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

For public – confidential information redacted

Technology appraisal committee C 09th January 2024

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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JAKi-naive population
JAKi-experienced population

Key and other issues for discussion

Table Key issues

Issue	Impact
JAKi-naive population: Appropriateness of cost comparison analysis	N/A
ESA usage during the SIMPLIFY trials	Unknown 

Table Other issues

Issue	Impact
Defining moderate to severe anaemia	Does not change direction of results 
JAKi-experienced population: Link between OS and transfusion status	Does not change direction of results 
JAKi-experienced population: Treatment with ruxolitinib as part of BAT after stopping momelotinib	Does not change direction of results 

Abbreviations: BAT, best available therapy; ESA, Erythropoiesis-stimulating agent; OS, overall survival

Momelotinib (Omjarra, GSK)

Table Technology details

Anticipated marketing authorisation	Momelotinib received a positive opinion from CHMP in November 2023 recommending that it is indicated for "the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib."
Mechanism of action	Momelotinib is an inhibitor of wild type Janus Kinase 1 and 2 (JAK1/JAK2) and mutant JAK2V617F. Momelotinib and its metabolite, M21, have higher inhibitory activity for JAK2 compared to JAK3. Momelotinib and M21 additionally inhibit activin A receptor type 1 (ACVR1), which subsequently down regulates liver hepcidin expression resulting in increased iron availability and red blood cell production.
Administration	200 mg orally once daily.
List price	£5,650 per 30-tablet pack (flat pricing across 200 mg, 150 mg and 100 mg)

Abbreviations: MF, myelofibrosis

Background on myelofibrosis

Causes

- Myelofibrosis is a cancer of the bone marrow in which the marrow is replaced by scar (fibrous) tissue
- It may be primary, or secondary to rare blood cancers (polycythaemia vera or essential thrombocythaemia)
- As the bone marrow becomes more scarred, it is less able to produce blood cells. To compensate for this, blood cell production occurs in the spleen and liver, causing these organs to enlarge.

Epidemiology

- Primarily affects older people - median age at diagnosis is 65 years. More common in men than women

Classification of disease

- MF can be graded into risk categories using prognostic tools (usually DIPSS and/or DIPSS Plus in the NHS)
- DIPSS uses five risk factors to predict survival: age >65 years, haemoglobin <10 g/dL, leukocytes >25x10^9/L, circulating blasts ≥1%, and constitutional symptoms (weight loss and/or unexplained fever or sweats)
- DIPSS Plus also includes unfavourable karyotypes, transfusion dependence, and platelet count <100x10^9/L
- Each criteria present adds 1 point to the score (except for haemoglobin <10 g/dL in DIPSS which adds 2)
- Risk category based on score is shown in the table below

	Low risk	Intermediate-1 risk	Intermediate-2 risk	High risk
DIPSS	0	1-2	3-4	5+
DIPSS Plus	0	1	2-3	4+

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis

Patient and clinical perspectives*

Submissions from clinical expert, patient expert, MPN Voice and Leukaemia Care

- Myelofibrosis affects many aspects of patients' lives and the people who care for them.
- There are multiple goals of treatment in myelofibrosis which depend on the age and disease status of the patient. Sometimes a cure is possible, more frequently managing quality of life and symptoms is the goal.
- There are a limited number of targeted treatments. This impacts elderly patients most as they are unlikely to be eligible for a stem cell transplant, the only curative treatment.
- A distinct advantage of momelotinib is its ability to manage anaemia, which is a common and challenging symptom of myelofibrosis
- Momelotinib will allow physicians to better tailor therapy to individual patient needs

*See appendix slides 35 and 36

Treatment pathway for myelofibrosis*

Comparator in model | Momelotinib | Other

JAKi-naive

PMF, post-ET MF and post-PV MF
Int-2 or high-risk category

Transplant ineligible

- Ruxolitinib
- Momelotinib
- Interferon-α
- Hydroxyurea

JAKi-experienced (int-2 or HR)

Ruxolitinib Or Momelotinib Or Fedratinib (CDF)

And other treatments which can include:

- Interferon-α
- Hydroxyurea
- Other chemotherapies
- Splenectomy
- Radiation therapy
- Palliative care

Anaemia supportive measures (as required) – EPO, Androgen (Danazol), RBC transfusion

Is the proposed positioning of momelotinib appropriate?

Return to questions

*See appendix slide 37 for full treatment pathway

Decision problem summary*

Table Decision problem summary

Populations in company submission	Type of model	Comparator	Trial	Subgroups considered in modelling
JAKi-naive	Cost comparison	Ruxolitinib	SIMPLIFY-1 (non-inferiority vs. ruxolitinib)	ITT (includes int-1 disease and people without moderate to severe anaemia) Int-2/HR Hb<12 g/dL Int-2/HR Hb<10 g/dL
JAKi-experienced* (ruxolitinib relapse, intolerant or still on ruxolitinib)	Cost-utility	BAT (including ruxolitinib)	SIMPLIFY-2 (vs BAT)	Int-2/HR Hb<12 g/dL Int-2/HR Hb<10 g/dL

*JAKi = ruxolitinib or fedratinib (CDF)

EAG Comments

Population

The population differs from the final scope by the inclusion of moderate to severe anaemia. This aligns with the positive CHMP opinion. Evidence is presented for both populations.

The ITT population for both trials included people with int-1 disease and without moderate to severe anaemia

*See appendix slides 38 and 39 for full decision problem

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Abbreviations: BAT, best available therapy; Hb, haemoglobin; HR, high risk; Int-1, intermediate-1 (risk); Int-2, intermediate-2 (risk); ITT, intention to treat

