating to the decision problem is provided in Sections 2.4.1 to 2.4.4.

Table 4 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	Adults with disease-related splenomegaly or symptoms of: • PMF (also known as chronic idiopathic MF • Post-PV MF or • Post-ET MF	Adults with **moderate to severe anaemia** and disease-related splenomegaly or symptoms of: • PMF (also known as chronic idiopathic MF), • Post-PV MF or • Post-ET MF The inclusion of moderate to severe anaemia [redacted]. Otherwise as per the NICE final scope	Evidence is presented for both the population in the final scope issued by NICE and for patients who may be considered to have moderate to severe anaemia (based on Hb levels) and disease-related splenomegaly or symptoms of MF (i.e., PMF, post-PV MF and Post-ET MF) [redacted]
Intervention	Momelotinib	Momelotinib	As per the final scope issued by NICE
Comparator(s)	For people eligible for treatment with ruxolitinib: • ruxolitinib For people whose	For people **with no previous treatment with JAKi and Int-2/HR disease**: • ruxolitinib For people with prior JAKi exposure, who may be	***JAKi-naïve population*** As per the final scope issued by NICE. Ruxolitinib was the SIMPLIFY-1 trial comparator. While patients treated with ruxolitinib in NHS clinical practice in England and Wales are required to have Int-2/HR disease, they are not required to have moderate to severe anaemia ***JAKi-experienced population***

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate **(including people with low or Int-1 risk disease)**: • established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion **and ruxolitinib**)	currently receiving JAKi or have discontinued but remain eligible for JAKi treatment: • established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion **and ruxolitinib**) No evidence is presented for people with low or Int-1 risk disease due to limitations of the available evidence. Otherwise as per the NICE final scope, noting that the revised wording more closely follows the structure of the evidence and economic modelling (see below)	As per the final scope issued by NICE. BAT was the comparator in the SIMPLIFY-2 trial. The company considered (CS, Table 7) that the BAT arm of the SIMPLIFY-2 trial reflects established NHS clinical practice. Clinical advice to the EAG is that, in NHS clinical practice, ruxolitinib (including dose-adjusted ruxolitinib) is the most common BAT for JAKi-experienced patients (see Section 2.3.2) In the MOMENTUM trial, all patients in the comparator arm received only danazol, an anaemia supportive measure; clinical advice to the EAG is that the limited availability of danazol means that it is rarely used in NHS clinical practice ***Low or Int-1 risk disease:*** The momelotinib trials all included patients with Int-1 risk disease (20.6% in the SIMPLIFY-1 trial, 25.0% in the SIMPLIFY-2 trial, 5.1% in the MOMENTUM trial); however, the company did not conduct subgroup analyses for these patients. The EAG considers subgroup analyses are not necessary for patients with Int-1 risk disease since it is unlikely that Int-1 risk patients will have moderate to severe anaemia; [redacted]

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	gens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion)		

Outcomes	The outcome measures to be considered include: • spleen size • symptom relief (including itch, pain and fatigue) • overall survival • leukaemia-free survival • response rate • haematologic parameters (including red blood cell transf	The outcome measures to be considered include: • spleen size (spleen response rate) • symptom relief (Total symptom score response rate) • overall survival • leukaemia-free survival • response rate • haematologic parameters (including red blood cell transfusion and blood count) • treatment-emergent/-related AEs • HRQoL	As per the final scope issued by NICE. The EAG notes that these are similar outcomes to those reported in the COMFORT-I and COMFORT-II trials; data from these trials were used to inform NICE TA386[11] (ruxolitinib for treating disease-related splenomegaly or symptoms in adults with MF)

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	usion and blood count) • AEs of treatment • HRQoL		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologi	<u>JAKi-naïve patients</u> Cost-comparison analysis. The technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication <u>JAKi-experienced patients</u> Cost utility analysis to be conducted as per NICE guidance Expressed in terms of incremental cost per QALY Time horizon for estimating clinical and cost-effectiveness will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from	The company has provided cost comparison analysis results for the JAKi-naïve population (10 year time horizon). The company has provided cost utility analysis results for the JAKi-experienced population (33 year time horizon). Cost utility analysis results are expressed in terms of incremental cost per quality adjusted life year gained. Costs were considered from an NHS and PSS perspective.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	es recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being	an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account The availability and cost of biosimilar and generic products will be taken into account	

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account The availability and cost of biosimilar and generic products should be taken into account		

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Subgroups	• People whose disease was previously treated with a JAKi • Prognostic factors such as Hb <10g/dL, leukocyte count >25 x 10^9/L, circulating blasts (immature blood cells) ≥1%, presence of constitutional symptoms or	The primary submission will focus on the **ITT** of the pivotal clinical trials of patients (i.e., those eligible for JAKi treatment). People whose disease was previously treated with JAKi will be included in the primary analysis, based on SIMPLIFY-2 data Subgroup analyses in anaemic patients (Hb <10g/dL and Hb <12g/dL) will also be included	The company presented post-hoc subgroup analysis results for both JAKi-naïve and JAKi-experienced populations: • patients with Int-2/HR Hb<10g/dL • patients with Int-2/HR Hb<12g/dL The company considered that these subgroups represent Int-2/HR populations with anaemia Clinical advice to the EAG is that patients with Int-2/HR disease and Hb<10g/dL are more likely to represent patients with moderate to severe anaemia in clinical practice than patients with Int-2/HR disease and Hb<12g/dL The EAG further notes that Hb<10g/dL is used to describe/define patients with anaemia in the following: • NCI criteria for anaemia • draft SmPC for momelotinib • company's AE subgroup analysis of patients with anaemia • SIMPLIFY-1 and MOMENTUM trial inclusion criteria

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	platelet count		

AE=adverse event; BAT=best alternative therapy; ET=essential thrombocythemia; Hb=haemoglobin; HRQoL=health-related quality of life; Int-1/LR=intermediate-1 risk disease; Int-2/HR=intermediate-2 or high risk; ITT=intention to treat; JAKi=Janus kinase inhibitor; MF=myelofibrosis; NCI=National Cancer Institute; PMF=primary myelofibrosis; PSS=Personal Social Services; PV=polycythemia vera; QALY=quality adjusted life year
Source: CS, Table 2 and EAG comment

2.4.1 Population and anticipated licensed indication of the intervention

The company's anticipated marketing authorisation for momelotinib (CS, Table 3) is "[redacted] The company's proposed positioning of momelotinib is as a treatment for patients with Int-2/HR disease (CS, Figure 4). The focus of the company's cost comparison analysis (JAKi-naïve population) is patients with Int-2/HR disease and anaemia (CS, p137); data from the SIMPLIFY-1 trial ITT population were used to populate the company's base case analysis. The focus of the company's cost utility model (JAKi-experienced population) is patients with Int-2/HR disease with moderate to severe anaemia (CS, Table 63); SIMPLIFY-2 trial data from patients with Int-2/HR disease and Hb<12g/dL (CS, 157) were used to populate the company's base case analysis.

Populations with moderate to severe anaemia

The company highlighted (CS, p12) that "anaemia is a particularly important symptom for the decision problem in this submission as momelotinib has a novel mechanism of action inhibiting the ACVR1 pathway and therefore reducing the symptoms of anaemia, in contrast to existing JAKis which tend to exacerbate the symptoms of anaemia".

Clinical advice to the company and the EAG is that moderate to severe anaemia should not be based solely on Hb levels. However, the NCI[8] uses the following levels to define moderate and severe anaemia:

- moderate: Hb 8.0g/dL to 9.9g/dL
- severe: Hb 6.5g/dL to 7.9g/dL.

Clinical advice to the EAG is that (as stated in Table 4) patients with Int-2/HR disease and Hb<10g/dL are more likely to represent NHS patients with moderate to severe anaemia in clinical practice than patients with Int-2/HR disease and Hb<12g/dL. Clinical advice to the EAG is that some, albeit very few, patients with Int-1 risk disease may have moderate to severe anaemia.

The EAG cautions that SIMPLIFY-1 and SIMPLIFY-2 analyses were not powered to demonstrate statistically significant differences between the intervention and comparator subgroups based on Hb levels; further, these subgroup analyses were not pre-specified.

2.4.2 Comparators

The comparator in the SIMPLIFY-1 trial for JAKi-naïve patients is ruxolitinib. The comparator in the SIMPLIFY-2 trial for JAKi-experienced patients is BAT; BAT consisted mainly (88.5%)

of dose-adjusted ruxolitinib. Clinical advice to the EAG is that most patients with Int-2/HR disease would receive ruxolitinib, whether JAKi-naïve or JAKi-experienced, as reflected in these trials.

Patients for whom ruxolitinib is not appropriate

The company has not explicitly presented any subgroup evidence to support using momelotinib to treat patients for whom ruxolitinib is not appropriate. The SIMPLIFY-1 trial comparator arm was ruxolitinib and therefore ruxolitinib would have been an appropriate treatment for all patients enrolled in the SIMPLIFY-1 trial. Over four-fifths (88.5%) of patients in the comparator (BAT) arm of the SIMPLIFY-2 trial received ruxolitinib; 11.5% of patients in the comparator arm received a BAT therapy that was not ruxolitinib. Clinical advice to the company and the EAG is that in clinical practice, ruxolitinib would be considered appropriate for most patients with Int-2/HR disease.

2.4.3 Outcomes

Clinical advice to the EAG is that the outcomes specified in the final scope issued by NICE are standard outcomes used in clinical trials of disease-related splenomegaly or symptoms in patients with MF and are the most important outcome measures for this appraisal. The EAG notes that these outcomes are similar to those reported in the COMFORT-I[18] and COMFORT-II[22] trials of ruxolitinib; data from these trials were used to inform the NICE appraisal of ruxolitinib for treating disease-related splenomegaly or symptoms in adults with MF (TA386[11]).

Regarding the key efficacy outcomes in the SIMPLIFY-1 and SIMPLIFY-2 trials, clinical advice to the EAG is that while all are considered important trial outcomes, as well as being meaningful measures in clinical practice, the trial specific definitions for these outcomes are not always used to determine treatment decisions in clinical practice (Table 5).

Table 5 SIMPLIFY-1 and SIMPLIFY-2 trial key efficacy outcomes and definitions

Outcome	Trial definition	EAG comment
Primary endpoint: Spleen response rate	The proportion of patients with ≥35% reduction in spleen volume from baseline at Week 24	Clinical advice to the EAG is that spleen volume reduction is an important clinical outcome, however a <35% reduction in spleen volume can be clinically meaningful for NHS patients, particularly when other key efficacy outcomes are considered
Secondary endpoint: TSS	≥50% reduction in mean TSS at Week 24 compared with baseline	Clinical advice to the EAG is that symptoms are important outcomes in clinical practice but they may not be routinely recorded using standard instruments and that consideration of individual items is clinically relevant. In the SIMPLIFY-1 and SIMPLIFY-2 trials, TSS was measured using the modified MPN-SAF v2.0 which has the following individual items: tiredness, early satiety, abdominal discomfort, night sweats, itching/pruritis, bone pain, pain under left ribs and inactivity (although this last item was excluded when calculating TSS in in the SIMPLIFY-1 and SIMPLIFY-2 trials)
Secondary endpoint: RBC TI	Proportion of patients who had no RBC transfusions and no Hb levels<8g/dl in the previous 12 weeks at Week 24	Clinical advice to the EAG is that in clinical practice, there is no standard definition of RBC TI. A recent recommendation[23] is it should be defined as not requiring an RBC transfusion over 3 months
Secondary endpoint: RBC TD	Proportion of patients who had 4 units of RBC transfusions or Hb levels<8g/dl in the previous 8 weeks at Week 24	Clinical advice to the EAG is that in clinical practice, there is no standard definition of RBC TD but that the trial definition may not capture clinically meaningful changes in transfusion requirements. A widely used definition is ≥1 RBC transfusions over a specified interval, the interval of which varies;[23] a recent recommendation[23] is it should be defined as requiring ≥2 units of RBC transfusions over 3 months

Hb=haemoglobin; MPN-SAF=Myeloproliferative Neoplasm Symptom Assessment Form RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent; TSS=total symptom score
Source: CS, Table 19; Gale 2021;[23] clinical advice to the EAG

The EAG notes that a reduced need for RBC transfusion is also considered an important outcome in clinical practice and that a patient who is not RBC TD may not be RBC TI (or vice versa). In the economic analysis the company also describes patients who are transfusion-requiring (TR), i.e., patients who still need RBC transfusions but who do not meet the strict trial definitions of RBC TD. TR is not an outcome that is reported in the clinical effectiveness evidence presented by the company. Clinical advice to the EAG is that all of efficacy outcomes should be considered when assessing the success of a treatment in clinical practice.

Regarding the key exploratory outcomes of overall survival (OS) and leukaemia-free survival (LFS), the EAG highlights that while patients in the SIMPLIFY-1 and SIMPLIFY-2 trials were followed up for up to 5 years following randomisation (final analysis), all patients continuing treatment from Week 24 received momelotinib. Therefore, interpretation of long-term OS data is difficult.

2.4.4 Economic analysis

The company has used the anticipated momelotinib PAS price to generate the company base cost effectiveness results presented in the CS, for both the JAKi-naïve population (cost comparison model) and JAKi-experienced population (cost utility model). Company and EAG cost effectiveness results using all available PAS prices and other confidential discounts are presented in the confidential appendix.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company in support of the use of momelotinib for disease-related splenomegaly or symptoms in patients with MF.

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify clinical effectiveness evidence of therapies for disease-related splenomegaly or symptoms in patients with MF were presented in the CS (CS, Appendix D). The company literature searches were comprehensive and were completed 6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's review was conducted in accordance with the LRiG in-house systematic review checklist is summarised in Table 6. The EAG considers that the company's systematic review methods were appropriate.

Table 6 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D, Table 3
Were appropriate sources searched?	Yes	CS, Appendix D, Section D.1.1.1
Was the timespan of the searches appropriate?	Yes	CS, Appendix D, Section D.1.1.1 Electronic databases were searched to identify relevant studies published since 2010
Were appropriate search terms used?	Yes	CS, Appendix D, Table 1
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D, Table 3
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D, Section D.1.1.2
Was data extracted by two or more reviewers independently?	Partial	CS, Appendix D, Section D.1.1.2 One reviewer extracted data and the data were then checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Section B.2.6.1 and CS, Appendix D, Section D.1.3
Was the quality assessment conducted by two or more reviewers independently?	Partial	CS, Appendix D, Section D.1.3 One reviewer quality assessed the primary publication for each included trial and a second (independent) reviewer then checked the quality assessments
Were attempts to synthesise evidence appropriate?	Yes	Narrative synthesis of trial data was reported in the CS; no meta-analyses or indirect comparisons were required

CS=company submission
Source: EAG in-house checklist

3.2 Critique of main trial of the technology of interest, the company's analysis and interpretation

3.2.1 Included trials

The company's systematic literature review (SLR) was broader with regard to population than the decision problem addressed in the CS as the SLR eligibility criteria did not specify moderate to severe anaemia. The company searched for studies of JAK inhibitors (fedratinib, momelotinib, ruxolitinib and pacritinib) or best available therapies (hydroxyurea, corticosteroids, interferon-alpha, immuno-modulating agents, danazol, decitabine, cytarabine, anagrelide, epoetin-alpha, purine analogues, melphalan, busulfan, pomalidomide, azacitidine).

The company SLR identified 14 RCTs that provided clinical effectiveness evidence of systemic therapies for treating disease-related splenomegaly or symptoms in patients with Int-2/HR MF. However, only three trials included momelotinib versus a comparator that the company considered to be relevant to this appraisal:

- SIMPLIFY-1 trial (momelotinib versus ruxolitinib for JAKi-naïve population)
- SIMPLIFY-2 trial (momelotinib versus BAT for JAKi-experienced population)
- MOMENTUM trial (momelotinib versus danazol for JAKi-experienced population).

The EAG agrees with the company in that the MOMENTUM trial offers supportive clinical evidence for patients with more severe disease (symptomatic [defined as TSS≥10] and anaemic [defined as Hb<10g/dL]), albeit for a comparator that is not widely used in the UK (and where it is used, only as an anaemia supportive measure rather than an intervention to treat disease). Further information about the MOMENTUM trial is therefore presented in Appendix 8, Section 8.8.

3.2.2 SIMPLIFY-1 trial conduct and baseline patient characteristics (JAKi-naïve)

SIMPLIFY-1 trial

The company provided details of the SIMPLIFY-1 trial in the CS (CS, Table 8). The trial was a Phase III, multicentre, international, double-blind, non-inferiority RCT (131 sites in 22 countries including the UK). Randomisation was stratified by RBC TD (yes or no; defined as ≥4 units of RBCs or Hb<8g/dL in the 8 weeks prior to randomisation excluding cases associated with clinically overt bleeding) and platelet count (<100x10^9/L, ≥100x10^9/L and ≤200x10^9/L or >200x10^9/L). The SIMPLIFY-1 trial included a 24-week double-blind randomised controlled period (primary data-cut: 12 September 2016) followed by an open-label phase (up to 5 years from randomisation) where patients randomised to momelotinib

could continue treatment with momelotinib and patients randomised to ruxolitinib could switch to treatment with momelotinib (data-cut: 12 September 2017); in the ruxolitinib arm, 197/201 (98.0%) patients who completed the 24-week randomised controlled treatment phase switched to treatment with momelotinib.

Key criteria regarding eligibility and concomitant therapy were as follows:

- Int-1 or Int-2/HR risk MF as defined by the IPSS associated with symptomatic splenomegaly, hepatomegaly, anaemia (Hb<10g/dL), and/or unresponsiveness to available therapy
- concomitant use of ESAs as anaemia supportive measures was prohibited during the 24-week randomised controlled period for patients in both treatment arms.

In relation to these criteria, the EAG notes:

- while patients may have had Int-2/HR risk and/or moderate to severe anaemia, this was not always the case
- clinical advice to the EAG is that patients with MF treated with ruxolitinib may also receive an ESA to control anaemia.

SIMPLIFY-1 trial baseline patient characteristics

A summary of the SIMPLIFY-1 trial patient (ITT, Hb<12g/dL, Hb<10g/dL) baseline characteristics is presented in Table 7. Clinical advice to the EAG is that the baseline characteristics of the SIMPLIFY-1 trial patients (ITT population) are representative of NHS patients with disease-related splenomegaly or symptoms of MF. The EAG notes that the Hb level post-hoc subgroups were intended to represent patients with moderate to severe anaemia. There were a few notable imbalances between Hb level subgroup treatment arms:

- fewer patients in the momelotinib arm had HR disease than in the ruxolitinib arm; the EAG considers this could bias results in favour of momelotinib
- fewer patients in the momelotinib arm had Hb≥8g/dL than in the ruxolitinib arm; the EAG considers this could bias results in favour of ruxolitinib
- in the Int-2/HR Hb<10g/dL subgroup, fewer patients in the momelotinib arm were RBC transfusion-independent (TI) than in the ruxolitinib arm; the EAG considers this could bias results in favour of ruxolitinib
- in the Int-2/HR Hb<10g/dL subgroup, more patients in the momelotinib arm were RBC TD than in the ruxolitinib arm; the EAG considers this could bias results in favour of ruxolitinib.

Table 7 Baseline characteristics of SIMPLIFY-1 trial patients (JAKi-naïve population)

Characteristic	ITT population		Int-2/HR Hb<12g/dL		Int-2/HR Hb<10g/dL	
	Momelotinib (N=215)	Ruxolitinib (N=217)	Momelotinib (N=137)	Ruxolitinib (N=143)	Momelotinib (N=84)	Ruxolitinib (N=90)
Mean age, years (SD)	65.0 (10.67)	64.4 (10.49)	[redacted]	[redacted]	[redacted]	[redacted]
Male sex, n (%)	124 (57.7)	120 (55.3)	[redacted]	[redacted]	[redacted]	[redacted]
MF subtype, n (%)						
PMF	128 (59.5)	116 (53.5)	[redacted]	[redacted]	[redacted]	[redacted]
Post-PV	48 (22.3)	50 (23.0)	[redacted]	[redacted]	[redacted]	[redacted]
Post-ET	39 (18.1)	51 (23.5)	[redacted]	[redacted]	[redacted]	[redacted]
Risk category, n (%)						
Int-1	46 (21.4)	43 (19.8)	NA	NA	NA	NA
Int-2	76 (35.3)	67 (30.9)	[redacted]	[redacted]	[redacted]	[redacted]
HR	93 (43.3)	107 (49.3)	[redacted]	[redacted]	[redacted]	[redacted]
TSS, mean (SD)	19.4 (13.18)	17.9 (11.47)	[redacted]	[redacted]	[redacted]	[redacted]
Mean Hb,g/dL (SD)	10.6 (2.10)	10.7 (2.38)	[redacted]	[redacted]	[redacted]	[redacted]
Hb≥8g/dL, n (%)	186 (86.5)	195 (89.9)	[redacted]	[redacted]	[redacted]	[redacted]
Mean platelet count, x10^3/µL	301.1 (207.03)	301.5 (255.88)	[redacted]	[redacted]	[redacted]	[redacted]
RBC TI, n (%)	147 (68.4)	150 (70.0)	[redacted]	[redacted]	[redacted]	[redacted]
RBC TD, n (%)	53 (24.7)	52 (24.0)	[redacted]	[redacted]	[redacted]	[redacted]

ET=essential thrombocythemia; Hb=haemoglobin; HR=high risk; Int-1=Intermediate-1; Int-2=Intermediate-2; ITT=intention-to-treat; JAKi=Janus kinase inhibitor; MF=myelofibrosis; NA=not applicable; PMF=primary myelofibrosis; PV=polycythaemia vera; RBC=red blood cell; SD=standard deviation; TD=transfusion dependence; TI=transfusion independence; TSS=total symptom score
Source: CS, Table 9 and Table 38 and clarification question A13, Table 35 and Table 36

3.2.3 SIMPLIFY-2 trial conduct and baseline patient characteristics (JAKi-experienced)

SIMPLIFY-2 trial

The company provided details of the SIMPLIFY-2 trial in the CS (CS, Table 8). The trial was Phase III, multicentre, international, open-label, superiority RCT (52 sites in 8 countries including the UK). Randomisation was stratified by RBC TD (yes or no; defined as ≥4 units of RBCs or Hb<8g/dL in the 8 weeks prior to randomisation excluding cases associated with clinically overt bleeding) and baseline TSS (<18 or ≥18). All patients in the trial had been previously treated with ruxolitinib. The SIMPLIFY-2 trial included an open-label 24-week randomised controlled period (primary data-cut: 12 September 2016) followed by an open-label phase (up to 5 years from randomisation) where patients randomised to momelotinib could continue treatment with momelotinib and patients randomised to BAT could switch to treatment with momelotinib (data-cut: 28 July 2016); in the BAT arm, all 40/40 patients who completed the randomised controlled period switched to treatment with momelotinib (100%). Key criteria regarding eligibility and concomitant therapy were as follows:

- current or previous treatment with ruxolitinib for MF for ≥28 days and characterised by the following:
    - requirement for RBC transfusions while on ruxolitinib treatment, or
    - dose adjustment of ruxolitinib to <20mg BID at the start of, or during, ruxolitinib treatment and at least one of the following while on ruxolitinib treatment:
        - Grade ≥3 thrombocytopenia
        - Grade ≥3 anaemia
        - Grade ≥3 haematoma (bleed)
- concomitant use of ESA as anaemia supportive measures was prohibited during the 24-week randomised controlled period for patients in the momelotinib arm[24] and while ESAs were permitted in the BAT arm, they were not commonly used (see Table 8).

In relation to these criteria, the EAG notes:

- while patients may have had Int-2/HR risk and/or moderate to severe anaemia, this was not always the case
- clinical advice to the EAG is that patients with MF treated with BAT (including ruxolitinib) may receive BAT (including ruxolitinib) in combination with an ESA to control anaemia but patients may have previously had anaemia supportive measures which is why they may not have received these again.

The composition of treatments that made up the BAT arm in the SIMPLIFY-2 trial ITT population are presented in Table 8. The composition of the BAT arm in the Int-2/HR Hb<10g/dL (and Int-2/HR Hb<12g/dL) subgroup is unknown.

Table 8 Composition of BAT arm in the SIMPLIFY-2 trial

BAT (N=52)	Used alone or in combination, n (%)	Used in combination with ruxolitinib, n (%)	Used in combination with another drug, n (%)
Any BAT	52 (100)	14 (26.9)	2 (3.8)
Ruxolitinib	46 (88.5)	--	0
Hydroxyurea	12 (23.1)	9 (17.3)	1 (1.9)
Prednisone / prednisolone	6 (11.5)	6 (11.5)	0
Danazol	3 (5.8)	2 (3.8)	1 (1.9)
ESA	2 (3.8)	1 (1.9)	1 (1.9)
Anagrelide	1 (1.9)	1 (1.9)	0
Aranesp	1 (1.9)	0	1 (1.9)
Aspegic	1 (1.9)	1 (1.9)	0
Thalidomide	1 (1.9)	1 (1.9)	0
No therapy	2 (3.8)	0	0

BAT=best available therapy; ESA=erythropoietin stimulating agent
Source: CS, Table 14 and CS, Table 15

SIMPLIFY-2 trial baseline patient characteristics

A summary of the SIMPLIFY-2 trial baseline patient characteristics is presented in Table 9. The EAG considers that most patient characteristics were well balanced between treatment arms, however, there were a few notable imbalances:

- in the ITT population, fewer patients had Int-1 disease and more patients had Int-2/HR disease in the momelotinib arm than in the BAT arm; the EAG considers this could bias results in favour of BAT
- in the Hb level subgroups, fewer patients in the momelotinib arm had Hb≥8g/dL than in the BAT arm; the EAG considers this could bias results in favour of BAT
- in the Int-2/HR Hb<10g/dL subgroup, fewer patients in the momelotinib arm were RBC TI than in the BAT arm; the EAG considers this could bias results in favour of BAT
- in the Int-2/HR Hb<10g/dL subgroup, more patients in the momelotinib arm were RBC TD than in the BAT arm; the EAG considers this could bias results in favour of BAT.

Clinical advice to the EAG is that the patient characteristics are representative of NHS patients with disease-related splenomegaly or symptoms of MF.

Table 9 Baseline characteristics of SIMPLIFY-2 trial patients (JAKi-experienced)

Characteristic	ITT population		Int-2/HR Hb<12g/dL		Int-2/HR Hb<10g/dL	
	Momelotinib (N=104)	BAT (N=52)	Momelotinib (N=77)	BAT (N=34)	Momelotinib (N=61)	BAT (N=32)
Mean age, years (SD or range)	66.4 (8.1)	69.4 (7.4)	[redacted]	[redacted]	[redacted]	[redacted]
Male sex, n (%)	69 (66)	24 (46)	[redacted]	[redacted]	[redacted]	[redacted]
MF subtype, n (%)						
PMF	64 (62)	30 (58)	[redacted]	[redacted]	[redacted]	[redacted]
Post-PV	18 (17)	12 (23)	[redacted]	[redacted]	[redacted]	[redacted]
Post-ET	22 (21)	10 (19)	[redacted]	[redacted]	[redacted]	[redacted]
Risk category, n (%)						
Int-1	23 (22)	16 (31)	NA	NA	NA	NA
Int-2	62 (60)	28 (54)	[redacted]	[redacted]	[redacted]	[redacted]
HR	19 (18)	8 (15)	[redacted]	[redacted]	[redacted]	[redacted]
TSS, mean (SD)	18.5 (13.0)	20.5 (16.0)	[redacted]	[redacted]	[redacted]	[redacted]
Mean Hb,g/dL (SD)	9.4 (1.9)	9.5 (1.6)	[redacted]	[redacted]	[redacted]	[redacted]
Hb ≥8g/dL, n (%)	77 (74)	46 (89)	[redacted]	[redacted]	[redacted]	[redacted]
Mean platelet count, $x10^3/\mu L$	170.8 (148)	126.5 (95.9)	[redacted]	[redacted]	[redacted]	[redacted]
RBC TI, n (%)	32 (31)	19 (37)	[redacted]	[redacted]	[redacted]	[redacted]
RBC TD, n (%)	58 (56)	27 (52)	[redacted]	[redacted]	[redacted]	[redacted]

ET=essential thrombocythemia; Hb=haemoglobin; HR=high risk; Int-1=Intermediate-1; Int-2=Intermediate-2; ITT=intention-to-treat; JAKi=Janus kinase inhibitor; MF=myelofibrosis; NA=not applicable; PMF=primary myelofibrosis; PV=polycythaemia vera; RBC=red blood cell; SD=standard deviation; TD=transfusion dependence; TI=transfusion independence; TSS=total symptom score
Source: CS, Table 11 and Table 40 and clarification question A13, Table 38

3.2.4 EAG assessment of the statistical approach adopted for the analysis of the SIMPLIFY-1 and SIMPLIFY-2 trials

Information relevant to the statistical approach taken by the company to analyse data from the SIMPLIFY-1 and SIMPLIFY-2 trials has been extracted from the Clinical Study Reports (CSRs),[24,25] the trial statistical analysis plans (TSAPs),[26,27] the trial protocols,[28,29] and the CS. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the SIMPLIFY-1 and SIMPLIFY-2 trials is provided in Appendix 1, Section 8.1, Table 54. The most important issues relating to the company's statistical approach are outlined in the text below.

Subgroup analysis of patients with Int-2/HR Hb<10g/dL and Int-2/HR Hb<12g/dL

The EAG notes that the subgroup analyses presented for patients with Int-2/HR disease Hb<10g/dL and Int-2/HR disease Hb<12g/dL were post-hoc. The EAG considers these post-hoc subgroup analyses were well-justified due to the proposed positioning of momelotinib in the treatment pathway.

Non-inferiority margins (SIMPLIFY-1 trial)

The non-inferiority margin for the primary outcome was set to test whether the spleen response rate of momelotinib at Week 24 is more than 60% of the spleen response rate of ruxolitinib at Week 24 (based on stratified Cochran-Mantel-Haenszel [CMH] proportions). Non-inferiority would only be demonstrated if the company's calculations indicated at the 95% confidence level that the spleen response rate of momelotinib at Week 24 is more than 60% of the spleen response rate of ruxolitinib at Week 24.

The non-inferiority margin for the secondary outcome of TSS was set to test whether the TSS rate of momelotinib at Week 24 is more than 67% of the TSS rate of ruxolitinib at Week 24. Non-inferiority would only be demonstrated if the company's calculations indicated at the 95% confidence level that the TSS rate of momelotinib at Week 24 is more than 67% of the TSS rate of ruxolitinib at Week 24.

