NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) [ID831]

Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

This premeeting briefing presents:

the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and

- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Ruxolitinib has a marketing authorisation for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF) and post essential thrombocythaemia myelofibrosis (PET-MF)'. However, the clinical effectiveness evidence is primarily from 2 RCTs (COMFORT-I and COMFORT-II), which included patients with intermediate-2 or high risk myelofibrosis and a platelet count of at least $100x10^9$/L, which is a subset of the licensed population. This is the evidence used to construct and populate the economic model. While the company also presented supporting evidence

from 4 non-RCT studies of ruxolitinib in patients with intermediate-1 risk myelofibrosis or a low platelet count, overall the submission addresses mainly the inter-mediate-2/high risk subgroup. How generalisable are the clinical effectiveness results to the UK population covered by the marketing authorisation?

- The COMFORT-II trial compared ruxolitinib with 'best available treatment' (BAT), which included a basket of therapies. The ERG heard from its clinical adviser that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is rarely used in UK practice. The ERG was of the opinion that the basket of therapies should have included allogeneic stem cell transplantation (allo-HSCT), although not suitable for all patients with myelofibrosis, it is the only curative therapy available for myelofibrosis and has been observed to result in significant survival benefit over other myelofibrosis therapies (excluding ruxolitinib). To what extent does the BAT basket of therapies reflect clinical practice in England?

Cost effectiveness

- The economic model assumed patients will continue to receive treatment if they meet response criteria at 24 weeks. Both the company and the ERG stated that the definition of response may be too strict and that in clinical practice, patients are likely to continue treatment if they show a more modest response to treatment. How plausible are the definitions of response used in the economic model?

- The economic model was primarily based on data from the COMFORT-II trial. However, this trial did not collect data on symptom response. This means that no data are available to model overall survival and discontinuation rates amongst symptom responders. The model therefore assumed that overall survival and discontinuation rates for symptom responders were the same as for spleen responders. This was justified by using data from the COMFORT-I trial. Is this assumption plausible?

- The ERG commented that the economic model does not allow for any drug wastage and considered this assumption optimistic as adverse events are often managed by dose reductions or interruptions. Analysis by the ERG showed this has some impact on the resulting ICER. Should the model allow for drug wastage?

End of life

- Does ruxolitinib meet NICE's 'end-of-life' criteria?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of ruxolitinib within its marketing authorisation for treating myelofibrosis.

Table 1: Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with disease-related splenomegaly or symptoms of: • primary myelofibrosis (also known as chronic idiopathic myelofibrosis) • post polycythaemia vera myelofibrosis • post essential thrombocythaemia myelofibrosis	Adults with disease-related splenomegaly or symptoms of: • primary myelofibrosis (also known as chronic idiopathic myelofibrosis) • post polycythaemia vera myelofibrosis • post essential thrombocythaemia myelofibrosis	None	Trial evidence presented only relates to a subset of the whole population
Intervention	Ruxolitinib with established clinical practice	Ruxolitinib with established clinical practice	None	Starting doses used in the trials appropriate.
Comparator	Established clinical practice without ruxolitinib	Established clinical practice without ruxolitinib, that is, best available treatment	None	Allogeneic haemato-poietic stem cell transplantation (Allo-HSCT) which is potentially curative should have been included in the basket of therapies that made up 'best available treatment'.
Outcomes	• symptom	• symptom relief	Progression	Company's

	relief (including itch, pain and fatigue) • overall survival • progression-free survival • changes in spleen size • adverse effects of treatment • health-related quality of life	(including itch, pain and fatigue) • overall survival • changes in spleen size • adverse effects of treatment • health-related quality of life	free survival (PFS) has not been included as an outcome because it is not a measure that is generally applied in myelo-fibrosis. There is no accepted definition of progression and therefore there is no accepted definition of PFS	justification for not including PFS is reasonable.

2 The technology and the treatment pathway

The technology

2.1 Ruxolitinib (Jakavi, Novartis) is a protein kinase inhibitor that targets Janus-associated kinase (JAK) signalling. Ruxolitinib received a marketing authorisation in the UK in August 2012.

Table 2: The technology

Marketing authorisation	Ruxolitinib is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.
Administration method	Orally administrated The recommended starting dose for continuous treatment (based on platelet count) is: 20 mg bid (patients with platelet count of > 200,000/mm^3) 15 mg bid (patients with platelet count of 100,000 to 200,000/mm^3) 5 mg bid and cautious titration (patients with platelet count of 50,000/mm^3 and < 100,000/mm^3) Doses may be titrated based on safety and efficacy.

Cost	List price (excluding VAT, British national formulary' [BNF] September 2014-March 2015): 5 mg × 56 tablets: £1,680 10 mg × 56 tablets: £3,360 15 mg × 56 tablets: £3,360 20 mg × 56 tablets: £3,360 The company has agreed a confidential patient access scheme with the Department of Health. The scheme is a fixed price simple discount scheme. [redacted].
Bid: twice daily	

See summary of product characteristics for details on adverse reactions and contraindications.

Treatment pathway

2.2 To guide treatment, myelofibrosis is classified into low, intermediate and high risk categories based on various prognostic factors such as age, presence of constitutional symptoms, haemoglobin level, white blood cell count, platelet count, circulating blast cells, transfusion dependence, and presence of unfavourable karyotype.

2.3 Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, however, it is only suitable for people who are fit enough to undergo treatment. For people who are not fit enough to undergo allogeneic stem cell transplant, treatment options aim to relieve symptoms and improve quality of life.

2.4 The British Committee for Standards in Haematology (BCSH, 2012) guideline 'for the diagnosis and management of myelofibrosis' recommends ruxolitinib as first line therapy for symptomatic splenomegaly and/or myelofibrosis-related symptoms. The guideline also gives guidance on modifying the dose of ruxolitinib and deciding if treatment should be discontinued. The guideline recommends that where the response is inadequate the dose should be modified to the maximum tolerated dose and that treatment should be continued for 24 weeks. The decision to stop ruxolitinib therapy should be dependent on a combination of different factors including the beneficial effect of

treatment on splenomegaly and/or symptoms and presence or absence of toxicity.

2.5 The BCSH guideline recommends the following for alternative medical treatments:

- Hydroxycarbamide for patients with symptomatic splenomegaly in the absence of cytopenias;
- Thalidomide plus prednisolone, or lenalidomide (for patients with anaemia and platelets over 100 $x10^9$/L), as an alternative to hydroxycarbamide for patients with symptomatic splenomegaly and cytopenias.
- Recombinant erythropoietin and androgens, particularly danazol, as therapeutic treatment of anaemia.