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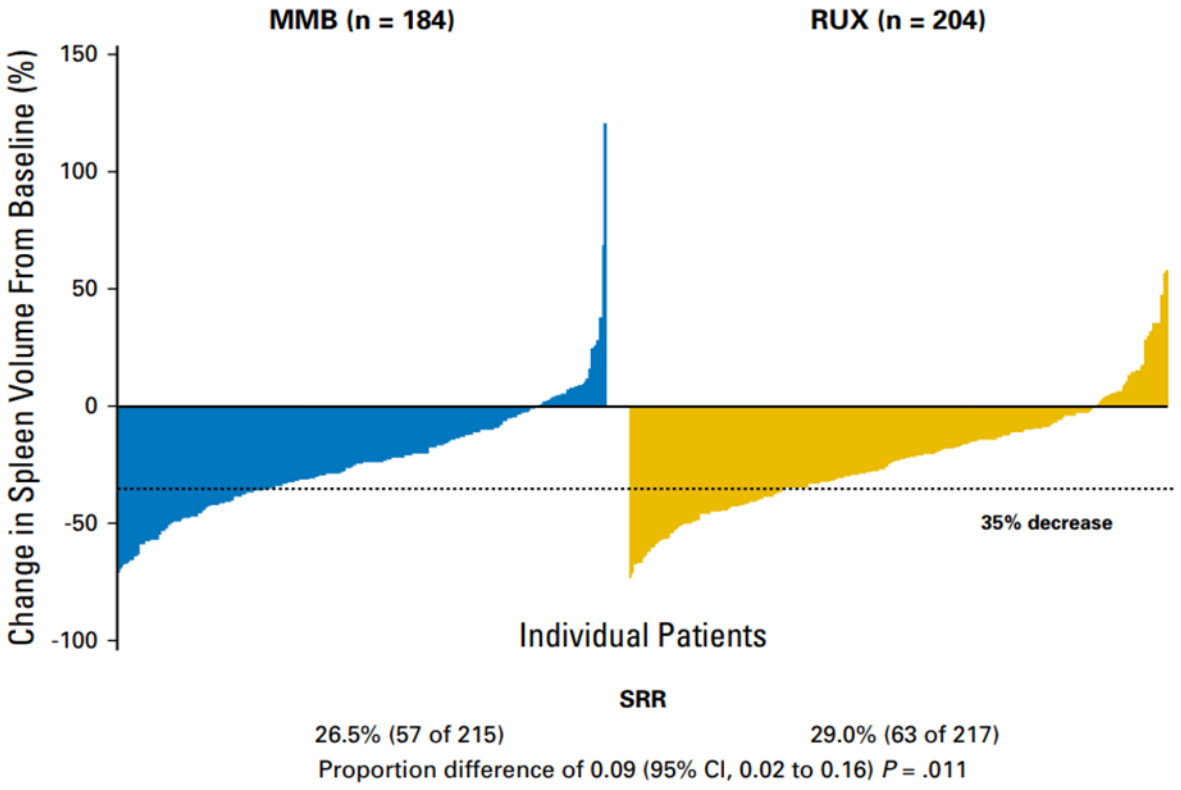
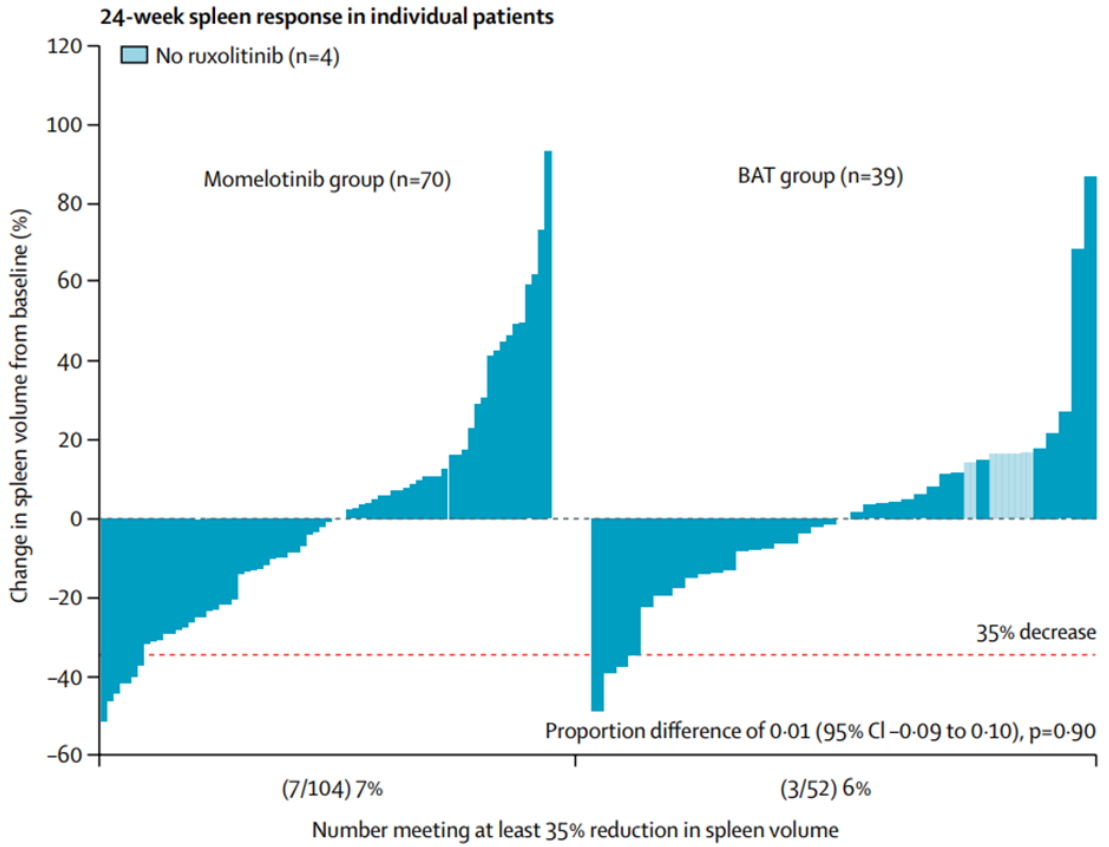
Key clinical trial results†

See appendix slides 40, 41, 42, 43, and 44 for full trial descriptions, designs, results, and AE



SIMPLIFY-1 – non-inferiority vs. ruxolitinib

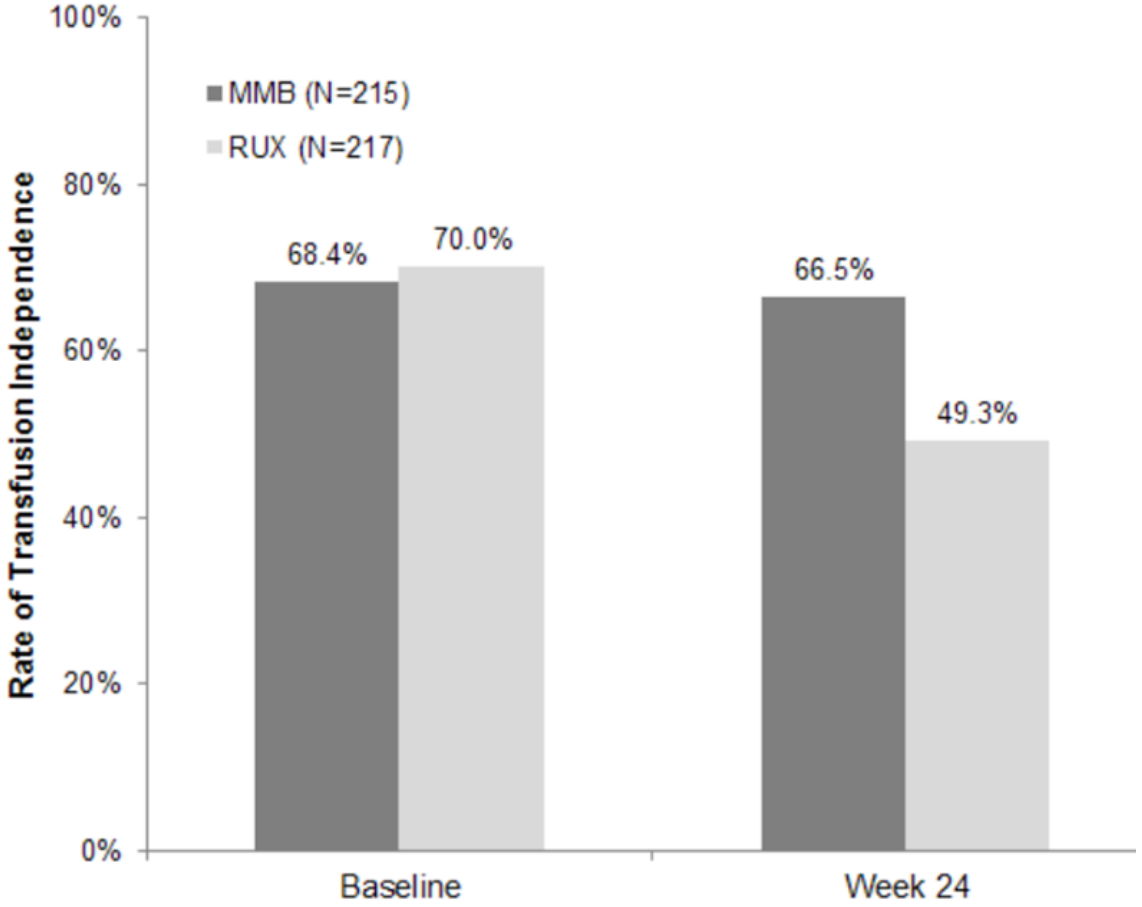


SIMPLIFY-2 – superiority vs. BAT

JAKi-naïve	Momelotinib	Ruxolitinib	Proportion difference (95% CI)
Spleen response rate*	26.5%	29.5%	0.09 (0.02, 0.16); p=0.014