The non-inferiority margins were derived from COMFORT-I trial[18] (ruxolitinib versus BAT in JAKi-naïve patients) results, using the lower margins of the CIs for each outcome (stated in the SIMPLIFY-1 trial CSR[25] to be [redacted] for spleen response rate and [redacted] for TSS [the mid-point estimates were 42% and 46%, respectively]) to derive the (largest) sample size. It was also noted in the SIMPLIFY-1 trial CSR[25] (Section 9.8.2.5.4) that [redacted]

Clinical advice to the EAG is that the statistically defined non-inferiority margins may be wider than the difference that could be considered clinically acceptable or tolerable and therefore momelotinib to be considered as 'similar' or 'not worse' than ruxolitinib in terms of symptom control.

Hierarchical testing

The company used a hierarchical approach to statistically test the primary endpoint (spleen response rate) and secondary endpoints (TSS response rate, RBC TI rate, RBC TD rate, rate of RBC transfusions) for both the SIMPLIFY-1 and SIMPLIFY-2 trials:

- SIMPLIFY-1 was designed to test non-inferiority of momelotinib versus ruxolitinib for spleen response rate and TSS response rate, as well as superiority of momelotinib versus ruxolitinib for primary and secondary efficacy outcomes (TSAP,[26] Section 3.5); non-inferiority of momelotinib to ruxolitinib was demonstrated for spleen response rate but not for TSS response rate, therefore analyses of all subsequent endpoints in the statistical hierarchy should be considered descriptive, with nominal significance reported
- SIMPLIFY-2 was designed to test superiority of momelotinib versus BAT for primary and secondary efficacy outcomes (TSAP,[27] Section 3.5); superiority of momelotinib compared to BAT was not achieved for spleen response rate, therefore analyses of all subsequent endpoints in the statistical hierarchy should be considered descriptive, with nominal significance reported.

The EAG is satisfied that the clinical effectiveness results presented in the CS were appropriately interpreted.

3.2.5 SIMPLIFY-1 trial quality assessment

The company assessed the quality of the SIMPLIFY-1 trial using the methodology checklist for randomised controlled trials from the Process and Methods: The social care guidance manual (PMG10),[30] published by NICE. The company's and EAG's assessment of the SIMPLIFY-1 trial and EAG comments are presented in Appendix 2, Section 8.2, Overall, the company found the overall risk of bias in the SIMPLIFY-1 trial to be low.

The EAG considers that the SIMPLIFY-1 trial was of good methodological quality but considers that the trial had an unclear risk of attrition bias.

3.2.6 SIMPLIFY-2 trial quality assessment

The company assessed the quality of the SIMPLIFY-2 trial using the methodology checklist for randomised controlled trials from PMG10.[30] The company's and EAG's assessment of the SIMPLIFY-2 trial and EAG comments are presented in in Appendix 3, Section 8.3. Overall, the company found the overall risk of bias in the SIMPLIFY-2 trial to be low.

The EAG considers that, overall, the SIMPLIFY-2 trial was of good methodological quality but considers that the trial had an unclear risk of attrition bias. The EAG agrees with the company that the primary endpoint (spleen volume response rate) and the secondary transfusion rate endpoints are at low risk of performance and detection bias because these are objective measures. However, the EAG considers that there was risk of performance and detection bias for the secondary endpoint, TSS response rate, because this is a subjective measure in an open-label study. The EAG therefore considers that TSS response rate could be biased in favour of momelotinib versus BAT.

The company considered (clarification question A12) that the SIMPLIFY-2 trial had less internal validity than the SIMPLIFY-1 trial because the SIMPLIFY-2 trial was open-label whereas the SIMPLIFY-1 trial included a double-blind randomised controlled treatment phase. However, the EAG considers that most of the checklist criteria have been met for the SIMPLIFY-2 trial and that the conclusions are unlikely to change, regardless of the level of blinding.

3.3 Key efficacy results: JAKi-naïve population (SIMPLIFY-1 trial)

The ITT population and Hb levels subgroup results from the key primary and secondary efficacy results at Week 24 are presented in Table 10. A summary of the key efficacy results with EAG comments is presented in Section 3.3.1 to 3.3.4. The EAG has focussed the emphasis of its summary and commentary on the Int-2/HR Hb<10g/dL subgroup. However, in general, for all outcomes, the results for the Int-2/HR Hb<10g/dL subgroup were similar to the results for the Int-2/HR Hb<12g/dL subgroup and ITT population. The EAG has highlighted where this was not the case.

The EAG highlights that ESAs as concomitant anaemia supportive measures were prohibited in both SIMPLIFY-1 trial treatment arms. Clinical advice to the EAG is that ESAs are often given alongside ruxolitinib in NHS clinical practice. The SIMPLIFY-1 trial efficacy results (particularly RBC TI and RBC TD outcomes) may have been different if ESAs had been permitted.

Table 10 Summary of SIMPLIFY-1 trial key efficacy results at Week 24

Outcome by population/subgroup	Momelotinib n/N (%)	Ruxolitinib n/N (%)	Proportion difference (95% CI) p-value
Spleen response rate[a]			
ITT population 95% CI (%)	[redacted]	[redacted]	[redacted][b]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][b]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][b]
TSS response rate[c]			
TSS population[c]	60/211 (28.4)	89/211 (42.2)	0.00 (-0.08 to 0.08) p=0.98[d]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][d]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][d]
RBC TI rate[e]			
ITT population	143/215 (66.5)	107/217 (49.3)	[redacted] nominal p<0.001[f]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][f]
RBC			
ITT population	65/215 (30.2)	87/217 (40.1)	[redacted] nominal p=0.019
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted] [f]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted] [f]

Note: Where p values have been generated by statistical tests that were not part of the pre-specified hierarchical testing strategy, the EAG has labelled these as 'nominal'

[a]Spleen response rate defined as the proportion of patients with ≥35% reduction in spleen volume from baseline at Week 24 (95% CI only reported for the ITT population)

[b]Stratified CMH analysis for non-inferiority hypothesis testing. If the company's calculations indicated at the 95% confidence level that the spleen response rate of momelotinib at Week 24 is more than 60% of the spleen response rate of ruxolitinib at Week 24 (stratum-adjusted CMH proportions), non-inferiority would be demonstrated
[c]TSS defined as the proportion of patients with a ≥50% reduction in mean MPN-SAF TSS at Week 24 compared with baseline. Measured all randomised patients with baseline TSS >0, or who had baseline TSS of 0 but with TSS >0 or missing at Week 24
[d]Stratified CMH analysis for non-inferiority hypothesis testing. If the company's calculations indicated at the 95% confidence level that the TSS response rate of momelotinib at Week 24 is more than 67% of the TSS response rate of ruxolitinib at Week 24 (stratum-adjusted CMH proportions), non-inferiority would be demonstrated
[e]RBC TI defined as the proportion of patients who had no RBC transfusions and no Hb levels<8g/dL in the previous 12 weeks at Week 24
[f]As non-inferiority was not achieved in the secondary endpoint of TSS response rate in the SIMPLIFY-1 trial, analyses of subsequent secondary endpoints are descriptive (nominal) only and statistical significance should not be inferred
[g] RBC TD defined as the proportion of patients who had 4 units of RBC transfusions or Hb levels<8g/dL in the previous 8 weeks at Week 24
CI=confidence interval; CMH=Cochran Mantel Haenzsel; Hb=haemoglobin; HR=high risk; Int-2=intermediate-2; ITT=intention-to-treat; MPN-SAF=Myeloproliferative Neoplasm Symptom Assessment Form; RBC=red blood cells; TD=transfusion dependent; Source: CS Table 19, Table 20, Table 39; clarification question A1; Mesa 2017[19]

3.3.1 SIMPLIFY-1 trial: spleen response rate

In the Int-2/HR Hb<10g/dL subgroup, a similar proportion of patients had a spleen response rate (≥35% reduction in spleen volume) in the momelotinib and ruxolitinib arms. The results demonstrated that momelotinib was nominally significantly non-inferior versus ruxolitinib (Table 10). While the EAG had concerns that the pre-specified non-inferiority margin was wider than the difference that could be considered clinically acceptable or tolerable for momelotinib to be considered as 'similar' or 'not worse' than ruxolitinib (see Section 3.2.4), clinical advice to the EAG was that the spleen response rates were similar in the momelotinib and ruxolitinib arms.

3.3.2 SIMPLIFY-1 trial: total symptom score response rate

In the Int-2/HR Hb<10g/dL subgroup, a higher proportion of patients had a TSS response (≥50% reduction in mean MPN-SAF TSS) in the ruxolitinib arm than in the momelotinib arm; it could not be concluded that treatment with momelotinib was nominally significantly non-inferior to treatment with ruxolitinib (Table 10).

The company (CS, p121) presented reasons why non-inferiority may not have been demonstrated, with reference to the ITT population as follows:

- at baseline, more patients were classified as "severe" (score of 7 to 9) for each individual TSS item in the momelotinib arm than in the ruxolitinib arm; hence, a ≥50% reduction in mean MPN-SAF TSS was harder to achieve for patients in the momelotinib arm
- TSS response is also difficult to detect when patients have low baseline scores; most patients generally had low symptom scores at baseline, with median individual symptom scores ranging from 2 to 4
- a higher proportion of patients in the momelotinib arm were classified as non-responders for TSS than in the ruxolitinib arm, due to scores being unavailable

While the EAG considers the company's explanation about why non-inferiority was not demonstrated seems reasonable, the EAG notes that the company did not provide baseline

TSS severity, individual item scores and non-responder information for the Hb levels subgroups.

The company also presented the following results from post-hoc analyses of TSS in the ITT population which showed that:

- the mean absolute change in TSS from baseline at Week 24 was [redacted] in the momelotinib arm and [redacted] in the ruxolitinib arm (CS, p70)
- median change from baseline at Week 24 for the seven individual MF-related symptoms from the modified MPN-SAF TSS v2.0 were similar for both treatment arms (CS, Figure 11)
- a similar proportion of patients met the derived meaningful change threshold (≥8 point improvement) in the momelotinib and ruxolitinib arms (CS, p121)
- an analysis of the cumulative distribution function of absolute change in MPN-SAF TSS from baseline to Week 24 in symptomatic patients (baseline TSS ≥10) showed similar results in the momelotinib and ruxolitinib arms (CS Figure 10).

The EAG highlights that the TSS post-hoc analyses results were not reported for the Int-2/HR Hb<10g/dL subgroup. Clinical advice to the EAG is that the TSS post-hoc ITT analyses results were reassuring; while a ≥50% reduction in TSS from baseline may be meaningful in a clinical trial context, it is not used to guide treatment decisions in clinical practice. Clinical advice to the EAG is that TSS scores are not routinely recorded in clinical practice but assessed subjectively as part of clinical assessment. In addition, clinical advice to the EAG also agreed with clinical advice to the company that the inability of the SIMPLIFY-1 trial to demonstrate non-inferiority for TSS response rate was not a major concern given many patients treated with momelotinib experienced improvements in the other key efficacy outcomes of RBC TI and TD (see Table 10).

3.3.3 SIMPLIFY-1 trial: red blood cell transfusion-independent rate

In the Int-2/HR Hb<10g/dL subgroup a higher proportion of patients in the momelotinib arm were RBC TI (no RBC transfusions and no Hb levels<8g/dL in the previous 12 weeks at Week 24) than in the ruxolitinib arm; momelotinib was nominally significantly superior to ruxolitinib (Table 10).

The EAG notes that for the ITT population and Hb levels subgroups, compared with patients in the ruxolitinib arm, more patients were RBC TI in the momelotinib arm at Week 24; this result is despite fewer patients in the momelotinib arm being TI at baseline, most notably in the Int-2/HR Hb<10g/dL subgroup. The numbers and proportions of patients who were RBC TI at baseline and at Week 24 are summarised in Table 11.

Table 11 Summary of SIMPLIFY-1 trial RBC TI data at baseline and at Week 24

Outcome by population/subgroup	Momelotinib n/N (%)	Ruxolitinib n/N (%)
ITT population Baseline RBC TI RBC TI at Week 24	 147/215 (68.4) 143/215 (66.5)	 150/217 (70.0) 107/217 (49.3)
Int-2/HR Hb<12g/dL Baseline RBC TI RBC TI at Week 24	[redacted]	[redacted]
Int-2/HR Hb<10g/dL Baseline RBC TI RBC TI at Week 24	[redacted]	[redacted]

Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; ITT=intention-to-treat; RBC=red blood count; TI=transfusion independence
Source: CS, Table 38 and Table 39

3.3.4 SIMPLIFY-1 trial: red blood cell transfusion-dependent rate

In the Int-2/HR Hb<10g/dL subgroup, fewer patients were RBC TD (4 units of RBC transfusions or Hb levels<8g/dL in the previous 8 weeks at Week 24) in the momelotinib arm than in the ruxolitinib arm; momelotinib was nominally significantly superior to ruxolitinib (Table 10).

The EAG notes that for the ITT population and Hb levels subgroups, compared with patients in the ruxolitinib arm, fewer patients were RBC TD in the momelotinib arm at Week 24; this result is despite more patients in the momelotinib arm being TD at baseline, most notably in the Int-2/HR Hb<10g/dL subgroup. The numbers and proportions of patients who were RBC TD at baseline and Week 24 are summarised in Table 12.

Table 12 Summary of SIMPLIFY-1 trial RBC TD data at baseline and at Week 24

Outcome by population/subgroup	Momelotinib n/N (%)	Ruxolitinib n/N (%)
ITT population Baseline RBC TD RBC TD at Week 24	 53/215 (24.7) 65/215 (30.2)	 52 217 (24.0) 87/217 (40.1)
Int-2/HR Hb<12g/dL Baseline RBC TD RBC TD at Week 24	[redacted]	[redacted]
Int-2/HR Hb<10g/dL Baseline RBC TD RBC TD at Week 24	[redacted]	[redacted]

Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; ITT=intention-to-treat; RBC=red blood count; TD=transfusion dependence
Source: CS, Table 38 and Table 39

3.4 Survival results: JAKi-naïve population (SIMPLIFY-1 trial)

The results from the exploratory analyses of OS and LFS at Week 24, as well as at later follow-up, are presented in Appendix 4, Section 8.4, Table 57. A summary of the results with EAG

comments is presented in Section 3.4.1 and 3.4.2. The EAG has focussed the emphasis of its summary and commentary on the Int-2/HR Hb<10g/dL subgroup.

3.4.1 SIMPLIFY-1 trial: overall survival

For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant OS differences between treatment arms at the time of the final analysis (up to 5 years from randomisation). Median OS was numerically shorter in the momelotinib arm than in the ruxolitinib arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup; median OS was not reached in the momelotinib arm for the ITT population.

Given that patients switched from ruxolitinib to momelotinib at Week 24, meaningful interpretation of long-term OS data is difficult. Rank preserving structural failure time model (RPSFTM) method analyses were conducted to account for the patients who switched from the ruxolitinib arm to the momelotinib arm at Week 24. These were conducted using ITT data only. All HRs generated by the RPSFTM analyses favoured momelotinib, with wide bootstrap confidence intervals (CIs) indicating uncertainty in the results of these analyses. The company did not provide detailed methods for any of the RPSFTM analyses that were conducted, and therefore the EAG is unable to determine which of the company's RPSFTM analyses was most appropriate.

3.4.2 SIMPLIFY-1 trial: leukaemia-free survival

In the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant differences between treatment arms in LFS at the time of the final analysis (up to 5 years from randomisation). Median LFS was numerically shorter in the momelotinib arm than in the ruxolitinib arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup but median LFS was not reached in the momelotinib arm for the ITT population. Given patients switched from ruxolitinib to momelotinib at Week 24, meaningful interpretation of long-term LFS data is difficult.

3.5 Key efficacy results: JAKi-experienced population (SIMPLIFY-2 trial)

The ITT population and Hb levels subgroup results from the key primary and secondary efficacy results at Week 24 are presented in Table 13. A summary of the key efficacy results with EAG comments is presented in Section 3.5.1 to 3.5.4. The EAG has focussed the emphasis of its summary and commentary on the Int-2/HR Hb<10g/dL subgroup. However, for all outcomes, in general, the results in the Int-2/HR Hb<10g/dL subgroup were mirrored in the Int-2/HR Hb<12g/dL subgroup and ITT population. The EAG has highlighted where this was not the case.

The EAG highlights that ESAs as concomitant anaemia supportive measures were not commonly used in the BAT arm of the SIMPLIFY-2 trial (and were prohibited in the momelotinib arm). Clinical advice to the EAG is that ESAs are often given alongside BAT (in particular, ruxolitinib) in NHS clinical practice. It is not clear why the use of ESAs was low in the BAT arm of SIMPLIFY-2 trial; however, clinical advice to the EAG is that this may reflect previous failure of ESAs and it is possible that trial efficacy results (particularly RBC TI and RBC TD outcomes) may have been different if ESAs had been more extensively used.

Table 13 Summary of SIMPLIFY-2 trial key efficacy results at Week 24

Outcome by population/subgroup	Momelotinib n/N (%)	BAT n/N (%)	Proportion difference (95% CI) p-value
Spleen response rate[a]			
ITT population 95% CI (%)	7/104 (6.7) (2.75 to 13.38)	3/52 (5.8) (1.21 to 15.95)	0.01 (-0.09 to 0.10) p=0.90[b]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][b]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][b]
TSS response rate[c]			
Overall TSS population[c]	27/103 (26.2)	3/51 (5.9)	[redacted] nominal p<0.001[b,d]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][b,d]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][b,d]
RBC TI rate[e]			
ITT population	45/104 (43.3)	11/52 (21.2)	[redacted] nominal p=0.0012[b,d]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][b,d]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][b,d]
ITT population	52/104 (50.0)	33/52 (63.5)	[redacted] nominal p=0.10[b,d]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][b,d]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][b,d]

Note: Where p values have been generated by statistical tests that were not part of the pre-specified hierarchical testing strategy, the EAG has labelled these as 'nominal'
[a]Spleen response rate defined as the proportion of patients with ≥35% reduction in spleen volume from baseline at Week 24 (95% CI only reported for the ITT population)
[b]Stratified CMH analysis for superiority hypothesis.
[c]TSS defined as the proportion of patients with a ≥50% reduction in mean MPN-SAF TSS at Week 24 compared with baseline. Measured all randomised patients with baseline TSS >0, or who had baseline TSS of 0 but with TSS >0 or missing at Week 24
[d]As superiority was not achieved in the primary endpoint of spleen response rate in the SIMPLIFY-2 trial, analyses of subsequent secondary endpoints are descriptive (nominal) only and statistical significance should not be inferred.
[e]RBC TI defined as the proportion of patients who had no RBC transfusions and no Hb levels<8g/dL in the previous 12 weeks at Week 24
[f]RBC TD defined as the proportion of patients who had 4 units of RBC transfusions or Hb levels<8g/dL in the previous 8 weeks at Week 24
BAT=best available treatment; CI=confidence interval; CMH=Cochran Mantel Haenzsel; Hb=haemoglobin; HR=high risk; Int-2=intermediate-2; ITT=intention-to-treat; MPN-SAF=Myeloproliferative Neoplasm Symptom Assessment Form; RBC=red blood cells; TD=transfusion dependent; TI=transfusion independent; TSS= total symptom score
Source: CS Table 19, Table 27, Table 41

3.5.1 SIMPLIFY-2 trial: spleen response

In the Int-2/HR Hb<10g/dL subgroup, few patients achieved a spleen response (≥35% reduction) in the SIMPLIFY-2 trial but a similar proportion of patients had a spleen response rate in the momelotinib and BAT arms. The results did not demonstrate statistical superiority of momelotinib versus BAT (Table 13).

The company stated (CS, p84) that failure to achieve the primary endpoint "may have been influenced by some inadvertent study design features" and the lack of a washout period. The cited "inadvertent study design features" were the BAT arm being largely composed of ruxolitinib-treated patients (88.5%) whereas the SIMPLIFY-2 statistical analysis plan was designed with a BAT treatment effect based on the BAT arm of the COMFORT-II trial;[22] in the COMFORT II trial of JAKi-naïve patients, spleen response was 0% in the BAT arm at Week 24 and Week 48, and 32% and 28% in the ruxolitinib arm at Week 24 and Week 48. The company highlighted that notably all patients achieving a response in the BAT arm of the SIMPLIFY-2 trial were treated with ruxolitinib.

Clinical advice to the company and the EAG agreed with the reasons given by the company for failing to achieve the primary endpoint. Furthermore, clinical advice to the EAG agrees with advice received by the company (CS, p126) that, "…considering the totality of efficacy evidence [summarised in Table 13] … momelotinib appeared to offer a greater overall benefit in more advanced JAKi-experienced patients than BAT."

3.5.2 SIMPLIFY-2 trial: total symptom score response rate

In the Int-2/HR Hb<10g/dL subgroup, more patients had a TSS response (≥50% reduction in mean MPN-SAF TSS) in the momelotinib arm than in the BAT arm. The results demonstrated that momelotinib was nominally significantly superior to BAT (Table 13).

As highlighted in Section 3.2.6, the EAG considers that given the subjective nature of the TSS outcome, the lack of blinding could have resulted in the TSS result being biased in favour of the momelotinib arm. In the discussion section of the published paper by Harrison 2018[17] reporting the SIMPLIFY-2 results, the authors agree the open-label nature of the trial may have contributed to the large difference. However, other reasons include the fact that ruxolitinib was usually given at lower doses in the SIMPLIFY-2 trial than the doses given to the JAKi-naïve patients treated with ruxolitinib in the SIMPLIFY-1 trial (dosing details are presented in Section 4.3.6, Table 27), and the use of non-ruxolitinib treatments in the BAT arm. Clinical advice to the EAG is that these reasons seem reasonable.

3.5.3 SIMPLIFY-2 trial: red blood cell transfusion-independent rate

In the Int-2/HR Hb<10g/dL subgroup, a higher proportion of patients in the momelotinib arm were RBC TI (no RBC transfusions and no Hb levels<8g/dL in the previous 12 weeks at Week 24) than in the BAT arm. Momelotinib was not nominally significantly superior to BAT in the Int-2/HR Hb<10g/dL subgroup but was nominally significantly superior to BAT in the Int-2/HR Hb<12g/dL subgroup and in the ITT population (Table 13).

The EAG notes that for the ITT population and Hb levels subgroups, compared with patients in the BAT arm, the proportion of patients who were RBC TI was higher in the momelotinib arm at Week 24; this result is despite a lower proportion of patients in the momelotinib arm being TI at baseline. The numbers and proportions of patients who were RBC TI at baseline and Week 24 are summarised in Table 14.

Table 14 Summary of RBC TI data at baseline and at Week 24 in the SIMPLIFY-2 trial

Outcome by population/subgroup	Momelotinib n/N (%)	BAT n/N (%)
ITT population Baseline RBC TI RBC TI at Week 24	 32/104 (30.8) 45/104 (43.3)	 19/52 (36.5) 11/52 (21.2)
Int-2/HR Hb<12g/dL Baseline RBC TI RBC TI at Week 24	[redacted]	[redacted]
Int-2/HR Hb<10g/dL Baseline RBC TI RBC TI at Week 24	[redacted]	[redacted]

Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; ITT=intention-to-treat; RBC=red blood count; TI=transfusion independence
Source: CS, Table 40 and Table 41

3.5.4 SIMPLIFY-2 trial: red blood cell transfusion-dependent rate

In the Int-2/HR Hb<10g/dL subgroup, a lower proportion of patients were RBC TD (4 units of RBC transfusions or Hb levels<8g/dL in the previous 8 weeks at Week 24) in the momelotinib arm than in the ruxolitinib arm; results were not nominally significantly different in this subgroup or in the Int-2/HR Hb<12g/dL subgroup or in the ITT population (Table 13).

The EAG notes that for the ITT population and Hb levels subgroups, compared with patients in the BAT arm, the proportion of patients who were RBC TD was lower in the momelotinib arm at Week 24; this result is despite a higher proportion of patients in the momelotinib arm being TD at baseline, most notably in the Int-2/HR Hb<10g/dL subgroup. The numbers and proportions of patients who were RBC TD at baseline and Week 24 are summarised in Table 15.

Table 15 Summary of RBC TD data at baseline and at Week 24 in the SIMPLIFY-2 trial

Outcome by population/subgroup	Momelotinib n/N (%)	BAT n/N (%)
ITT population Baseline RBC TD RBC TD at Week 24	 58/104 (55.8) 52/104 (50.0)	 27/52 (51.9) 33/52 (63.5)
Int-2/HR Hb<12g/dL Baseline RBC TD RBC TD at Week 24	[redacted]	[redacted]
Int-2/HR Hb<10g/dL Baseline RBC TD RBC TD at Week 24	[redacted]	[redacted]

Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; RBC=red blood count; TD=transfusion dependence
Source: CS, Table 40 and CS, Table 41

3.6 Survival results: JAKi-experienced population (SIMPLIFY-2 trial)

The results from the exploratory analyses of OS and LFS at Week 24, as well as at later follow-up, are presented in Appendix 5, Section 8.5, Table 58. A summary of the results with EAG comments is presented in Section 3.6.1 and 3.6.2. The EAG has focussed the emphasis of its summary and commentary on the Int-2/HR Hb<10g/dL subgroup.

3.6.1 SIMPLIFY-2 trial: overall survival

For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant OS differences between treatment arms at the time of the final analysis (up to 5 years from randomisation). Median OS was numerically longer in the momelotinib arm than in the BAT arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup; median OS was numerically shorter in the momelotinib arm than in the BAT arm for the ITT population.

Given that patients switched from ruxolitinib to momelotinib at Week 24, meaningful interpretation of long-term OS data is difficult. RPSFTM analyses were conducted to account for the patients who switched from the BAT arm to the momelotinib arm at Week 24. These were conducted using ITT data only. All HRs generated by the RPSFTM analyses favoured momelotinib, with wide bootstrap CIs indicating uncertainty in the results of these analyses. The company did not provide detailed methods for any of the RPSFTM analyses that were conducted, and therefore the EAG is unable to determine which of the company's RPSFTM analyses was most appropriate.

3.6.2 SIMPLIFY-2 trial: leukaemia-free survival

For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant LFS differences between treatment arms at the time of the final analysis (up to 5 years from randomisation). LFS results were very similar to OS results, i.e., median LFS was numerically longer in the momelotinib arm than in the BAT arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR

Hb<12g/dL subgroup but was shorter in the ITT population. Given patients switched from BAT to momelotinib at Week 24, meaningful interpretation of long-term LFS data is difficult.

3.7 Patient reported outcomes from the included trials

All HRQoL results from the SIMPLIFY-1 and SIMPLIFY-2 trials were considered exploratory. For the SIMPLIFY-1 and SIMPLIFY-2 trials, the company reported change from baseline to Week 24 for the following outcomes:

- Short Form-36 (SF-36) version 2
- EuroQoL 5-Dimensions Visual Analogue Scale (EQ-5D VAS)
- Patient Global Impression Change (PGIC).

3.7.1 HRQoL at Week 24: JAKi-naïve population (SIMPLIFY-1 trial)

The company presented HRQoL data for all patients in the SIMPLIFY-1 trial in the CS (CS, Section B.2.7.1.7) and provided HRQoL data for the Hb levels subgroups at clarification (clarification question A9). A summary of HRQoL results for the SIMPLIFY-1 trial is provided in Appendix 6, Section 8.6, Table 59. The company considered (CS, pp78-79) that momelotinib demonstrated a comparable benefit to ruxolitinib at Week 24 in all reported HRQoL outcomes for the ITT population.

The EAG considers that momelotinib demonstrated a comparable benefit to ruxolitinib at Week 24 in all reported HRQoL outcomes for the ITT population, Int-2/HR Hb<12g/dL and the Int-2/HR Hb<10g/dL subgroups (see clarification question A9, Table 9 to Table 11, Table 14 to Table 16).

3.7.2 HRQoL at Week 24: JAKi-experienced population (SIMPLIFY-2 trial)

The company presented HRQoL data for all patients in the SIMPLIFY-2 trial (CS, Section B.2.7.2.7) and provided HRQoL data for Hb levels subgroups at clarification (clarification question A9). A summary of HRQoL results for the SIMPLIFY-2 trial is provided in Appendix 7, Section 8.7, Table 60. The company reported (CS, pp95-96) that there was a numerically larger median maximum percentage change from baseline to Week 24 in SF-36 scores (physical function component score (PCS) and mental health component score [MCS]) and higher proportion of patients reported an improvement in symptoms measured by the PGIC in the momelotinib arm compared with the BAT arm.

The EAG agrees that for the ITT population, Int-2/HR Hb<12g/dL and the Int-2/HR Hb<10g/dL subgroups, there was a numerically larger median percentage change from baseline to Week 24 in SF-36 PCS in the momelotinib arm compared with the BAT arm. The EAG highlights that median percentage change from baseline to Week 24 in SF-36 MCS showed a small reduction

in the momelotinib arm and a small increase in the BAT arm. The EAG also highlights that for the Int-2/HR Hb<10g/dL subgroups, there was a numerically smaller mean percentage change from baseline to Week 24 in EQ-5D VAS in the momelotinib arm compared with the BAT arm. The EAG agrees that a higher proportion of patients reported an improvement in symptoms measured by the PGIC in the momelotinib arm compared with patients in the BAT arm. The EAG considers that momelotinib demonstrated a comparable benefit to BAT at Week 24 in all reported HRQoL outcomes for the ITT population, Int-2/HR Hb<12g/dL and the Int-2/HR Hb<10g/dL subgroups (see clarification question A9, Table 19 to Table 21 and Table 24 to Table 26).

3.8 Safety and tolerability outcomes from the included trials

Pooled safety analyses were reported in the main body of the CS, Section B.2.11, based on the pooled data from all three trials plus the extended access programme for patients regardless of their risk status (n=725). The median duration of momelotinib exposure was 11.3 months (range: 0.1 to 90.4 months).

The company also presented individual trial safety results from the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials in the CS, Appendix F, including summaries of the overall safety profile for the double-blind phases of the trials (Week 0 to 24) and from an interim analysis at Week 48 (SIMPLIFY-1 and SIMPLIFY-2 trials only). It was reported in the CS (p125 and p128) that, in the SIMPLIFY-1 and SIMPLIFY-2 trials, there were no notable differences in AEs between patients with/without anaemia or with/without thrombocytopenia. The data to support these statements were presented during the clarification process (clarification question A11).

The safety findings are summarised in Section 3.8.1 to 3.8.4. Overall, clinical advice to the EAG agrees with the company's interpretation of the safety evidence (CS, p125 and p128) that the safety findings provide strong evidence for the safety and tolerability of momelotinib.