2.6 NICE Technology appraisal guidance 289 'Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis' (June 2013) does not recommend ruxolitinib for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

2.7 Ruxolitinib is currently available through the Cancer Drug Fund, as a first or second line treatment for symptomatic splenomegaly in people with intermediate or high risk primary myelofibrosis, post polycythaemia myelofibrosis, and post essential thrombocytosis myelofibrosis when stem cell transplantation is not suitable.

2.8 This appraisal is a review of NICE Technology appraisal guidance 289. In September 2014, NICE's Guidance Executive agreed that a review of the guidance should be undertaken because updated data on longer term survival had become available. It was believed that this data would address the key uncertainties surrounding the progression of

myelofibrosis with and without ruxolitinib and the effect of the drug on survival. In addition, it would also support changes to the economic model.

3 Comments from consultees

3.1 The professional group stated that there are few treatment options for patients with symptomatic myelofibrosis. The clinical expert stated that some patients are offered allogeneic bone marrow transplant, but this treatment is associated with significant procedure related morbidity and mortality and would only be offered to patients who were less than 65 years of age and who had intermediate-high and high risk disease. The clinical expert stated that other treatment options include hydroxyurea, interferons and immunomodulatory imide drugs such as thalidomide.

3.2 The patient group explained that there is an unmet need for treatment which prolong life and improve the management of the symptoms of myelofibrosis. The patient expert also explained that there is a need for treatments which offer patients the possibility of maintaining independence and help relieve psychological distress for patients and their families who would be comforted by knowing that should their disease progress, an effective treatment is available.

3.3 The clinical expert stated that the UK incidence rate of myelofibrosis is approximately 0.5 to 1 per 100,000 population per year. The clinical expert also noted that clinical gains associated with ruxolitinib in the clinical trials may be difficult to quantify in clinical practice, for example the clinical trials show that even a 10% reduction in spleen volume is hard to equate to a reduction in spleen length in clinical practice. The clinical expert stated that therefore decisions about whether treatment with ruxolitinib is successful and hence whether to continue treatment is likely to be made on an individual patient basis in clinical practice.

3.4 The professional and patient groups agreed there is a high level of clinical need for this treatment because there are currently no current treatments which prolong life and improve the management of the symptoms of mylofibrosis and therefore ruxolitinib represents and innovative treatment.

4 Clinical-effectiveness evidence

4.1 The company conducted a systematic literature review for clinical trials investigating ruxolitinib that included patients with primary myelofibrosis or post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. Two randomised controlled trials were identified that met the inclusion criteria: COMFORT-I and COMFORT-II. The company also included supportive evidence from 4 non-randomised controlled studies of ruxolitinib in patients with intermediate-1 risk myelofibrosis or a low platelet count (ROBUST, JUMP, Study 258, and EXPAND).

Overview of the randomised controlled trials

4.2 COMFORT-I is a multicentre (USA, Canada and Australia), phase III, randomised, double-blinded trial that compared ruxolitinib (15 mg or 20 mg twice daily, n=155) with placebo (n=154) in people with primary myelofibrosis (45.2% of ruxolitinib group; 54.5% of placebo group), or myelofibrosis secondary to polycythaemia vera (32.3% of ruxolitinib treatment arm; 30.5% of placebo treatment arm) or essential thrombocytopenia (22.6% of ruxolitinib group; 14.3% of placebo group). Patients who enrolled on the trial, had resistant or refractory myelofibrosis, or available therapy was contraindicated or not tolerated. All patients on the trial had intermediate-2 risk or high-risk myelofibrosis, a platelet count of at least $100x10^9$/L and a palpable spleen length of at least 5 cm. The duration of the study was 24 weeks, after which patients could enter an open-label extension phase. In COMFORT-I, patients were eligible to crossover to ruxolitinib treatment. Before week 24, patients on placebo were required to have

symptom worsening and ≥ 25% spleen volume increase from baseline. After week 24, patients were required to have ≥ 25% spleen volume increase from baseline.

4.3 COMFORT-II is a multicentre (Europe, including sites in the UK), phase III, randomised, open-label trial that compared ruxolitinib (15 mg or 20 mg twice daily, n=146) with best available therapy (n=73) in people with primary myelofibrosis (53% of ruxolitinib group, 53% of the best available therapy [BAT] group), or myelofibrosis secondary to polycythaemia vera (33% of ruxolitinib group; 27% of BAT group) or essential thrombocythaemia (14% of ruxolitinib group; 19% of BAT group). BAT comprised a range of treatments. The most frequently used were hydoxycaramide, prednisolone and epoetin alfa. Other treatment used as BAT included lenalidomide and thalidomide. All patients on the trial had intermediate-2 risk or high-risk myelofibrosis, a platelet count of at least $100x10^9$/L and a palpable spleen length of at least 5 cm. The company stated that the trial population may be heathier than the general population with myelofibrosis because of the exclusion criteria of the trial which included uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. The duration of the trial was 48 weeks, after which patients could enter an open-label extension phase. In COMFORT-II, patients were eligible to crossover to ruxolitinib treatment. Patients on BAT whose disease progressed (defined according to the study protocol as either 25% or greater increase in spleen volume from on-study nadir, including baseline, or a splenectomy) could crossover to receive ruxolitinib at any time.

4.4 The primary outcome for both COMFORT-I and COMFORT-II was the proportion of patients achieving a spleen volume reduction of 35% or more from baseline, assessed by magnetic resonance imaging (MRI) or computed tomography (CT) scan. The measure for the primary efficacy outcome was taken at 24 weeks in COMFORT-I and at 48 weeks in COMFORT-II.

4.5 Secondary outcomes for the COMFORT-I trial included maintenance of reduction in spleen reduction, reduction in palpable spleen length, change in total symptom score ([TSS] measured using the modified myelofibrosis symptom assessment form [MF-SAF] v2.0 diary), overall survival and health-related quality-of-life measures. Secondary outcomes for the COMFORT-II trial included those in the COMFORT-I trial, as well as the time to achieve a spleen volume reduction of 35% or more, progression-free survival, leukaemia-free survival and transfusion dependency. In COMFORT- II additional overall survival analyses were carried out at 3.5 years follow up.