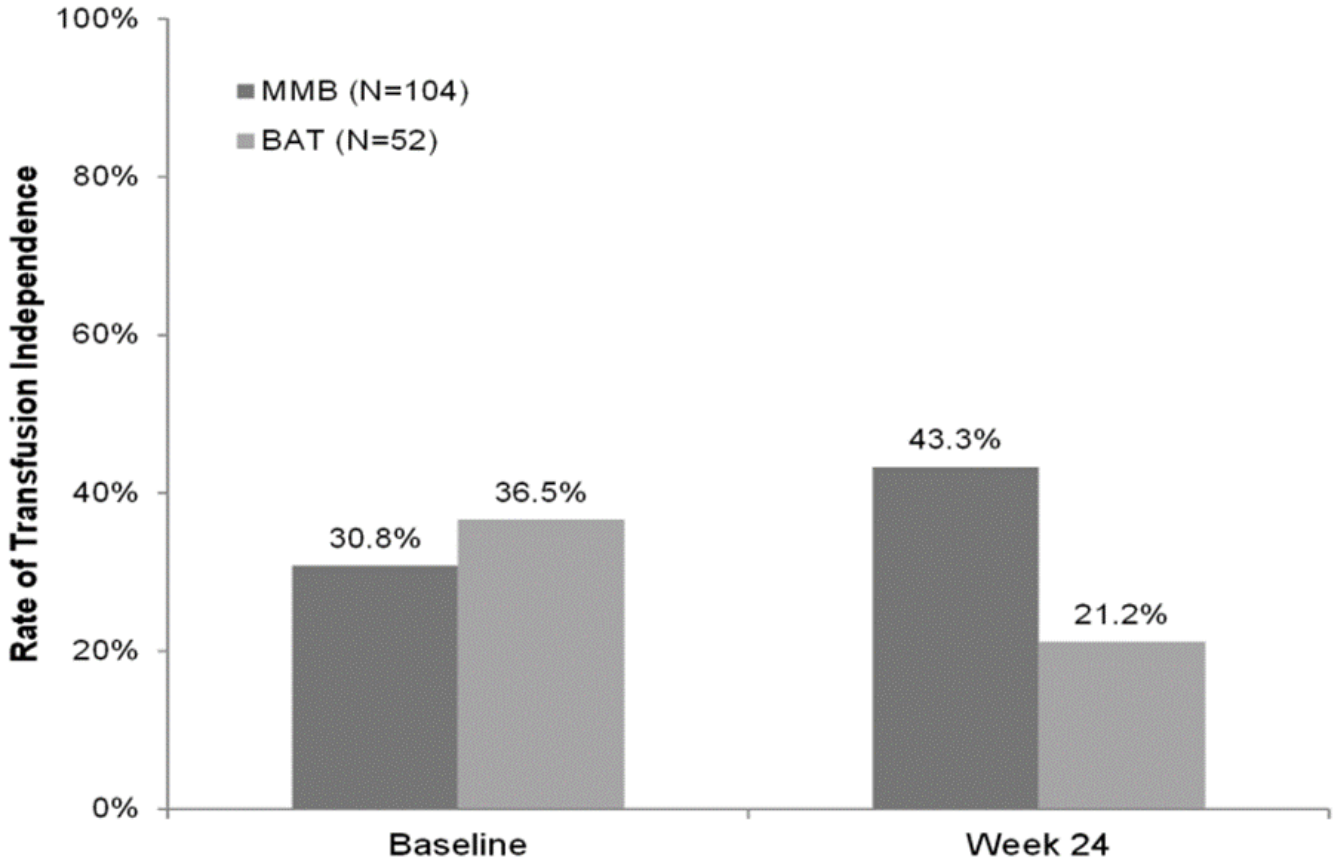
Currently/ previous ruxolitinib	Momelotinib	BAT	Proportion difference (95% CI)
Spleen response rate*	6.7%	5.8%	0.01 (-0.09, 0.10); p=0.90

Key clinical trial results – transfusion status ITT population



Proportion difference (95% CI)	[redacted] p<0.001*

Figure SIMPLIFY-1 – transfusion independence rate at baseline and week 24 – ITT population



Proportion difference (95% CI)	[redacted] p=0.0012*

Figure SIMPLIFY-2 – transfusion independence rate at baseline and week 24 – ITT population

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Abbreviations: BAT, best available therapy; ITT, intention to treat; MMB, momelotinib; RUX, ruxolitinib

Key clinical trial results – transfusion status - subgroups

Proportion difference (95% CI)	[redacted]

Proportion difference (95% CI)	[redacted]

Figure SIMPLIFY-1 – transfusion independence rate at baseline and week 24 – Int-2/HR and Hb <12 g/dL population

Figure SIMPLIFY-2 – transfusion independence rate at baseline and week 24 – Int-2/HR and Hb <12 g/dL population

Abbreviations: BAT, best available therapy; ITT, intention to treat; MMB, momelotinib; RUX, ruxolitinib

Key issue: Appropriateness of cost comparison analysis

Company believe cost comparison is most suitable, EAG believes evidence is mixed

Background

- The results from the SIMPLIFY-1 trial were mixed. Compared to treatment with ruxolitinib, momelotinib was:
  - statistically significantly non-inferior in terms of spleen response rate using a non-inferiority margin of 60%
  - not statistically significantly non-inferior in terms of total symptom score (TSS)
  - nominally significantly superior red blood cell transfusion independence (RBC TI)/ transfusion dependence

Company

- Study design may have impacted the assessment of TSS and symptom response
- RBC TI rate was much higher in the momelotinib arm compared to the ruxolitinib arm at week 24 (67% vs 49%)
- Overall efficacy profiles indicates holistic benefits are comparable

EAG comments

- Clinical advice suggested the non-inferiority margin (60%) was wider than considered acceptable in clinical practice but spleen response rates were similar in the momelotinib and ruxolitinib arms
- Non-inferiority not met for TSS – may cast doubt on the suitability of cost-comparison
  - However post-hoc analysis indicated there was little difference between treatment arms when assessing individual symptom scores and absolute change in TSS from baseline
- Clinical advice suggested TSS response rate was not a major concern because of improvements in RBC TI

Return to questions

Is a cost comparison appropriate for the JAKi-naive population?

Key issue: Appropriateness of cost comparison analysis

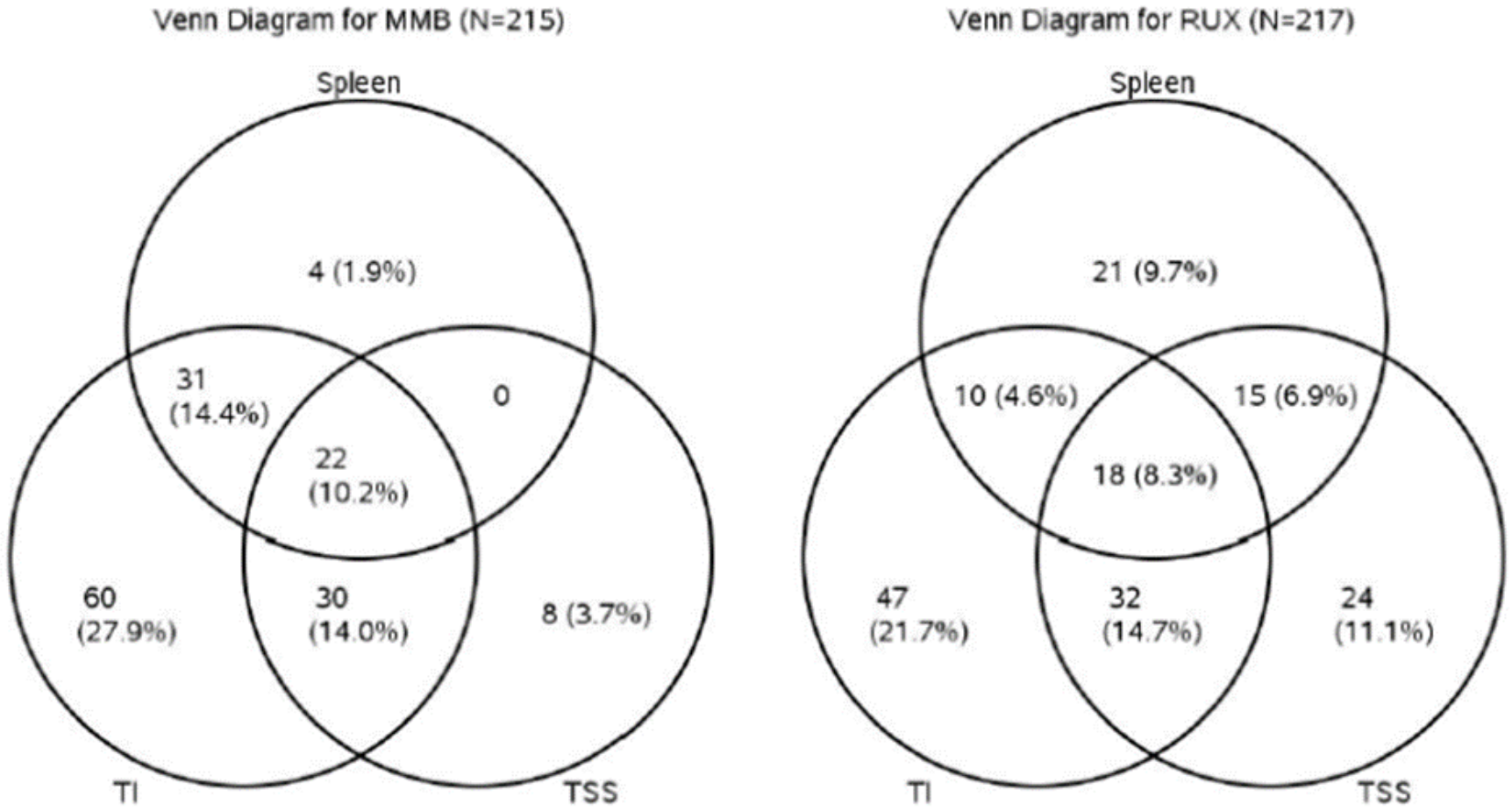

Figure Response rates for spleen response, transfusion independence, and total symptom score from SIMPLIFY-1 for momelotinib and ruxolitinib at week 24