3.8.1 Safety during the randomised treatment phases, Week 0 to 24

Since, in all three trials, patients switched from the comparator arm to momelotinib at Week 24, AEs for patients who only received ruxolitinib, BAT or danazol were only available during the randomised treatment phase. The safety profiles are presented in Table 16.

Table 16 Individual and pooled safety profiles of individual trials of momelotinib and comparators (randomised treatment phase, Week 0 to 24)

Type of AE	JAKi-naïve population		JAKi-experienced population			
	SIMPLIFY-1		SIMPLIFY-2		MOMENTUM	
	Momelotinib (n=214)	Ruxolitinib (n=216)	Momelotinib (n=104)	BAT (n=52)	Momelotinib (n=130)	Danazol (n=65)
Any TEAE, n (%)	198 (92.5)	206 (95.4)	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 TEAEs, n (%)	[redacted]	94 (43.5)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related TEAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAEs, n (%)	49 (22.9)	39 (18.1)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to premature discontinuation of study drug, n (%)	[redacted]	12 (5.6)	[redacted]	[redacted] [a]	[redacted]	[redacted]
TEAE leading to dose reduction/interruption of study drug, n (%)	[redacted]	79 (36.6)	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to deaths, n (%)	7 (3.3)	7 (3.2)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3/4 haematological TEAEs / abnormalitiies [b]						
Thrombocytopenia	15 (7.0)	10 (4.6)	[redacted]	[redacted]	[redacted] [c]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] The company state (CS, Appendix F, Table 27 footnote) that in the SIMPLIFY-2 trial: "The difference in study drug discontinuation rates may be due to the study design and execution, as changes in therapy and no-therapy were both permissible options for the BAT treatment group, this may have resulted in BAT discontinuations being inconsistently reported and reported in smaller numbers. Based on data collected for the BAT group, 11 of 52 patients in the BAT group discontinued BAT treatment during the randomised treatment phase; pooled data included in the table only include [redacted] of 52 patients.

[b] Grade 3/4TEAEs reported in the SIMPLIFY-1 and SIMPLIFY-2 trials, Grade≥3 haematological abnormalities reported for MOMENTUM trial are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase, regardless of whether this grade was a change from baseline.

[c] Proportion erroneously reported to be 23% in the CS, Appendix F, Table 31; this is a typographical error (see Verstovsek , 2023b[31])

AE=adverse event; BAT=best available therapy; JAKi=Janus kinase inhibitor; SAE-serious adverse event; TEAE=treatment-emergent adverse event

Source: CS, Appendix F, Tables 23, 27 and 31

Except for drug-related TEAEs (SIMPLIFY-2 trial) and TEAE leading to dose reduction/interruption of study drug (MOMENTUM trial), there were fewer TEAEs in the momelotinib arm of the SIMPLIFY-1 trial than in the momelotinib arms of the SIMPLIFY-2 and MOMENTUM trials, i.e., fewer AEs in the JAKi-naïve population than in the JAKi-experienced populations.

TEAEs leading to dose reduction / interruption of study drug and TEAEs leading to death were higher in the momelotinib arm of the MOMENTUM trial than in either of the momelotinib arms of the SIMPLIFY-1 or SIMPLIFY-2 trials; AEs leading to death were also higher in the comparator arm of the MOMENTUM trial than in either of the comparator arms of the SIMPLIFY-1 or SIMPLIFY-2 trials. Frequencies of Grade 3/4 anaemia and thrombocytopenia were noticeably higher in both arms of the MOMENTUM trial than in either arm of the SIMPLIFY-1 or SIMPLIFY-2 trials. In addition, as reported in CS, Appendix F.1.3, (Table 32), any grade anaemia was experienced by [redacted]% of patients in the momelotinib arm and [redacted]% of patients in the danazol arm; any grade thrombocytopenia was experienced by [redacted]% of patients in the momelotinib arm and by [redacted]% of patients in the danazol arm. The higher frequencies of the aforementioned AEs in the MOMENTUM trial, particularly haematological AEs, may reflect the fact that 92.8% of patients in this trial had Int-2/HR disease and also likely reflect the fact that all patients were considered to be both anaemic (Hb<10g/L) and symptomatic (MFSAF TSS ≥10).

3.8.2 Pooled trial safety data at Week 48 (patients who were ever exposed to momelotinib)

As shown in Table 17, of the AEs reported in the CS (p119), proportionately more patients experienced AEs (other than anaemia) at Week 48 than at Week 24, reflecting the fact that additional patients received momelotinib from Week 24, i.e., the patients who had switched from ruxolitinib/BAT/danazol.

Table 17 Pooled safety data for patients receiving momelotinib at Week 24 and Week 48

Type of AE	Week 24 (N=448) [a]	Week 48 (N=725) [b]
TEAE leading to premature discontinuation of study drug, n (%)	[redacted]	229 (31.6)
TEAE leading to dose reduction / interruption of study drug, n (%)	[redacted]	262 (36.1)
AEs leading to deaths, n (%)	[redacted]	102 (14.1)
Grade 3/4 haematological TEAEs		
Thrombocytopenia	[redacted]	119 (16.4)
Anaemia	[redacted]	107 (14.8)

[a] Patients initially randomised to momelotinib, only
[b] Patients who were ever exposed to momelotinib
AE=adverse event; TEAE=treatment-emergent adverse event
Source: CS, Appendix F, Tables 23, 27 and 31 and CS, pp118-119

The company reported that:

- thrombocytopenia and infections and infestations (including pneumonia) were the most common reasons for discontinuation (3.7% and 4.0%, respectively) and dose reduction/interruption (10.5 and 7.0%, respectively) (CS, p119)
- Grade ≥3 pneumonia (8.4%) was the only non-haematologic TEAE that occurred in >5% of patients (CS, Table 43)
- fatal AEs related to momelotinib were only reported in 5 (0.7%) patients, all of whom were in the JAKi-experienced population; the causes of death were cardiac arrest, severe respiratory failure, nephritis (SIMPLIFY-2 trial), rotavirus gastroenteritis and staphylococcal pneumonia (MOMENTUM trial) (clarification question A10).

3.8.3 Longer term pooled trial safety data

'Clinically important AEs' (which included but were not limited to haematological AEs and opportunistic infections) were reported in the CS at various time-points, each time point covering a period of several weeks (see CS, Table 44 for detail). The company reported that the frequency of pre-specified clinically important AEs did not increase in incidence over time.

3.8.4 Safety profiles in subgroups of patients with/without anaemia or with/without thrombocytopaenia

The following data were reported for all patients who were ever exposed to momelotinib, i.e., including patients who were initially randomised to ruxolitinib in SIMPLIFY-1 or to BAT in SIMPLIFY-2:

- any grade TEAEs reported in ≥5% of patients
- Grade 3 or 4 TEAEs in ≥5% of patients.

Company AE data were summarised in response to clarification question A11, Table 27 to Table 34. Overall, in both the SIMPLIFY-1 and SIMPLIFY-2 trials, Grade 3/4 TEAEs were more common in the Hb<10g/dL subgroup than in the Hb≥10g/dL subgroup and less common in the platelet >200 $x10^3$/uL subgroup than in either the platelet count <100 $x10^3$/uL or platelet count 100-200 (inclusive) $x10^3$/uL subgroups (Table 18). As expected, individual types of AEs (any grade or Grade 3/4 TEAEs) that differed in frequency by subgroup were anaemia (in subgroups defined by Hb levels) and thrombocytopenia (in subgroups defined by platelet count). Some non-haematological TEAEs of any grade were also found to differ in frequency by >5% between subgroups in the SIMPLIFY-1 and SIMPLIFY-2 trials, most notably pneumonia (any grade and Grade 3/4) which was notably greater in patients with Hb<10g/dL than patients with Hb≥10g/dL in both the SIMPLIFY-1 and SIMPLIFY-2 trials.

Table 18 Safety profiles in subgroups of patients with/without anaemia or with/without thrombocytopaenia (all exposed to momelotinib)

Type of AE	JAKi-naïve population					JAKi-experienced population				
	SIMPLIFY-1 Hb levels		SIMPLIFY-1 Platelet count			SIMPLIFY-2 Hb levels		SIMPLIFY-2 Platelet count		
	<10g/dL (n=171)	≥10g/dL (n=240)	<100 x10^3/uL (n=35)	100-200 x10^3/uL (n=123)	>200 x10^3/uL (n=253)	<10g/dL (n=96)	≥10g/dL (n=48)	<100 x10^3/uL (n=66)	100-200 x10^3/uL (n=47)	>200 x10^3/uL (n=31)
Any TEAE, n (%)	[redacted]									
Thrombocytopenia	[redacted]									
Anaemia	[redacted]									
Grade 3/4 TEAEs, n (%)	[redacted]									
Thrombocytopenia	[redacted]									
Anaemia	[redacted]									
[redacted]										

AE=adverse event; JAKi=Janus kinase inhibitor; NR=not reported; TEAE=treatment-emergent adverse event
Source: clarification question A11, Table 27 to Table 34

3.9 Conclusions of the clinical effectiveness section

The company has provided evidence to support the clinical effectiveness of momelotinib as a treatment for patients with MF who have moderate to severe anaemia from the SIMPLIFY-1 trial (JAKi-naïve population) and the SIMPLIFY-2 trial (JAKi-experienced population). In both trials, clinical effectiveness results are available for the ITT population, Int-2/HR Hb<12g/dL and Int-2/HR Hb<10g/dL subgroups. Clinical advice to the EAG is that efficacy and HRQoL results from the Int-2/HR Hb<10g/dL subgroup are likely to be most relevant to the company's decision problem; results for this subgroup were similar to those reported for the Int-2/HR Hb<12g/dL subgroup and ITT population.

SIMPLIFY-1 trial results at Week 24 were mixed. Although the non-inferiority margin was wide, compared to ruxolitinib, momelotinib was non-inferior in terms of spleen response rate (primary outcome) but was not non-inferior in terms of TSS rate. In terms of RBC TI rate and RBC TD rate, momelotinib was nominally significantly superior to ruxolitinib. However, it is unclear whether the differences between treatment arms would have been similar had ESAs been permitted alongside treatment with ruxolitinib. There were little or no differences in HRQoL outcomes between treatment arms.

SIMPLIFY-2 trial results at Week 24 were also mixed. Compared to BAT, momelotinib was not superior for the primary endpoint of spleen volume reduction. However, momelotinib was nominally significantly superior to BAT in terms of TSS rate and numerically superior to BAT for RBC TI rate and RBC TD rate; momelotinib was nominally significantly superior to BAT in terms of TI (but not TD) in the ITT population and Int-2/HR Hb<12g/dL subgroup. However, it is unclear whether the differences between treatment arms would have been similar had ESAs and/or other anaemia supportive measures been more widely used in the BAT arm. There were little or no differences in HRQoL outcomes between treatment arms.

Exploratory analyses of OS and LFS were not presented at Week 24 for the Int-2/HR Hb<10g/dL subgroup in either trial. Since, in both trials, patients switched from ruxolitinib/BAT to momelotinib at Week 24, longer term OS and LFS results (up to 5 years from randomisation) are difficult to interpret. The company's attempts to adjust for switching using the RPSFTM method (ITT population only) were inconclusive.

Safety outcomes were not available for the Int-2/HR Hb<10g/dL subgroup. Individual and pooled data from the safety populations of the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials (i.e., all patients who received momelotinib up to Week 24 or after switching to momelotinib at Week 24; median duration of momelotinib exposure of 11.3 months) provide strong evidence for the safety and tolerability of momelotinib.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of momelotinib as an option for treating disease-related splenomegaly or symptoms in patients with MF and moderate to severe anaemia. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluations for (i) the JAKi-naïve population and (ii) the JAKi-experienced population. The company has provided electronic copies of the two economic models; both models were developed in Microsoft Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook a systematic literature review to identify published cost effectiveness studies of treatments for adult patients with MF. Database searches were designed to retrieve articles published between 2012 and February 2023. The results of the literature search were validated via manual review of recently published relevant systematic review bibliographies identified from the database searches. The company also searched conference abstracts (2020 onwards) and submission documents published by Health Technology Assessment (HTA) agencies. Full details of the methods used by the company to identify and select relevant cost effectiveness evidence are presented in the CS (Appendix G).

The company's review identified eight publications; all except one publication included ruxolitinib as an intervention, none included momelotinib. Two of the identified publications were journal articles,[32,33] one was an abstract[34] and five were HTA submissions.[11,12,35-37]

4.1.1 EAG critique of the company's literature review

A summary of the EAG's critique of the company's economic literature review methods is provided in Table 19. The company's database searches used appropriate filters and search terms, although other relevant sources, such as the NHS Economic Evaluation Database (NHS EED), could have been included within the search. Overall, the EAG considers the company's systematic review of cost effectiveness evidence was carried out to a good standard.

Table 19 EAG appraisal of systematic review methods

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not specified
Were attempts to synthesise evidence appropriate?	NA

NA=not applicable
Source: LRiG in-house checklist

4.1.2 EAG conclusion

The EAG is satisfied that the company's systematic review of relevant cost effectiveness literature was carried out to a high standard and no important studies were missed.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 20 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	Partially – the population is restricted to patients with Int-2/HR disease (in accordance with the NICE recommendation for ruxolitinib) [redacted]
Comparators	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	NA
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes

Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EQ-5D=EuroQol-5 Dimension; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NA=not applicable; PSS=Personal Social Services; QALY=quality adjusted life year
Source: EAG assessment of NICE Reference Case[38]

Table 21 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	No	Clinical advice to the EAG is that, in the NHS, EPO is commonly used alongside ruxolitinib to manage anaemia. Therefore, SIMPLIFY-1 and SIMPLIFLY-2 trial outcomes (and cost effectiveness results) may not be generalisable to NHS patients
Was the effectiveness of the programme or services established?	No	**JAKi-naïve population** i) the EAG has concerns about the wide non-inferiority margin used in the SIMPLIFY-1 trial (spleen response rate; primary endpoint) ii) the SIMPLIFY-1 trial did not demonstrate non-inferiority of momelotinib compared to ruxolitinib (TSS; secondary endpoint) **JAKi-experienced population** The SIMPLIFY-2 trial did not demonstrate superiority of momelotinib compared to BAT
Were all the important and relevant costs and consequences for each alternative identified?	Partially	**JAKi-experienced population** OS was inappropriately modelled by transfusion status
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	

BAT=best available therapy; EPO=erythropoietin; JAKi=Janus kinase inhibitor; OS=overall survival
Source: Drummond and Jefferson 1996[39] and EAG comment

4.3 Cost comparison analysis: JAKi-naïve population

The company conducted a cost comparison analysis to compare the cost of treatment with momelotinib versus ruxolitinib for JAKi-naive patients with Int-2/HR MF and moderate to severe anaemia.

4.3.1 Model structure

The cost comparison model was developed in Microsoft Excel. The company included all relevant costs (drug acquisition, blood transfusions, AEs, and concomitant and subsequent treatments) that were considered to differ substantially between patients treated with

momelotinib and patients treated with ruxolitinib. The company did not include resource use costs associated with MF disease management as MF clinical outcomes for patients treated with either drug were assumed to be equivalent.

4.3.2 Population

The company defined the population of interest for the cost comparison analysis as JAKi-naive patients with Int-2/HR MF and anaemia. The SIMPLIFY-1 trial included patients with Int-1 risk disease who had evidence of splenomegaly; there was no specific inclusion criterion relating to anaemia. The company used SIMPLIFY-1 trial ITT data to generate results for the cost comparison analysis; momelotinib and ruxolitinib treatment costs were not expected to differ between disease risk or concomitant anaemia subgroups (CS, Table 46).

4.3.3 Interventions and comparators

Momelotinib drug acquisition costs are presented in Table 22. The company assumed no momelotinib wastage; momelotinib doses were assumed to align with the tablet strengths available. The company assumed all patients received the recommended dose of 200mg once per day as the price per tablet (list price: £5,273.33 per 28 days) is equal across different formulations (therefore any dose adjustments have no impact on costs). The company applied a confidential PAS discount to the momelotinib list price.

The company sourced ruxolitinib drug costs from the British National Formulary (BNF); prices are equivalent across the 10mg, 15mg and 20mg formulations (Table 22). Ruxolitinib is available to the NHS at a confidential discounted price; this price is not known to the company. The company modelled different ruxolitinib dose distributions before and after Week 12 to reflect the frequent dose adjustments observed over time in the SIMPLIFY-1 trial (CS, Figure 34). The company assumed no ruxolitinib wastage and considered this was a conservative assumption as, compared to momelotinib, the more frequent ruxolitinib dose titration could lead to some loss of tablets.

Table 22 Ruxolitinib dosing information and drug acquisition costs (list price)

Dose	Dosing regimen	Cost per unit	Dose share		Average cost per 28 days	
			Weeks 0-12	After Week 12	Weeks 0-12	After Week 12
0mg	-	£0	1.10%	0.30%	£2,592	£2,574
5mg	Twice daily	£1,428	17.28%	21.74%		
10mg	Twice daily	£2,856	13.70%	16.20%		
15mg	Twice daily	£2,856	19.20%	22.70%		
20mg	Twice daily	£2,856	48.00%	36.00%		
25mg	Twice daily	£4,284	0.80%	2.90%		

Source: CS, Table 49 and Table 50

4.3.4 Perspective, time horizon and discounting

The company stated that the model perspective was the NHS and PSS, the time horizon was 10 years, and the cycle length was 1 year. In line with the NICE Reference Case,[38] a discount rate of 3.5% per annum was applied.

4.3.5 Treatment effectiveness

The company considered the assumption of equivalent clinical outcomes between momelotinib and ruxolitinib was supported by SIMPLIFY-1 trial results which demonstrated that treatment with momelotinib was non-inferior versus ruxolitinib for the primary endpoint of spleen response rate.

The company did not explicitly model mortality; OS was assumed to be equivalent for all patients. The company cited SIMPLIFY-1 trial OS data and a post-hoc crossover-adjusted analysis[40] as supporting evidence of comparable survival for patients treated with either momelotinib or ruxolitinib (CS, p77).

4.3.6 Resources and costs

Anaemia management costs

Costs associated with red blood cell (RBC) transfusions, including supportive iron chelation therapy (ICT), were included in the cost comparison analysis.

The cost per RBC transfusion unit was sourced from a previous NICE appraisal[12] and inflated to 2022 costs (£399.77). In the base case, the company used adjusted mean RBC transfusion rates for the ITT population, calculated from the number of transfusion units that patients required during the SIMPLIFY-1 trial (Weeks 0-24). An adjusted RBC transfusion rate for patients receiving BAT was estimated using SIMPLIFY-2 trial data. The cost per unit of blood

was multiplied by the transfusion rates to calculate the annual cost of RBC transfusion for each treatment (Table 23).

Table 23 Annual cost of RBC transfusion by treatment

Treatment	RBC transfusion rate (units per month)	Annual cost of RBC transfusions
Momelotinib	[redacted]	[redacted]
Ruxolitinib	[redacted]	[redacted]
BAT	[redacted]	[redacted]

BAT=best available therapy; RBC=red blood cell
Source: CS, Table 53

Company clinical experts considered that patients requiring regular RBC transfusions would receive ICT (deferasirox) to mitigate complications resulting from the iron overload associated with repeated transfusions. The company included the cost of treating patients with deferasirox using the electronic Market Information Tool (eMIT) price of a pack of 30 tablets (Table 24) and the mean baseline weight of the SIMPLIFY-1 trial population (72.5kg).

Table 24 Cost of ICT

Treatment	Cost per pack	Cost per mg	Dose	Cost per person per 28 days
Deferasirox 360mg	£165.45	£0.02	21mg/kg/day	£653.07

ICT=iron chelation therapy
Source: CS Table 54

Using data from the SIMPLIFY-1 trial at Week 24, the company assumed that only patients who were transfusion-dependent (defined as patients who, in the prior 8 weeks, had required ≥4 RBC transfusion units) would be eligible for ICT. The company assumed the proportions of patients who were transfusion-dependent did not vary by treatment. The cost per person of ICT was multiplied by the proportion of patients receiving ICT to estimate the average annual ICT cost for each treatment (Table 25).

Table 25 Modelled cost of patient ICT

Treatment	Proportion of patients transfusion-dependent	Proportion of patients receiving ICT (conditional on transfusion dependence)	Proportion of patients receiving ICT	Average annual ICT cost
Momelotinib	[redacted]	37%	[redacted]	[redacted]
Ruxolitinib/BAT	[redacted]		[redacted]	[redacted]

BAT=best available therapy; ICT=iron chelation therapy
Source: CS, Table 55

Adverse event costs

The company base case analysis included the cost of Grade 3/4 AEs with an incidence of ≥5% in any SIMPLIFY-1 trial and SIMPLIFY-2 trial treatment arm (Table 26). Trial incidence rates were converted into annual probabilities and multiplied by AE unit costs to estimate annual AE costs (for the proportion of patients receiving each treatment).

Table 26 Incidence of Grade 3/4 AEs in any treatment arm of the SIMPLIFY-1 trial and associated costs

AE	AE unit cost	Incidence in SIMPLIFY-1		
		Momelotinib	Ruxolitinib	BAT
Anaemia	£194.02	[redacted]	[redacted]	[redacted]
Thrombocytopenia	£948.22	[redacted]	[redacted]	[redacted]
Asthenia	£13.73	[redacted]	[redacted]	[redacted]
Neutropenia	£1,303.42	[redacted]	[redacted]	[redacted]
Abdominal pain	£0	[redacted]	[redacted]	[redacted]
AE cost applied in cost comparison		[redacted]	[redacted]	[redacted]

AE=adverse event; BAT=best available therapy
Source: CS, Table 56 andTable 57; company model

Time to discontinuation or death (TTDD)

The company used SIMPLIFY-1 trial time to discontinuation or death (TTDD) data to model the time points when patients discontinued treatment with momelotinib or ruxolitinib and initiated BAT as a subsequent treatment. SIMPLIFY-1 trial momelotinib TTDD data are mature (data are available for up to 4.6 years); however, ruxolitinib data are only available up to Week 24 as all ruxolitinib patients crossed over to momelotinib at the end of the randomised treatment phase. The company considered the lower discontinuation rate observed in the ruxolitinib arm up to Week 24 was driven by the high number of patients who received low ruxolitinib doses and the high number of ruxolitinib dose adjustments permitted in the trial protocol before mandatory unblinding.

The company considered that, in clinical practice, treatment discontinuation rates would be comparable for momelotinib and ruxolitinib and assumed that TTDD was equivalent in the cost comparison analysis. The company modelled treatment discontinuation at a constant rate (exponential distribution) using SIMPLIFY-1 trial momelotinib TTDD data.

Subsequent treatment costs

In the company's base case analysis, on discontinuation of treatment with momelotinib or ruxolitinib, all patients were assumed to receive BAT; BAT mainly comprised dose-adjusted ruxolitinib. The proportions of patients receiving different types of BAT were sourced from the SIMPLIFY-2 trial and are presented in Table 27. Clinical advice to the company was that, in

NHS practice, patients rarely discontinue ruxolitinib, instead doses are titrated to lower levels to manage toxicities and maintain disease control.

Table 27 Composition of SIMPLIFY-2 trial BAT arm treatments

Subsequent treatment	SIMPLIFY-2 trial BAT composition
Ruxolitinib - 5mg BID	17.3%
Ruxolitinib - 10mg BID	35.3%
Ruxolitinib - 15mg BID	20.7%
Ruxolitinib - 20mg BID	15.1%
Hydroxyurea	23.1%
Prednisone / prednisolone	11.5%
Danazol	5.8%
ESA (assumed as epoetin alfa)	3.8%
No therapy	3.8%
Anagrelide	1.9%
Aranesp (darbepoetin alfa)	1.9%
Aspegic	1.9%
Thalidomide	1.9%

BAT=best available therapy; BID=twice daily; ESA=erythropoiesis-stimulating agent
Source: CS, Table 102

4.4 Cost utility analysis for the JAKi-experienced population

The company conducted a cost utility analysis to demonstrate the cost effectiveness of momelotinib versus BAT for JAKi-experienced patients with Int-2/HR MF and moderate to severe anaemia.

4.4.1 Model structure

The company developed a cohort-based Markov model constructed in Microsoft Excel to estimate costs and QALYs for JAKi-experienced patients treated with momelotinib or BAT over a lifetime horizon. The company used this model structure to allow changes in transfusion status to be captured over time as transfusion rates are likely to differ between patients treated with momelotinib and those treated with BAT (suboptimal ruxolitinib). The model includes the death health state and three transfusion health states (Figure 1), defined to align with definitions used in the SIMPLIFY-1/2 trials, namely:

- transfusion-independent (TI): an absence of RBC transfusions and no haemoglobin level <8g/dL in the three prior model cycles (12 weeks)
- transfusion-dependent (TD): at least four units of RBC transfusions, or a haemoglobin level <8g/dL in the two prior model cycles (8 weeks)
- transfusion-requiring (TR): not meeting the TI or TD criteria.

The company adopted a model cycle length of 4 weeks and, in each model cycle, patients can either remain in the same transfusion health state, transition to a different transfusion health state (including an improvement in transfusion status) or move to the death health state, which is an absorbing health state.

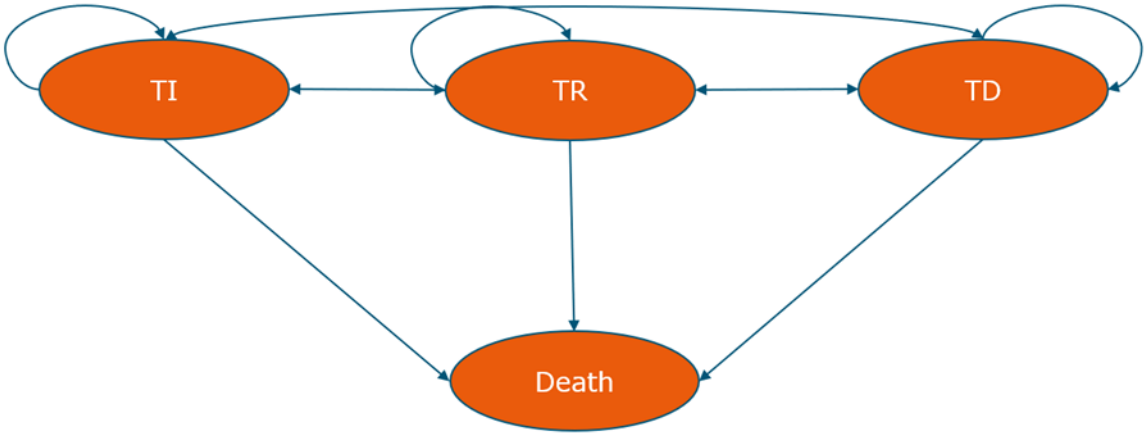

Figure 1 Markov model structure: JAKi-experienced population

JAKi=Janus kinase inhibitor; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Figure 37

4.4.2 Population

The company considered that patients with an Hb level of >12g/dL were unlikely to require anaemia treatment. Clinicians advised the company that although some patients with an Hb level below this cut-off may not be considered to have moderate or severe anaemia, a lower Hb threshold would exclude patients with clinically relevant treatment-requiring anaemia. In the base case analysis, the company generated cost effectiveness estimates using Int-2/HR Hb<12g/dL subgroup data from the SIMPLIFY-2 trial.

4.4.3 Perspective, time horizon and discounting

In the base case, the company selected a time horizon of 33 years, a length that was expected to be long enough to capture costs and health outcomes over the lifetime of the average patient (based on the average baseline age of the SIMPLIFY-2 trial population [67.4 years] and average cohort age reaching 100 years by the end of the model). In line with the NICE Reference Case[38], a discount rate of 3.5% per annum was applied to costs and outcomes and the analysis adopted an NHS/PPS perspective.

4.4.4 Intervention and comparators

The company applied a confidential PAS discount to the momelotinib list price.

The proportion of patients receiving each BAT treatment was sourced from the SIMPLIFY-2 trial; this approach is consistent with the cost comparison analysis (Table 27). The mean or median doses for each BAT treatment could not be estimated from the SIMPLIFY-2 trial, therefore, the company used the lowest dose from the SmPC for all treatments[41-44] except ruxolitinib. Company clinical experts advised that most of the assumed dosages for BAT treatments aligned with UK clinical practice but suggested alternative doses for hydroxyurea and ESAs, which the company used in their analysis. The weighted average total BAT acquisition cost per model cycle was £2,396.04.

The company assumed there was no drug wastage as momelotinib and all BAT treatments were expected to be administered at fixed dosages that were either equivalent to, or divisible by, the number of mg per unit for each dose size available. The company considered that as darbepoetin alfa and deferasirox (ICT) are weight-based, wastage may occur in clinical practice but excluding this cost is conservative as darbepoetin alfa and deferasirox costs are higher for patients treated with BAT than for patients treated with momelotinib.

4.4.5 Treatment effectiveness and extrapolation

Transition probabilities

SIMPLIFY-2 trial patient level data were used to inform the transition probabilities between the TI, TR and TD health states for patients treated with momelotinib or BAT (Figure 1). The baseline distribution of patients in each health state was derived from the SIMPLIFY-2 trial pooled distribution and was set equal for the two treatments (Table 28).

Table 28 Mean baseline health state distributions for the base case population (Int-2/HR Hb<12g/dL)

Health state	Pooled momelotinib and BAT	Momelotinib	BAT
TI	[redacted]	[redacted]	[redacted]
TR	[redacted]	[redacted]	[redacted]
TD	[redacted]	[redacted]	[redacted]

BAT=best available therapy; Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Table 65

Due to the SIMPLIFY-2 trial TI definition, post-baseline transfusion status estimates were not available until Week 12. In the absence of data between baseline and Week 12, the company assumed that for the first and second model cycles (Weeks 0-8), patients would experience no change from baseline transfusion status following treatment initiation. SIMPLIFY-2 trial changes observed at Week 12 were applied in the third model cycle (Weeks 8-12).

SIMPLIFY-2 trial data were only used for deriving transition probabilities in the first six model cycles due to the crossover from BAT to momelotinib after Week 24. The company applied a modified transition probability matrix to extrapolate health state membership for both treatment arms after model cycle 6 (Table 29). The company used the transition probabilities estimated for cycle 6, assuming they were representative of subsequent movements, and assumed patients treated with momelotinib or BAT could not experience an improvement in transfusion status. Pooled data from the momelotinib and BAT arms were applied in the base case analysis.