4.6 Patients were analysed on an intention-to-treat (ITT) basis for all efficacy endpoints. Patients who discontinued treatment or crossed over before 24 weeks (in COMFORT-I) or did not have a 48-week assessment of spleen volume (in COMFORT-II because of discontinuation and entering the open-label extension phase) were counted as non-responders (for change in spleen volume and symptom score.

ERG comments

4.7 The ERG was satisfied that all relevant studies had been included in the company's submission. The ERG stated that the COMFORT trials were of good quality and appropriate for addressing the decision problem.

4.8 The ERG commented that the COMFORT trials were conducted only in patients with splenomegaly and intermediate-2 or high-risk myelofibrosis, who had a platelet count ≥ 100 x 10^9/L and an absolute neutrophil count >1 x 10^9/L. In addition, patients suitable for allogeneic haematopoietic stem cell transplantation (allo-HSCT) at the time of study enrolment were excluded from the trials. Therefore the population represented in the trials were narrower than that covered by the marketing authorisation.

4.9 The COMFORT-II trial compared ruxolitinib with BAT, including observation alone (33% patients), hydroxycarbamide (47% patients), glucocorticoids (16% patients), epoetin-alpha (7% patients), immunomodulators (thalidomide and lenalidomide, 7% patients), purine analogs (6% patients), androgens (4% patients), interferons (4% patients), nitrogen mustard analogues (3% patients) and pyrimidine analogues (3% patients). The ERG considered the comparators to be generally appropriate, although the clinical adviser to the ERG stated that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and that lenalidomide is rarely used in UK practice.

4.10 The COMFORT-I trial compared ruxolitinib with placebo. The ERG highlighted that as patients in the trial were refractory to, or were not considered candidates for available therapies or had side effects requiring their discontinuation, and were not candidates for allo-HSCT, there were no alternative therapies for these patients; therefore the comparator in this trial could be interpreted as a form of BAT for this population.

Randomised controlled trials results

Spleen volume

Table 3: Summary of spleen volume results – COMFORT- I and II trials (from table 4 on page 35 of the ERG report])

Outcome	COMFORT-II	COMFORT-I (n=309)
	Ruxolitinib vs. Best available therapy	**Ruxolitinib vs. placebo**
Spleen volume		
Patients achieving ≥ 35% spleen volume reduction		
at week 12	29.5% vs. 1.4% (n=144/146 ruxolitinib, n=72/73 BAT)	39.4% vs. 0% (n=155/155 ruxolitinib, n=153/154 placebo)
at week 24	32% vs. 0%, p < 0.001 (n=144/146 ruxolitinib, n=72/73 BAT)	41.9% vs. 0.7% (p < 0.001) (n=155/155 ruxolitinib, n=153/154 placebo)
at week 48	28% vs.0%, p < 0.001 (n=144/146 ruxolitinib, n=72/73 BAT)	−
Mean change in spleen volume		
at week 24	−29.2% vs.+2.7%, p < 0.001 (n=125/146 ruxolitinib, n=45/73 BAT)	−31.6% vs. +8.1% (n=139/155 ruxolitinib, n=106/154 placebo)
at week 48	−30.1% vs.+7.3%,p < 0.001 (n= 98/146 ruxolitinib, n=34/73 BAT)	−
at week 156	Approximately –35% in ruxolitinib responders (n=16)	−
BAT: Best available therapy		

Total symptom score (TSS)

4.11 Only the COMFORT-I trial assessed symptom reduction (see table 4). The company also undertook a post hoc exploratory analysis of data from COMFORT-1 to examine whether there was a correlation between improvements in TSS with ruxolitinib and improvements in

health-related quality-of-life. For further details see pages 91-92 of the company submission.

Table 4: Summary of total symptom score results – COMFORT- I trial (from table 4, page 35 of the ERG report)

Outcome	COMFORT-I (n=309)
	Ruxolitinib vs. placebo
Patients achieving ≥ 50% reduction in TSS at week 24	45.9% vs.5.3% p < 0.001
Mean change from baseline in TSS at week 24	46.1% vs.−41.8%, p < 0.001 Mean absolute change in symptom score: -8.6 vs 3.2
TSS: Total symptom score.	

4.12 While symptom reduction was not specifically assessed in the COMFORT-II trial, the company undertook a post hoc exploratory analysis of health-related quality-of-life and symptom analyses on the primary analysis data set (at 48 weeks) from COMFORT-II. Of the 9 symptom scores assessed by the EORTC QLQ-C30, 6 (appetite loss, dyspnoea, fatigue, insomnia, pain and diarrhoea) were improved with ruxolitinib compared with best available care. See Figure 26 on page 93 of the company submission for further details.

Health related quality of life

4.13 Health-related quality-of-life was assessed in the COMFORT trials using the Global Health Status (EORTC QLQ-C30) and FACT-Lyn questionnaires (see table 5).

Table 5: Summary of health-related quality of life results – COMFORT- I and II trials (from table 4, page 38 of the ERG report)

Outcome	COMFORT-II	COMFORT-I
Mean change from baseline in Global Health Status/QoL (EORTC QLQ-C30)	At week 48: +9.1 vs +3.4 (n= 66/146 ruxolitinib, n=27/73 BAT)	At week 24: +12.3 vs −3.4, p < 0.001 (n=136/155 ruxolitinib, n=104/154 placebo)
Mean change from baseline in FACT-Lym total score at week 48	At week 48: + 11.3 vs −0.9 (n= 70/146 ruxolitinib, n=29/73 BAT)	−
BAT: best available therapy		

Overall survival

4.14 Overall survival was a secondary endpoint in both COMFORT trials and neither trial was designed to be sufficiently powered to detect a statistically significant difference in overall survival between treatment groups.

4.15 In COMFORT-I, overall survival was statistically significantly improved with ruxolitinib over placebo at a median follow-up of 51 weeks; 91.6% versus 84.4% (hazard ratio [HR] 0.50, 95% confidence intervals [CI] 0.25 to 0.98) and 102 weeks (HR 0.58, 95% CI 0.36 to 0.95). At a median follow-up of 3 years, 42 patients in the ruxolitinib group and 54 patients in the placebo group had died and the difference in overall survival was no longer statistically significant (HR 0.69, 95% CI 0.46 to 1.03. As crossover was permitted during the treatment period of the study, the company provided an analysis which adjusted for crossover using the Rank Preserving Structural Failure Time (RPSFT) method. The HR was 0.36 for ruxolitinib compared with placebo (95% C.I 0.20 to 1.04).