Criteria met	Momelotinib
≥1	72.1%
≥2	38.6%
3	10.2%

Criteria met	Ruxolitinib
≥1	77.0%
≥2	34.5%
3	8.3%

Tables Proportions of patients meeting 1 or more, 2 or more, or all 3 response criteria after receiving momelotinib or ruxolitinib at week 24

Abbreviations: MMB, momelotinib; RUX, ruxolitinib; TI, transfusion independence; TSS, total symptom score

Key issue: ESA usage during the SIMPLIFY trials

EAG believe that ESA usage differs from NHS practice and may have impacted results, company disagree

Background

- Use of ESAs as anaemia support were prohibited in SIMPLIFY-1 and in momelotinib arm of SIMPLIFY-2
- ESAs were also not commonly used in the BAT arm of SIMPLIFY-2 (5.8%)
- ESAs stimulate the bone marrow to produce red blood cells which helps reduce anaemia
- Expert input to NICE suggests ESA response is unpredictable in MF, unclear how ESAs would impact trials

Company

- Data from UK REALISM study of 200 MF patients show that anaemia was common but only 5% of patients had anaemia supportive therapy
- No clear evidence that ESA use improves clinical outcomes in ruxolitinib-treated patients
- Data from COMFORT-2 trial suggest that concomitant ruxolitinib and ESA treatment did not improve the proportion of patients who were transfusion-independent or increase Hb levels.
- UK HMRN registry reports lifetime use of ESAs of 25.5% in JAKi-treated patients, study was only 24 weeks

EAG comments

- Clinical advisors said that ESAs are often given alongside BAT (especially ruxolitinib) in NHS clinical practice
- Clinical advice suggests in NHS clinical practice, ESAs are used by 20% to 60% of ruxolitinib patients
- Possible that efficacy results (particularly RBC TI and RBC TD) may have been different if ESAs were used

Return to questions

Can the results from the SIMPLIFY trials be generalised to UK clinical practice?

Key issue: Defining moderate to severe anaemia

EAG believe that Hb<10g/dL better represents moderate to severe anaemia than company's Hb<12g/dL assumption

Background

- The positive CHMP opinion for momelotinib specifies its use in adults with moderate to severe anaemia
- The company define moderate to severe anaemia as 'treatment-requiring anaemia' using **Hb<12g/dL** where a specific threshold is required
- Clinical advice to the company and EAG suggests moderate to severe anaemia should not be based solely on Hb levels and should include other factors such as age, fitness, and comorbidities
- Expert advice to NICE suggests 8-10g/dL would be considered moderate to severe anaemia

Company

- While not all patients with Hb<12 g/dL would be considered moderately or severely anaemic, clinicians advised a lower Hb threshold would omit patient groups with clinically relevant treatment-requiring anaemia

EAG comments

- Clinical advice suggests patients with Int-2/HR disease and **Hb<10g/dL** are more likely to represent NHS patients with moderate to severe anaemia
- NCI defines moderate to severe anaemia as Hb <10 g/dL
- Conducted scenario analysis for both subgroups, direction of results was unchanged

Is Hb<12g/dL or Hb<10g/dL more likely to represent NHS patients with moderate to severe anaemia?

Return to questions

Abbreviations: Hb, haemoglobin; int-2, intermediate-2 (risk); MA, marketing authorisation; NCI, National Cancer institute

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Company's model overview

RBC transfusion costs - JAKi-naive population

- EAG considers cost per RBC transfusion (£399.77) reasonable and in line with weighted average NHS Cost Collection unit costs for simple blood transfusions (£374.33)
- RBC transfusion costs are calculated by multiplying the unit cost by the monthly RBC transfusion rates observed in SIMPLIFY-1, over a 10-year time horizon

Table Model overview – **JAKi-naive population**

Model type	Cost comparison
Perspective	UK NHS and PSS
Time horizon	10 years
Cycle length	N/A
Discounting	3.5% per annum for costs and benefits
Subgroups	ITT, Int-2/HR Hb<12 g/dL, Int-2/HR Hb<10 g/dL

Figure Model structure – **JAKi-experienced population**

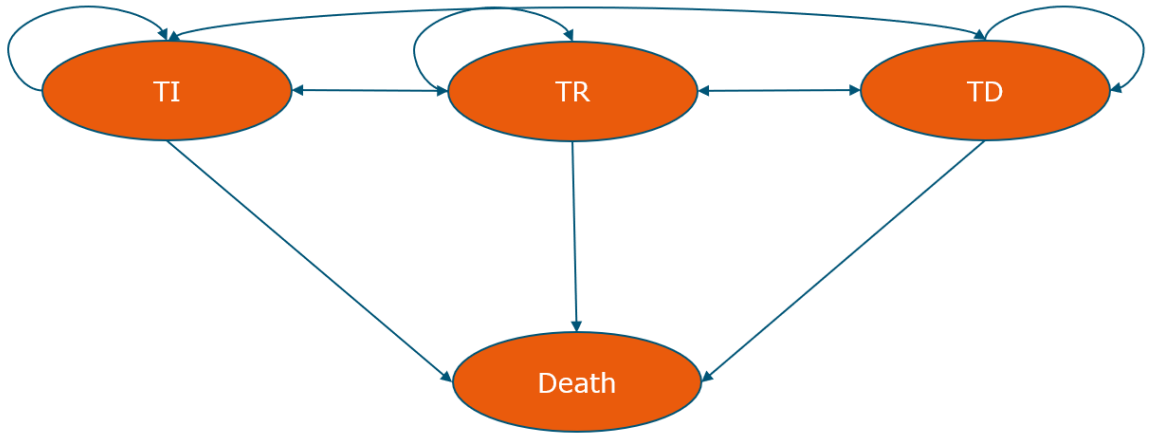

Table Model overview – **JAKi-experienced population**

Model type	4-state Markov model
Perspective	UK NHS and PSS
Time horizon	33 years
Cycle length	4 weeks
Discounting	3.5% per annum for costs and benefits
Subgroups	Int-2/HR Hb<12 g/dL, Int-2/HR Hb<10 g/dL

Abbreviations: Hb, haemoglobin; HR, high risk; Int-2, intermediate-2 (risk); ITT, intention to treat, TD, transfusion dependence; TI, transfusion independence; TR, transfusion requiring

Key issue: Link between OS and transfusion status

Company assume transfusion status is linked to OS, EAG does not

Background

- Up to 24 weeks, survival in the model is derived from SIMPLIFY-2 and is the same for both arms
- After 24 weeks, survival based on transfusion status (TI or non-TI) from SIMPLIFY-2 momelotinib arm OS
- Pooled analysis of COMFORT trials (which assessed ruxolitinib) indicated that for patients treated with ruxolitinib, there was no statistically significant difference in 5-year OS by transfusion status at Week 24
- Analysis of SIMPLIFY-2 included 68 people, the pooled COMFORT analysis included 123 people

Company

- Survival in SIMPLIFY-2 is confounded due to crossover of patients from the BAT arm to momelotinib
- Results from SIMPLIFY-2 indicated that transfusion status at Week 24 was predictive of survival
- The assumption of transfusion status impacting OS was validated by clinical experts
- The results from the pooled COMFORT trials were unlikely to give significant results due to sample size

EAG comments

- The differences in OS by transfusion status from SIMPLIFY-2 may have been caused by differences in the proportions of TI and non-TI patients who were still being treated with momelotinib at Week 24
- 88.5% of SIMPLIFY-2 trial BAT arm patients were treated with ruxolitinib, COMFORT trial results are relevant
- SIMPLIFY-2 was also not powered to show a difference in OS for subgroups by transfusion status
- Conducted scenario analysis removing OS impact, direction of results was unchanged

Abbreviations: BAT, best available therapy; OS, overall survival; TI, transfusion independence