Table 29 Extrapolated transition probability matrix for cycle 7+ (Week 24+) base case population (Int-2/HR Hb<12g/dL)

From/to health state	Pooled momelotinib and BAT (base case)			Momelotinib			BAT		
	TI	TR	TD	TI	TR	TD	TI	TR	TD
TI	[redacted]								
TR									
TD									

BAT=best available therapy; Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Table 71

Overall survival

Transition probabilities to the death health state during the first six model cycles (Weeks 0-24) were estimated using the pooled mortality risk across the SIMPLIFY-2 trial momelotinib and BAT arms. The company considered that comparison of survival outcomes between treatments after Week 24 was confounded due to crossover of patients from the BAT arm to momelotinib. After Week 24, the company assumed mortality was dependent on transfusion status (whether a patient was TI or non-TI); the company cited evidence from the SIMPLIFY-2 trial that transfusion status at Week 24 was predictive of survival (CS, Figure 25) and this assumption was validated by clinical experts. The company considered that the number of TR patients in the SIMPLIFY-2 trial was too small to detect a meaningful difference in survival between patients who were TR or TD.

In the model, after cycle 6, the company applied a TI mortality risk to the proportion of patients who were TI and a non-TI mortality risk to the proportion of patients who were either TR or TD. Since all patients crossed over from BAT to momelotinib at Week 24, the company used the SIMPLIFY-2 trial TI and non-TI OS curves from the momelotinib arm only to calculate the mortality risks. In line with the NICE DSU guidance,[45] six parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma) were fitted to the SIMPLIFY-2 TI and non-TI OS K-M data after Week 24 for the Int-2/HR Hb<12g/dL population. After

assessment of log-cumulative hazard plots and Schoenfeld residuals, the company considered the proportional hazards assumption was violated and separately fitted independent parametric models to the TI and non-TI OS K-M curves. The company selected the best fitting distribution according to statistical fit, visual inspection of the fitted curves to the OS K-M data, plausibility based on clinical expert feedback and internal consistency of results between population subgroups.

For TI patients at Week 24, all distributions provided a similar statistical fit and reasonable visual fit to the OS K-M data. The company selected the log-normal distribution to extrapolate survival as the log-normal distribution 5 and 10-year survival rates (Table 30) were consistent with the results for other subgroups (ITT, Hb<10g/dL) and clinical expert opinion. SIMPLIFY-2 trial patients who were non-TI and had a Hb<12g/dL at Week 24 were assumed to correspond to the non-TI ITT population. All distributions provided a similar statistical fit and reasonable visual fit to the OS K-M data. The company selected the exponential distribution to extrapolate survival as long-term survival rates generated by other distributions were considered implausible (similar to, or greater than, the estimated survival rates for the TI population) (Table 30).

Table 30 Company base case OS parametric distributions for TI and non-TI populations (Int-2/HR, Hb<12g/dL)

Population	Distribution	AIC	AIC ranking	BIC	BIC ranking	5-year survival	10-year survival
TI	Lognormal	[redacted]	1	[redacted]	1	[redacted]	[redacted]
Non-TI	Exponential	[redacted]	1	[redacted]	1	[redacted]	[redacted]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; OS=overall survival; TI=transfusion-independent
Source: CS, Tables 76, 78, 79, 81

All OS distributions were capped by age and sex-matched general population mortality rates sourced from the Office for National Statistics (ONS) national life tables.[46] Non-TI OS distributions were capped by TI OS distributions so that the risk of death for a non-TI patient could not exceed that for a TI patient. The same mortality risks were applied to patients treated with momelotinib or BAT therefore the modelled treatment effect on survival was determined by the difference in proportion of patients who were TI at Week 24.

4.4.6 Health-related quality of life

SIMPLIFY-2 trial patients completed the EQ-5D-5L questionnaire at baseline and every 4 weeks thereafter during the randomised treatment period. EQ-5D-5L responses were mapped to EQ-5D-3L utility values using the crosswalk algorithm developed by Hernandez-Alava .[47] In

the base case analysis, the company used treatment independent health state utility values (Table 31).

Table 31 EQ-5D-3L health state utility values (SIMPLIFY-2 trial)

Health state	Utility value (SE)
TI	[redacted]
TR	[redacted]
TD	[redacted]

EQ-5D-3L=EuroQol 5-dimensions 3-levels; SE=standard error; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Table 87

Health state utility values were age-adjusted using age and sex-matched general population utility values from Hernandez-Alava[48] to account for the decline in HRQoL with age.

AE disutilities were included in the base case analysis; these were sourced from the literature[49,50] and previous NICE appraisals[12,51,52] (Table 32). The company applied utility decrements in each model cycle for patients treated with momelotinib and BAT after adjusting for the probability of each AE.

Table 32 AE disutilities in JAKi-experienced population

Adverse event	Disutility
Anaemia	0.090
Thrombocytopenia	0.050
Asthenia	0.090
Neutropenia	0.050
Abdominal pain	0.110

AE=adverse event; JAKi=Janus kinase inhibitor
Source: CS, Table 86

4.4.7 Resources and costs

Administration costs

No treatment administration costs were modelled for momelotinib or ruxolitinib as both are oral treatments. In the BAT arm, ESAs (epoetin alfa, darbepoetin alfa, and dalteparin) are administered via subcutaneous (SC) injection using pre-filled syringes. The company assumed that patients receiving these treatments incur a one-off administration cost for attending a training session where they receive education and support with SC administration. The training session is assumed to take place in a hospital with a nurse (Band 6) and to last for 20 minutes with no further administration costs incurred thereafter. The one-off training cost is applied to the proportion of patients who receive SC injections as part of BAT in model cycle one.

Anaemia and disease management costs

In line with the cost comparison analysis, costs associated with RBC transfusions and ICT (Table 25) were included for patients treated with momelotinib and BAT in each model cycle. Health state specific RBC transfusion rates were estimated (rather than treatment-specific rates) from a post-hoc analysis of patients in each health state at Week 24 (Table 33). Health state specific ICT rates were elicited from clinical experts.[53]

Table 33 SIMPLIFY-2 trial RBC transfusion and ICT rates for the JAKi-experienced Int-2/HR Hb <12g/dL population

Health state	Mean number of RBC transfusion units per model cycle	Proportion of patients receiving ICT (per model cycle)*
TI	0	0%
TR	0.83	14.17%
TD	2.77	37.08%

*Mean of clinician responses
Hb=haemoglobin; HR=high risk; ICT=iron chelation therapy; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Table 94

Resource use associated with blood test monitoring and follow-up haematology appointments for the management of MF was obtained from a HCRU questionnaire sent to six clinicians who participated in an advisory board.[53] Resource use costs per cycle in each health state are presented in Table 34.

Table 34 Total resource use cost per cycle by health state for the JAKi-experienced Int-2/HR Hb<12g/dL population

Resource	Cost per cycle		
	TI	TR	TD
Blood test monitoring	£0.64	£1.89	£4.77
Follow-up haematology appointment	£50.40	£95.34	£204.31
ICT (deferasirox)	£0.00	£97.24	£752.50
RBC transfusion	£0.00	£332.12	£1,107.06
Total resource use costs per cycle	**£182.28**	**£625.54**	**£2,076.94**

ICT=iron chelation therapy; JAKi=Janus kinase inhibitor; RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Table 95

Adverse event costs

In line with the cost comparison analysis, costs for Grade 3/4 AEs with incidence ≥5% in any of the SIMPLIFY-2 trial treatment arms were included. AE unit costs were sourced from the NHS Cost Collection[54] by calculating a weighted average of costs for different settings. The company considered that abdominal pain was a symptom of MF resulting from splenomegaly and therefore assumed the cost of treatment for this AE was captured within disease

management costs. Incidence rates from the SIMPLIFY-2 trial were converted into event rates per cycle and multiplied by AE unit costs to estimate total AE costs per cycle (Table 35).

Table 35 Total adverse event costs per model cycle for the JAKi-experienced Int-2/HR Hb<12g/dL population

Adverse event	Momelotinib	BAT
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Total	[redacted]	[redacted]

Hb=haemoglobin; ICT=iron chelation therapy; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; RBC=red blood cell; TD=transfusion-dependent; TI=transfusion-independent; TR=transfusion-requiring
Source: CS, Table 101

Time to treatment discontinuation or death (TTDD)

The company assumed that patients receiving BAT did not discontinue treatment; instead, patients were assumed to switch to one of the treatments in an alternative subsequent treatment basket (Table 36).

SIMPLIFY-2 trial momelotinib TTDD data for the Int-2/HR Hb<12g/dL population were analysed in line with the methodology used to analyse OS data (Section 4.4.5). Although the generalised gamma distribution produced the best statistical fit to the K-M OS data, the company considered the sharp drop in TTDD at the beginning of the curve was implausible and selected the Gompertz distribution to model TTDD for patients treated with momelotinib. TTDD was capped by OS to prevent the proportion of patients remaining on treatment exceeding the proportion alive.

Subsequent treatment costs

The company assumed that patients who discontinue treatment with momelotinib receive BAT. Clinicians advising the company considered that JAKi-experienced patients would be unlikely to be re-treated with ruxolitinib following momelotinib discontinuation due to lack of NHS funding for ruxolitinib re-treatment. In the base case analysis, the company assumed that patients who discontinued momelotinib treatment would not receive ruxolitinib and the distribution of other BAT treatments was adjusted according to their proportional distribution in the SIMPLIFY-2 trial (Table 36).

Table 36 BAT subsequent treatment distributions

Subsequent treatment	SIMPLIFY-2 trial BAT composition	BAT composition excluding ruxolitinib (base case)	BAT composition with 39% receiving ruxolitinib (scenario)
Ruxolitinib - 5mg BID	17.3%	0.0%	7.6%
Ruxolitinib - 10mg BID	35.3%	0.0%	15.6%
Ruxolitinib - 15mg BID	20.7%	0.0%	9.1%
Ruxolitinib - 20mg BID	15.1%	0.0%	6.7%
Hydroxyurea	23.1%	59.7%	43.5%
Prednisone / prednisolone	11.5%	29.8%	21.8%
Danazol	5.8%	14.9%	10.9%
ESA (assumed as epoetin alfa)	3.8%	9.9%	7.3%
No therapy	3.8%	9.9%	7.3%
Anagrelide	1.9%	5.0%	3.6%
Aranesp (darbepoetin alfa)	1.9%	5.0%	3.6%
Aspegic	1.9%	5.0%	3.6%
Thalidomide	1.9%	5.0%	3.6%

BAT=best available therapy; BID=twice daily; ESA=erythropoiesis-stimulating
Source: CS, Table 102

Terminal care

The company included a terminal care cost. This was applied as a one-off cost for all patients who enter the death state at each model cycle and was considered to represent the increased cost of providing health and social care to patients near the end of life. The end of life cost was sourced from Round[55] and inflated to cost year 2022.

4.4.8 Severity modifier

The company calculated the QALY shortfall assuming a mean cohort age of 67 years and 60% male, representing the pooled baseline characteristics of the SIMPLIFY-2 trial population. The total expected QALYs for patients with MF treated with current standard of care corresponded to the total (discounted) QALYs in the BAT arm of the base case analysis population (Int-2/HR Hb<12g/dL) generated by the economic model. Expected general population QALYs were calculated using mortality rates from the ONS life tables[46] and age/gender-specific health state utility values from Hernandez-Alava.[48] The company estimated absolute QALY shortfall was 7.649 and the company estimated proportional shortfall was 78.6%. A QALY weight of 1.0 was therefore applied.

5 COST EFFECTIVENESS RESULTS

5.1 Cost comparison analysis for JAKi-naïve population

The company base case results using the confidential PAS price for momelotinib are presented in Table 37.

Table 37 Company base case cost comparison results (momelotinib PAS price)

Treatment	Drug acquisition cost	Subsequent treatment cost	ICT cost	RBC transfusion cost	AE cost	Total costs	Incremental costs
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021	-

AE=adverse event; ICT=iron chelation therapy; PAS=Patient Access Scheme; RBC=red blood cell
Source: CS, Table 59

5.1.1 Sensitivity analyses

The company considered that deterministic and probabilistic sensitivity analyses were not required due to the simplicity of the cost comparison model.

5.1.2 Scenario analyses

The company conducted several scenario analyses. These were designed to test the sensitivity of model results to alternative model input values and assumptions; results are presented in Table 38.

Table 38 Company scenario analyses results (momelotinib PAS price)

Scenario analysis	Incremental cost
3-year time horizon with no TTDD	[redacted]
RBC transfusion cost source: Agrawal (2006)[56]	[redacted]
Removal of ICT costs	[redacted]
ICT dose of 14mg/kg	[redacted]
TTDD and unadjusted RBC transfusion rates from Hb<12g/dL population	[redacted]
Extrapolation of ruxolitinib TTDD SIMPLIFY-1 trial data	[redacted]
RBC transfusion rate ratio of 0.43	[redacted]
Exclusion of ruxolitinib from BAT for patients discontinuing momelotinib treatment	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICT=iron chelation therapy; PAS=Patient Access Scheme; RBC=red blood cell; TTDD=time to discontinuation or death
Source: CS, Table 61

5.1.3 Subgroup analyses

The company did not present any subgroup results.

5.2 Cost utility analysis for JAKi-experienced population

The company base case deterministic and probabilistic results are presented in Table 39 and Table 40 respectively.

Table 39 Company base case deterministic results for the JAKi-experienced Int-2/HR Hb<12g/dL population (momelotinib PAS price)

Intervention	Mean total costs	Mean total QALYs	Mean incremental costs	Mean incremental QALYs	ICER £/QALY	Incremental NMB (WTP = £30,000)
BAT	[redacted]	1.898				
Momelotinib	[redacted]	2.043	[redacted]	0.145	Dominant	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost-effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; PAS=Patient access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
Source: Company clarification addendum Table 9

Table 40 Company base case probabilistic results (1,000 iterations) for the JAKi-experienced Int-2/HR Hb<12g/dL population (momelotinib PAS price)

Intervention	Mean total costs	Mean total QALYs	Mean incremental costs	Mean incremental QALYs	ICER £/QALY	Incremental NMB (WTP = £30,000)
BAT	[redacted]	1.831	-	-	-	
Momelotinib	[redacted]	2.018	[redacted]	0.187	Dominant	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost-effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; PAS=Patient access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
Source: Company clarification addendum Table 12

5.2.1 Deterministic sensitivity analyses

The company varied parameter input values individually in deterministic sensitivity analyses (DSA). Upper and lower values were based on confidence intervals or an assumed standard error of 10% of the mean base case value. The key drivers of cost effectiveness were OS model parameters (for non-TI and TI states), the overall proportion of patients receiving ruxolitinib as BAT and TD health state utility values (CS, Figure 51).

5.2.2 Scenario analyses

The company conducted several scenario analyses exploring alternative survival extrapolations and data sources. Cost effectiveness results were most sensitive to use of subsequent ruxolitinib (following discontinuation of momelotinib) and a shorter (5-year) time horizon (CS, Table 116).

5.2.3 Subgroup analyses

A subgroup analysis was performed for the Int-2/HR Hb<10g/dL population to explore the impact of applying a more restrictive interpretation of moderate to severe anaemia on cost effectiveness results (Table 41).

Table 41 Company subgroup results for the JAKi-experienced Int-2/HR Hb<10g/dL population (momelotinib PAS price)

Intervention	Mean total costs	Mean total QALYs	Mean incremental costs	Mean incremental QALYs	ICER £/QALY	Incremental NMB (WTP = £30,000)
BAT	[redacted]	1.709	-	-	-	
Momelotinib	[redacted]	1.762	[redacted]	0.053	Dominant	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost-effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; PAS=Patient access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
Source: Company model

5.3 Validation

The company JAKi-experienced population cost effectiveness model was assessed for conceptual validity using the AdViSHE framework.[57] Technical validation was based on relevant checklists from the TECH-VER framework.[58] The modelling approach, assumptions and outputs were validated through consultation with six UK clinical experts and two health economists. The proportion of TI patients at Week 24 in the SIMPLIFY-2 trial was compared to the predicted proportions in the economic model to ensure results were internally consistent. Survival estimates were also compared to those of presented as part of previous NICE MF appraisals.[11,12]

6 EAG CRITIQUE OF COMPANY ECONOMIC MODELS

The company has submitted two economic models for the comparison of momelotinib versus a relevant comparator for the treatment of disease-related splenomegaly or symptoms in adults with MF:

- momelotinib versus ruxolitinib (JAKi-naïve patients, cost comparison model)
- momelotinib versus BAT (JAKi-experienced patients, cost utility model).

The EAG has provided critiques of these models and alternative cost effectiveness results in Section 6.2 and Section 6.3 respectively.

6.1 Introduction: cost comparison model

The company's cost comparison model is a simple model, developed in Microsoft® Excel. The company has started discounting costs and benefits in Year 1 rather than from the start of Year 2. The EAG corrected this error and generated corrected company base case cost effectiveness results. Other than discounting, the EAG is satisfied that the company model algorithms are accurate and that parameter values in the model match the values presented in the CS.

Table 42 Summary of EAG critique of company cost comparison model

Aspect considered	EAG comment	Section of EAG report
Cost comparison analysis (JAKi-naïve population)		
Data/type of analysis	• The SIMPLIFY-1 trial non-inferiority margin (used to calculate statistical significance for the primary endpoint of spleen response rate) may be wider than the difference that could be considered clinically acceptable or tolerable for momelotinib to be considered as 'similar' or 'not worse' than ruxolitinib • SIMPLIFY-1 trial results failed to demonstrate that treatment with momelotinib was non-inferior to treatment with ruxolitinib in terms of TSS (a secondary endpoint)	6.2.1 and 6.2.4
Population	• Cost comparison results were generated using SIMPLIFY-1 trial ITT data. Int-2/HR population and anaemia (i.e., the Int-2/HR Hb<10g/dL population or Int-2/HR Hb<12g/dL population) should have been used	6.2.2
Comparators	• The comparator (ruxolitinib) represents standard of care in the NHS for patients with Int-2/HR MF	NA
Transfusion rates	• The RBC transfusion rate for NHS patients treated with ruxolitinib is likely to be lower than the SIMPLIFY-1 trial (and therefore in the model)	6.2.3
Treatment costs	• The EAG has no concerns about the company's treatment cost estimates	NA
Healthcare resource use	• The company's resource use estimates are reasonable and well justified • Clinical advice to the EAG is that SIMPLIFY-1 trial ruxolitinib arm transfusion rates may not be generalisable to NHS patients as, in the trial, ESAs were prohibited	NA
Discounting	• The EAG has corrected the company model so that discounting starts in Year 2 rather than Year 1	6.1
Adverse events	• The EAG has no concerns about the company's AE cost estimates	NA
Deaths	• The EAG has no concerns that no deaths occur over the model time horizon (10 years)	6.2.5

AE=adverse event; ESA=erythropoiesis-stimulating agent; Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; ITT=intention to treat; JAKi=Janus kinase inhibitor; NA=not applicable; RBC=red blood cell; TSS=total symptom score

6.2 Cost comparison analysis: JAKi-naïve population

The following key assumptions have been used in the company cost comparison analysis:

- with the exception of transfusion rates and AEs, all clinical outcomes are the same for patients treated with momelotinib and patients treated with ruxolitinib
- no patients die over the 10-year model time horizon
- discontinuation rates and subsequent treatments are the same for patients initially treated with momelotinib and those initially treated with ruxolitinib
- in line with the SIMPLIFY-1 trial, ESAs were a disallowed concomitant medication for patients receiving first-line treatment
- the proportion of patients who discontinue treatment with momelotinib and are then treated with ruxolitinib was sourced from the BAT arm of the SIMPLIFY-2 trial.

6.2.1 Data/type of analysis: use of SIMPLIFY-1 trial results to justify a cost comparison analysis

The SIMPLIFY-1 trial primary endpoint is spleen response rate. Statistical significance was tested using a non-inferiority margin of 60%. Clinical advice to the EAG is that this statistically defined non-inferiority margin is wider than the difference that could be considered clinically acceptable or tolerable for momelotinib to be considered as 'similar' or 'not worse' than ruxolitinib. The size of the non-inferiority margin does not affect the endpoint but does affect the calculation of confidence intervals; the wider the margin, the higher the likelihood is that the statistical result will lead to the conclusion that momelotinib is non-inferior to ruxolitinib (Section 3.2.4). However, clinical advice to the EAG was that the spleen response rates were similar in the momelotinib and ruxolitinib arms (Section 3.3.1).

The failure of SIMPLIFY-1 trial results to demonstrate that treatment with momelotinib is non-inferior to treatment with ruxolitinib for the secondary endpoint of TSS, could cast doubt about whether momelotinib and ruxolitinib can be assumed to be so clinically similar that any differences in patient outcomes can be ignored, i.e., that it is appropriate to carry out a cost comparison analysis. However, post-hoc analyses suggest there appeared to be little difference between treatment arms when assessing individual symptom scores and absolute change in TSS from baseline (Section 3.3.2). Clinical advice to the company and EAG was that the inability of the SIMPLIFY-1 trial to demonstrate non-inferiority for TSS response rate was not a major concern given many patients treated with momelotinib experienced improvements in the other key efficacy outcomes of RBC TI (Section 3.3.3) and RBC TD (3.3.4).

6.2.2 Modelled population

In the CS (CS, p137), the company states that the cost comparison evaluation is designed to support the reimbursement of momelotinib as a treatment for JAKi-naïve patients with Int-2/HR MF and anaemia. However, the company's base case results were generated using SIMPLIFY-1 trial ITT data (Table 45); [redacted]. In response to clarification (clarification question B1), the company stated that using ITT data was appropriate as differences in data inputs were not expected to vary between Hb subgroups and use of the data inputs from the full ITT population maximises the available sample size and minimised any parameter uncertainty.

The EAG considers that data from the Hb level subgroups should be used to populate the cost comparison model. The company model has the functionality to generate results for the Int-2/HR Hb<12g/dL subgroup; the EAG asked the company (clarification question B1) to provide

cost comparison results for the Int-2/HR Hb<10g/dL subgroup. The company also provided rates of RBC transfusions by Hb level subgroup (Table 43). Adjusted rates were used in the company base case (ITT) analysis and in the company Int-2/HR Hb<10g/dL subgroup analysis. The EAG has used adjusted rates to generate Int-2/HR Hb<10g/dL subgroup and the Int-2/HR Hb<12g/dL subgroup results. As the company model does not provide TTD data for the Int-2/HR Hb<10g/dL subgroup, the EAG used Int-2/HR Hb<12g/dL TTD data as a proxy. The EAG considers that it is more appropriate to use adjusted RBC transfusion rates as these account for differences in baseline patient characteristics.

Table 43 Rates of RBC transfusions by subgroup

	Int-2/HR with Hb<10g/dL		Int-2/HR with Hb<12g/dL	
	Momelotinib	**Ruxolitinib**	**Momelotinib**	**Ruxolitinib**
RBC transfusion rate in RT phase (unadjusted)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) units per month	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusion rate in RT phase, adjusted for strata				
Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

CI=confidence interval; Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; RBC=red blood cell; RT=randomised treatment; SD=standard deviation
Source: clarification question Table 41

6.2.3 Generalisability of SIMPLIFY-1 trial ruxolitinib arm transfusion rates

SIMPLIFY-1 trial 24 Week ITT results show that, compared with patients treated with ruxolitinib, a higher proportion of patients treated with momelotinib were TI and RBC transfusion rates were lower; these results hold for the two Hb level subgroups.

In the company base case analysis, [redacted]% of the estimated cost savings associated with treatment with momelotinib (using the momelotinib confidential PAS price) can be attributed to lower RBC transfusion costs. This proportion will increase after the application of the confidential ruxolitinib PAS discount; the difference in SIMPLIFY-1 trial momelotinib and ruxolitinib arm RBC transfusion rates is a key driver of cost comparison results.

ESAs (as concomitant medications) were prohibited in the SIMPLIFY-1 trial. Clinical advice to the EAG is that ESAs (e.g., darbepoetin alfa) are commonly used in the NHS as a supportive measure for patients with anaemia and that, of those patients prescribed ESAs, approximately:

- 25% respond and do not require any transfusions (i.e., remain TI)
- 25% partially respond and require a small number of transfusions (i.e., become TR) and
- the remainder fail treatment and require regular transfusions (i.e., become TD).

The EAG does not know what the impact on RBC transfusion rates would be if more patients received ESAs (in either or both trial arms) but considers that the RBC transfusion rate for NHS patients treated with ruxolitinib is likely to be lower than the rate observed in the SIMPLIFY-1 trial. The implications for the cost comparison analysis are unclear as, although ESA usage means that transfusion rates (and ICT rates) will be lower in the NHS than in the company model, drug acquisition costs associated with ESAs are unknown as the costs depend on dosages and response to treatment. Further, information on how long ESAs delay the need for, or totally replace, RBC transfusions is required. It is also unknown as to whether patients treated with momelotinib in NHS clinical practice would receive concomitant ESAs and the magnitude of any reduction in RBC transfusions.

6.2.4 Discontinuation rates and subsequent treatments

In the model, the company has assumed that the SIMPLIFY-1 trial momelotinib arm discontinuation rate (5.9% per month) can be applied to treatment with momelotinib and to treatment with ruxolitinib, and that following discontinuation of initial treatment, patients are prescribed BAT. As such, the assumption of equal discontinuation rates for momelotinib and ruxolitinib does not have a significant impact on costs.

In the model, in line with the SIMPLIFY-2 trial, the company has assumed that patients who discontinue treatment with momelotinib are treated with BAT; for 88.5% of patients who discontinue momelotinib BAT is ruxolitinib. The EAG considers that this assumption is reasonable as the NICE recommendation for ruxolitinib[11] is for all patients with Int-2/HR disease and is not limited by previous treatments. However, if it is not appropriate to offer ruxolitinib to patients who have discontinued treatment with momelotinib, then long-term patient outcomes may differ by first-line treatment; if outcomes do differ by first-line treatment then a cost comparison analysis is not appropriate.

6.2.5 No deaths in the cost comparison model

The company cost comparison model assumes that, over the 10-year time horizon, there are no deaths. The EAG considers that there is no approach that could be used to robustly introduce mortality into the company model. If mortality is assumed to be independent of treatment, it is unlikely that introducing mortality into the model would make the treatment that was the least costly become the most costly.

6.2.6 JAKi-naïve population: impact of EAG amendments on company base case results

The EAG has corrected the company base case so that discounting occurs from Year 2 onwards. Deterministic cost comparison analysis results are presented in Table 44 to Table

47. The EAG highlights that despite the company's cost comparison evaluation being designed to support the reimbursement of momelotinib as a treatment for JAKi-naïve patients with Int-2/HR MF and anaemia, the company's base case results were generated using SIMPLIFY-1 trial ITT data. The company and EAG cost comparison analysis results, generated using the PAS price for momelotinib and list prices for all other drugs, all demonstrate that treatment with momelotinib is [redacted] compared to ruxolitinib.

Details of EAG revisions to the company cost comparison model are presented in Appendix 9, Section 0 of this EAG report. Cost comparison analysis results using discounted prices for all drugs (where appropriate) are provided in a confidential appendix.

Table 44 Company base case results: ITT population (PAS price momelotinib, list prices all other treatments)

	Drug acquisition costs	Subsequent medicine cost	ICT cost	RBC transfusion costs	AE costs	Total costs
Ruxolitinib	£42,175	£219,056	£5,157	£57,507	£2,126	£326,021
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental momelotinib cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse events; ICT=iron chelation treatment; ITT=intention to treat; LY=life years; PAS=Patient Access Scheme; RBC=red blood cell

Table 45 EAG corrected company base case results: ITT population (PAS price momelotinib, list prices all other treatments)

	Drug acquisition costs	Subsequent medicine cost	ICT cost	RBC transfusion costs	AE costs	Total costs
Ruxolitinib	£43,704	£227,001	£5,344	£59,593	£2,203	£337,846
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental momelotinib cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse events; ICT=iron chelation treatment; ITT=intention to treat; PAS=Patient Access Scheme; RBC=red blood cell

Table 46 EAG corrected base case results: Int-2/HR Hb<12g/dL subgroup (PAS price momelotinib, list prices all other treatments)

	Drug acquisition costs	Subsequent medicine cost	ICT cost	RBC transfusion costs	AE costs	Total costs
Ruxolitinib	£40,789	£229,714	£5,344	£59,505	£2,197	£337,550
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental momelotinib cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse events; Hb=haemoglobin; ICT=iron chelation treatment; Int-2/HR=intermediate-2 or high risk; PAS=Patient Access Scheme; RBC=red blood cell

Table 47 EAG corrected base case: Int-2/HR Hb<10g/dL subgroup (PAS price momelotinib, list prices all other treatments)

	Drug acquisition costs	Subsequent medicine cost	ICT cost	RBC transfusion costs	AE costs	Total costs
Ruxolitinib	£40,789	£229,714	£5,344	£61,485	£2,197	£339,529
Momelotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental momelotinib cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse events; Hb=haemoglobin; ICT=iron chelation treatment; Int-2/HR=intermediate-2 or high risk; PAS=Patient Access Scheme; RBC=red blood cell

6.3 Cost utility analysis for JAKi-experienced population

6.3.1 Introduction

The company's cost utility model is a cohort-based Markov model constructed in Microsoft® Excel. The company has started discounting costs and benefits in Year 1 rather than from the start of Year 2. The EAG corrected this error and generated a corrected company base case ICER per QALY gained. Other than discounting, the EAG is satisfied that the company model algorithms are accurate and that parameter values in the model match the values presented in the CS.