4.16 In COMFORT-II, overall survival was not statistically significantly different between ruxolitinib and BAT at a median follow-up of 61 weeks, although it reached borderline statistical significance at a median of 112 weeks of follow-up; 86% versus 78% (HR 0.52, 95% CI

0.27 to 1.00). At median follow-up of 3 years, 20% (29 patients) in the ruxolitinib group and 30% (22 patients) in the BAT group had died and ruxolitinib was associated with a 52% reduction in the risk of death compared with BAT (HR 0.48, 95% CI 0.28 to 0.85). The probability of survival at 144 weeks was 81% in the ruxolitinib group and 61% in the BAT group.

4.17 The company provided the results of a further analysis performed at median follow-up of 3.5 years, which included additional survival information for 15 of 41 patients who were previously deemed lost to follow-up. At 3.5 years of follow-up, 27% (40 patients) in the ruxolitinib group and 40% (30 patients) in the BAT group had died. Ruxolitinib was associated with a 42% reduction in the risk of death compared with BAT (HR 0.58, 95% CI 0.36 to 0.93); median overall survival has not yet been reached. The probability of survival at 3.5 years was 71% in the ruxolitinib group and 54% in the BAT group (p=0.02).

4.18 As the majority of patients randomised to receive BAT crossed over to receive ruxolitinib (at a median of 66 weeks); the company was requested during the clarification stage to provide an overall survival analysis with adjustment for crossover using the rank-preserving structural failure time (RPSFT) for the COMFORT-II trial. Ruxolitinib was associated [redacted]

4.19 Because median overall survival was not reached in the ruxolitinib group it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT. The company included a summary of an indirect comparison made between the ruxolitinib treatment arm of COMFORT-II and the Dynamic International Prognostic Scoring System (DIPSS) cohort. The number of observed deaths in the two cohorts were 30 (30%) on ruxolitinib and 256 (86%) on conventional care, generating estimates of median survival of

5 years from diagnosis (95% CI: 2.9-7.8) on ruxolitinib compared with 3.5 years (95% CI: 3.0- 3.9) for the DIPSS cohort. For further details, see pages 48-49 of the ERG report.

ERG comments

4.20 The ERG noted that only the COMFORT-I trial assessed symptom reduction. The ERG judged the tool used to measure the ≥ 50% reduction in TSS was appropriate and that the TSS result was reliable.

4.21 The ERG noted that the *post hoc* analysis of the COMFORT-II trial data had shown that ruxolitinib was associated with clinically meaningful improvements in myelofibrosis symptoms but the number of patients included in this analysis was not reported and therefore the completeness of the data is unknown. The ERG also noted that no data were reported for diarrhoea or the 3 symptoms which were not improved with ruxolitinib.

4.22 The ERG commented that there were many patients missing from the analysis of health related quality of life in the COMFORT- II trial (66/146 for ruxolitinib and 27/73 for BAT) and the number of patients included in the 144 week analysis of health-related quality-of-life in COMFORT-I was not reported. Therefore these results should be interpreted with caution.

4.23 The ERG stated that overall survival was a secondary endpoint in both the COMFORT trials and that neither trial had sufficient power to detect a statistically significant difference in overall survival between treatments. The ERG noted that all methods to adjust for crossover have limitations, but the methods used by the company were appropriate.

Meta-analyses/indirect comparison/MTC

4.24 The company carried out a pooled analysis using the results of the COMFORT-I and II trials. The company stated that a meta-analysis could not be undertaken because the trials were considerably different

in terms of patient populations, treatment received and study duration. The data from the 2 trials were analysed as a single dataset and the analysis included a correction for crossover. A statistically significant overall survival gain in favour of ruxolitinib was identified (HR =0.29, 95% C.I 0.13 to 1.15). A multivariate cox regression model was used to identify factors which influenced overall survival. The analyses found increased baseline spleen size and greater spleen reduction in response to treatment were associated with greater overall survival.

ERG comments

4.25 The ERG noted the company's statement that there were considerable differences between the trials regarding the patient population, treatments, and trial durations. The ERG commented that if the data from the 2 trials were analysed as a single dataset, then randomisation would have been broken and the study should be considered as a comparative observational study. The ERG concluded that given the lack of information about the methodology and statistical methods used for this analysis in the company submission, the results should be interpreted with caution.

Adverse effects of treatment

4.26 Adverse events data were collected in COMFORT-I at 28 weeks and at 48 weeks in COMFORT-II. In COMFORT-II, the most common adverse event was diarrhoea, and it was more frequently reported with ruxolitinib compared with BAT (23% vs.12%). There were a greater number of grade 3-4 adverse events with ruxolitinib compared with BAT (42% vs.25%). In the ruxolitinib group 12 people (8%) and 4 people (5.5%) in the BAT group discontinued treatment because of adverse events.

ERG comments

4.27 The ERG noted that the reported adverse event data from the COMFORT trials did not include people who had dropped out of the trials because of adverse events. Although adverse event data was

only collected at 48 weeks in COMFORT-II, the ERG noted that at the end of the 3.5 years follow-up period, 60% of patients treated with ruxolitinib had discontinued treatment and of these 20% did so as a result of adverse events.

Summary of the non-randomised controlled trials

ROBUST

4.28 The ROBUST study was a phase II study which was undertaken in the UK (n = 48). In addition to involving patients with intermediate-2 and high-risk disease, ROBUST also included patients with intermediate-1 risk disease. At week 48, 40% of patients achieved reduction in spleen length of at least 50% and 21% achieved a reduction in TSS of at least 50% (as assessed using the Myelofibrosis Symptom Assessment Form, MF-SAF). Treatment success, defined as a 50% or greater decrease in spleen length and/or TSS at week 48, was achieved by 50.0% of the overall population and 57.1%, 38.5% and 52.4% of the intermediate-1 risk, intermediate-2 risk and high-risk disease groups, respectively. Consistent with findings from the COMFORT trials, the most common haematological adverse events were anaemia (45.8% of patients) and thrombocytopenia (37.5%). The most common non-haematological adverse events were abdominal pain (27.1%), epistaxis (27.1%), diarrhoea (25.0%), confusion (22.9%), fatigue (22.9%), headache (22.9%) and lethargy (20.8%), and were primarily grade 1/ 2.