Key issue: Link between OS and transfusion status

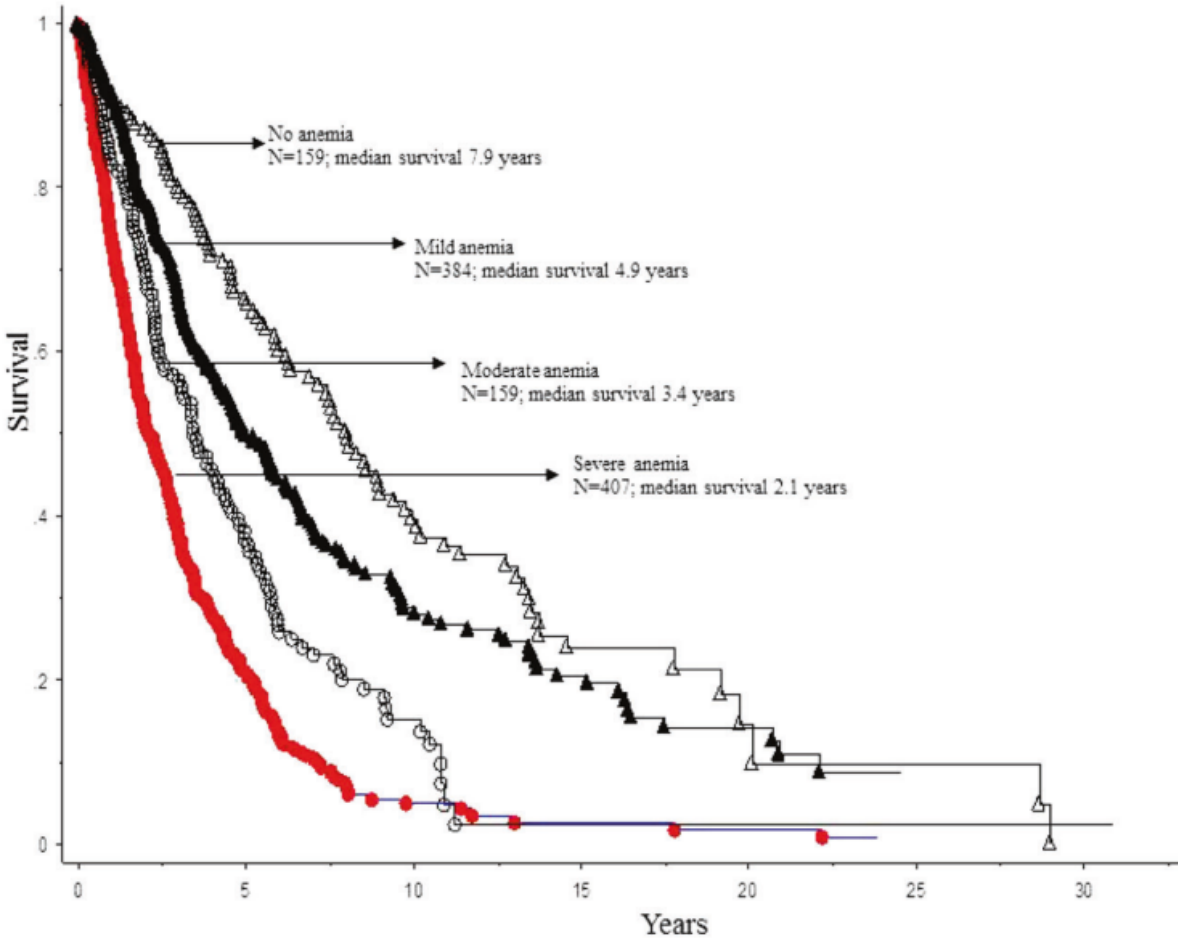

Figure Survival of MF patients by severity of anaemia

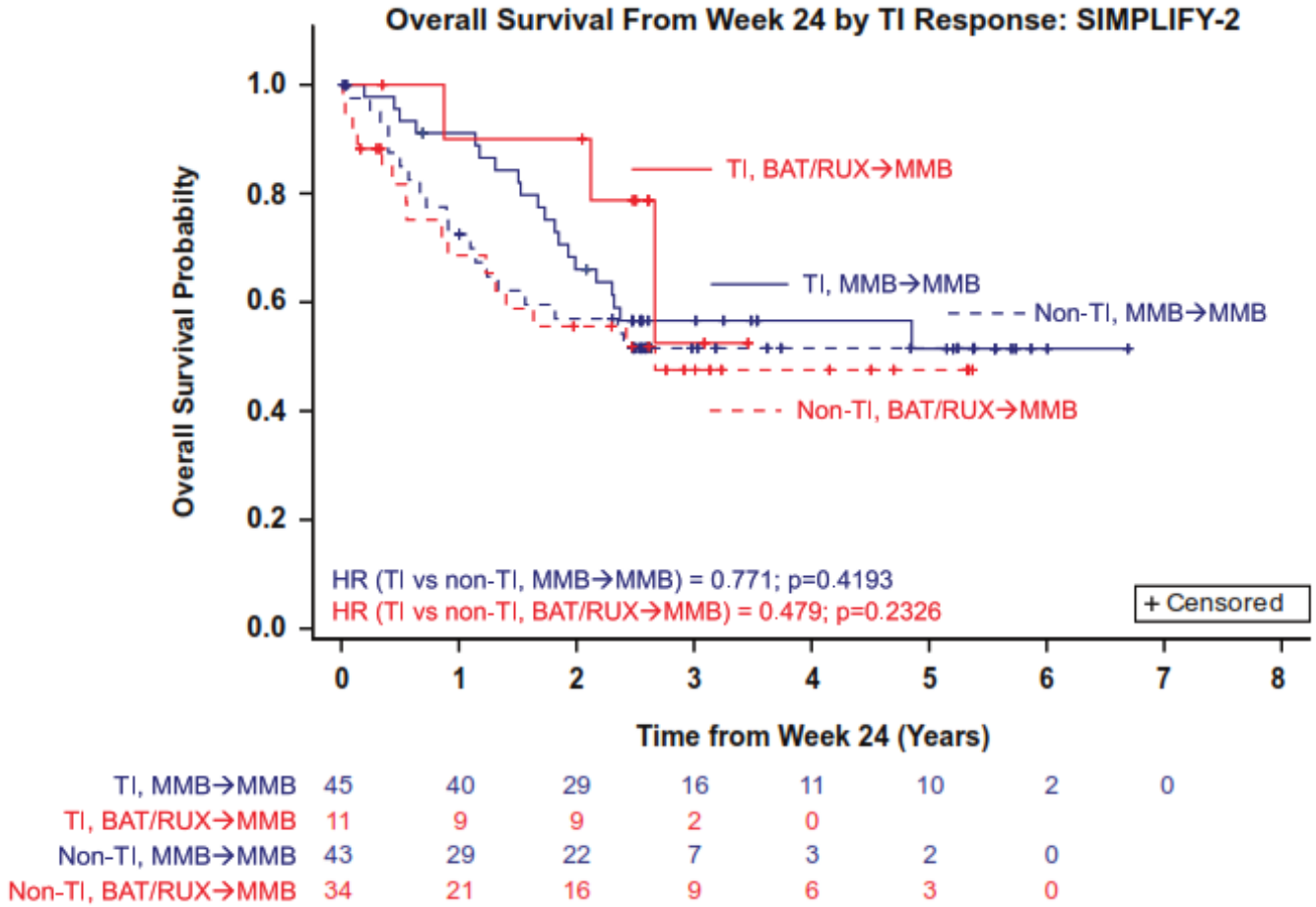

Figure Overall survival from week 24 by transfusion status in SIMPLIFY-2

Return to questions

Should transfusion status impact survival in the model?

Key issue: Ruxolitinib as part of BAT after stopping momelotinib

EAG believe treatment with ruxolitinib should be included after momelotinib is stopped, the company disagrees

Background

- In the company model, 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)

Company

- Clinicians stated that retreatment with ruxolitinib was unlikely after discontinuing momelotinib
- The EAGs base case vastly overestimates the proportion of patients would be able to receive ruxolitinib (88.5%)
- A clinician survey gave a mean estimation of 39% of patients receiving ruxolitinib after discontinuing momelotinib, which should be considered as a pessimistic alternative to the company base-case.

EAG comments

- Adds further challenge to company approach to modelling improved OS for momelotinib compared to BAT
- Clinicians would like to have the option to re-treat some eligible patients with ruxolitinib however in NHS practice, there may be restrictions to re-treatment with ruxolitinib
- The EAG's preferred assumption is that all patients who stop treatment with momelotinib 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 time.
- Analysis with ruxolitinib as part of BAT after stopping momelotinib did not change the direction of results

Return to questions

Should treatment with ruxolitinib be included in the model after momelotinib is stopped?

Company and EAG preferred base case assumptions

Table Company and EAG preferred base case assumptions

Base case preferred assumptions (JAKi-experienced)	Company	EAG
OS impacted by transfusion status	TI patients have a lower mortality than non-TI patients	Transfusion status has no impact on mortality
Ruxolitinib included in BAT after discontinuing momelotinib	Ruxolitinib is not included in BAT after discontinuing momelotinib	BAT composition for patients discontinuing momelotinib is the same as the BAT arm (88.5% receive ruxolitinib)

Note: the EAG's and company's base case assumptions for the JAKi-naive population are the same

Abbreviations: BAT, best available therapy; OS, overall survival; TI, transfusion independence

See appendix slides 43, 44, 45 and 46 for part 1 list price results

Cost-effectiveness results

Confidential discounts are available for momelotinib and subsequent treatments in the pathway. ICERs including confidential discounts will be presented in Part 2.

