EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136076

Completed 12 October 2023
Updated 31 October 2023

CONTAINS [redacted] DATA

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A MEMBER OF THE RUSSELL GROUP

Title: Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]

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Date completed: 12 October 2023 (Updated 31 October following company factual accuracy and confidential marking check)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136076

Acknowledgements: The EAG would like to thank Bethan Psaila (Associate Professor of Haematology, Oxford University Hospital NHS Foundation Trust) who provided peer review on a draft version of the report as well as additional clinical advice. The EAG would also like to thank Joanne Ewing (Consultant Haematologist, University Hospitals Birmingham) who also provided peer review on a draft version of the report.

Declared competing interests of the authors: Nauman Butt has received consultancy fees, reimbursement for attending a conference, fees for speaking and funding for research from Novartis

Declared competing interests of the peer reviewers: Bethan Psaila has received consultancy fees from GSK, reimbursement for attending a conference and fees for speaking by Novartis, and funding for research and a member of staff from Incyte. Joanne Ewing has received consultancy fees, reimbursement for attending a conference, fees for speaking and hospitality from GSK

This report should be referenced as follows: Fleeman N, Bresnahan R, Mahon J, Bryning S, Beale S, Boland A, Chaplin M, Nevitt S, Dundar Y, McEntee J and Butt, NM. Momelotinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis [ID6141]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2023

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LIST OF ABBREVIATIONS

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.

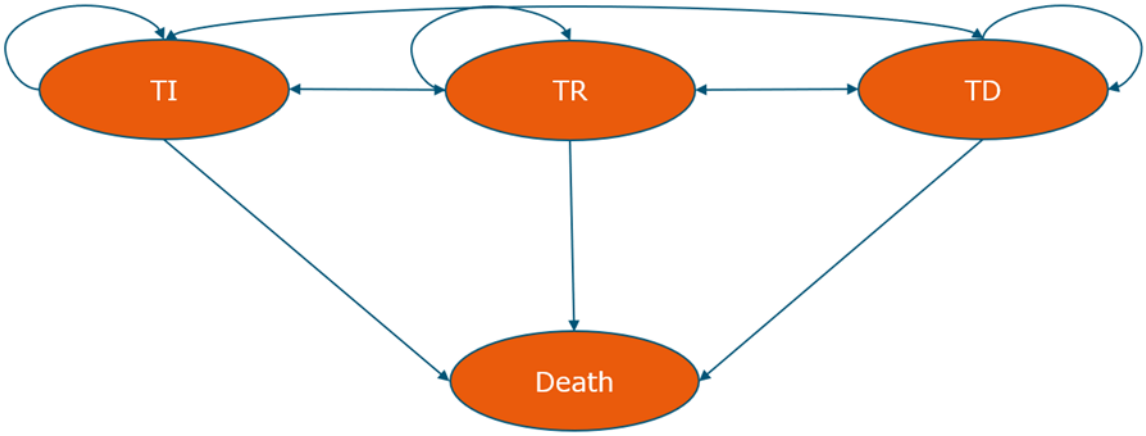

Figure 1 Markov model structure: JAKi-experienced population

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]	[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]

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

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