JUMP

4.29 The phase III expanded-access, JAK inhibitor rUxolitinib in MF Patients (JUMP) trial was also designed to assess the safety and efficacy of ruxolitinib in patients with high-risk, intermediate-2 risk or intermediate-1 risk disease. As of September 2014, 2138 patients had been enrolled in 25 countries and data had been reported for an analysis of 1144 patients who had received ruxolitinib for a median of 11.1 months. At week 48, 61% of patients achieved at least a 50% reduction from baseline in palpable spleen length. Clinically meaningful improvements

in symptoms were seen as early as week 4 and were maintained during the study. Ruxolitinib was generally well tolerated, with 14% of patients discontinuing treatment as a result of adverse events. The most common grade 3 or 4 haematological adverse events were anaemia (33.0%), thrombocytopenia (12.5%) and neutropenia (3.9%); each of these rarely led to discontinuation of ruxolitinib. The incidences of grade 3 or 4 non-haematological adverse events were low, with pneumonia being the only event reported in over 2% of patients (3.6%).

4.30 The JUMP study included patients with low platelet counts (at least 50 to under 100 x 10^9/L). In this patient population, ruxolitinib was initiated at a dose of 5 mg twice daily and could be increased to 10 mg twice daily at week 4 in patients with inadequate efficacy if platelet counts were at least 50 x 10^9/L and there had been no treatment-related toxicities that resulted in dose reduction, interruption, or discontinuation during treatment at the 5 mg twice daily dose. Results for an interim analysis for 6 months of therapy in the first 50 patients with low platelet counts have been reported. At this time point, 82% of patients (31 of 38 patients starting therapy on 5 mg twice daily) remained on the 5 mg twice daily dose and 18% had undergone dose escalation to 10 mg twice daily. At week 24, 38.2% (13 of 34 evaluable patients) achieved a reduction of at least 50% from baseline in palpable spleen length; overall, 44.7% of patients (21/47) achieved at least a 50% reduction from baseline in spleen length at any time. Clinically meaningful improvements in symptoms, as assessed using the FACT-Lym total score, were seen as early as week 4 (mean change from baseline, 8.2) and were durable through week 12 (change from baseline, 9.6). The reduction in splenomegaly and improvements in symptoms observed in this subgroup of patients are however inferior to those achieved for the overall JUMP population.

4.31 Overall, the adverse effect profile was consistent with previous studies in patients with platelet counts under 100 x10^9/L. The most common grade 3 or 4 haematological adverse events were thrombocytopenia

(30%) and anaemia (28%): 3 patients (6%) discontinued owing to thrombocytopenia and 1 (2%) discontinued owing to anaemia. Grade 1/2 haemorrhages were reported in 4 (8%) patients and grade 3 or 4 haemorrhages in 2 (4%) patients. Rates of grade 3 or 4 non-haematological adverse events were low, with only the following occurring in more than one patient: pyrexia (6.0%); septic shock (4.0%); and arthralgia (4.0%). Nine patients (18%) discontinued therapy because of adverse events. The company commented that this analysis suggested that ruxolitinib doses of 5 to 10 mg twice daily were generally well tolerated and efficacious in patients with myelofibrosis who have platelet counts of at least 50 to under 10 x 10^9/L.

Study 258

4.32 Study 258 was a phase II dose-finding study investigated the efficacy and safety of ruxolitinib in patients with low platelet counts (50 to 100 x 10^9/L) when initiated at a dose of 5 mg twice daily with the option to increase to 10 mg twice daily if platelet counts remained adequate. An interim analysis of data from this study reported that by week 24, 62% of patients achieved stable doses of at least 10 mg twice daily. A median percentage reduction in spleen volume of 24.2% was achieved at 24 weeks and 20% of patients achieved a reduction in spleen volume of at least 35%. When evaluated by titrated dose (average dose over the last 4 weeks of the study, up to week 24), median percentage reductions from baseline in spleen volume at week 24 were 16.7% for patients who received 5 mg once or twice daily (n = 7) and 28.5% for patients who received 10 mg twice daily (n = 20). Decreases in TSS were also observed in patients who completed 24 weeks of therapy (n = 32). The median percentage reduction from baseline in TSS for those who completed 24 weeks of therapy was 43.8% and was 13.0% for patients receiving 5 mg once or twice daily (n = 8) and 63.5% for patients receiving 10 mg twice daily (n = 21). In the 3 patients who had their dose escalated to over 10 mg twice daily because of inadequate response, median percentage reduction from baseline in

TSS at week 24 was 33.8%. The study reported a mean change in EORTC QLQ-C30 GHS score from baseline of approximately 13 at week 24.

4.33 Thrombocytopenia was the most frequently reported grade 3 or 4 adverse events occurring in 56% of patients and grade 3 or 4 anaemia was reported in 42% of patients. Most other adverse events were grade 1 or 2 and no other grade 3 or 4 adverse events were reported in more than 2 (4%) patients. Non-haematological adverse events (any grade) reported in over 10% of patients were diarrhoea (28%), peripheral oedema (26%), nausea (24%), abdominal pain (24%) and fatigue (22%). Thrombocytopenia necessitating dose reductions and dose interruptions occurred in 12 (24%) and 8 (16%) patients, respectively, and occurred mainly in patients with baseline platelet counts of 75 x 10^9/L or less. Two patients discontinued as a result of adverse events: in 1 patient this was grade 4 thrombocytopenia. The company stated that the results of this study therefore indicated ruxolitinib, initiated at a dose of 5 mg twice daily, can benefit patients with low platelet counts.

EXPAND

4.34 EXPAND was an open-label, phase Ib, dose-finding study which investigated the optimum dose of ruxolitinib in patients with low baseline platelet counts. This on-going study investigates 15 mg twice daily in patients with platelet counts of 75 to 99 x 10^9/L and doses of up to 10 mg twice daily in patients with the lower platelet levels. Results for a preliminary analysis of data for 34 patients have shown that most (97%) patients achieved reductions in palpable spleen length and 50% of patients achieved a reduction in spleen length of at least 50% as their best response. Improvements in symptoms, as assessed using the MF-SAF TSS, were also observed; a reduction from baseline of at least 50% at any time in TSS was achieved by 43% (6/14) of patients with platelet counts of 75 to 99 x 10^9/L and 66.7% (8/12) of patients with platelet counts of 50 to 74 x 10^9/L. The reported adverse effects were consistent with the known safety profile of ruxolitinib.