Table 48 Summary of EAG critique of company cost effectiveness model

Aspect considered	EAG comment	Section of EAG report
Model structure	• The EAG considers that the company model structure is appropriate	NA
Population	• Given the uncertainty around identifying patients with moderate to severe anaemia, the EAG considers that results from both the SIMPLIFY-2 trial Int-2/HR Hb<10g/dL subgroup and the Int-2/HR Hb<12g/dL subgroup (company base case) should be used to inform decision making	6.3.2
Comparators	• The comparator represents standard of care in the NHS for the Int-2/HR Hb<10g/dL subgroup and for the Int-2/HR Hb<12g/dL subgroup	NA
Overall survival	• The company approach to modelling survival by transfusion status is not supported by the evidence	6.3.3
Transition probabilities	• The company has assumed that transition probabilities do not change after Week 24; the EAG is satisfied that this assumption aligns with SIMPLIFY-2 trial data	6.3.5
Transfusion rates	• The RBC transfusion rate for NHS patients treated with BAT is likely to be lower than the SIMPLIFY-2 trial (and therefore in the model)	6.3.6
Treatment costs	• Treatment costs have been appropriately calculated; however, for patients who stop treatment with momelotinib, the EAG has run a scenario in which ruxolitinib is available, as part of BAT	6.3.4
Healthcare resource use	• The company's resource use estimates are reasonable and well justified	NA
Utility values	• The utility values used in the company model conform to the NICE Reference Case and are appropriate • Clinical advice to the EAG is that regular blood transfusions impose a significant HRQoL burden on patients and this is fairly reflected in the company's utility decrements	NA
Adverse events	• The EAG has no concerns about the company's AE cost estimates	NA
Discounting	• The EAG has corrected the company model so that discounting starts in Year 2 rather than Year 1	NA
Company severity modifier	• The company appropriately does not claim that a severity modifier should be applied	NA
PSA	• The PSA was appropriately specified and correctly implemented	NA

AE=adverse event; BAT=best available therapy; Hb=haemoglobin; HRQoL=health-related quality of life; Int-2/HR=intermediate-2 or high risk; NA=not applicable; PSA=probabilistic sensitivity analysis; RBC=red blood cell transfusion

The company cost utility analysis employs the following key assumptions:

- OS benefit is linked to whether a patient is TI or non-TI (TD and TR) and not by treatment
- in the model, at Week 24, the probabilities of transitioning between transfusion states are fixed for the remainder of the model time horizon and are independent of treatment received and whether patients remain on treatment or move onto subsequent treatment(s)
- patients receiving momelotinib and BAT are assumed to be treated with ESAs in the same proportions as patients in the SIMPLIFY-2 trial momelotinib (0.0%) and BAT (5.7%) arms.

6.3.2 JAKi-experienced subgroup populations

The company base case analysis has been populated with data from the SIMPLIFY-2 trial Int-2/HR Hb<12g/dL subgroup. The EAG considers that it is also important to assess results from the Int-2/HR Hb<10g/dL subgroup as clinical advice to the EAG is that patients with Hb<10g/dL are more likely to represent NHS patients with moderate to severe anaemia than patients with Hb<12g/dL.

6.3.3 Overall survival benefit by transfusion status

In the company model, up until Week 24, OS for patients receiving momelotinib and BAT are assumed to be the same. After Week 24, the company has modelled OS for all patients based on whether a patient is TI or non-TI at Week 24, using data from the SIMPLIFY-2 trial momelotinib arm; data from the SIMPLIFY-2 trial BAT arm were not used as BAT arm patients were able to cross over to receive momelotinib at Week 24.

In line with the NICE DSU guidance,[45] the company fitted standard parametric distributions (n=6) to Int-2/HR Hb<12g/dL subgroup SIMPLIFY-2 trial TI and non-TI momelotinib arm OS K-M data after Week 24; separate distributions were fitted to the TI and non-TI OS K-M data. The best fitting distribution was identified based on statistical fit (Akaike Information Criterion [AIC] and Bayesian Information [BIC] statistics), visual inspection of the fitted distributions to the OS K-M data, plausibility based on clinical expert feedback and internal consistency of results between subgroups.

It is not possible to choose the most appropriate distribution based solely on AIC/BIC statistics as all AIC statistics have a relative fit classification compared to the best fitting distribution of 'good' (AIC difference of ≤4) and all BIC statistics have a relative fit classification compared to the best fitting distribution of 'reasonable' (BIC difference of ≤10) (CS, Table 77). This is problematic as, whilst the six distributions are statistically indistinguishable, they generate very different medium and long-term OS estimates (Table 49).

Table 49 Landmark survival rates for pure momelotinib SIMPLIFY-2 OS parametric distributions, TI, from Week 24 (base case Int-2/HR and Hb<12 g/dL subgroup)

Landmark survival rates	1 year	3 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; OS=overall survival; TI=transfusion-dependent
Source: CS, Table 78

The company's modelling approach means that, for a JAKi-experienced population, TI patients /treated with BAT have longer OS than non-TI patients treated with BAT; 88.5% of SIMPLIFY-2 trial BAT arm patients were treated with ruxolitinib. Results from a pooled analysis of COMFORT-I and COMFORT-II trial[59] OS data for patients with Int-2/HR disease and anaemia demonstrated that, for patients treated with ruxolitinib, there was no statistically significant difference in 5-year OS by transfusion status at Week 24. These published results suggest that, for patients treated with BAT, modelling differential survival by transfusion status at Week 24 is not appropriate.

The company provided information in response to clarification questions B2 and B3 to justify why, for patients treated with momelotinib and BAT, OS would vary by transfusion status. The EAG has some reservation about the information provided by the company:

- The company stated that results from the pooled analysis of COMFORT-I and COMFORT-II trial[59] data were uninformative as comparisons involved data from subgroups of subgroups (baseline anaemia status and transfusion status at Week 24) and were unlikely to be powered to show a difference in OS by transfusion status at Week 24.
    - The EAG highlights that the SIMPLIFY-2 trial was also not powered to show a difference in OS for the ITT population and, by extension, was also not powered to show a difference in OS for subgroups by transfusion status. The SIMPLIFY-2 trial subgroup OS analysis (38 TI and 30 non-TI patients [CS, Figure 38]) included fewer patients overall than the COMFORT-I and COMFORT-II trial[59] analysis (26 TI patients and 97 non-TI patients). If results from the COMFORT-I and COMFORT-II trial[59] analysis cannot robustly evidence survival by transfusion status at 24 Weeks for patients receiving ruxolitinib, then SIMPLIFY-2 trial data cannot robustly evidence survival by transfusion status at 24 Weeks for patients receiving momelotinib.

- The company stated that the Response to Ruxolitinib at 6 months (RR6) model[60] uses transfusion status for all patients receiving ruxolitinib at 6 months as a predictive factor for OS.
    - The EAG highlights that, for patients treated with ruxolitinib who have Int-2/HR disease and anaemia, the RR6 model does not estimate the additional risk of being TI versus non-TI at Week 24.
- The company presented a targeted literature review to support transfusion status being a predictor of OS.
    - The EAG highlights that this review did not provide any additional information to support the company's view that OS differs by transfusion status at Week 24 for patients with Int-2/HR disease and anaemia who are treated with ruxolitinib.

In summary, the EAG considers the evidence that transfusion status at Week 24 is a predictor of OS for patients with Int-2/HR disease and anaemia who are treated with a ruxolitinib is limited, and that the most robust evidence is provided by the analysis of COMFORT-I and COMFORT-II trial[59] data. The EAG therefore considers that it is not appropriate to model a difference in OS by transfusion status.

The EAG acknowledges that results from a company post-hoc analysis show that, for the ITT population, TI at Week 24 was associated with a non-significant trend towards longer survival for patients randomised to receive momelotinib (univariate analysis) (CS, p93). However, the EAG considers that these results may be due to differences in the proportions of TI and non-TI patients who were still being treated with momelotinib at Week 24. The EAG asked the company to provide SIMPLIFY-2 trial patient level OS, TTD and transfusion status data (clarification question B2). The company was unable to provide this information.

6.3.4 Ruxolitinib retreatment

In the company model, it is assumed that patients who stop treatment with momelotinib will not receive ruxolitinib. This results in patients in the momelotinib arm being on treatment with a JAKi for a shorter time than patients in the BAT arm (where 88.5% of patients alive are always receiving ruxolitinib). For example, at 3 years the company model predicts that 77 patients in the momelotinib arm will still be treated with a JAKi but that 400 patients in the BAT arm will still be treated with a JAKi. The large disparity in JAKi treatment rates between the momelotinib and BAT arms adds further challenge to the company approach to modelling improved OS for momelotinib compared to BAT.

Clinical advice to the EAG and to the company is that, following cessation of treatment with momelotinib, clinicians would like to have the option to re-treat some eligible patients with ruxolitinib. However, clinical advice to the EAG is that, in NHS practice, there may be restrictions to re-treatment with ruxolitinib. BlueTeq criteria[61] state that if treatment is stopped for more than 3 months, a treatment break form is required to restart ruxolitinib treatment.

The EAG has amended the company model so that all patients who stop treatment with momelotinib go on to receive BAT as per SIMPLIFY-2 trial proportions. This approach may overestimate retreatment rates, but means that patients in both arms of the model receive a JAKi for a similar period of time, which further justifies the EAG approach to modelling OS (i.e., no difference in OS by transfusion status).

6.3.5 Transitions between transfusion states

The company has used SIMPLIFY-2 trial data to estimate the probabilities of transitioning between transfusion states (TI, TR and TD) up to Week 24; probabilities differ by treatment. For the remainder of the model time horizon, for both model treatments, the company has used the momelotinib arm Week 24 transition probabilities. This means that stopping treatment with momelotinib after Week 24 has no impact on transition probabilities. The EAG has no concerns about transitions between transfusion states. For information, evidence provided by the company (clarification question B3) showed that the momelotinib transition probabilities from TI to non-TI states used in the model were pessimistic compared to the long-term SIMPLIFY-2 trial evidence (Figure 2).

Figure 2 Time to loss of TI response from 24 weeks or death from SIMPLIFY-2 trial compared to momelotinib TI health state membership from 24 weeks in the cost effectiveness model (base case Int-2/HR Hb<12g/dL population)

Source: clarification question B3, Figure 3

Hb=haemoglobin; Int-2/HR=intermediate-2 or high risk; TI=transfusion independent

6.3.6 Generalisability of transfusion rates in the SIMPLIFY-2 trial BAT arm

In contrast to SIMPLIFY-1 trial criteria, patients randomised to the SIMPLIFY-2 trial BAT arm were permitted to receive ESAs; however, ESA utilisation rates were low (5.7%) (CS, p164). Clinical advice to the EAG is that ESA usage would be higher in the NHS than in the SIMPLIFY-2 trial and therefore the proportion of NHS Int-2/HR BAT patients requiring RBC transfusions may be lower than the proportion of SIMPLIFY-2 trial Int-2/HR BAT patients requiring RBC transfusions. The implication of this difference in ESA usage on the size of the ICER per QALY gained is unknown as the impact extends beyond the direct cost impact of fewer RBC transfusions and affects model health state transition probabilities, OS and HRQoL. Further, it is also unknown as to whether patients treated with momelotinib in NHS clinical practice would receive concomitant ESAs and the magnitude of any reduction in RBC transfusions.

6.3.7 JAKi-experienced population: impact of EAG amendments on the company base case cost utility results

The EAG has corrected the company base case so that discounting occurs from Year 2 onwards. Deterministic and probabilistic cost utility analysis results are presented in Table 50 to Table 53; these results have been generated using the PAS price for momelotinib and list prices for all other drugs.

The EAG has made two revisions to the corrected company base case model:

- R1) No difference in OS by transfusion status
- R2) Patients who stop treatment with momelotinib are treated with ruxolitinib as part of BAT (in the same proportions as per patients in the SIMPLIFY-2 trial BAT arm [ruxolitinib: 88.5%]).

The EAG highlights that the company's base case cost utility analysis was populated with SIMPLIFY-2 trial Int-2/HR MF and Hb<12g/dL data; however, the EAG considers that it is important to also review results for the Int-2/HR MF and Hb<10g/dL subgroup. The company and EAG cost utility analysis results, generated using the PAS price for momelotinib and list prices for all other drugs, all demonstrate that treatment with momelotinib dominates treatment with ruxolitinib.

Details of EAG revisions to the company cost utility model are presented in Appendix 9, Section 8.9.2 of this EAG report. Cost effectiveness results generated using discounted prices for all drugs (where relevant) are provided in a confidential appendix.

Table 50 JAKi-experienced Int-2/HR Hb<12g/dL population: deterministic base case results with EAG revisions, momelotinib versus BAT (PAS price momelotinib, list prices all other treatments)

Analysis	Momelotinib		BAT		Incremental		ICER per QALY gained	Incremental NMB (WTP threshold £30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
Company base case*	[redacted]	2.043	[redacted]	1.898	[redacted]	0.145	Momelotinib dominates	[redacted]
EAG corrected company base case**	[redacted]	2.053	[redacted]	1.907	[redacted]	0.146	Momelotinib dominates	[redacted]
R1) No difference in OS by transfusion status	[redacted]	2.036	[redacted]	1.971	[redacted]	0.066	Momelotinib dominates	[redacted]
R2) Patients who stop treatment with momelotinib are treated with ruxolitinib as part of BAT	[redacted]	2.053	[redacted]	1.907	[redacted]	0.146	Momelotinib dominates	[redacted]
EAG preferred base case (R1+R2)	[redacted]	2.036	[redacted]	1.971	[redacted]	0.066	Momelotinib dominates	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
*Company corrected model submitted after clarification
**EAG revisions are applied to the EAG corrected company base case

Table 51 JAKi-experienced Int-2/HR Hb<10g/dL population: deterministic base case results with EAG revisions, momelotinib versus BAT (PAS price momelotinib, list prices all other treatments)

Analysis	Momelotinib		BAT		Incremental		ICER per QALY gained	Incremental NMB (WTP threshold £30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
Company base case*	[redacted]	1.762	[redacted]	1.709	[redacted]	0.053	Momelotinib dominates	[redacted]
EAG corrected company base case**	[redacted]	1.773	[redacted]	1.719	[redacted]	0.054	Momelotinib dominates	[redacted]
R1) No difference in OS by transfusion status	[redacted]	1.830	[redacted]	1.783	[redacted]	0.047	Momelotinib dominates	[redacted]
R2) Patients who stop treatment with momelotinib are treated with ruxolitinib as part of BAT	[redacted]	1.773	[redacted]	1.719	[redacted]	0.054	Momelotinib dominates	[redacted]
EAG preferred base case (R1+R2)	[redacted]	1.830	[redacted]	1.783	[redacted]	0.047	Momelotinib dominates	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
*Company corrected model submitted after clarification
**EAG revisions are applied to the EAG corrected company base case

Table 52 JAKi-experienced Int-2/HR Hb<12g/dL population: probabilistic company base case and EAG preferred base case, momelotinib versus BAT (PAS price momelotinib, list prices all other treatments)

Analysis	Momelotinib		BAT		Incremental		ICER per QALY gained	Incremental NMB (WTP threshold £30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
Company base case*	[redacted]	2.030	[redacted]	1.834	[redacted]	0.196	Momelotinib dominates	[redacted]
EAG corrected company base case**	[redacted]	2.037	[redacted]	1.843	[redacted]	0.195	Momelotinib dominates	[redacted]
EAG preferred base case (R1+R2)	[redacted]	2.193	[redacted]	2.112	[redacted]	0.081	Momelotinib dominates	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; PAS=Patient Access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
*Company corrected model submitted after clarification
**EAG revisions are applied to the EAG corrected company base case

Table 53 JAKi-experienced Int-2/HR Hb<10g/dL population: probabilistic company base case and EAG preferred base case, momelotinib versus BAT (PAS price momelotinib, list prices all other treatments)

Analysis	Momelotinib		BAT		Incremental		ICER per QALY gained	Incremental NMB (WTP threshold £30,000)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
Company base case*	[redacted]	1.739	[redacted]	1.642	[redacted]	0.096	Momelotinib dominates	[redacted]
EAG corrected company base case**	[redacted]	1.749	[redacted]	1.652	[redacted]	0.097	Momelotinib dominates	[redacted]
EAG preferred base case (R1+R2)	[redacted]	1.795	[redacted]	1.744	[redacted]	0.051	Momelotinib dominates	[redacted]

BAT=best available therapy; Hb=haemoglobin; ICER=incremental cost effectiveness ratio; Int-2/HR=intermediate-2 or high risk; JAKi=Janus kinase inhibitor; NMB=net monetary benefit; PAS=Patient Access Scheme; QALY=quality adjusted life year; WTP=willingness to pay
*Company corrected model submitted after clarification
**EAG revisions are applied to the EAG corrected company base case

6.4 Cost effectiveness conclusions

These conclusions are based on cost effectiveness results generated using the PAS price for momelotinib and list prices for all other drugs.

Results for patients with Int-2/HR Hb<12g/dL and patients with Int-2/HR Hb<10g/dL should be used to inform decision making.

6.4.1 JAKi-naïve population: cost comparison analysis:

If the NICE Appraisal Committee considers that the benefits delivered by treatment with momelotinib and ruxolitinib are so clinically similar that any differences in patient outcomes can be ignored, then a cost comparison analysis is appropriate. Company and EAG cost effectiveness results show that, compared with ruxolitinib, momelotinib is [redacted] over a time horizon of 10 years.

6.4.2 JAKi-experienced population: cost utility analysis

The EAG considers that OS does not vary by transfusion status and that patients who stop treatment with momelotinib could receive ruxolitinib as part of BAT. After implementing EAG revisions to the company corrected base case model, treatment with momelotinib dominates BAT.

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8 APPENDICES

8.1 Appendix 1: SIMPLIFY-1 trial and SIMPLIFY-2 trial statistical approaches

Table 54 EAG summary and critique of statistical approaches used to analyse SIMPLIFY-1 and SIMPLIFY-2 trial data

Item	EAG assessment	Statistical approach with EAG comments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary efficacy endpoint of the SIMPLIFY-1 and SIMPLIFY-2 trials was spleen response rate, defined as the proportion of patients with ≥35% reduction in spleen volume from baseline at Week 24 (CS, Table 12). Secondary efficacy endpoints were MPN-SAF TSS response rate, RBC TI rate, RBC TD rate, rate of RBC transfusions at Week 24 and exploratory outcomes relevant to the final scope issued by NICE were ORR, LFS and OS (CS, Table 8). Endpoint definitions and analysis approaches were pre-specified in the TSAPs (Section 6.1 to Section 6.3, Section 7.6.1). The EAG is satisfied that the SIMPLIFY-1 and SIMPLIFY-2 trial pre-specified primary, secondary and exploratory efficacy outcomes have been analysed appropriately
Was an appropriate sample size calculation and study design pre-specified?	Yes	The SIMPLIFY-1 and SIMPLIFY-2 trial sample size and power calculations were outlined (CS, Table 12) and were pre-specified (TSAPs, Section 1.3 and Section 6.1). A hierarchical approach to statistical testing of the primary endpoint (spleen response rate) and secondary endpoints (TSS response rate, RBC TI rate, RBC TD rate, rate of RBC transfusions) was also pre-specified for both trials (TSAPs, Section 6.2.1). The EAG is satisfied that the SIMPLIFY-1 and SIMPLIFY-2 trials pre-specified sample size calculations, statistical power calculations and hierarchical approach to statistical testing are appropriate and were correctly implemented. The EAG is also satisfied that clinical effectiveness results presented in the CS are appropriately interpreted with respect to the hierarchical approach
Were all changes in the conduct of the study or planned analysis made prior to analysis?	No	Latest versions of the SIMPLIFY-1 trial protocol (Amendment 3, 20 July 2017) and the SIMPLIFY-2 trial protocol (Amendment 2, 20 July 2017) were amended after the data-cut off dates for the analyses of Week 24 data (SIMPLIFY-1: 12 September 2016 and SIMPLIFY-2: 28 July 2016) but before the data cut-off dates for the follow-up analysis of open-label phase data (12 September 2017 for both trials). The TSAPs were also finalised after the data-cut off dates for the analyses of Week 24 data (SIMPLIFY-1 TSAP, version 1.0: 11 October 2016; SIMPLIFY-2 TSAP, version 1.0: 6 September 2016). Changes to planned analyses are outlined in the TSAPs (Section 6.4) and CSRs (Section 9.8) The company presented results from various post-hoc analyses in the CS. The post-hoc analyses presented for the SIMPLIFY-1 trial were: • an analysis of the cumulative distribution function of absolute change in MPN-SAF TSS from baseline to Week 24 in symptomatic patients (baseline TSS ≥10) (CS, Figure 10) • long term analyses comparing i) OS and ii) LFS between patients randomised to momelotinib versus patients randomised to ruxolitinib who switched to momelotinib after Week 24 (CS, Figure 16 and Appendix M, Figure 16)

Item	EAG assessment	Statistical approach with EAG comments
		For the SIMPLIFY-2 trial, post-hoc long-term analyses were conducted to compare i) OS and ii) LFS in ITT patients randomised to momelotinib versus patients randomised to BAT who switched to momelotinib after Week 24 (CS, Figure 23 and Appendix M, Figure 17) Several post-hoc subgroup analyses (see 'Were all subgroup and sensitivity analyses pre-specified?' Item) were presented for both trials. The EAG considers that all post-hoc analyses should be considered as exploratory in nature and should not be used to determine statistical significance
Were all analysis populations clearly defined & pre-specified?	Yes	Efficacy analysis populations of the SIMPLIFY-1 and SIMPLIFY-2 trials were the ITT population (all randomised patients) and all randomised patients with baseline TSS >0, or baseline TSS of 0 but with TSS missing or >0 at Week 24 for TSS response. OS was analysed within the safety population (all randomised patients who received ≥1 dose of study drug). The EAG is satisfied that the analysis populations of the SIMPLIFY-1 and SIMPLIFY-2 trials were appropriate and pre-specified (TSAPs, Section 3.1 and Section 6.2)
Was a suitable approach used for handling missing data?	Yes	The company's approach to handling missing data were outlined in the CS (Table 12) and further details are provided in the TSAPs (Section 3.6 and Section 6.1). The EAG is satisfied that the approach described was appropriate and was pre-specified in the TSAPs (Section 3.6 and Section 6.1)
Was the analysis approach for PROs appropriate and pre-specified?	Partly	PROs presented in the CS (Section B.2.7.1.7 and Section B.2.7.2.7) and analysed using a stratified ANCOVA approach were the absolute change and percentage change from baseline at Week 24 in SF-36 and EQ-5D-5L VAS score. The proportion of patients with an improvement or worsening of MF symptoms according to PGIC up to and at Week 24 was analysed using a stratified CMH approach. PROs were analysed in the ITT population and all analyses of PROs were considered exploratory. The EAG is satisfied that the analysis approaches of pre-specified PROs were appropriate (TSAP, Section 6.3.1.23 and Section 6.3.2). Additional post-hoc exploratory HRQoL utility MMRM analyses were conducted to assess the impact of variables including treatment arm and transfusion status on utility (CS, Table 26 and Table 32). The company also presented a SF-36 by transfusion state for pooled data from the SIMPLIFY-1 and SIMPLIFY-2 trials (CS, Appendix M, Table 77). The EAG considers that all post-hoc analyses should be considered as exploratory in nature and should not be used to determine statistical significance
Was the analysis approach for AEs appropriate and pre-specified?	Partly	AEs were assessed according to MedDRA version 22.0 and graded according to the CTCAE version 4.03 within the safety population (all randomised patients who received at least one dose of study drug [TSAPs, Section 3.1.3]). AEs were presented as numbers and percentages of patients experiencing events by treatment arm and by CTCAE grade (any Grade and Grade 3 to 4). AEs were presented in the double-blind treatment phase (Week 0 to 24) and in the open-label phase (Week 24 to 48) of the SIMPLIFY-1 and SIMPLIFY-2 trials. An overview of safety, TEAEs leading to study drug discontinuation and TEAEs reported in at least 5% of patients were presented in the CS separately for SIMPLIFY-1 and SIMPLIFY-2 trials (Appendix F.1.1 and F.1.2), as well as a pooled safety analysis of the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM trials (CS, Section B.2.11).

Item	EAG assessment	Statistical approach with EAG comments
		No formal statistical analyses of AEs were conducted. The EAG is satisfied that the analysis approach for AEs was pre-specified (TSAPs, Section 7.1) and is appropriate
Were all subgroup and sensitivity analyses pre-specified?	No	Pre-planned and post-hoc subgroups of primary and secondary efficacy endpoints were presented in the CS for both the SIMPLIFY-1 and SIMPLIFY-2 trials (Table 8, Figure 25, Figure 33, Section 2.8, Appendix E.1.1 and E.1.2). The EAG notes that the subgroup analyses presented for patients with Int-2/HR disease and Hb<10g/dL and Int-2/HR disease and Hb<12g/dL were post-hoc. The EAG considers these post-hoc subgroup analyses were well-justified, due to the proposed positioning of momelotinib in the treatment pathway. No sensitivity analyses were presented in the CS

AE=adverse event; ANCOVA=analysis of covariance; BAT=best available treatment; CMH=Cochran-Mantel-Haenszel; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; EQ-5D-5L=European Quality of Life 5 Dimensions 5 Level Version; Hb=haemoglobin; HRQoL=health related quality of life; Int-2/HR=intermediate-2 or high risk; ITT=intention-to-treat; LFS=leukaemia-free survival; MedDRA=Medical Dictionary for Regulatory Activities Terminology; MPN-SAF=Myeloproliferative Neoplasm Symptom Assessment Form; MF=myelofibrosis MMRM=mixed model for repeated measures; ORR=objective response rate; OS=overall survival; PGIC=patient global impression of change; PRO=patient-reported outcome; RBC=red blood cells; SF-36=Short Form 36; TD=transfusion-dependent; TI=transfusion-independent TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan; TSS=total symptom score; VAS=visual analogue scale
Source: CS, SIMPLIFY-1 TSAP[26] and CSR,[25] SIMPLIFY-2 TSAP[27] and CSR,[24] GSK Myelofibrosis HRQoL analysis[62]

8.2 Appendix 2: Quality assessment of the SIMPLIFY-1 trial

Table 55 Quality assessment for the SIMPLIFY-1 trial

Checklist	Company assessment	EAG assessment	EAG comment
Selection Bias (systematic differences between the comparison groups)			
An appropriate method of randomisation was used to allocate participants to intervention groups (which would have balanced any confounding factors equally across groups)	Yes	Yes	Stratified randomisation (SIMPLIFY-1 TSAP, Section 1.2)
There was adequate concealment of allocation (such that investigators, social care practitioners, healthcare professionals and participants cannot influence enrolment or allocation to groups)	Yes	Yes	Interactive web response system (SIMPLIFY-1 TSAP, Section 1.2)
The groups were comparable at baseline, including all major confounding factors	Yes	Yes	CS, Table 9
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	-
Performance Bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			
The comparison groups received the same care and support apart from the intervention(s) studied	Yes	Yes	-
Participants receiving care and support were kept 'blind' to intervention allocation	Yes	Yes	Patients in the momelotinib arm received momelotinib QD+ruxolitinib placebo BID and patients in the ruxolitinib arm received momelotinib placebo QD+ruxolitinib BID (SIMPLIIFY-1 TSAP, Section 1.2); all patients and carers were effectively blinded to treatment allocation.
Individuals administering care and support were kept 'blind' to intervention allocation	Yes	Yes	
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	-
Attrition Bias (systematic differences between the comparison groups with respect to loss of participants)			
All groups were followed up for an equal length of control group time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	Yes	The SIMPLIFY-1 trial included a 24-week randomised treatment phase (SIMPLIFY-1 TSAP, Section 1). All endpoints were measured at Week 24 for both treatment arms (SIMPLIFY-1 TSAP, Section 1.1)

Checklist	Company assessment	EAG assessment	EAG comment
How many participants did not complete the intervention in each group?	Momelotinib: 40/215 (18.6%) Ruxolitinib: 16/217 (7.4%)	Momelotinib: 40/215 (18.6%) Ruxolitinib: 16/217 (7.4%)	CS, Appendix D.1.2, Figure 3
The groups were comparable for intervention completion (that is, there were no important or systematic differences between groups in terms of those who did not complete the intervention)	Yes	No	The EAG considers that the discontinuation rate was notably higher in the momelotinib arm than the ruxolitinib arm (CS, Appendix D.1.2, Figure 3)
For how many participants in each group were no outcome data available?	Momelotinib: 31/215 (14.4%) Ruxolitinib: 13/217 (6.0%)	Momelotinib: 31/215 (14.4%) Ruxolitinib: 13/217 (6.0%)	Mesa 2017, Supplementary Appendix, Figure A1
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes	Yes	-
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?	Low risk of bias	Unclear risk of bias	The EAG considers that the SIMPLIFY-1 trial had unclear risk of attrition bias due to imbalances in intervention completion and availability of outcome data. It is unclear which treatment arm attrition bias would favour
Detection Bias (bias in how outcomes are ascertained, diagnosed, or verified)			
The study had an appropriate length of follow-up	Yes	Yes	The SIMPLIFY-1 trial included a 24-week randomised treatment phase and an extended treatment phase of up to 5 years (SIMPLIFY-1 TSAP, Section 1.2). Clinical advice to the EAG is that 24 weeks is a sufficient time frame to demonstrate efficacy for the key outcomes (i.e., spleen response, TSS and transfusion rate endpoints). In the ruxolitinib arm, 197/201 (98.0%) patients who completed the 24-week randomised controlled treatment phase switched to treatment with momelotinib, therefore, meaningful interpretation of long-term OS and LFS data is difficult despite follow-up of up to 5 years
The study used a precise definition of outcome	Yes	Yes	The SIMPLIFY-1 trial pre-specified primary, secondary and exploratory efficacy outcomes were appropriately defined (SIMPLIFY-1 TSAP, Section 6.1 to Section 6.3)

Checklist	Company assessment	EAG assessment	EAG comment
A valid and reliable method was used to determine the outcome	Yes	Yes	The SIMPLIFY-1 trial pre-specified primary, secondary and exploratory efficacy outcomes were appropriately assessed (SIMPLIFY-1 TSAP, Section 6.1 to Section 6.3)
Investigators were kept 'blind' to participants' exposure to the intervention	Yes	Yes	The primary endpoint (≥ 35% reduction from baseline to Week 24), spleen volume was assessed by a blinded central imaging laboratory (SIMPLIFY-1 TSAP, Section 6.1.1). The EAG considers that is was unclear whether investigators who assessed the secondary and exploratory efficacy outcomes were blind to treatment allocation. However, the EAG considers that the secondary transfusion rate endpoints are objective measures and therefore are not susceptible to investigator bias
Investigators were kept 'blind' to other important confounding factors	Yes	Yes	The EAG considers that it is unclear whether investigators in the SIMPLIFY-1 trial were blind to confounding factors but considers that spleen volume response rate and secondary transfusion rate endpoints are objective measures and therefore have low risk of investigator bias
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	-
Overall assessment of internal validity. Are the study results internally valid?			
Rate the study for internal validity below	++	++	The EAG agrees that most of the checklist criteria have been met for the SIMPLIFY-1 trial and that conclusions are unlikely to change
Overall assessment of external validity – Are the study results externally valid (i.e., generalisable to the whole source population)? Consider participants, interventions, settings, comparisons, and outcomes			
Rate the study for external validity below	++	++	Clinical advice to the EAG is that the SIMPLIFY-1 trial population is reflective of patients with MF in NHS clinical practice

BID=twice daily; MF=myelofibrosis; OS=overall survival; LFS=leukaemia-free survival; QD=once daily; TSAP=trial statistical analysis plan; TSS=total symptom score
Source: CS, Appendix D.1.3, Table 8; SIMPLIFY-1 TSAP;[25] Mesa 2017[19]