Summary of confidential results

JAKi-naive population

- Company's base case has **lower** total costs than ruxolitinib
- EAG's base case has **lower** total costs than ruxolitinib
- A scenario where momelotinib is assumed to have no transfusion benefit is considered in part 2. Momelotinib has **higher** total costs than ruxolitinib

JAKi-experienced population

- Company's base case is **below** the lower end of what would usually be considered cost-effective use of NHS resources
- EAG's base case is **below** the lower end what would usually be considered cost-effective use of NHS resources

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- ❑ Summary

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Other considerations

Equality considerations

- Age over 65 years old is a prognostic factor for myelofibrosis and so there is potential for clinical efficacy and cost effectiveness to vary for populations over and under 65 years.

Severity

- Company and EAG consider momelotinib is not expected to meet the severity modifier criteria

Innovation

- Company does not suggest there are any additional benefits not captured in the modelling

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JAKi-naive population
JAKi-experienced population

Key and other issues for discussion

Table Key issues

Issue	Impact
**JAKi-naive population: Appropriateness of cost comparison analysis	N/A
ESA usage during the SIMPLIFY trials	Unknown 

Table Other issues

Issue	Impact
Defining moderate to severe anaemia ***What threshold should be used for moderate to severe anaemia?***	Does not change direction of results 
JAKi-experienced population: Link between OS and transfusion status ***Should transfusion status impact survival?*	Does not change direction of results 
JAKi-experienced population: Treatment with ruxolitinib as part of BAT after stopping momelotinib ***Should ruxolitinib be included as a treatment after momelotinib has stopped?*	Does not change direction of results 

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Abbreviations: BAT, best available therapy; ESA, Erythropoiesis-stimulating agent; OS, overall survival

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Thank you.

Appendix

Clinical perspectives

Submission from clinical expert

- There are multiple goals of treatment in myelofibrosis which depend on the age and disease status of the patient.
- Sometimes cure is possible, more frequently the goal of therapy is to improve quality of life and reduce impact of symptoms
- JAK2 inhibitors are effective treatments for patients with myelofibrosis who have significant disease-related symptoms
- One of the distinctive advantages of momelotinib is its ability to manage anaemia, which is a common and challenging symptom of myelofibrosis
- The population of patients who have myelofibrosis-related anaemia would be better off having momelotinib therapy as their first line JAK2 inhibitor
- Momelotinib will allow physicians to better tailor therapy to individual patient needs, especially considering factors like symptom profile, disease severity and side effect tolerance

"Momelotinib would provide an alternative for patients who might not respond well to or cannot tolerate ruxolitinib."

"[Momelotinib] could be particularly beneficial for patients who suffer from significant anaemia and may reduce the need for regular blood transfusions"

Patient perspectives

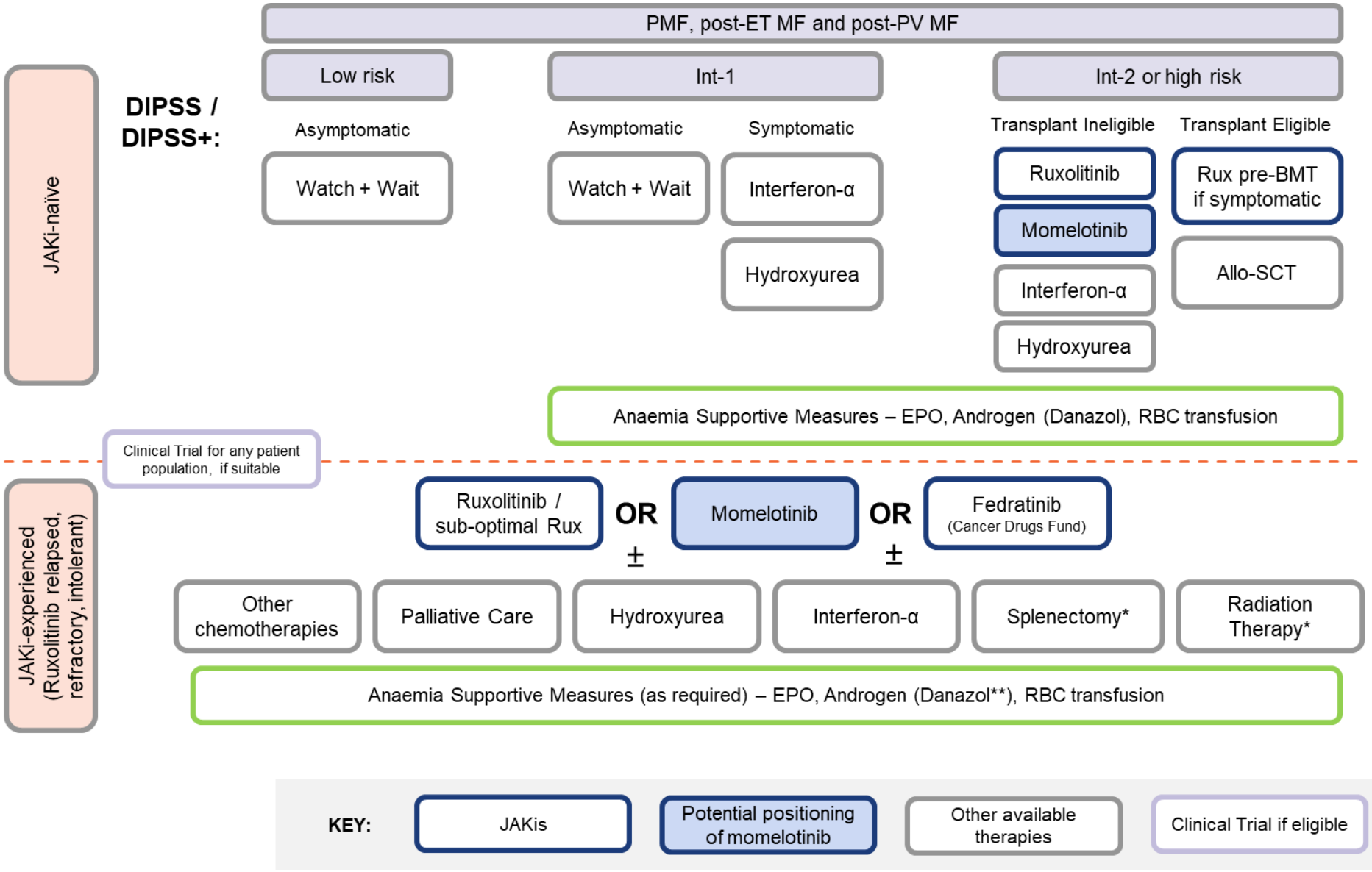
Submissions from patient expert, MPN Voice and Leukaemia Care

- Myelofibrosis affects many aspects of patients' lives
- The impact of the disease is also felt by the people who care for myelofibrosis patients
- There are a limited number of current treatments for myelofibrosis and a significant number of patients are, or become in time, intolerant of or unresponsive to them, with poor outcomes once treatment is ended
- The lack of other alternative treatments is a particular problem for elderly patients and/or those with other illnesses, who are unlikely to be eligible for stem cell transplantation, which is the only potential cure for myelofibrosis
- Momelotinib has an improved side-effect profile and a convenient delivery method and reduces the need for blood transfusions for anaemic patients.