5 Cost-effectiveness evidence

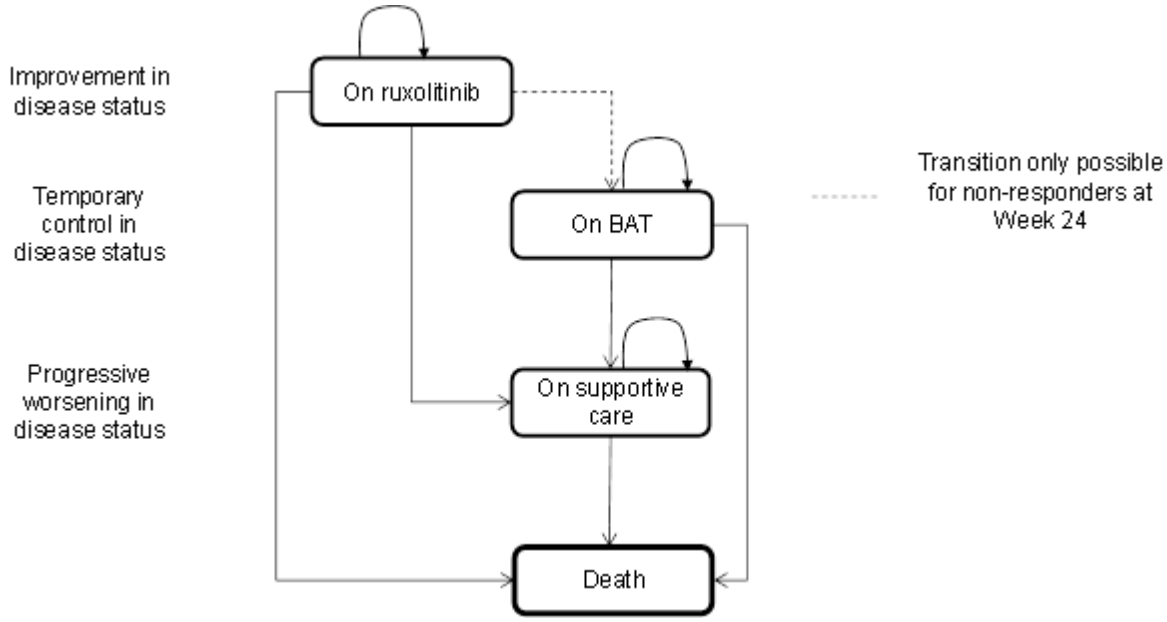
5.1 The company conducted a systematic literature review of existing cost effectiveness studies. Only a Canadian study which was not relevant to the UK and a UK study which was included in the submission during the development of NICE technology appraisal guidance 289.

Model structure

5.2 The company submitted an individual patient discrete event simulation model comparing ruxolitinib with best available care. The company considered this design to be more appropriate because it is more flexible and transparent compared with a Markov cohort approach, which would require the use of tunnel states and lead to the model being convoluted. The model had a lifetime horizon of 35 years. Although the model did not use time cycles, it effectively had a cycle length of 1 week as this was the shortest unit of time in the model. The company based the analysis from an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%.

5.3 There were 4 heath states in the model: on ruxolitinib; on BAT; on supportive care or death (see figure 1).

Figure 1: Model Structure



5.4 Hypothetical patients in the BAT group were assumed to begin in the BAT health state. In this health state, patients received a basket of treatments that constitute BAT which reflects the treatment received by patients in the control group of the COMFORT-II trial. Patients on BAT were assumed to achieve some control of symptoms but not splenomegaly. Patients could continue to receive BAT until death or they could stop receiving BAT (after exhaustion of possible options) and progress to the supportive care health state. In this health state patients experienced a gradual worsening of the disease (symptoms and haematological parameters) and health-related quality-of- life until death. No formal stopping rule was applied to patients receiving BAT and discontinuation was modelled on discontinuation observed during the COMFORT-II trial.

5.5 Hypothetical patients who entered the model on ruxolitinib were categorised into 4 groups based on their outcomes at 24 weeks in the COMFORT trials and patients considered as non-responders were subject to a stopping rule. This stopping rule was based on criteria set out in the International Working Group for Myelofibrosis Research and Treatment/ European LeukemiaNet (IWG-MRT/ELN) guidelines. This

stopping rule was not applied in the COMFORT-I or COMFORT-II trials. The 4 categories of response were as follows:

- Responders: which consisted of spleen responders who achieved a spleen response at week 24 (with or without a symptom response) and symptom responders, who achieved a symptom response at week 24 but who do not achieve the required level of spleen response. Responders continued treatment with ruxolitinib until either death or failure of treatment response. On failure of treatment, response patients moved to the supportive care health state, which implied gradually declining health-related quality-of-life until death.
- Non-responders: These patients were alive at the end of treatment, but failed to meet the criteria for spleen or symptom response at week 24. For these patients, treatment with ruxolitinib was discontinued and they moved into the BAT health state. They progressed through the model as for patients initiating on BAT.
- Early discontinuation group: These were patients who were alive at week 24 but who discontinued therapy before week 24. These were considered treatment failures and were assumed to move to the supportive care health state.
- Early death group: These were patients who died before the application of the week 24 stopping rule.

ERG comments

5.6 The ERG commented that the use of an individual patient discreet event simulation model can be considered novel because the majority of oncology models are cohort Markov structures. The ERG stated that the use of this type of modelling approach appears justified given the progressive nature of the disease and has the advantage of increased flexibility and is appropriate for the decision problem.

5.7 The ERG stated that the model design placed considerable demands on the data and small number of patients transition through the

different states of the model. The ERG stated that the model design required a number of assumptions to be made which were subject to a degree of uncertainty.

5.8 The economic model was considered by the ERG to meet the NICE reference case and was broadly in-line with the final scope issued by NICE.

Model details

5.9 Clinical effectiveness data used in the model was primarily obtained from the COMFORT-II trial, which enrolled intermediate-2 and high risk patients who were not refractory to other therapies. Additional data was used from the COMFORT -1 trial which enrolled intermediate-2 and high risk patients who were refractory to all other therapies.

Intervention and comparators

5.10 Ruxolitinib dosing was subject to dose-intensity adjustment and varied according to platelet count, patient's tolerance of therapy and efficacy. To reflect this, individual patient data from the COMFORT-II trial were used to estimate dose given. Based on this data, the dose of ruxolitinib used in the model varied between 5 mg to 25 mg twice daily or 5 mg and 35 mg once per day. For a small proportion of treatment days (1.38%) dose interruptions were also accounted for, that is 0 mg dose. The most common doses used in the model were 5 mg twice daily (14.50% of treatment days), 10 mg twice a day (25.93% of treatment days), 15 mg twice daily (20.14% of treatment days) and 20 mg twice daily (30.66% of treatment days).