8.3 Appendix 3: Quality assessment of the SIMPLIFY-2 trial

Table 56 Quality assessment for the SIMPLIFY-2 trial

Checklist	Company assessment	EAG assessment	EAG comment
Selection Bias (systematic differences between the comparison groups)			
An appropriate method of randomisation was used to allocate participants to intervention groups (which would have balanced any confounding factors equally across groups)	Yes	Yes	Stratified randomisation (SIMPLIFY-2 TSAP, Section 1.2)
There was adequate concealment of allocation (such that investigators, social care practitioners, healthcare professionals and participants cannot influence enrolment or allocation to groups)	Yes	Yes	Interactive web response system (SIMPLIFY-2 TSAP, Section 1.2)
The groups were comparable at baseline, including all major confounding factors	Yes	Yes	CS, Table 10
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	-
Performance Bias (systematic differences between groups in the care provided, apart from the intervention under investigation)			
The comparison groups received the same care and support apart from the intervention(s) studied	Yes	Yes	-
Participants receiving care and support were kept 'blind' to intervention allocation	No	No	The SIMPLIFY-2 trial was open-label and patients and carers were not blinded to treatment allocation (SIMPLIFY-2 TSAP, Section 1.2)
Individuals administering care and support were kept 'blind' to intervention allocation	No	No	
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?	Low risk of bias	Unclear risk of bias	The EAG considers that the SIMPLIFY-2 trial was at risk of performance bias for the secondary endpoint, TSS response rate (≥50% reduction from baseline to Week 24), because this is a subjective measure and could be biased in favour of momelotinib versus BAT. The EAG considers that the primary endpoint, spleen volume response rate (≥ 35% reduction from baseline to Week 24) and the secondary transfusion rate endpoints are at low risk of performance bias because these are objective measures

Checklist	Company assessment	EAG assessment	EAG comment
Attrition Bias (systematic differences between the comparison groups with respect to loss of participants)			
All groups were followed up for an equal length of control group time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	Yes	The SIMPLIFY-2 trial included a 24-week randomised treatment phase (SIMPLIFY-2 TSAP, Section 1). All endpoints were measured at Week 24 for both treatment arms (SIMPLIFY-2 TSAP, Section 1.1)
How many participants did not complete the intervention in each group?	Momelotinib: 35/104 (33.7%) BAT: 12/52 (23.1%)	-	-
The groups were comparable for intervention completion (that is, there were no important or systematic differences between groups in terms of those who did not complete the intervention)	Unclear	No	The company considered (clarification question A12) that the discontinuation rate for the BAT arm was uncertain because discontinuations were inconsistently reported in the BAT arm. The company therefore considered that it was difficult to compare the discontinuation rate between treatment arms in the SIMPLIFY-2 trial. The EAG considers that the discontinuation rate was notably higher in the momelotinib arm than in the BAT arm (CS, Appendix D.1.2, Figure 4)
For how many participants in each group were no outcome data available?	Momelotinib: 34/104 (32.7%) BAT: 13/52 (25.0%)	-	Spleen volume data (primary endpoint) were available 70/104 (67.3%) patients in the momelotinib arm and 39/52 (75.0%) patients in the BAT arm. TSS data (secondary endpoint) were available for 72/104 (69.2%) patients in the momelotinib arm and 38/52 (73.1%) patients in the BAT arm
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes	Yes	-
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?	Low risk of bias	Unclear risk of bias	The EAG considers that the SIMPLIFY-2 trial had unclear risk of attrition bias due to the high discontinuation rate (>20%) in both treatment arms. The EAG also considers that there were imbalances in intervention completion rate. It is unclear which treatment arm attrition bias would favour

Checklist	Company assessment	EAG assessment	EAG comment
Detection Bias (bias in how outcomes are ascertained, diagnosed, or verified)			
The study had an appropriate length of follow-up	Yes	Yes	The SIMPLIFY-2 trial included a 24-week randomised treatment phase and an extended treatment phase of up to 5 years (SIMPLIFY-2 TSAP, Section 1.2). Clinical advice to the EAG is that 24 weeks is a sufficient time frame to demonstrate efficacy for the key outcomes (i.e., spleen response, TSS and transfusion rate endpoints). In the BAT arm, all patients (40/40, 100.0%) who completed the 24-week randomised controlled treatment phase switched to treatment with momelotinib, therefore, meaningful interpretation of long-term OS and LFS data is difficult despite follow-up of up to 5 years
The study used a precise definition of outcome	Yes	Yes	The SIMPLIFY-2 trial pre-specified primary, secondary and exploratory efficacy outcomes were appropriately defined (SIMPLIFY-2 TSAP, Section 6.1 to Section 6.3)
A valid and reliable method was used to determine the outcome	Yes	Yes	The SIMPLIFY-2 trial pre-specified primary, secondary and exploratory efficacy outcomes were appropriately assessed (SIMPLIFY-2 TSAP, Section 6.1 to Section 6.3)
Investigators were kept 'blind' to participants' exposure to the intervention	NA	Unclear	The primary endpoint (≥ 35% reduction from baseline to Week 24), spleen volume was assessed by a blinded central imaging laboratory (SIMPLIFY-2 TSAP, Section 6.1.1). The EAG considers that it was unclear whether investigators who assessed the secondary and exploratory efficacy outcomes were blind to treatment allocation and confounding factors. However, the EAG considers that the secondary transfusion rate endpoints are objective measures and therefore are not susceptible to investigator bias. The secondary outcome of TSS response is a subjective measure and may have been prone to bias
Investigators were kept 'blind' to other important confounding factors	NA	Unclear	
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?	Low risk of bias	Low risk of bias	The EAG agrees that, overall, the SIMPLIFY-2 trial has low risk of detection bias

Checklist	Company assessment	EAG assessment	EAG comment
Overall assessment of internal validity. Are the study results internally valid?			
Rate the study for internal validity below	+	++	The company considered (clarification questions A12) that the SIMPLIFY-2 trial had less internal validity than the SIMPLIFY-1 trial because the SIMPLIFY-2 trial was open-label whereas the SIMPLIFY-1 trial included a double-blind randomised controlled treatment phase. However, the EAG considers that most of the checklist criteria have been met for the SIMPLIFY-2 trial and that conclusions are unlikely to change, regardless of the level of blinding
Overall assessment of external validity – Are the study results externally valid (i.e., generalisable to the whole source population)? Consider participants, interventions, settings, comparisons, and outcomes			
Rate the study for external validity below	++	++	Clinical advice to the EAG is that the SIMPLIFY-2 trial population is reflective of patients with MF in NHS clinical practice

BAT=best available therapy; MF=myelofibrosis; NA=not applicable; OS=overall survival; LFS=leukaemia-free survival; TSAP=trial statistical analysis plan; TSS=total symptom score
Source: CS, Appendix D.1.3, Table 8; SIMPLIFY-2 TSAP;[27] Harrison 2018[17]

8.4 Appendix 4: SIMPLIFY-1 trial OS and LFS results

Table 57 OS and LFS results in the SIMPLIFY-1 trial

Timepoint	Outcome	OS		LFS	
		Momelotinib	Ruxolitinib	Momelotinib	Ruxolitinib
Week 24 interim analysis (safety population) [a]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Week 48 interim analysis (safety population)	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Long term follow-up (safety population) [b]	Events, n/N (%)	66/214 (30.8)	73/216 (33.8)	78 / 214 (36.4%)	82 / 216 (38.0%)
	Median (95% CI) months	NE [c]	NE [c]	NE [c]	NE [c]
	Stratified HR (95 CI%) log rank test p-value	1.02 (0.73 to 1.43) p=not reported		1.08 (0.78 to 1.50) p=not reported	
Final analysis (safety population) [d]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Final analysis (Int-2/HR Hb<12g/dL) [d]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Final analysis (Int-2/HR Hb<10g/dL) [d]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	

[a] Following the 24 week randomised treatment phase, all patients in the ruxolitinib arm who continued in the extended treatment phases of SIMPLIFY-1 trial switched to receive momelotinib.
[b] Median follow-up was 3.43 years among patients randomised to momelotinib and 3.47 years among patients randomised to ruxolitinib
[c] Median OS and LFS were reached in both arms of the SIMPLIFY-1 trial at the final analysis, but not at the long-term follow-up analysis. This is because the long-term follow-up analysis included additional follow-up time and additional patients at risk at later time points compared with the final analysis, affecting the calculation of median OS and LFS (clarification question A8).
[d] Final analysis is up to 5 years after randomisation
CI=confidence interval; HR=hazard ratio; Int-2/HR=intermediate-2 or high risk; LFS=leukaemia-free survival; NE=not estimable; OS=overall survival
Source: CS Table 21, Section B.2.7.1.6; CS Appendix M, Table 73; Mesa 2022;[40] SIMPLIFY-1 Data on File Table 2.1002, Table 2.1003, Table 2.1102, Table 2.1103

8.5 Appendix 5: SIMPLIFY-2 trial OS and LFS results

Table 58 OS and LFS results in the SIMPLIFY-2 trial

Timepoint	Outcome	OS		LFS	
		Momelotinib	BAT	Momelotinib	BAT
Week 24 interim analysis (safety population) [a]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Week 48 interim analysis (safety population)	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Long term follow-up (safety population) [b]	Events, n/N (%)	47 / 104 (45.2)	23 / 52 (44.2)	54 / 104 (51.9%)	24 / 52 (46.2%)
	Median (95% CI) months	34.8 (27.6 to NE)	37.2 (21.6 to NE)	37.2 (20.4 to NE)	33.3 (27.6 to NE)
	Stratified HR (95 CI%) log rank test p-value	0.98 (0.59 to 1.62) p=not reported		0.97 (0.59 to 1.60) p=not reported	
Final analysis (safety population) [c]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Final analysis (Int-2/HR Hb<12g/dL) [c]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	
Final analysis (Int-2/HR Hb<10g/dL) [c]	Events, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI) months	[redacted]	[redacted]	[redacted]	[redacted]
	Stratified HR (95 CI%) log rank test p-value	[redacted]		[redacted]	

[a] Following the 24 week randomised treatment phase, all patients in the BAT arm who continued in the extended treatment phase switched to receive momelotinib.
[b] Median follow-up was 3.07 years among patients randomised to momelotinib and 3.22 years among patients randomised BAT
[c] Final analysis is up to 5 years after randomisation
BAT=best available treatment; CI=confidence interval; Hb=haemoglobin; HR=hazard ratio; Int-2/HR=intermediate-2 or high risk; LFS=leukaemia-free survival; NE=not estimable; NR=not reached; OS=overall survival
Source: CS Table 28, Section B.2.7.2.6; CS Appendix M, Table 74; Mesa 2022;[40] SIMPLIFY-2 Data on File Table 2.0701, Table 2.4102, Table 2.0802, Table 2.4702

8.6 Appendix 6: SIMPLIFY-1 HRQoL results

Table 59 Summary of HRQoL results for the SIMPLIFY-1 trial at Week 24: ITT populations and key subgroups

Outcome by population/subgroup	Momelotinib	Ruxolitinib	LSMD (95% CIs)
Median percentage CFB in SF-36 PCS, % (Q1 to Q3)			
ITT population	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted]
Median percentage CFB in SF-36 MCS, % (Q1 to Q3)			
ITT population	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted]
Mean percentage CFB in EQ-5D VAS, % (SD)			
ITT population	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted]
PGIC improvement, n/N (%)			
ITT population	[redacted]	[redacted]	[redacted][a]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][a]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][a]

[a] Proportion difference (95% CIs)
CFB=change from baseline; CI=confidence interval; EQ-5D VAS=EuroQoL 5-Dimensions Visual Analogue Scale; Hb=haemoglobin; HRQoL=health-related quality of life; Int-2/HR=intermediate-2 or high risk; ITT=intention to treat; LSMD=least squares mean difference; MCS=mental health component score; PCS=physical function component score; PGIC=Patient Global Impression Change; SD=standard deviation; SF-36=Short Form-36
Source: CS, Table 23 to Table 25, clarification question A9, Table 9 to Table 11 and Table 14 to Table 16

8.7 Appendix 7: SIMPLIFY-2 HRQoL results

Table 60 Summary of HRQoL results for the SIMPLIFY-2 trial at Week 24: ITT populations and key subgroups

Outcome by population/subgroup	Momelotinib	BAT	LSMD (95% CIs)
Median percentage CFB in SF-36 PCS, % (Q1 to Q3)			
ITT population	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted]
Median percentage CFB in SF-36 MCS, % (Q1 to Q3)			
ITT population	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted]
Mean percentage CFB in EQ-5D VAS, % (SD)			
ITT population	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted]
PGIC improvement, n/N (%)			
ITT population	[redacted]	[redacted]	[redacted][a]
Int-2/HR Hb<12g/dL	[redacted]	[redacted]	[redacted][a]
Int-2/HR Hb<10g/dL	[redacted]	[redacted]	[redacted][a]

[a] Proportion difference (95% CIs)
BAT=best available therapy; CFB=change from baseline; CI=confidence interval; EQ-5D VAS=EuroQoL 5-Dimensions Visual Analogue Scale; Hb=haemoglobin; HRQoL=health-related quality of life; Int-2/HR=intermediate-2 or high risk; ITT=intention to treat; LSMD=least squares mean difference; MCS=mental health component score; PCS=physical function component score; PGIC=Patient Global Impression Change; SD=standard deviation; SF-36=Short Form-36
Source: CS, Table 29 to Table 31, clarification question A9, Table 19 to Table 21 and Table 24 to Table 26

8.8 Appendix 8: MOMENTUM trial

8.8.1 MOMENTUM trial conduct

The company provided details of the MOMENTUM trial in the CS (CS, Table 8). The MOMENTUM trial was a Phase III, multicentre, international, double-blind, non-inferiority and superiority RCT (107 sites in 21 countries, including the UK). Randomisation was stratified by TSS (<22 or ≥22), spleen size (<12cm or ≥12cm), red blood cell or whole blood units transfused in the 8 weeks before randomisation (0 units versus 1–4 units versus ≥5 units) and study site. The EAG notes:

- the MOMENTUM trial also included a washout period prior to the trial entry during which patients were required to taper any treatment with JAKis and patients must have completely discontinued JAKi treatment ≥2 weeks prior to randomisation; clinical advice to the EAG is that in NHS clinical practice, patients who discontinue treatment with ruxolitinib would not undergo a washout period before receiving a subsequent treatment
- after the double blind 24-week randomised controlled period (data-cut: 3 December 2021) patients randomised to momelotinib could continue treatment with momelotinib and patients randomised to danazol could switch to treatment with momelotinib. In the MOMENTUM trial, the proportion of patients who completed treatment at Week 24 and who switched from danazol to treatment with momelotinib was 94.68% (n=35/37)
- while in the final scope issued by NICE, androgens (including danazol) were listed as a relevant comparator, danazol is not widely available in NHS clinical practice and the BSH[7] only recommend danazol for patients with RBC TD anaemia; not all patients had RBC TD anaemia (see Table 61)
- where danazol is available, although it can be used alone (as in the MOMENTUM trial), clinical advice to the EAG is that danazol is usually used in combination with an active MF therapy
- given danazol is used alone in the comparator arm, the comparator arm could be considered to be a proxy for 'watch and wait'; however, clinical advice is that 'watch and wait' would not considered to be a relevant comparator for patients with Int-2/HR disease.

The non-inferiority margin for the primary outcome was set to test whether the RBC TI rate (co-primary outcome) of momelotinib at Week 24 was more than 80% of the RBC TI rate of danazol (based on stratified CMH proportions). Non-inferiority would only be demonstrated if the company's calculations indicated at the 95% confidence level that the spleen RBC TI rate of momelotinib at Week 24 is more than 80% of the spleen response rate of danazol at Week 24.

8.8.2 MOMENTUM trial baseline patient characteristics

A summary of the baseline patient characteristics are presented in Table 61. The EAG considers that most patient characteristics were well balanced between treatment arms, the exception being there were fewer Int-2 risk and more high risk patients in the momelotinib arm versus the danazol arm.

Table 61 Baseline characteristics of the MOMENTUM trial patients

Characteristic	Momelotinib (N=130)	Danazol (N=65)
Mean age, years (range)	71 (65 to 75)	72 (67 to 78)
Male sex, n (%)	79 (61)	44 (68)
MF subtype, n (%)		
PMF	78 (60)	46 (71)
Post-PV	27 (21)	11 (17)
Post-ET	25 (19)	8 (12)
Risk category, n (%) Int-1	7 (5)	3 (5)
Int-2	72 (55)	40 (62)
HR	50 (38)	19 (29)
TSS, mean (SD)	28.0 (13.8)	25.7 (12.8)
Mean Hb,g/dL (SD)	8.1 (1.1)	7.9 (0.8)
Hb ≥8g/dL, n (%)	67 (52)	33 (51)
Mean platelet count, $x10^3/\mu L$	151.7 (130.9)	130.7 (101.0)
RBC TI, n (%)	17 (13)	10 (15)
RBC TD, n (%)	63 (48)	34 (52)

ET=essential thrombocythemia; Hb=haemoglobin; Int-1=Intermediate-1; Int-2=Intermediate-2; HR=high risk; MF=myelofibrosis; PMF=primary myelofibrosis; ; PV=polycythaemia vera; SD=standard deviation; TD=transfusion dependence; RBC TI=transfusion independence; TSS=total symptom score
Source: CS, Table 40 and clarification response, A13, Table 38

8.8.3 MOMENTUM trial efficacy results

The key efficacy results from the MOMENTUM trial are summarised in Table 62. For spleen response rate, TSS response rate and RBC TI rate at Week 24, the results were statistically significantly in favour of momelotinib versus danazol. For TD, the results were numerically in favour of momelotinib versus danazol.

OS data were only available at Week 24 in the MOMENTUM trial. Median OS was not reached in either treatment arm but OS rates were numerically higher in the momelotinib arm (88%) compared with the danazol arm (80%). In a post-hoc subgroup analysis, RBC TI at Week 24 was associated with statistically significantly longer OS in patients randomised to receive momelotinib ([redacted]; CS Figure 33). LFS data were not reported in the MOMENTUM trial.

The EAG highlights when interpreting the results, it should be noted that patients in the comparator arm of the MOMENTUM trial only received danazol, an anaemia supportive measure, i.e., no active treatment for MF in the comparator arm. While danazol could be a proxy for 'watch and wait' the BSH[7] only recommend it for patients with RBC TD (approximately half of the patients in the trial were not TD) and danazol is not widely available in NHS clinical practice.

Table 62 Summary of results for MOMENTUM trials efficacy endpoints at Week 24: ITT population

Outcome	Momelotinib n/N (%)	Danazol n/N (%)	Proportion difference (95% CI)
Spleen response rate [a]	29/130 (22.3%)	2/65 (3.1%)	[redacted] [b]
TSS response rate c	32/130 (24.6%)	6/65 (9.2%)	[redacted] p=0.0095 [b]
RBC TI rate [d]	39/130 (30.0%)	13/65 (20.0%)	[redacted] one-sided p=0.0116 [e]
RBC TD rate [f]	[redacted]	[redacted]	[redacted] [b]

[a] Spleen response rate defined as the proportion of patients with ≥35% reduction in spleen volume from baseline at Week 24; unlike the SIMPLIFY-1 and SIMPLIFY-2 trials, spleen response rate was a secondary outcome in the MOMENTUM trial
[b] Stratified CMH analysis for superiority hypothesis.
[c] TSS defined as the proportion of patients with a ≥50% reduction in mean MF-SAF (MOMENTUM) at Week 24 compared with baseline; unlike the SIMPLIFY-1 and SIMPLIFY-2 trials, TSS response rate was measured in the overall ITT population and was co-primary outcome in the MOMENTUM trial
[d] RBC TI defined as the proportion of patients who had no RBC transfusions or no Hb levels<8g/dL in the previous 12 weeks at Week 24; unlike the SIMPLIFY-1 and SIMPLIFY-2 trials, RBC TI was co-primary outcome in the MOMENTUM trial
[e] If the company's calculations indicated at the 95% confidence level that the RBC TI rate of momelotinib at Week 24 is more than 80% of the spleen response rate of ruxolitinib at Week 24 (stratum-adjusted CMH proportions), non-inferiority would be demonstrated
[f] RBC TD defined as the proportion of patients who required ≥ 4 RBC or whole blood units with each such transfusion in response to a Hb assessment of ≤9.5g/dL and ≥2 Hb assessments with time between the earliest and latest Hb assessments ≥28 days in an 8-week period immediately before the end of Week 24
CI=confidence interval; CMH=Cochran Mantel Haenzsel; CSR=clinical study report; Hb=haemoglobin; ITT=intention-to-treat; MF-SAF=Myelofibrosis Symptom Assessment Form; RBC=red blood cell; TD=transfusion-dependent; RBC TI=transfusion-independent; TSS=total symptom score
Source: CS Table 19; MOMENTUM CSR,[63] Table 36, Verstovsek 2023a;[20] clarification questions A1 and A2

8.8.4 MOMENTUM trial patient reported outcomes

The company presented HRQoL data for all patients in the MOMENTUM trial (CS, Section B.2.7.3.8). HRQoL results from the MOMENTUM trial were considered exploratory. For the MOMENTUM trial, the company reported the following HRQoL outcomes:

- change from baseline to Week 24 in disease-related fatigue measured by Myelofibrosis Symptom Assessment Form (MF-SAF)
- change from baseline to Week 24 in cancer-related fatigue measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
- percentage change from baseline to Week 24 in EQ-5D VAS.

In the MOMENTUM trial, mean disease-related fatigue and cancer-related fatigue scores and EQ-5D VAS improved from baseline to Week 24 in both the momelotinib and danazol treatment arms (CS, Table 35). The mean change from baseline at Week 24 in:

- disease-related fatigue was numerically greater in the momelotinib arm (least squares mean [standard error, SE]: [redacted]) than in the danazol arm (least squares mean [SE]: [redacted])
- cancer-related fatigue was numerically significantly greater (p=[redacted]) in the momelotinib arm (least squares mean [SE]: [redacted]) than in the danazol arm (least squares mean [SE]: [redacted])
- EQ-5D VAS was numerically greater in the momelotinib arm (mean [SD]: [redacted]) than in the danazol arm (mean [SD]: [redacted]).

8.9 Appendix 9: EAG revisions to the company models

8.9.1 EAG revisions to the company JAKi-naïve (cost comparison) model

EAG revisions	Implementation instructions
Correct discounting	**Insert sheet "EAG Revisions"** Set value in cell C3 = "C1" Set value in cell D3 = 1 Select Sheet 'Outputs' Set value in cell C29=R29*IF('EAG Revisions'!D3=1,1,(1-$D$12)^C$28) Set value in cell C30= R30*IF('EAG Revisions'!D3=1,1,(1-$D$12)^C$28) Set value in cell D29= S29*(1-$D$12)^IF('EAG Revisions'!$D$3=1,C$28,D$28) Set value in cell D30= S30*(1-$D$12)^IF('EAG Revisions'!$D$3=1,C$28,D$28) Copy formula in range D29:D30 Paste tin range E29:L30 Set value in cell C37=R37*IF('EAG Revisions'!$D$3=1,1,(1-$D$12)^C$34) Copy formula in cell C37 Paste in range C38:C45 and in range C50:C58 Set value in cell D37= =S37*(1-$D$12)^IF('EAG Revisions'!$D$3=1,C$34,D$34) Copy formula in cell D37 Paste in range D37:L45 and in range D50:L58
Int-2/HR Hb<10g/dL subgroup results	Select Sheet 'Outputs' Set value in cell D7 = "Int2/HR, Hb<12" Set value in cell E7=1 Select Sheet 'RBCT Costs' Set value in cell L17 = 0.86 Set value in cell L18 = 1.84 Copy formula in cell G17 Paste to range M17:M18 Set value in cell H17 =IF(Outputs!$E$7=1,L17, IF(Outputs!$D$7="ITT",'RBCT Costs'!B17,'RBCT Costs'!F17)) Copy formula in cell H17 Paste to range H17:I18

8.9.2 EAG revisions to the company JAKi-experienced (cost utility) model

EAG revisions	Implementation instructions
Correct discounting	**Insert sheet "EAG Revisions"** Set value in cell C3 = "C1" Set value in cell D3 = 1 Select Sheets "Markov Trace (BAT 2L)" and "Markov Trace (Momeltonib 2L)" Set value in cell C9= =IF('EAG Revisions'!D$3=1,0,(D9-1)/model_cycles_per_yr) Copy formula in cell C9 and paste to range C10:C21
R1: No difference in OS by transfusion status	Select Sheet "Clinical inputs – JAKi exp" Set value in cell D126 = "Overall cohort" For Int2/HR & Hgb<12 g/dL subgroup: Set value in cell G122 = "Gompertz" For Int2/HR & Hgb<10 g/dL subgroup: Set value in cell G122 = "Weibull"
R2: Patients who stop treatment with momelotinib are treated with ruxolitinib as part of BAT	Select Sheet 'EAG Revisions' Set value in cell C5 = "R2" Set value in cell D5 = 1 Select Sheet "Data Store" Set value in cell D649 =IF('EAG Revisions'!D5=1,88.5%,0%)

PRE-ACM1 EAG APPENDIX

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

Pre-ACM1 External Assessment Group Appendix

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136076

Completed 20 December 2023

Contains [redacted] data

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 EAG ADDITIONAL ANALYSES

Following on from the pre-meeting briefing (PMB), NICE requested the following actions:

- determining how the costs of blood transfusion were calculated in the JAKi-naive population and whether they are appropriate (Section 1.1)
- scenario including no benefit to transfusion status for momelotinib (Section 1.2)
- analysis of time to treatment discontinuation for patients treated with ruxolitinib and momelotinib, if possible (Section 1.3)
- confirming the tables in the confidential appendix, particularly the JAKi-naive Hb<12g/dL and Hb<10g/dL subgroups (confidential appendix 3 [20 December 2023])

1.1 Red blood cell transfusion costs

In both the cost comparison and cost utility models, the company applied a red blood cell (RBC) transfusion cost of £399.77 per unit. This cost was sourced from TA756[1] and inflated to 2022 prices.

In TA756,[1] the cost per RBC transfusion unit was sourced from Varney 2003;[2] the unit cost by dividing the NHS hospital resource use attributable to blood transfusions (e.g., hospital stays, managing blood transfusion-related complications) plus the total costs incurred by the blood transfusion services (collecting, testing, processing and issuing blood products), by the estimated number of transfusions. The EAG considers the cost per RBC transfusion unit is reasonable and is in line with the weighted average of NHS Cost Collection[3] unit costs for simple blood transfusions (£374.33). In the cost comparison model, RBC transfusion costs are calculated by multiplying the RBC transfusion cost by the monthly RBC transfusion rates observed in the SIMPLIFY-1 trial, over a 10-year time horizon. Similarly, in the cost utility model, SIMPLIFY-2 trial RBC transfusion rates are multiplied by the RBC transfusion cost (different rates for different health states).

1.2 EAG scenario analysis

The EAG considers the SIMPLIFY-1 and SIMPLIFY-2 trials provide evidence that patients treated with momelotinib require fewer RBC transfusions than patients treated with ruxolitinib/BAT; however, the magnitude of the benefit associated with reduced RBC transfusions is likely to be lower in the NHS as, in the SIMPLIFY trials, ESAs were prohibited or used infrequently (EAR, Section 6.2.3 and Section 6.3.6).

The EAG has carried out a scenario analysis assuming no transfusion benefit for JAKi-naïve patients treated with momelotinib (confidential PAS prices). The EAG preferred scenario for JAKi-experienced patients assumes no difference in OS by transfusion status for patients still on treatment with a JAKi. By assuming no transfusion benefit (i.e., equal proportion of patients

in each transfusion health state over time), the cost utility analysis becomes a cost comparison analysis as the efficacy of momelotinib and BAT are approximately equivalent.

1.3 Time to treatment discontinuation or death

SIMPLIFY-1 trial time to treatment discontinuation (TTTD) K-M data for the Int-2/HR Hb<12g/dL and Hb<10g/dL populations are presented in Figure 1 and Figure 2 respectively. The company did not provide TTDD K-M data for the Int-2/HR Hb<10g/dL population. Ruxolitinib arm TTDD K-M data are very immature; all patients crossed over to momelotinib at Week 24.

The EAG considers that in the SIMPLIFY-1 trial, the momelotinib discontinuation rate was likely higher than the ruxolitinib discontinuation rate due to the lower number of permitted dose reductions for patients treated with momelotinib. Up to five ruxolitinib dose adjustments were permitted before mandatory unblinding; in contrast, only three momelotinib dose adjustments were permitted. Subsequently, [redacted]% and 36.6% of patients treated with momelotinib and ruxolitinib respectively experienced treatment-related AEs leading to a dose reduction. The rate of treatment-related AEs leading to treatment discontinuation were [redacted]% and 5.6% for patients treated with momelotinib and ruxolitinib respectively (CS, Appendix F, Table 23).

Figure 1 SIMPLIFY-1 trial TTDD K-M data: Int2-HR Hb<12 g/dL population

Source: Company model

Figure 2 SIMPLIFY-1 trial TTDD K-M data: Hb<10 g/dL population

Source: Company model

In the cost comparison analysis (JAKi-naïve patients), the company assumed that discontinuation rates were equivalent for patients treated with momelotinib or ruxolitinib (see EAR, Section 6.2.4). The company considered that in NHS clinical practice (without the influence of trial protocols), treatment discontinuation would be comparable for patients treated with momelotinib and ruxolitinib (CS, p140). The assumption of equivalent treatment discontinuation rates may slightly underestimate ruxolitinib treatment costs; however, upon discontinuation of ruxolitinib, patients are assumed to continue receiving sub-therapeutic ruxolitinib doses as part of subsequent treatment with BAT.

SIMPLIFY-2 trial momelotinib and BAT arm TTDD K-M data for the Int-2/HR Hb<10g/dL and Int-2/HR Hb<12g/dL populations are presented in Figure 3 and Figure 4, respectively. In contrast to the SIMPLIFY-1 trial, SIMPLIFY-2 trial momelotinib and BAT arm treatment discontinuation rates were similar. At the start of the trial, most patients in the BAT arm who were receiving ruxolitinib had already had dose reductions and were receiving sub-therapeutic doses of ruxolitinib. This means that the number of dose reductions available to patients treated with momelotinib and ruxolitinib were likely more similar than if, at the start of the trial, all patients treated with ruxolitinib had been receiving the full dose.