"Extreme fatigue and bone pain make it impossible on some days to stand and cook, walk dog, play with kids, socialise"

"Was working full time in demanding job but have taken early retirement due to constant fatigue and recurring infections"

Full treatment pathway for myelofibrosis



Decision problem

Table Decision problem

	Final scope	Company	EAG comments
Population	Adults with disease-related splenomegaly or symptoms of: • PMF • Post-PV MF or • Post-ET MF	Adults with **moderate to severe anaemia** and disease-related splenomegaly or symptoms of: • PMF • Post-PV MF or • Post-ET MF	The inclusion of moderate to severe anaemia aligns with the positive CHMP opinion. Evidence is presented for both populations
Intervention	Momelotinib	Momelotinib	As per final scope
Comparators	For people eligible for treatment with ruxolitinib: • ruxolitinib For people whose disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate **(including people with low or Int-1 risk disease):** • established clinical practice*	For people **with no previous treatment with JAKi and Int-2/HR disease:** • ruxolitinib For people with prior JAKi exposure, who may be currently receiving JAKi or have discontinued but remain eligible for JAKi treatment: • established clinical practice* **including ruxolitinib**	**JAKi-naïve population** As per the final scope **JAKi-experienced population** EAG's clinician advised ruxolitinib is the most common BAT used for JAKi-experienced patients **Low or Int-1 risk disease** It is unlikely that Int-1 risk patients will have moderate to severe anaemia

Decision problem

Table Decision problem

	Final scope	Company	EAG comments
Outcomes	The outcome measures to be considered include: • spleen size • symptom relief (including itch, pain and fatigue) • overall survival • leukaemia-free survival • response rate • haematologic parameters (including red blood cell transfusion and blood count) • AEs of treatment • HRQoL	The outcome measures to be considered include: • spleen size • symptom relief (including itch, pain and fatigue) • overall survival • leukaemia-free survival • response rate • haematologic parameters (including red blood cell transfusion and blood count) • AEs of treatment • HRQoL	As per final scope. Similar to TA386 (ruxolitinib for treating disease-related splenomegaly or symptoms in adults with MF)

Key clinical trials

	SIMPLIFY-1	SIMPLIFY-2	MOMENTUM*
Design	Multicentre, randomised, double-blind, Phase III, non-inferiority trial	Multicentre, randomised, open-label, Phase III, superiority trial	Multicentre, randomised, double-blind, Phase III trial
Population	JAKi-naïve patients aged ≥18 years with PMF or post-PV/-ET MF	Currently or previously ruxolitinib-treated patients aged ≥18 years with PMF or post-PV/-ET MF, who had suboptimal response[a] or haematological toxicity[b] after receiving ruxolitinib	JAKi-experienced, symptomatic and anaemic patients aged ≥18 years with PMF or post-PV/-ET MF
Intervention	Momelotinib 200mg once daily	Momelotinib 200mg once daily	Momelotinib 200mg once daily
Comparator	Ruxolitinib 20mg twice daily	BAT	Danazol 300mg twice daily
Duration	Primary outcome: 24 weeks Follow up: 216 weeks	Primary outcome: 24 weeks Follow up: 204 weeks	Primary outcome: 24 weeks Follow up: 151 weeks
Primary outcome	Splenic Response Rate at Week 24	Splenic Response Rate at Week 24	Total Symptom Score (TSS) Response Rate at Week 24
UK participants?	Yes	Yes	Yes
Used in model?	Yes	Yes	No

Study design

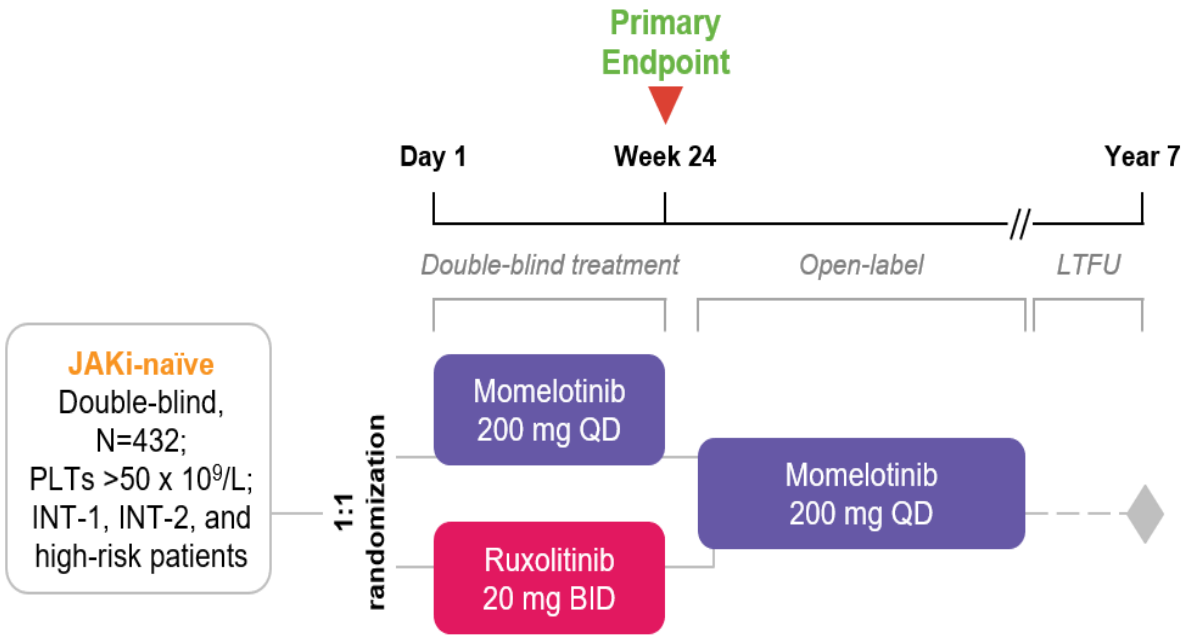


Figure Study design of SIMPLIFY-1

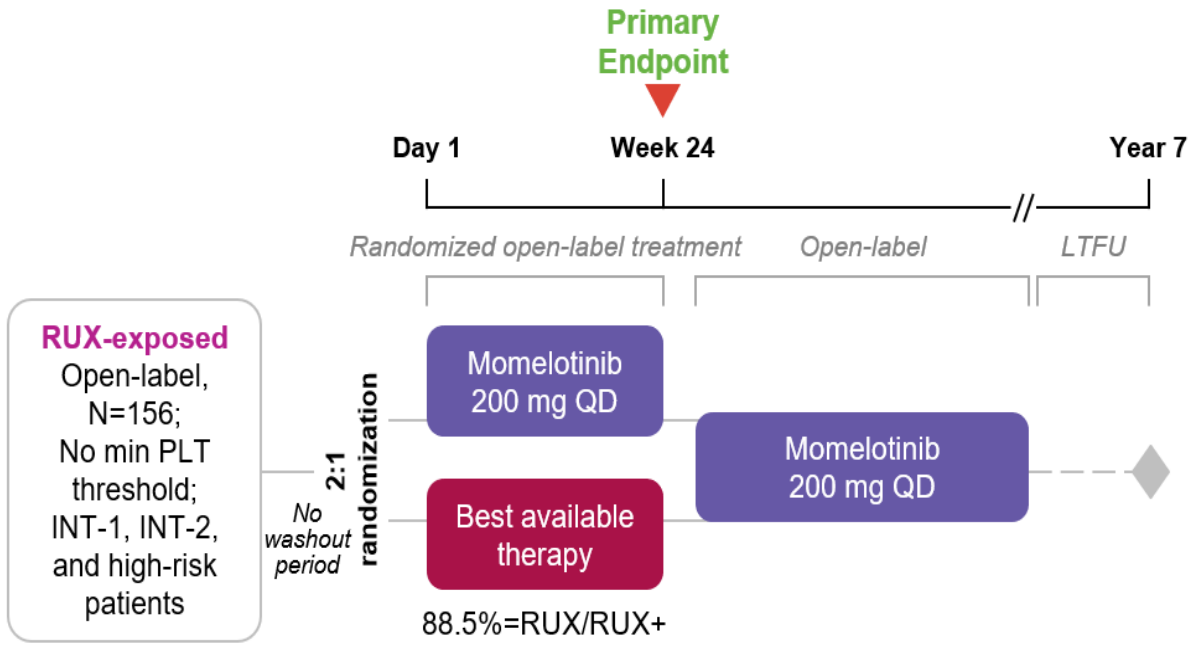


Figure Study design of SIMPLIFY-2

Primary analysis

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Trial	SIMPLIFY-1 (ITT)			SIMPLIFY-2 (ITT)			MOMENTUM (ITT)		
	MMB	RUX	Proportion difference (95% CI)	MMB	BAT	Proportion difference (95% CI)	MMB	Danazol	Treatment difference (95% CI)
Primary efficacy endpoints									
Spleen response rate	[redacted]	[redacted]	[redacted]	6.7%	5.8%	0.01 (-0.09, 0.10); p=0.90	-	-	-
MF-SAF TSS response rate	-	-	-	-	-	-	Coprimary endpoint: 24.6%	Coprimary endpoint: 9.2%	Coprimary endpoint: [redacted] p=0.0095