5.11 The comparator in the model, BAT, consisted of a number of different treatments for myelofibrosis based on data from the COMFORT II trial. Dose intensity, duration, treatment or order of treatment were not recorded in the COMFORT-II trial. For the purpose of calculating cost of BAT a number of assumptions were made to account for this lack of data.

Response and stopping rule

5.12 Patients who received ruxolitinib were subject to a stopping rule at 24 weeks. The 24 week stopping rule and decision was based on the BCSH guideline that state that treatment should be discontinued after 6 months if there has been no reduction in splenomegaly or improvement in symptoms since initiation of therapy. The definition of response was based on the IWG-MRT/ELN guidelines, and defined in terms of either a spleen response or a symptom response. Patients were therefore considered responders if they met the following criteria:

- Spleen response: non-palpable spleen in a patient with splenomegaly at baseline that is palpable at 5-10 cm below the left costal margin (LCM), or spleen decreases by ≥50% in a patient with splenomegaly at baseline that is palpable at > 10 cm below the LCM, or
- Symptom response: a ≥ 50% reduction from baseline in the MF-SAF TSS.

The company noted that these response criteria were quite stringent and that in clinical practice achieving a smaller reduction in spleen size or smaller decrease in symptoms may be considered clinically meaningful and patients may continue to receive treatment. Therefore the company also presented a number of scenario analyses using alternative definitions of response.

5.13 Within the model, the proportions of patients gaining a spleen response, discontinuing ruxolitinib treatment, and experiencing early death were based on data from the COMFORT-II trial. However, the COMFORT-II trial did not record symptom response and therefore it was not possible to estimate the proportion of symptom responders from the COMFORT-II trial. The proportion of patients gaining a symptom response, but no spleen response was therefore based on data from the COMFORT-I trial. As there were no data to model overall survival and discontinuation rates in a response group that included both spleen and symptom responders, the company assumed that

overall survival and discontinuation rates were the same for both spleen and symptom responders.

Mortality

5.14 For patients starting on BAT, death could occur either while on BAT or after discontinuation of BAT when patients had moved to the supportive care state. The number of patients dying on BAT was based on data from the COMFORT-II trial and time to death for this group was based on time to discontinuation of therapy. This was justified by the company on the basis that 4/73 patients discontinued because of death. For patients starting on ruxolitinib therapy, all patients faced the same mortality risk in the first 24 weeks and a proportion of patients were assumed to die within this initial 24 week treatment phase. Both the rate and mean survival time were obtained from the COMFORT-II trial. After the initial treatment phase, treatment responders, non-responders and early discontinuers each faced different mortality rates. As with BAT, ruxolitinib treatment responders could die either while on treatment or post discontinuation. Data for both of these were obtained from the COMFORT-II trial. In the baseline model the mortality rate for ruxolitinib responders was assumed to be 0.0% i.e. no patients die while on ruxolitinib.

5.15 For patients discontinuing ruxolitinib (both during the initial 24 week period and for responders after this initial period), duration alive following discontinuation was modelled based on observed survival in the COMFORT-II trial. The same curve was used for both groups as the number of patients discontinuing early was very small (11 patients). The company presented scenario analyses in which separate survival curves were used for each group.

5.16 Non-responders to ruxolitinib were assumed to move to BAT after 24 weeks and mortality was modelled in the same way as patients starting on BAT except that patients who were non-responders to ruxolitinib were assumed to receive a mortality benefit of an additional

24 weeks of life. This was justified by the company on the basis of clinical opinion and no-empirical evidence was presented. The company presented a scenario analysis in which time on ruxolitinib was assumed to be part of the time patients would have been treated with BAT. Non-responders were therefore treated as far as possible as if they had never received ruxolitinib.

Discontinuation

5.17 For patients starting on ruxolitinib, the model used 2 alternative discontinuation rates, one for the initial 24 week treatment phase of the model, and one which was applied to spleen and symptom responders (who continue treatment) post 24 weeks. Both rates were obtained from the COMFORT-II trial. Patients discontinuing treatment early were assumed to receive treatment for a total of 14.083 weeks, based on the mean time on treatment for this group in the COMFORT-II trial. This parameter was not varied on the probabilistic sensitivity analysis. In the post 24 week the rate of discontinuation was based on analysis of time to discontinuation for spleen responders. A range of parametric survival models were considered to extrapolate beyond the observed data, and based on Akaike information criteria (AIC) and Bayesian information criterion (BIC), a Gompertz distribution was considered the most appropriate. Scenario analyses using the alternative distributions were also presented. A differential of discontinuation was not applied for spleen responders and symptom responders; this was justified on evidence from the COMFORT-I trial which demonstrated no statistically significant rate in the discontinuation rate for these two groups. The company did not present a scenario analysis exploring this assumption.

5.18 A single rate of discontinuation was used for patients on BAT based on data from the COMFORT-II trial as no stopping rule was applied to BAT. As with discontinuation from ruxolitinib, a number of parametric survival models were considered. The Gompertz distribution was found to be the most appropriate. The company also presented scenario analyses using alternative distributions. Reasons for discontinuing BAT

included: adverse events, withdrawal of consent, disease progression or other reasons (38.4% of patients); and cross-over to ruxolitinib (61.6% of patients).

Leukaemic transformation

5.19 Leukaemic transformation (LT) is a potential risk for patients with myelofibrosis and has significant impact on a patient's life expectancy, health-related quality-of-life, as well as having resource implications. The model included the possibility of LT by allowing this to occur as an "adverse event" with disutility and cost applied. The company justified not having LT as a separate health state on the grounds that the effectiveness data used in the model included the impact on life expectancy, and to do so would double count the impact of LT. The company used the same rate of LT from the COMFORT-II trial for patients in both the ruxolitinib and BAT groups.

Health related quality of life

5.20 The COMFORT-I and II trials did not include a generic measure of health-related quality of life (such as the EQ–5D). However the company explained that although it would have been possible to do so, it was not considered appropriate to use a mapping algorithm to develop health-related quality-of-life based on EQ-5D. Instead a condition-specific preference-based measure for myelofibrosis, the MF-8D, was developed using existing measures, the MF-SAF and EORTC QLQ-C30. The model used changes in health-related quality-of-life on a continuous scale according to different phases of the myelofibrosis disease state. Patients were assumed to experience constant benefits with ruxolitinib and BAT, but health-related quality-of-life was assumed to steadily decline in the supportive care health state.