Figure 3 SIMPLIFY-2 trial TTDD K-M data: Int2-HR Hb<12 g/dL population

Source: Company model

Figure 4 SIMPLIFY-2 trial TTDD K-M data: Int2-HR Hb<10 g/dL population

Source: Company model

2 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis. Technology appraisal guidance [TA756]. Published 16 December 2021; Available from: https://www.nice.org.uk/guidance/ta756/. Accessed 23 August 2023.
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3. NHS England. 2021/22 National Cost Collection data. Published 19 May 2023; Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Accessed 14 September 2023.

Single Technology Appraisal

Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 23 October 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Major factual inaccuracies: response to issues raised by EAG (and related sections)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Issue 2 JAKi-naïve population: anaemia supportive measures</u> • Section 1.4, p12 • Section 3.2.2 and 3.3 JAKi-naïve component of issue 5 • Section 1.5, p13 Critique of cost comparison model • Section 6.1 Table 42, p79) GSK believes that the description of the issue omits important context that should be added.	Modify "SIMPLIFY-1 trial efficacy result, particularly RBC TI and RBC TD outcomes, may have differed had ESAs been permitted." to "SIMPLIFY-1 trial efficacy result, particularly RBC TI and RBC TD outcomes, may have **differed slightly** had ESAs been permitted." We would ask that comments relating to the generalizability of transfusion rates in SIMPLIFY-1 includes additional context relating to the uncertainty associated with the effectiveness of ESAs when used alongside JAKis, and that by allowing ESA use in the trial both treatment arms could have benefited equally.	The statements regarding the use of ESA in JAKi-naive patients are potentially misleading because they imply there is a strong clinical consensus that ESAs are a material part of MF management in the NHS and been proven to be efficacious in ruxolitinib-treated patients. Furthermore, it implies that had ESA use been allowed in SIMPLIFY-1 only ruxolitinib arm would have benefitted from their use. Data from 200 MF patients from the UK REALISM study suggest that, although anemia is common, only a small number of patients received supportive therapies for anemia during the 6-month period after initiation of a new core management strategy (9 patients received	This is not a factual inaccuracy. Clinical advice to the EAG is that patients with MF and moderate to severe anaemia, i.e., the population of interest to this appraisal, are often treated with ESAs. As stated in the CS (p29) and cited in the EAG report (p22), clinical advice to the company is that in NHS clinical practice, ESAs are used by 20% to 60% of patients treated with ruxolitinib. The EAG has not stated that ESAs have been proven to be efficacious (although it is likely they are efficacious for at least some patients, or they would not be used). The extent to which use of ESAs (in either or both SIMPLIFY-1 trial arms) would reduce transfusion rates

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		erythropoietin and 1 patient received danazol).(1) Moreover, per Table 1 in the EAG report, only patients with endogenous erythropoietin <125µ/L should be considered candidates for erythropoietin, indicating that this treatment is only relevant for a subset of MF patients. There is also no clear evidence that ESA use can improve clinical outcomes in ruxolitinib-treated patients. For example, data from the COMFORT-2 trial suggest that concomitant ruxolitinib and ESA treatment did not improve the proportion of patients in TI or increase Hb levels. In the 13 patients who received concomitant ruxolitinib and ESA, the worst Hb value within 12 weeks of ESA administration improved in 3 patients, worsened in 2	is unclear. However, the EAG considers that it is likely that the RBC transfusion rate for NHS patients treated with ruxolitinib is lower than the rate observed in the SIMPLIFY-1 trial. Text changed on p81 from: The EAG therefore considers that the RBC transfusion rate for NHS patients treated with ruxolitinib is likely to be lower than the rate observed in the SIMPLIFY-1 trial To: The EAG does not know what the impact on RBC transfusion rates would be if more patients received ESAs (in either or both trial arms) but considers that the RBC

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		patients, and did not change in 7 patients.(2)	transfusion rate for NHS patients treated with ruxolitinib is likely to be lower than the rate observed in the SIMPLIFY-1 trial The EAG acknowledges that in Issue 2 (Section 1.4, p12), it is stated that "Clinical advice to the EAG is that patients with MF treated with ruxolitinib may also receive an ESA to control anaemia" and that this could imply only patients treated with ruxolitinib would receive ESAs. Clinical advice to the EAG is that it is unknown if patients treated with momelotinib would also receive an ESA. Text changed from: Clinical advice to the EAG is that patients with MF treated with ruxolitinib may also

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			receive an ESA to control anaemia. To: Clinical advice to the EAG is that patients with MF treated with ruxolitinib may also receive an ESA to control anaemia (but it is unknown if patients treated with momelotinib would also receive ESAs). In Section 6.3.2 of the EAG report, the EAG also acknowledges there is uncertainty around the cost impact of ESA treatment for patients treated with ruxolitinib, given that any cost savings from fewer RBC transfusions may be partially offset by an increase in ESA drug costs. The EAG has clarified in Section 6.2.3 of the EAG report that it is unknown

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			whether patients treated with momelotinib would also receive ESAs in NHS clinical practice and the magnitude of any benefit. New text added to the end of the paragraph of this section: "It is also unknown whether patients treated with momelotinib in NHS clinical practice would receive concomitant ESAs and the magnitude of any associated reduction in RBC transfusions."
<u>Issue 3 JAKi-experienced population: anaemia supportive measures</u> • Section 1.4, p12 • Section 3.2.2 and 3.3 JAKi-experienced component of Issue 5 • Section 1.5, p13	We would ask that this issue and associated paragraphs be removed from the EAG report as they are factually inaccurate.	The EAG report that anaemia supportive measures were not commonly used in the BAT arm (5.8%). This is incorrect, 11.5% of patients received anaemia supportive measures within the 24-week randomised period of SIMPLIFY-2, including both ESAs and Danazol. Other therapies which can be used to manage cytopenias such as	This is not a factual inaccuracy. Issue 3 (and Issue 2), and the associated report sections, are intended to specifically focus on the use of ESAs as anaemia supportive measures. The difference between NHS practice and the SIMPLIFY-2 trial was the use of ESAs (5.8%) in the BAT arm of the SIMPLIFY-2 trial

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Statement in Section 3.5 (p46) "it is not clear why [...]." Generalisability of transfusion rates • Section 6.3.6 p89 GSK feels that the issue regarding the use of anaemia supportive measures in JAKi-experienced patients potentially results from a misinterpretation of the SIMPLIFY-2 trial and should be removed.		thalidomide (1.9%) and corticosteroids (11.5%) were also recorded as being used during the trial period. Clinical advice received by GSK supported the distribution of concomitant therapies in SIMPLIFY-2.(3, 4) In addition, the EAG are contrasting clinical advice on lifetime use of ESAs to use of anaemia agents within the 24-week randomised period. We believe that 11.5% usage of anaemia supportive measures within the trial period is consistent with clinical advice relating to the use of anaemia treatment at any point. Furthermore, the latest available data from the UK HMRN registry reports lifetime use of ESAs to be 25.5% in JAKi-treated patients.(5)	(as opposed to danazol [5.8%]) as expanded upon below. The EAG has changed the text of these Issues and the report sections from "anaemia supportive measures" to "ESAs as anaemia supportive measures" to reflect this. Similar changes have been made to the related text in the following places: • Section 1.5, p13 • Section 3.2.2, p33 • Section 3.2.3, p35 • Section 3.3, p41 • Section 3.5, p46 As highlighted above, it is stated in the CS (p29) and cited in the EAG report (p22), that clinical advice to the company was that in NHS clinical practice, 20% to 60% of patients treated with

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			ruxolitinib would receive ESAs (and data presented here from the UK HMRN registry show 25.5% are treated with ESAs); in the SIMPLIFY-2 trial, the proportion of patients in the BAT arm receiving ESAs was much lower (5.8%). While it is possible that UK HMRN data may refer to lifetime use of ESAs as opposed to 24 weeks (from the UK HMRN registry data provided, it is unclear how long patients were treated with ruxolitinib for), it should be noted that clinical advice to the EAG was that ESAs would be preferred as an anaemia treatment before resorting to RBC transfusions. The proportion of patients who had RBC transfusions was much higher in the BAT arm of the SIMPLIFY-2 trial than the

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			proportion of patients who received an ESA. A final point in relation to ESAs is that clinical advice to the EAG was that patients may previously have failed on ESAs, which is why they did not receive them again in the SIMPLIFY-2 trial.
<u>Issue 4 JAKi-naïve population: appropriateness of a cost comparison analysis</u> • Section 1.5, p13 • Section 6.2.1 and Table 42 Critique of cost comparison model • Section 6.2.1 Table 42, p79 Data/type of analysis	We would ask that the description of the issue be amended to emphasise that there is no disagreement between the Company and EAG.	GSK believe it should be noted that the decision to proceed with a cost-comparison analysis for JAKi-naive patients was discussed with the EAG and agreed at the decision problem stage. Therefore, it is critical context for the Committee to understand that there is no disagreement between the Company and EAG that this is the most appropriate model structure.	This is not a factual inaccuracy. At the decision problem meeting, NICE stated that they were happy that a cost comparison evaluation could be submitted for the JAKi-naïve population. Technically, a cost comparison is appropriate if the clinical effectiveness data supports one. A judgement on whether the clinical effectiveness data supports a cost comparison falls within the remit of the NICE Appraisal Committee.

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• Section 6.2.1, p80 GSK feel that statements regarding the appropriateness of the cost-comparison analysis omits critical context and should be modified.			As the EAG concluded in Section 6.4.1: > If the NICE Appraisal Committee considers that the benefits delivered by treatment with momelotinib and ruxolitinib are so clinically similar that any differences in patient outcomes can be ignored, then a cost comparison analysis is appropriate The EAG included a similar statement in Issue 4. However, the EAG has now also added additional context to Issue 4 and Section 6.2.1 (i.e., clinical advice to the EAG in relation to spleen response rate and reference to company post-hoc analyses in relation to TSS) and deleted the statement that “These results cast some uncertainty around

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			the validity of carrying out a cost comparison analysis" in Issue 4.
Issue 7 JAKi-experienced population: treatment with ruxolitinib as part of BAT after stopping treatment with momelotinib The EAG amendment for implementing their preferred assumption of 88.5% of patients discontinuing momelotinib receiving ruxolitinib is based on changing cell G322 on the "Cost Inputs" sheet of the model. This overestimates the subsequent treatment costs for momelotinib as it does not rescale the proportion of patients on other (i.e. non-ruxolitinib) subsequent therapies to match the original	Remove EAG amendment from cell G322 on the "Cost Inputs" sheet, and instead implement the EAG scenario on the "Data store" sheet as follows: Set value in cell D649 = IF('EAG Revisions'!D5=1,88.5%,0%) We would ask that the EAG accept that 88.5% retreatment with ruxolitinib is an excessively conservative assumption and modify the input and associated paragraphs accordingly.	As indicated in Section B.3.3.6.5 and Table 102 of the original CS, the proportion of patients on different therapies within BAT post-momelotinib in the model are derived using the distribution of therapies in the BAT comparator arm from SIMPLIFY-2 and rescaling the proportions on non-ruxolitinib therapies upwards to account for removal or lowering of the proportion post-momelotinib patients receiving ruxolitinib and prevent underestimation of subsequent treatment costs for momelotinib. When changing cell G322 on the "Cost Inputs" sheet to 88.5%, this reintroduces the cost of ruxolitinib without readjusting the proportions of patients receiving non-ruxolotinib	The EAG agrees with the suggested change to the "Cost Inputs" sheet and the results presented in Tables 50, 51, 52 and 53 of the EAG report have been updated. Model instructions in Appendix 8.9.2 have also been updated. The EAG accepts that the rate of retreatment with ruxolitinib following discontinuation with momelotinib is unknown. If patients are not retreated with ruxolitinib (or another JAKi) following discontinuation of momelotinib treatment, this will result in lower proportions of patients in the momelotinib arm of the model having lower rates of JAKi treatment than patients in the BAT arm of the model. This is the case in the

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BAT distribution from SIMPLIFY-2. • Appendix 8.9.2, p. 116 Statements regarding composition of treatments after stopping treatment with BAT represent and unnecessarily conservative viewpoint and are not reflective of NHS clinical practice. • Section 1.5, p14 • Section 6.3.3 • Section 6.3.7, Table 48, Table 50 and Table 51		therapies, and therefore overestimates the cost of momelotinib subsequent treatment. GSK acknowledges the EAG's concerns regarding the subsequent treatment composition for patients who discontinue momelotinib. As part of the company submission, GSK has sought clinical advice at the clinical-HEOR advisory board. Similar to the clinical advice the EAG received (EAG report 6.3.4), GSK was informed by clinical experts that there may be restrictions to re-treatment with ruxolitinib in NHS, following momelotinib discontinuation. Three reasons for this restriction may be relevant: i) Patients may not be	company submitted base case model and company ruxolitinib retreatment scenario. The impact, on patient outcomes and costs, of differential proportions of patients in the momelotinib and BAT arms receiving JAKi treatment should be included in the economic model. Further, if patients cannot be retreated with ruxolitinib after having stopped treatment with momelotinib, clinical advice to the EAG was that this would make clinicians reluctant to switch patients to momelotinib. The EAG considers that, in the JAKi experienced population, retreatment rates with ruxolitinib (or another JAKi) following discontinuation of momelotinib is an area of uncertainty. The EAG has presented one scenario that removes the need to consider

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		clinically suitable for re-treatment with a previously trialed JAKi, following discontinuation of a second-line JAKi, MMB. ii) NHS funding is not available for ruxolitinib re-treatment following initial discontinuation. iii) Blueteq criteria state that a treatment break >12 weeks beyond the 4 weekly cycle length is needed, a treatment break form is needed to restart treatment. GSK has received clinical advice that re-access is not routinely successful.(6) This appears to align with a statement in Section 2.3.2 (p21) of the EAG report: "Clinical advice to the EAG is that for patients who experience toxicity during ruxolitinib treatment, the ruxolitinib dose would be reduced; patients would not be	the impact of differential proportions of patients in the momelotinib and BAT arms being treated with a JAKi; however, this scenario may overestimate the proportion of patients retreated with ruxolitinib. The company has provided alternative scenarios which assess the effect of lower retreatment with ruxolitinib; however, these scenarios do not account for differential JAKi use on patient outcomes. The EAG has amended the text in Section 6.3.4 to the following to make these issues clearer: In the company model, it is assumed that patients who stop treatment with momelotinib will not receive ruxolitinib. This results in patients in the

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		re-treated with ruxolitinib following an extended break in treatment with ruxolitinib." We are concerned that EAG's scenario analysis does not reflect the expected NHS practice, as indicated by both GSK's and EAG's clinical experts, where EAG assumes that 88.5% of patients who stop treatment with momelotinib are treated with ruxolitinib as part of BAT. Therefore, this scenario analysis would not be plausible and unlikely to inform the committee's decisions. A conservative scenario analysis, informed by expert opinion, allowing for 39% of patients to receiving JAKi retreatment was the CS and should be considered as a pessimistic alternative to the company base-case.	momelotinib arm being on treatment with a JAKi for a shorter time than patients in the BAT arm (where 88.5% of patients alive are always receiving ruxolitinib). For example, at 3 years, the company model predicts that 77 patients in the momelotinib arm will still be treated with a JAKi but that 400 patients in the BAT arm will still be treated with a JAKi. The large disparity in JAKi treatment rates between the momelotinib and BAT arms adds further challenge to the company approach to modelling improved OS

			for momelotinib compared to BAT. Clinical advice to the EAG and to the company is that, following cessation of treatment with momelotinib, clinicians would like to have the option to re-treat some eligible patients with ruxolitinib. However, clinical advice to the EAG is that, in NHS practice, there may be restrictions to re-treatment with ruxolitinib. BlueTeq criteria[61] state that if treatment is stopped for more than 3 months, a treatment break form is required to restart ruxolitinib treatment. The EAG has amended the company model so that all patients who stop treatment with momelotinib go on to

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			receive BAT in the same proportions as in the SIMPLIFY-2 trial. This approach may overestimate retreatment rates but means that patients in both arms of the model receive a JAKi for a similar period of time, which further justifies the EAG approach to modelling OS (i.e., no difference in OS by transfusion status).

Issue 2 Additional inaccuracies related to Introduction and Background section

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<u>Text error</u> • List of abbreviations, p8 Typo “Baysian”	Update wording to: “Bayesian”	Typo	Thank you for highlighting this error.

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			Text amended
<u>Text error</u> • Section 2.2, p.17 Text: “peripheral blood blasts >1%”	Update wording to: "peripheral blood blasts ≥1%”	Correction of peripheral blood blasts threshold (O’Sullivan 2018, CS p.19 Table 4)	Thank you for highlighting this error. Text amended
<u>Text error</u> • Section 2.2, p.18 “As shown in the CS, Table 4, patients classified as having Int-2 risk have a life expectancy of 3 to 4 years and those classified as high risk (HR) have a life expectancy of 1.3 to 2.3 years”	Update wording to: “As shown in the CS, Table 4, patients classified as having Int-2 risk have a life expectancy of 2.9 to 4 years and those classified as high risk (HR) have a life expectancy of 1.3 to 2.3 years”	Precise life expectancy of patients classed as intermediate-2 (O’Sullivan 2018, Reilly 2012, CS p.19 Table 4)	Thank you for highlighting this error. Text amended
<u>Updated indication</u> • Section 2.1, p.24, Table 4 • Section 2.4.1, p.47 Text: “[redacted]	Update wording to: “[redacted]	Updated indication in the latest SmPC.(7)	Thank you for this updated information. Updated text in EAG report in:

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[redacted]"	[redacted]		• Issue 1 (p11) • Section 2.1, p.24, Table 4 (p24) • Section 2.4.1, p47
<u>Text error</u> • Section 2.4.3, Table 5, p.29 Incorrect definition of RBC TI and RBC TD	Update RBC TI and TD trial definitions in Table 5 to: • RBC TI: Proportion of patients who had no RBC transfusions and no Hb levels<8g/dL in previous 12 weeks at Week 24 • RBC TD: Proportion of patients who had 4 units of RBC transfusion or Hb levels<8g/dL in the previous 8 weeks at Week 24	Correction of RBC TI and TD definitions for SIMPLIFY-1 and SIMPLIFY-2	Thank you for highlighting this error. Text amended as suggested. The EAG notes that the erroneous definition of

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			RBC TI was copied from the definition of this outcome reported in the CS, Tables 19, 39 and 41.

Issue 3 Additional inaccuracies related to clinical effectiveness section

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Text error • Section 3.2.1, p.32 Text: "The EAG agrees with the company in that the MOMENTUM trial offers supportive clinical evidence for patients with more severe disease (symptomatic [defined as	Update wording to: "The EAG agrees with the company in that the MOMENTUM trial offers supportive clinical evidence for patients with more severe disease (symptomatic [defined as TSS ≥10] and anaemic [defined as Hb<10g/dL]), albeit for a comparator that is not widely used in the UK (and where it is	Correction of MOMENTUM TSS threshold	Thank you for highlighting this error. Text amended.

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TSS>10] and anaemic [defined as Hb<10g/dL]), albeit for a comparator that is not widely used in the UK (and where it is used, only as an anaemia supportive measure rather than an intervention to treat disease)."	used, only as an anaemia supportive measure rather than an intervention to treat disease)."		
<u>Text error</u> • Section 3.9, p.57 Text: "However, momelotinib was nominally significantly superior to BAT in terms of TSS rate and numerically superior to BAT for RBC TI rate and RBC TD rate; momelotinib was nominally significantly superior to ruxolitinib in terms of TI (but not TD) in the ITT population and Int-2/HR Hb<12g/dL subgroup."	Update wording to: "However, momelotinib was nominally significantly superior to BAT in terms of TSS rate and numerically superior to BAT for RBC TI rate and RBC TD rate; momelotinib was nominally significantly superior to BAT in terms of TI (but not TD) in the ITT population and Int-2/HR Hb<12g/dL subgroup."	Correction of SIMPLIFY-2 comparator.	Thank you for highlighting this error. Text amended.

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Text error • Section 3.2.2, p.32 Text: "Randomisation was stratified by RBC TD (yes or no; defined as ≥4 units of RBCs or Hb≤8g/dL in the 8 weeks prior to randomisation excluding cases associated with clinically overt bleeding) and platelet count (<100x10^9/L, ≥100x10^9/L and ≤200x10^9/L or >200x10^9/L"	Update wording to: "Randomisation was stratified by RBC TD (yes or no; defined as ≥4 units of RBCs or Hb<8g/dL in the 8 weeks prior to randomisation excluding cases associated with clinically overt bleeding) and platelet count (<100x10^9/L, ≥100x10^9/L and ≤200x10^9/L or >200x10^9/L"	Correction of Hb threshold.	Thank you for highlighting this error. Text amended.
Text error • Section 3.3, p.42, Table 10 Proportion differences for the spleen response rate endpoint for both Int-2/HR Hb <10 g/dL and int-2/HR Hb <12 g/dL are incorrectly	Update Table 10 proportion difference column for spleen response rate to: • Int-2/HR Hb <12 g/dL: [redacted] • Int-2/HR Hb <10 g/dL: [redacted]	Proportion differences for the spleen response rate endpoint for both Int-2/HR Hb <10 g/dL and int-2/HR Hb <12 g/dL were significantly non-inferior to ruxolitinib.	As statistical testing of outcomes in the Int-2/HR Hb <10g/dL and Int-2/HR Hb <12g/dL subgroups did not form part of the pre-specified hierarchical testing strategy in the SIMPLIFY-1 trial, the EAG has labelled the p-values from these statistical tests as nominal. Footnote

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marked as nominally significant			added to Table 10 to clarify the EAG approach (a similar footnote has also been added to Table 13 regarding the SIMPLIFY-2 trial).
<u>Text error</u> • Section 3.3, p.42, Table 10 footnote Text: "[e]RBC TI defined as the proportion of patients who had no RBC transfusions or no Hb levels<8g/dL in the previous 12 weeks at Week 24" • Section 3.3.3, p.44 Text: "In the Int-2/HR Hb<10g/dL subgroup a higher proportion of patients in the momelotinib arm were RBC TI (no RBC transfusions or no Hb levels <8g/dL in the previous 12	The text should be updated to reflect the following definitions of TI: RBC TI defined as the proportion of patients who had no RBC transfusions and no Hb levels <8g/dL in the previous 12 weeks at Week 24	Correction of RBC definition TI	Thank you for highlighting these errors. Text amended as suggested in both places of the EAG report. The EAG notes that the erroneous definition of RBC TI was copied from the definition of this outcome reported in the CS, Tables 19, 39 and 41.

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weeks at Week 24) than in the ruxolitinib arm; momelotinib was nominally significantly superior to ruxolitinib"			
<u>Text error</u> • Section 3.3, p.42, Table 10 footnote Text: "[g] RBC TD defined as the proportion of patients who had 4 units of RBC transfusions or Hb levels<8g/dL in the previous 12 weeks at Week 24" • Section 3.3.4, p.45 Text: "In the Int-2/HR Hb<10g/dL subgroup, fewer patients were RBC TD (4 units of RBC transfusions or Hb levels<8g/dL in the previous 12 weeks at Week 24) in the momelotinib arm than in the ruxolitinib arm;	The text should be updated to reflect the following definitions of TD: RBC TD defined as the proportion of patients who had 4 units of RBC transfusions or Hb levels<8g/dL in the previous 8 weeks at Week 24	Correction of RBC definition TD	Thank you for highlighting these errors. Text amended in both places.

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momelotinib was nominally significantly superior to ruxolitinib.”			
<u>Text error</u> • Section 3.3.3, p. 43 Text: “a similar proportion of patients met the derived meaningful change threshold (≥8 point improvement) in the momelotinib and ruxolitinib arms (CS, p131)”	Update wording to: “a similar proportion of patients met the derived meaningful change threshold (≥8 point improvement) in the momelotinib and ruxolitinib arms (CS, p121)”	Correction of CS page number (change page 131 to page 121).	Thank you for highlighting this error. Text amended.
<u>Proposed inclusion of SIMPLIFY-1 RBC TI p-values</u> • Section 3.3.3, p.44, Table 11 No p-values have been included for RBC TI data	Update Table 11 to: • ITT population: Proportion difference (95% CI) p-value: [redacted] nominal p<0.001 • Int-2/HR Hb <12 g/dL: Proportion difference (95% CI) p-value: [redacted]	GSK propose to add p-values to the table for completeness and to demonstrate the proportion difference between treatment arms is nominally significant.	The purpose of this table is simply to highlight the differences in the proportions of patients who were RBC TI at baseline and at Week 24 within and between treatment arms; the EAG considers that the inclusion of p-values would be misleading as the proportion differences and reported p-values were

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	• Int-2/HR Hb <10 g/dL: Proportion difference (95% CI) p-value: [redacted]		only assessed between treatment arms at Week 24. These proportion differences and p-values are presented in Table 10 of the EAG report. For clarity, cross references to Table 10 have been added throughout the text in Sections 3.3.1 to 3.3.4.
<u>Text error</u> • Section 3.3.4, p.45 Text: "The numbers and proportions of patients who were RBC TI at baseline and Week 24 are summarised in Table 12"	Update wording to: "The numbers and proportions of patients who were RBC TD at baseline and Week 24 are summarised in Table 12"	Correction of table description, should refer to RBC TD (not RBC TI).	Thank you for highlighting this error. Text amended.
<u>Proposed inclusion of SIMPLIFY-1 RBC TD p-values</u> • Section 3.3.4, p.46, Table 12	Update Table 12 to: • ITT population: Proportion difference (95% CI) p-value: [redacted]; nominal p=0.019	GSK propose to add p-values to the table for completeness and to demonstrate the proportion difference between treatment arms is nominally significant.	The purpose of this table is simply to highlight the differences in the proportions of patients who were RBC TD at baseline and at Week 24 within and between treatment arms;

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No p-values have been included for RBC TD data	• Int-2/HR Hb <12 g/dL: Proportion difference (95% CI) p-value: [redacted] • Int-2/HR Hb <10 g/dL: Proportion difference (95% CI) p-value: [redacted]		the EAG considers that the inclusion of p-values would be misleading as the proportion differences and reported p-values were only assessed between treatment arms at Week 24. These proportion differences and p-values are presented in Table 10 of the EAG report. For clarity, cross references to Table 10 have been added throughout the text in Sections 3.3.1 to 3.3.4.
<u>Text error</u> • Appendix 8.4, p.107, Table 57 Incorrect OS stratified HR for final analysis (int-2/HR Hb <12 g/dL) Incorrect LFS median (95% CI) for final analysis (Int-2 Hb <10 g/dL)	Update table to: • Final analysis (Int-2/HR Hb <12 g/dL): OS stratified HR: [redacted] • Final analysis (Int-2/HR Hb <10 g/dL): median LFS [redacted]	Correction of OS stratified HR for final analysis (int-2/HR Hb <12 g/dL) and LFS median (95% CI) for final analysis (Int-2 Hb <10 g/dL).	Thank you for highlighting these errors. Text amended.