Adverse events – full momelotinib population

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

Pooled from SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM

Adverse events comparison

Table SIMPLIFY-1 safety profile week 0-24

	MMB (n=214)	RUX (n=216)
Any TEAE, n (%)	198 (92.5)	206 (95.4)
Grade ≥3 TEAEs, n (%)	[redacted]	94 (43.5)
Drug-related TEAEs, n (%)	[redacted]	[redacted]
Serious TEAEs, n (%)	49 (22.9)	39 (18.1)
Drug-related SAEs, n (%)	[redacted]	[redacted]
TEAE leading to premature discontinuation of study drug, n (%)	[redacted]	12 (5.6)
TEAE leading to dose reduction or temporary interruption of study drug, n (%)	[redacted]	79 (36.6)
AEs leading to deaths, n (%)	7 (3.3)	7 (3.2)
Grade 3 or 4 TEAE (≥5% patients)	[redacted]	94 (43.5)
Thrombocytopenia	15 (7.0)	10 (4.6)
Anaemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Table SIMPLIFY-2 safety profile week 0-24

	MMB (n=104)	BAT (n=52)
Any TEAE, n (%)	[redacted]	[redacted]
Grade ≥3 TEAEs, n (%)	[redacted]	[redacted]
Drug-related AEs, n (%)	[redacted]	[redacted]
Serious TEAE, n (%)	[redacted]	[redacted]
Drug-related SAEs, n (%)	[redacted]	[redacted]
TEAE leading to premature discontinuation of study drug, n (%)	[redacted]	[redacted]
TEAE leading to dose reduction or temporary interruption of study drug, n (%)	[redacted]	[redacted]
AEs leading to deaths, n (%)	[redacted]	[redacted]
Grade 3 or 4 TEAEs	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]

Clinical trial results – time to treatment discontinuation

Figure SIMPLIFY-1 – time to treatment discontinuation - Int2-HR **Hb<12 g/dL** population

Figure SIMPLIFY-2 – time to treatment discontinuation - Int2-HR **Hb<12 g/dL** population

EAG comments

- SIMPLIFY-1 - momelotinib discontinuation rate was likely higher than for ruxolitinib due to lower number of permitted dose reductions for patients having momelotinib (3 vs. 5).
- The rate of TEAEs leading to a dose reduction were [redacted]% (momelotinib) and 36.6% (ruxolitinib). The rate of TEAEs leading to discontinuation were [redacted]% (momelotinib) and 5.6% (ruxolitinib)
- SIMPLIFY-2 - TTD was likely more similar because BAT patients were at lower starting doses of ruxolitinib, so number of dose reductions for momelotinib and ruxolitinib were likely more similar

Company scenario results

Table Company scenario results

#	Base-case input	Scenario analysis description	Technology	Total Costs	Incremental costs
1	Ten-year time horizon with equivalent TTD	Three-year time horizon with no TTD	Ruxolitinib	£116,771	-
			Momelotinib	[redacted]	[redacted]
2	RBC transfusion cost source: Varney and Guest, 2003; TA756	Agrawal et al. 2006	Ruxolitinib	£335,675	-
			Momelotinib	[redacted]	[redacted]
3	Inclusion of ICT costs	Removal of ICT costs	Ruxolitinib	£320,864	-
			Momelotinib	[redacted]	[redacted]
4	ICT dose: 21 mg/kg	ICT dose: 14 mg/kg	Ruxolitinib	£324,302	-
			Momelotinib	[redacted]	[redacted]
5	TTD and RBC transfusion rates from S1 ITT population	TTD and unadjusted RBC transfusion rates from Hb<12 population	Ruxolitinib	£325,735	-
			Momelotinib	[redacted]	[redacted]
6	Equivalent TTD rates between momelotinib and ruxolitinib	Ruxolitinib d/c: constant extrapolation of S1 ruxolitinib d/c	Ruxolitinib	£334,519	-
			Momelotinib	[redacted]	[redacted]
7	RBC transfusion rate ratio: [redacted]	RBC transfusion rate ratio: [redacted]	Ruxolitinib	£326,021	-
			Momelotinib	[redacted]	[redacted]
8	Momelotinib subsequent treatment costs include ruxolitinib	Momelotinib subsequent treatment costs do not include ruxolitinib	Ruxolitinib	£326,021	-
			Momelotinib	[redacted]	[redacted]

Company scenario results

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JAKi-experienced population

Table Company scenario results

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case	[redacted]	0.346	Dominant
5-year time horizon	[redacted]	0.179	Dominant
10-year time horizon	[redacted]	0.266	Dominant
Discount rate (cost and health outcomes) of 1.5%	[redacted]	0.396	Dominant
TP extrapolation: Average of cycle 4-6 probabilities	[redacted]	0.342	Dominant
TP extrapolation: Assume no movement between health states after 24 weeks	[redacted]	0.429	Dominant
TP extrapolation: Cap probability of improvement in transfusion status by probability of worsening transfusion status	[redacted]	0.350	Dominant
TP extrapolation: Treatment specific transition probabilities	[redacted]	0.308	Dominant
TI OS: log-logistic	[redacted]	0.307	Dominant
Non-TI OS: Weibull	[redacted]	0.363	Dominant
Momelotinib TTDD: exponential	[redacted]	0.346	Dominant
Apply KOL RBC transfusion unit data	[redacted]	0.346	Dominant
Momelotinib subsequent treatment: 39% receiving ruxolitinib	[redacted]	0.346	Dominant
Exclude terminal care costs	[redacted]	0.346	Dominant
Treatment specific HSUVs	[redacted]	0.407	Dominant
Scenario 15 + Assume patients have BAT utility upon discontinuation of momelotinib	[redacted]	0.359	Dominant
Higher anaemia AE cost	[redacted]	0.346	Dominant
Alternative RBC transfusion unit costs (Agrawal 2006)	[redacted]	0.346	Dominant
Exclude ICT costs	[redacted]	0.346	Dominant
Higher anaemia AE cost	[redacted]	0.346	Dominant

JAKi-naive population cost-comparison results - list price

Table Company's base case results – **ITT population**

	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]
Incr. momelotinib cost	Decrease	Equal	Decrease	Decrease	Decrease	Decrease

Table EAG corrected base case results: Int-2/HR **Hb<12g/dL** subgroup

	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]
Incr. momelotinib cost	Decrease	Equal	Decrease	Decrease	Decrease	Decrease

Table EAG corrected base case results: Int-2/HR **Hb<10g/dL** subgroup

	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]
Incr. momelotinib cost	Decrease	Equal	Decrease	Decrease	Decrease	Decrease

EAG corrected company results - JAKi experienced - list price

Table Company's **deterministic** results – Int-2/HR **Hb<12g/dL** population

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
BAT	[redacted]	1.907	-	-	-
Momelotinib	[redacted]	2.053	[redacted]	0.146	Dominant

Table Company's **probabilistic** results – Int-2/HR **Hb<12g/dL** population

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
BAT	[redacted]	1.843	-	-	-
Momelotinib	[redacted]	2.037	[redacted]	0.195	Dominant

Table Company's **deterministic** results – Int-2/HR **Hb<10g/dL** population

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
BAT	[redacted]	1.719	-	-	-
Momelotinib	[redacted]	1.773	[redacted]	0.054	Dominant

Table Company's **probabilistic** results – Int-2/HR **Hb<10g/dL** population

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
BAT	[redacted]	1.652	-	-	-
Momelotinib	[redacted]	1.749	[redacted]	0.097	Dominant

EAG's preferred assumptions and base case – JAKi experienced – list price

Table EAG preferred assumptions and base case - Int-2/HR **Hb<12g/dL** population

Analysis	Momelotinib		BAT		Incremental		ICER per QALY gained
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
EAG corrected company base case	[redacted]	2.053	[redacted]	1.907	[redacted]	0.146	Momelotinib dominates
R1) No difference in OS by transfusion status	[redacted]	2.036	[redacted]	1.971	[redacted]	0.066	Momelotinib dominates
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
EAG preferred base case (R1+R2)	[redacted]	2.036	[redacted]	1.971	[redacted]	0.066	Momelotinib dominates

Abbreviations: BAT, best available therapy; Hb, haemoglobin; HR, high risk; Int-2, intermediate-2 (risk); OS, overall survival

EAG's preferred assumptions and base case – JAKi experienced population

Table EAG preferred assumptions and base case - Int-2/HR **Hb<10g/dL** population

Analysis	Momelotinib		BAT		Incremental		ICER per QALY gained
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
EAG corrected company base case	[redacted]	1.773	[redacted]	1.719	[redacted]	0.054	Momelotinib dominates
R1) No difference in OS by transfusion status	[redacted]	1.830	[redacted]	1.783	[redacted]	0.047	Momelotinib dominates
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
EAG preferred base case (R1+R2)	[redacted]	1.830	[redacted]	1.783	[redacted]	0.047	Momelotinib dominates

Abbreviations: BAT, best available therapy; Hb, haemoglobin; HR, high risk; Int-2, intermediate-2 (risk); OS, overall survival