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Text error • Section 3.2.3, p.35 Text: "Randomisation was stratified by RBC TD (yes or no; defined as ≥4 units of RBCs or Hb≤8g/dL in the 8 weeks prior to randomization excluding cases associated with clinically overt bleeding) and baseline TSS (<18 or ≥18)."	Update text to: "Randomisation was stratified by RBC TD (yes or no; defined as ≥4 units of RBCs or Hb<8g/dL in the 8 weeks prior to randomization excluding cases associated with clinically overt bleeding) and baseline TSS (<18 or ≥18)."	Correction of Hb threshold.	Thank you for highlighting this error. Text amended.
Text error • Section 3.2.3, p.35 Text: "The SIMPLIFY-2 trial included an open-label 24-week randomised controlled period (primary data-cut: 12 September 2016) followed by an open-label phase"	Update text to: "The SIMPLIFY-2 trial included an open-label 24-week randomised controlled period (primary data-cut: 28 July 2016) followed by an open-label phase"	Correction of primary data-cut date.	Thank you for highlighting this error. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Error in description of SIMPLIFY-2 trial conduct • Section 3.2.3, p.36 Text: "in the ITT population, fewer patients had Int-1 disease and more patients had Int-2 disease in the momelotinib arm than in the BAT arm; the EAG considers this could bias results in favour of BAT"	Add more patients had HR in the momelotinib group. Update text to: "in the ITT population, fewer patients had Int-1 disease and more patients had Int-2 disease and HR in the momelotinib arm than in the BAT arm; the EAG considers this could bias results in favour of BAT"	Provides more accurate description of the patient characteristics across the momelotinib and BAT treatment arms.	For clarity, text amended to: "…in the ITT population, fewer patients had Int-1 disease and more patients had Int-2/HR disease in the momelotinib arm than in the BAT arm; the EAG considers this could bias results in favour of BAT"
Text error • Section 3.2.3, p.37, Table 9 Table 9 states the ITT population comparator is ruxolitinib, however the comparator in SIMPLIFY-2 is BAT	In Table 9, update comparator in the ITT population column to from ruxolitinib to BAT	Correction of the SIMPLIFY-2 comparator.	Thank you for highlighting this error. Text amended.
Text error • Section 3.2.3, p.37, Table 9	In Table 9, TSS mean for int-2/HR Hb<10 g/dL BAT should be corrected from [redacted] to [redacted]	Correction of TSS mean for int-2/HR Hb<10 g/dL BAT arm.	Thank you for highlighting this error. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect mean TSS for int-2/HR Hb <10 g/dL			The EAG notes that this error was originally made in the CS, Table 40.
<u>Text error</u> • Section 3.5, p.47, Table 13 Incorrect spleen response rate 95% CIs for momelotinib and BAT arms	Update Table 13: SRR: • Momelotinib ITT population (95% CI) from 2.75 to 13.38 to [redacted] • BAT ITT population (95% CI) from 1.21 to 15.95) to [redacted]	Correction of spleen response rate 95% CIs for momelotinib and BAT.	This is not a factual inaccuracy. The confidence intervals reported by the company were expressed as proportions (i.e., numerical values that fall between 0 and 1), the confidence intervals reported by the EAG have been converted to percentages (as labelled in the first column of the table). The EAG highlights that the same approach was taken when presenting the confidence intervals for spleen response in Table 10 (which has not been raised as a problem by the company).
<u>Text error</u>	Update text to:	Correction of RBC TI definition	Thank you for highlighting these errors. Text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 3.5, p.47, Table 13 footnote Text: "[e]RBC TI defined as the proportion of patients who had no RBC transfusions or no Hb levels<8g/dL in the previous 12 weeks at Week 24" • Section 3.5.2, p.48 Text: "In the Int-2/HR Hb<10g/dL subgroup, a higher proportion of patients in the momelotinib arm were RBC TI (no RBC transfusions or no Hb levels<8g/dL in the previous 12 weeks at Week 24) than in the BAT arm.	"[e]RBC TI defined as the proportion of patients who had no RBC transfusions and no Hb levels<8g/dL in the previous 12 weeks at Week 24"		amended as suggested in both places of the EAG report. The EAG notes that the erroneous definition of RBC TI was copied from the definition of this outcome reported in the CS, Tables 19, 39 and 41.
<u>Text error</u> • Section 3.5, p.47, Table 13 footnote "[f] RBC TD defined as the proportion of patients who	Update text to: "[f] RBC TD defined as the proportion of patients who had 4 units of RBC transfusions or Hb levels<8g/dL in the previous 8 weeks at Week 24"	Correction of RBC TD definition	Thank you for highlighting these errors. Text amended in both places.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
had 4 units of RBC transfusions or Hb levels<8g/dL in the previous 12 weeks at Week 24” • Section 3.5.4, p.49 Text: “In the Int-2/HR Hb<10g/dL subgroup, a lower proportion of patients were RBC TD (4 units of RBC transfusions or Hb levels<8g/dL in the previous 12 weeks at Week 24) in the momelotinib arm than in the ruxolitinib arm”			
<u>Text error</u> • Section 2.5.1, p.48 Text: “Furthermore, clinical advice to the EAG agrees with advice received by the company (CS, p125) that, “…considering the totality of efficacy evidence [summarised in Table 13]	Update text to: “Furthermore, clinical advice to the EAG agrees with advice received by the company (CS, p126) that, “…considering the totality of efficacy evidence [summarised in Table 13] … momelotinib appeared to offer a greater overall benefit in more advanced JAKi-experienced patients than BAT.”	Correction of CS page cited	Thank you for highlighting this error. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
… momelotinib appeared to offer a greater overall benefit in more advanced JAKi-experienced patients than BAT.”			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Lack of p-values</u> • Section 3.5.3, p.49, Table 14 No p-values have been included for RBC TI data	Update Table 14 to: • ITT population: Proportion difference (95% CI) p-value: [redacted] nominal p=0.0012 • Int-2/HR Hb <12 g/dL: Proportion difference (95% CI) p-value: [redacted] • Int-2/HR Hb <10 g/dL: Proportion difference (95% CI) p-value: [redacted]	GSK propose to add p-values to the table for completeness and to demonstrate the proportion difference between treatment arms is nominally significant.	The purpose of this table is simply to highlight the differences in the proportions of patients who were RBC TI at baseline and at Week 24 within and between treatment arms; the EAG considers that the inclusion of p-values would be misleading as the proportion differences and reported p-values were only assessed between treatment arms at Week 24. These proportion differences and p-values are presented in Table 13 of the EAG report. For clarity, cross references to Table 13 have been added throughout the text in Sections 3.5.1 to 3.5.4.
<u>Lack of p-values</u> • Section 3.5.4, p.50, Table 15	Update Table 15 to:	GSK propose to add p-values to the table for completeness.	The purpose of this table is simply to highlight the differences in the proportions of patients who

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
No p-values have been included for RBC TD data	• ITT population: Proportion difference (95% CI) p-value: [redacted] nominal p=0.10 • Int-2/HR Hb <12 g/dL: Proportion difference (95% CI) p-value: [redacted] • Int-2/HR Hb <10 g/dL: Proportion difference (95% CI) p-value: [redacted]		were RBC TD at baseline and at Week 24 within and between treatment arms; the EAG considers that the inclusion of p-values would be misleading as the proportion differences and reported p-values were only assessed between treatment arms at Week 24. These proportion differences and p-values are presented in Table 13 of the EAG report. For clarity, cross references to Table 13 have been added throughout the text in Sections 3.5.1 to 3.5.4.
<u>Text error</u> • Section 3.6.1, p.50 Text: "For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant OS differences between treatment arms at	Text refers to ruxolitinib as the comparator, however in SIMPLIFY-2, BAT is the comparator. Update text to: "For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant OS differences between treatment arms at the time of the final analysis (up to 5 years from	Correction of comparator in SIMPLIFY-2	Thank you for highlighting these errors. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the time of the final analysis (up to 5 years from randomisation). Median OS was numerically longer in the momelotinib arm than in the ruxolitinib arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup; median OS was numerically shorter in the momelotinib arm than in the ruxolitinib arm for the ITT population."	randomisation). Median OS was numerically longer in the momelotinib arm than in the BAT arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup; median OS was numerically shorter in the momelotinib arm than in the BAT arm for the ITT population."		
<u>Text error</u> • Section 3.6.2, p.50 Text: "For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant LFS differences between treatment arms at the time of the final analysis (up to 5 years from randomisation). LFS results were very similar to OS results, i.e., median LFS	Text refers to ruxolitinib as the comparator, however in SIMPLIFY-2, BAT is the comparator. Update text to: Text: "For the Int-2/HR Hb<10g/dL subgroup, there were no nominally significant LFS differences between treatment arms at the time of the final analysis (up to 5 years from randomisation). LFS results were very similar to OS results, i.e., median LFS was numerically longer in the momelotinib arm than in the BAT arm for both the Int-2/HR Hb<10g/dL	Correction of comparator in SIMPLIFY-2	Thank you for highlighting these errors. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
was numerically longer in the momelotinib arm than in the ruxolitinib arm for both the Int-2/HR Hb<10g/dL subgroup and Int-2/HR Hb<12g/dL subgroup but was shorter in the ITT population. Given patients switched from ruxolitinib to momelotinib at Week 24, meaningful interpretation of long-term LFS data is difficult.”	subgroup and Int-2/HR Hb<12g/dL subgroup but was shorter in the ITT population. Given patients switched from BAT to momelotinib at Week 24, meaningful interpretation of long-term LFS data is difficult.”		
<u>Text error</u> • Section 3.8 p52 Error in the statement "Pooled safety analyses were reported in the main body of the CS, Section B.2.11, and, in line with the draft SmPC, these are based on the pooled data from all three trials for	Change sentence to: Pooled safety analyses were reported in the main body of the CS, Section B.2.11, based on the pooled data from all three trials plus the extended access programme for patients regardless of their risk status (n=725).	The pooled safety analysis presented in the CS is indeed from all three trials plus the extended access programme (n=725). However, the pooled safety analysis shown in the draft SmPC is from the three trials during respective randomised phases only (n = 448). Furthermore, the draft SmPC has not yet been approved by the	Thank you for highlighting this error. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients regardless of their risk status (n=725).		appropriate regulatory body and is subject to change. This information does not change the interpretation of safety data, but GSK feel that clarification is important to avoid the appearance of inconsistency in reporting.	
<u>Data clarification</u> • Section 3.8.2, Table 16 p53 MOMENTUM 24 weeks haematological adverse events	Include table footnote linked to Grade 3/4 haematological TEAEs reported under the MOMENTUM trial: **Haematological abnormalities reported for MOMENTUM trial are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase of the study, regardless of whether this grade was a change from baseline.*	Although labelled as Treatment Emergent Adverse Events (TEAEs) in the MOMENTUM publication, a footnote clarifies that 'haemotological abnormalities' reported are based on laboratory values only and don't reflect a change from baseline (8). We would ask that a similar footnote should be included to make clear that MOMENTUM anaemia and thrombocytopenia outcomes are recorded differently to those in SIMPLIFY-1 and SIMPLIFY-2.	Thank you for this clarification. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		This clarification should have been included in the original CS, Appendix Table 32 but was omitted.	
<u>Data error</u> • Section 3.8.2, Table 17 p54 Pooled haematological adverse events at week 24	Change grade 3/4 thrombocytopenia and anaemia incidence at week 24 to [redacted] and [redacted] respectively.	See justification above, grade 3/4 TEAEs reported as 'haemotological abnormalities' in the MOMENTUM publication are based off laboratory values only and do not align with how TEAEs are reported in SIMPLIFY-1 and SIMPLIFY-2. Therefore, it is inappropriate to pool these results. However, grade 3/4 TEAEs considered related to MMB in MOMENTUM, as reported in the CSR should be used to calculate the pooled safety values at week 24, because these data are in line with the TEAEs at week 24 for	Thank you for this clarification. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		SIMPLIFY-1 and SIMPLIFY-2. Grade 3/4 TEAEs in MOMENTUM randomised phase were [redacted] for grade 3/5 thrombocytopenia and [redacted] for grade 3/4 anaemia (CSR, table 49, page 169).(9) Together with SIMPLIFY, these values add to the final correct incidence values shown in this correction. Furthermore, the integrated safety analysis of 3 trials confirms the incidence of grade 3/4 TEAEs at week 24 (Integrated Safety, table 25, page 83).(10)	
<u>Missing context in safety outcomes (mortality)</u> • Section 3.8.1, p54 Statement "TEAEs leading to death were higher in the momelotinib arm of the	Inclusion of AEs leading to death (as a percentage) in the BAT and Danazol arms in SIMPLIFY-2 and MOMENTUM compared to MMB arm in both trials	It is misleading to state that the deaths in the momelotinib arm were higher in MOMENTUM than the SIMPLIFY trials without adding that deaths in the	The percentages are reported in Table 16 of the EAG report. For clarity, new text has been added on p54 of the EAG report as follows: “AEs leading to death were also higher in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
MOMENTUM trial than in either of the momelotinib arms of the SIMPLIFY-1 or SIMPLIFY-2 trials." omits relevant context		comparator arm were higher as a proportion of patients.	the comparator arm of the MOMENTUM trial than in either of the comparator arms of the SIMPLIFY-1 or SIMPLIFY-2 trials.”
Text error • Section 8.8.1, p. 111 Text: “RBC TD (yes or no; defined as ≥4 units of RBCs or Hb level ≤8g/dL in the 8 weeks prior to randomisation excluding cases associated with clinically overt bleeding)”	Update text to: “baseline RBC or whole blood units transfused in the 8-week period prior to randomization (0, 1-4, ≥ 5 units)”	Correction of RBC TD definition for stratification	Thank you for highlighting this error. Text amended.
Text error • Section 8.8.3, p113, Table 62, footnote f TD is defined incorrectly.	Change footnote f to: “RBC TD defined as defined as proportion of patients who required ≥ 4 RBC or whole blood units with each such transfusion in response to a Hb assessment of ≤ 9.5 g/dL and ≥ 2 Hb assessments with time between the earliest and latest Hb assessments ≥ 28 days in an 8-week period	In MOMENTUM transfusion dependence at week 24 was defined as requirement of ≥ 4 RBC or whole blood units with each such transfusion in response to a Hb assessment of ≤ 9.5 g/dL and ≥ 2 Hb assessments with time between the earliest and	Thank you for highlighting this error. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	immediately before the end of week 24."	latest Hb assessments ≥ 28 days in an 8-week period immediately before the end of week 24.	

Issue 4 Potential errors and reproducibility issues with EAG economic model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Reproducibility of EAG subgroup analysis results for JAKi-naïve population</u> • Section 6.2.2, p. 80 Text: "The EAG considers that data from the Hb level subgroups should be used to populate the cost comparison model. The company model has the functionality to generate results for the Int-2/HR Hb<12g/dL subgroup; the EAG asked the company (clarification question B1) to provide cost comparison	GSK request that the EAG clarify which input data were used or updated for the subgroup analyses for the CCM for the JAKi-naïve population in the EAR, and/or provide an updated copy of the EAG version of the CCM which includes the EAG preferred input data used for these subgroup analyses.	EAG approach for generating subgroup results in the CCM for the JAKi-naïve population is unclear. In the EAR, the EAG it is stated that "the EAG considers that data from the Hb level subgroups should be used to populate the cost comparison model". However, only information on adjusted RBC transfusion rates are presented as amended input data for these analyses.	Thank you for highlighting this error. Model instructions (Appendix 8.9.1) have been revised to include details of how Int-2/HR Hb<10g/dL subgroup results were generated. In addition, new text has been added to Section 6.2.2 of the EAG report as follows: "As the company model does not include TTD data for the Int-2/HR Hb<10g/dL subgroup, the EAG used Int-2/HR Hb<12g/dL TTD data as a proxy." As noted in Section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
results for the Int-2/HR Hb<10g/dL subgroup. The company also provided rates of RBC transfusions by Hb level subgroup (Table 43). Adjusted rates were used in the company base case (ITT) analysis and in the company Int-2/HR Hb<10g/dL subgroup analysis. The EAG has used adjusted rates to generate Int-2/HR Hb<10g/dL subgroup and the Int-2/HR Hb<12g/dL subgroup results. The EAG considers that it is more appropriate to use adjusted RBC transfusion rates as these account for differences in baseline patient characteristics." • Section 6.2.6, p. 83, Tables 46 and 47 GSK are unable to reproduce the EAG corrected base case results presented in Tables 46 and 47 for the Int-2/HR		GSK are currently unable to reproduce the subgroup analysis results using the EAG version of the CCM and adjusted RBC transfusion rates presented in the EAR.	6.6.2 of the EAG report, subgroup specific RBC transfusion rates were used (Table 43). The results in Table 46 and Table 47 of the EAG report have been updated.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Hb<12g/dL and Int-2/HR Hb<10 subgroups, respectively, using the EAG version of the cost comparison model and information provided in the EAR.			
<u>Reproducibility of EAG Int-2/HR Hb<12g/dL population results for JAKi-experienced population</u> • Section 6.3.7, p. 90, Table 50 GSK are unable to reproduce the EAG results in terms of total and incremental costs when amending the model to assume no differences in transfusion status (rows 3 and 5) using the EAG corrected model. For example, when switching on components of the EAG model to reproduce results in row 3 of Table 50, the QALY and incremental NMB values	GSK request that the EAG check the total and incremental cost results for scenarios for the Int-2/HR Hb<12g/dL population using the JAKi-experienced CEM where no differences in OS is assumed for TI and non-TI patients.	GSK are unable to reproduce some results for the JAKi-experienced Int-2/HR Hb<12g/dL population presented in Table 50 of the EAR.	Thank you for highlighting this error. The results in Table 50 of the EAG report have been updated following implementation of the suggested changes to the EAG revisions highlighted in Issue 1 and Issue 5.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
match those presented. However, total costs of £104,452 for momelotinib and £176,164 are produced instead of £104,511 and £176,260, respectively, with incremental costs of -£7,133 rather than -£7,170.			
<u>Final company base case results and EAG scenario results for Int-2/HR Hb<10g/dL population results for JAKi-experienced population</u> • Section 5.2.3, p. 77, Table 41 Company base case INMB results presented in Table 41 (£53,120) for the Int-2/HR Hb<10g/dL population do not match the revised base case INMB value presented in Tables 68 and 69 of the company results addendum.	Correct INMB value in Table 41 to £53,210. Correct the company base case results in row 1 of Table 51 to align with the revised base case values presented in the company results addendum as follows: • Update momelotinib total costs from £[redacted] to £[redacted] and BAT total costs from £143,936 to £145,111. • Update momelotinib total QALYs from 1.762 to 1.800 and BAT total	Company base case results presented in Table 51 of the EAR JAKi-experienced Int-2/HR Hb<10g/dL population appear incorrect in relation to those presented in the company results addendum. All results presented in Table 51 of the EAG cannot be reproduced using the EAG corrected version of the JAKi-experienced CEM.	The EAG highlights that the results presented in the company October addendum (Table 19) for the JAKi-experienced Int-2/HR Hb<10g/dL population do not match the results in the company October model. The EAG revisions have been made to the company October model. The EAG report Table 41 has been updated to present company October model results.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 6.3.7, p. 90, Table 51 Company base case results presented in row 1 of Table 51 do not match the revised base case results presented in Tables 68 and 69 of the company results addendum, as well as those presented in Table 41 of the EAR. GSK are also unable to reproduce all results presented in Table 51 using the EAG corrected model.	QALYs from 1.709 to 1.723. • Update incremental costs from [redacted] to [redacted] and incremental QALYs from 0.053 to 0.077. • Update INMB from £[redacted] to £[redacted]. GSK also request that the EAG review all results presented in Table 51 for the Int-2/HR Hb<10g/dL population using the JAKi-experienced CEM to ensure they are correct.		

Issue 5 Implementation of ERG corrections and amendments for JAKi-experienced population CEM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>EAG discounting corrections</u> • Section 6.1, p. 78	GSK request that the EAG provide clarification on why they believe the implementation of discounting	Discounting in the JAKi-experienced model was conducted on a per cycle basis, with discounting	The EAG considers that discounting should not take place in the first year. The company is correct that annual

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: “The company has started discounting costs and benefits in Year 1 rather than from the start of Year 2. The EAG corrected this error and generated corrected company base case cost effectiveness results” • Section 6.1, p. 79, Table 42 Text: “The EAG has corrected the company model so that discounting starts in Year 2 rather than Year 1” • Section 6.2.6, p. 82 Text: “The EAG has corrected the company base case so that discounting occurs from Year 2 onwards” • Section 6.3.1, p. 84 Text: “The company has started discounting costs and benefits in Year 1 rather than from the start of Year 2. The	in the JAKi-experienced cost-effectiveness model is incorrect.	formulas accounting for more granular time increments of 4 weeks rather than discounting on an annual basis. EAG rationale for removing discounting in Year 1 of the model is unclear, and the implementation produces an inconsistent discounting approach with no discounting in Year 1 followed by per cycle discounting from Year 2 onwards (rather than implementing discounting on an annual basis, for example).	rather than per cycle discounting from Year 2 would have been preferable, however using annual rather than per cycle discounting would not have made a materially important difference to cost effectiveness results.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG corrected this error and generated a corrected company base case ICER per QALY gained. Other than discounting, the EAG is satisfied that the company model algorithms are accurate and that parameter values in the model match the values presented in the CS” • Section 6.3.1, p. 84, Table 48 Text: “The EAG has corrected the company model so that discounting starts in Year 2 rather than Year 1” • Section 6.3.7, p. 89 Text: “The EAG has corrected the company base case so that discounting occurs from Year 2 onwards” • Appendix 8.9.2, p. 115 Description of EAG amendment indicates that			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
both model engine sheets were adjusted such that discounting does not occur in the first year.			
<u>Implementation of EAG amendment assuming equal OS regardless of transfusion dependence status at 24 weeks</u> • Appendix 8.9.2, p. 115 Description of EAG amendment indicates that non-TI (i.e. TR and TD) OS was set equivalent to TI OS when assuming no difference in survival for TI and non-TI patients.	Remove EAG amendments from "Markov Trace (BAT 2L)" and "Markov Trace (momelotinib 2L)". Generate scenario results for no differences in OS by transfusion status at 24 weeks using overall OS cohort data as follows: • Switching cell D126 on the "Cost Inputs" sheet to the "Overall cohort" option • Switching the selected overall OS extrapolation in cell G122 on the "Cost Inputs" sheet to the preferred parametric model, e.g. as proposed in the	Overall cohort OS based on pooled data for TI and non-TI is more robust given larger sample size available to inform parametric survival extrapolations.	The EAG agrees with the suggested change to the revision and the results in Tables 50, 51, 52 and 53 of the EAG report have been updated.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	company results addendum: ○ Gompertz distribution for the base case Hb <12 g/dL population ○ Weibull distribution for the Hb <10 g/dL population		
<u>Implementation of EAG amendment assuming 88.5% of patients receive ruxolitinib as subsequent treatment after momelotinib</u> • Appendix 8.9.2, p. 116 The EAG amendment for implementing their preferred assumption of 88.5% of patients discontinuing momelotinib receiving ruxolitinib is based on changing cell G322 on the	Remove EAG amendment from cell G322 on the "Cost Inputs" sheet, and instead implement the EAG scenario on the "Data store" sheet as follows: Set value in cell D649 = IF('EAG Revisions'!D5=1,88.5%,0%)	As indicated in Section B.3.3.6.5 and Table 102 of the original CS, the proportion of patients on different therapies within BAT post-momelotinib in the model are derived using the distribution of therapies in the BAT comparator arm from SIMPLIFY-2 and rescaling the proportions on non-ruxolitinib therapies upwards to account for removal or lowering of the proportion post-momelotinib patients receiving ruxolitinib	The EAG agrees with the suggested change to the revision and the results in Tables 50, 51, 52 and 53 of the EAG report have been updated.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Cost Inputs" sheet of the model. This overestimates the subsequent treatment costs for momelotinib as it does not rescale the proportion of patients on other (i.e. non-ruxolitinib) subsequent therapies to match the original BAT distribution from SIMPLIFY-2.		and prevent underestimation of subsequent treatment costs for momelotinib. When changing cell G322 on the "Cost Inputs" sheet to 88.5%, this reintroduces the cost of ruxolitinib without readjusting the proportions of patients receiving non-ruxolotinib therapies, and therefore overestimates the cost of momelotinib subsequent treatment.	

Issue 6 Other errors and points of clarification related to economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Clarification of EAG comment</u> • Section 4.2.1, p. 61, Table 21 In response to the question "Were all the important and relevant costs and consequences for each	GSK requests that the EAG clarify that this comment applies only to the JAKi-experienced population.	Table 20 summarises EAG responses to the NICE reference case checklist in relation to both the JAKi-naïve population cost comparison model and JAKi-experienced cost-effectiveness model.	Text has been added to Table 21 to make it clear that this comment refers to the JAKi-experienced population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
alternative identified?", the EAG responded that "OS was inappropriately modelled by transfusion status".		As this comment only applies to the JAKi-experienced population cost-effectiveness model, and the EAG distinguishes separate responses for each population in the comment above in Table 20, clarification should be added to avoid potential misinterpretation that this comment applies to both populations.	
<u>Rate ratio labelled as rate</u> • Section 5.1.2, p. 75, Table 38 The EAG describes one of the company scenarios for the JAKi-naïve cost comparison model as "RBC transfusion rate of 0.43".	Change scenario description to "RBC transfusion rate ratio of 0.43".	Scenario is incorrectly stated as an adjustment of an RBC transfusion rate instead of a rate ratio between momelotinib and ruxolitinib.	Thank you for highlighting this error. The wording has been changed as suggested.
<u>Erroneous statement</u> • Section 6.2.3, p81	Remove statement "The EAG therefore considers that the RBC transfusion rate for NHS patients treated with ruxolitinib	GSK believe that the same rationale / outcome regarding the prohibition of ESA treatment in SIMPLIFY-1	This is not a factual inaccuracy. Clinical advice to the EAG is that ESAs can be effective at preventing or

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Statement regarding effect of ESA prohibition on RBC transfusion rate outcomes is misleading attributed only to ruxolitinib-treated patients	is likely to be lower than the rate observed in the SIMPLIFY-1 trial"	should apply to each treatment arm/scenario. Therefore, it is expected that this would have little impact on the net transfusion outcomes observed and applied to the cost-comparison model. We would re-iterate the weak evidence base supporting the use of ESAs concomitantly with JAKi in MF patients. As described above, data from the COMFORT-2 trial suggest that concomitant ruxolitinib and ESA treatment did not improve the proportion of patients in TI or increase Hb levels. In the 13 patients who received concomitant ruxolitinib and ESA, the worst hemoglobin value within 12 weeks of ESA administration improved in 3 patients, worsened in 2 patients, and	reducing the number of RBC transfusions in patients requiring treatment for anaemia. Due to the small number of patients, the study referenced by the company cannot provide reliable information on the effectiveness of concomitant ESAs. As per the response above, the EAG has clarified in Section 6.3.6 of the EAG report that it is unknown whether patients treated with momelotinib would also receive ESAs in NHS clinical practice and the magnitude of any benefit is also unknown. New text has been added to the end of the paragraph in this Section: “It is also unknown whether patients treated with momelotinib in NHS clinical practice would receive concomitant ESAs and the magnitude of any

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		did not change in 7 patients.(2)	associated reduction in RBC transfusions is also unknown.”
<u>Minor grammatical error</u> • Section 6.3.1, p. 84, Table 48 Text: “The company appropriately does not claim that a severity modify should be applied”	Adjust text to: “The company appropriately does not claim that a severity modifier should be applied”	Minor grammar correction.	Thank you for highlighting this error. The wording has been corrected as suggested.
<u>Missing context</u> • Section 6.3.3, p86 Statement "there was no difference in 5-year OS by transfusion status at Week 24" requires additional context to accurately understand conclusion	Modify statement "there was no difference in 5-year OS by transfusion status at Week 24" to "there was no **statistically significant** difference in 5-year OS by transfusion status at Week 24	Visual inspection of the survival curves indicates nominal difference in survival outcomes, however this was not statistically significant. GSK would like to reiterate the key limitations associated with the conclusion from Verstovsek et el. 2017. It is unclear whether this study was sufficiently powered to detect potential differences in OS according to transfusion	The wording has been amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		status in either of the anaemia-status subgroups.(11)	
Text error • Section 6.3.4 p87 GSK believe that the statement "clinicians would like to have the option to re-treat patients with ruxolitinib" implies all patients may be re-treated and is therefore inaccurate	Modify sentence to state "clinicians would like to have the option to re-treat **some eligible** patients with ruxolitinib"	GSK acknowledges the EAG's concerns regarding the subsequent treatment composition for patients who discontinue momelotinib. Per clinical feedback received by GSK, it is clear that not all patients would be re-treated with ruxolitinib due to reasons of suitability and access issues.(3, 4) This appears to align with a statement in Section 2.3.2 (p21) of the EAG report: "Clinical advice to the EAG is that for patients who experience toxicity during ruxolitinib treatment, the ruxolitinib dose would be reduced; patients would not be re-treated with ruxolitinib	The wording has been amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		following an extended break in treatment with ruxolitinib."	
Text error • Section 6.3.4 p87 GSK believe that the statement "However, the EAG has been unable to identify any such restrictions described in the NICE recommendation for ruxolitinib (or other published guidance)." can be removed	Remove statement "However, the EAG has been unable to identify any such restrictions described in the NICE recommendation for ruxolitinib (or other published guidance)."	This statement is misleading because it implies the restriction on re-use of ruxolitinib comes from a NICE recommendation. Instead, it comes from Blueteq criteria stating that where a treatment break >12 weeks beyond the 4 weekly cycle length is needed, a treatment break form is needed to restart treatment.(6) GSK has received advice that re-access is not routinely successful.(3, 4)	The EAG has removed the sentence as suggested and amended the following text from: However, clinical advice to the EAG is that, in NHS practice, there may be restrictions to re-treatment with ruxolitinib. However, the EAG has been unable to identify any such restrictions described in the NICE recommendation for ruxolitinib11 (or other published guidance). To: However, clinical advice to the EAG is that, in NHS practice, there may be

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			restrictions to re-treatment with ruxolitinib. BlueTeq criteria[61] state that if treatment is stopped for more than 3 months, a treatment break form is required to restart ruxolitinib treatment."
Text error • Section 6.3.6 p89 GSK believe the statement "The implication of this difference in ESA usage on the size of the ICER per QALY gained is unknown as the impact extends beyond the direct cost impact of fewer RBC transfusions and affects model health state transition probabilities, OS and HRQoL" inaccurately proposes that ESA can improve survival	Modify statement to remove OS	To GSK's knowledge there are no published evidence that support the notion that ESA can improve survival in MF patients.	This is not a factual inaccuracy. The sentence refers to the potential impact of changes in RBC transfusions on model outcomes. Transfusion rates are used to determine health state occupancy and different health states are associated with different costs, health-related quality of life and survival outcomes.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text error • Section 6.4.2 p92 Comparator in cost-utility analysis incorrectly labelled as "ruxolitinib"	Change text to: "momelotinib dominates BAT."	The comparator in the submitted cost-utility analysis is BAT	Thank you for highlighting this error. The text has been amended as suggested.

Issue 7 Check of confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
<u>Missing confidential marking</u> • Section 3.3, Table 10, p.42	SRR ITT population data should be confidential	Update table to: [redacted]	The EAG has marked these data as confidential. However, these data were not marked as confidential in the company response to clarification, clarification question A1, Table 1. As explained by the company in their clarification response: "Data reported in the CSR and CS are based on the final analysis, whereas data reported in the Mesa et al 2017 publication are derived from the interim Week 24 data cut. Because the data from the final analysis (taken from the CSR) were not in the

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
			public domain at the time of writing the dossier, they have been marked as confidential. However, since the same final analysis was used in the draft Summary of Product Characteristics (SmPC), which will be in the public domain following regulatory approval at the time of publishing this information, it is no longer necessary to mark this information up."
<u>Missing confidential marking</u> • Section 3.5, Table 13, p.47	RBC TI rate ITT population proportion difference (95% CI) should be confidential	Update table to:	Thank you for highlighting this error. Data marked as confidential.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		[redacted]	
Missing confidential marking • Section 3.8.1, p.53, Table 16	MOMENTUM safety data in Table 16 should be marked as confidential	Update table to: [redacted]	The EAG has marked these data as confidential. However, these data were not marked as confidential in CS, Appendix F.1.3, Table 31.
Missing confidential marking • Section 3.8.1, p.54 Text: "In addition, as reported in CS,	MOMENTUM safety data should be marked as confidential	Update wording to: Text: "In addition, as reported in CS, Appendix F.1.3, (Table 32), any grade anaemia was experienced by [redacted]% of patients in the momelotinib arm and 100% of patients in the danazol arm; any grade thrombocytopenia was experienced by [redacted]% of patients in the momelotinib arm and by [redacted]% of patients in the danazol arm. The higher	The EAG has marked these data as confidential. However, these data were not marked as confidential in CS, Appendix F.1.3, Table 32.

Appendix F.1.3, (Table 32), any grade anaemia was experienced by 99.2% of patients in the momelotinib arm and 100% of patients in the danazol arm; any grade thrombocytopenia was experienced by 76.1% of patients in the momelotinib arm and by 61.5% of patients in the danazol arm. The higher frequencies of the aforementioned AEs in the MOMENTUM trial, particularly haematological AEs, may reflect the fact that 92.8% of patients in this trial had Int-2/HR disease and also likely reflect the fact that all patients were considered to be both		frequencies of the aforementioned AEs in the MOMENTUM trial, particularly haematological AEs, may reflect the fact that [redacted]% of patients in this trial had Int-2/HR disease and also likely reflect the fact that all patients were considered to be both anaemic (Hb <10g/L) and symptomatic (MFSAF TSS ≥10).”	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
anaemic (Hb<10g/L) and symptomatic (MFSAF TSS ≥10)."			
<u>Missing confidential marking</u> • Section 6.3.7, Table 52 and 53, p.91	Incremental NMB in tables 52 and 53 should be marked as confidential.	Update table to: [redacted]	Thank you for highlighting this error. Data marked as confidential.

References

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