Table 6: Summary of the utility values used in the company's cost effectiveness analysis (from table 37, page 186 of the company submission)

	Utility value: mean (standard error)	Standard error	Source
Baseline HRQoL			
Unadjusted baseline	[redacted]	[redacted]	COMFORT-I
Adjustment applied to baseline	0		
Change in HRQoL			
On BAT			
in patients treated with BAT	0		Assumption
On ruxolitinib			
change in HRQoL at week 4 in patients achieving a spleen (Group 1) and or symptom response (Group 2)	[redacted]	[redacted]	COMFORT-I
change in HRQoL at week 4 in patients achieving neither a spleen nor a symptom response (Group 3-5)	[redacted]	[redacted]	COMFORT-I
On supportive care			
every 24 weeks	[redacted]	[redacted]	COMFORT-I
Events (decrement in QALYs)			
AML	0.15		Assumption
BAT: best available therapy; HRQoL: health-related quality of life; QALY: quality adjusted life year; AML: acute myeloid leukaemia			

Resources and costs

5.21 The costs associated with management of the myelofibrosis were obtained from the Haematological Malignancies Research Network (HMRN) audit and the ROBUST study. The HMRN audit provided information on the number of hospital nights, outpatient visits and laboratory tests. ROBUST, provided data on resource use. Data from the JUMP study were used to represent the reduction in resource use associated with the use of ruxolitinib. These data were supplemented

by information from the COMFORT trials and assumptions when appropriate. For further details, see pages 202-207 of the ERG report.

Table 7: Cost of the technologies (from page 193 of the company submission)

Technology	Dosage	Total cost per day	Total cost per 1 week cycle
Ruxolitinib	25 mg per day (1x10 mg tablet and 1x15 mg tablet)	£113.33	£793.30
Best available therapy	N/A	£4.34	£30.37
Supportive care		£0.17	£1.18

Table 8: Cost estimates used in the company's economic model (from table 44, page 207 of the company submission)

Resource use	Unit cost	Source
Follow-up appointment at the haematology clinic	£92.00	NHS Reference cost HRG (WF01A); Service Code (303): Non-Admitted Face to Face Attendance, Follow-up – Non-consultant led
Hospital night	£170.82	PSSRU (2010) uplifted to 2014
GP visit	£46.00	PSSRU (2014)
Accident & Emergency visit	£162.17	PSSRU (2010) uplifted to 2014
Urgent care visit	£47.57	PSSRU (2010) uplifted to 2014
FBCs	£6.21	Private Patient Tariff 2008–2009192 at the Sheffield Teaching Hospital NHS Foundation Trust uplifted to 2014 based on the PSSRU inflation indices58
Full profile (U&E, LFT, Ca)	£16.93	Private Patient Tariff 2008–2009192 at the Sheffield Teaching Hospital NHS Foundation Trust uplifted to 2014 based on the PSSRU inflation indices58
RBC unit	£361.85	Varney (2003) uplifted to 2014
HRG: Healthcare Resource Group; NHS: National Health Service; Ca: calcium; FBC: full blood count; LFT: liver function test; NHS:National Health Service; PSSRU:Personal Social Services Research Unit; U&E: urea and electrolytes.		

5.22 The company explained that based on advice received from its clinical advisers it assumed that resource use increased in the 3-6 month period preceding death, because of an increased need for transfusions, thrombotic complications, pain control and other factors. This was not

included as a separate health state to limit the number of assumption required. Based on clinical advice, the company assumed that patients typically received 2 units of transfused blood every week. Patients were also assumed to visit their haematologist every week leading to a one-off cost of £14, 687 at the time of death. In addition to the cost associated with an increased requirement for transfusions, it was assumed that there was an additional cost associated with palliative care based on the community and inpatient hospital care cost for patients with cancer in the last 8 weeks of life. Patients were assumed to incur a one off cost of £6,016 at the time of death. These assumptions were varied in sensitivity analyses.

5.23 The cost estimates associated with the management of adverse events were taken from a range of sources. The annual costs associated with the management of grade 3 or 4 non-haematological adverse events were estimated to be £61.11 for patients receiving ruxolitinib and £46.75 for patients receiving BAT. Patients were assumed to experience no adverse events while receiving supportive care. For a summary of the costs for management of adverse events, see table 46, page 210 of the company submission.

ERG comments

5.24 The ERG noted that the population in the model pragmatically reflected the patients in COMFORT-II which represent a subset of the population specified in the marketing authorisation for ruxolitinib, that is Intermediate-2 and high risk patients. The ERG commented that the modelling presented therefore reflects the cost-effectiveness of ruxolitinib in this more restricted population.

5.25 The ERG had a number of concerns about the composition of BAT used in the model. The clinical adviser to the ERG indicated that lenalidomide is rarely used in the UK, and the HMRN audit appeared to confirm this. The ERG stated that it was also clear from the published literature that there are other treatments used in the UK which are not

included in the BAT basket. In particular, the BCSH guideline indicates that allo-HSCT is a potential therapy for myelofibrosis and is the only curative treatment for patients. The ERG was of the opinion that allo-HSCT should have been considered either within the BAT basket or as an alternative comparator as significant survival benefits have been observed using allo-HSCT. However, the ERG recognised that this treatment option would not be suitable for all patients and has a different treatment goal (curative as opposed to management of symptoms).

5.26 The ERG agreed with the company that in clinical practice a less stringent definition of response is likely to be used. The ERG commented that response to treatment in patients receiving ruxolitinib is often observed relatively quickly and therefore in clinical practice a stopping rule may be applied earlier than 24 weeks. The company was requested during the clarification stage for a 12 week stopping rule scenario to be added to the model. The company's response indicated that they did not consider this a plausible scenario and would be difficult to apply given the available data. The ERG stated that the impact of using a shorter initial treatment period would be to lower the estimated ICER.

5.27 The ERG had concerns about the use of data from COMFORT-I to obtain the proportion of patients gaining a symptom response, but no spleen response. The ERG stated that the use of this data may not be entirely appropriate and it added additional uncertainty regarding the effectiveness of ruxolitinib, as the patients enrolled in COMFORT-I differed significantly from those in COMFORT-II. Specifically, the COMFORT-I trial limited enrolment to patients who were refractory to all other therapies while COMFORT-II included patients who were or were not refractory to other therapies. The ERG also stated that this assumption also had a number of other implications for the model. Most importantly there was no data available to model overall survival and rates of discontinuation rates in a response group that included

both spleen and symptom responders. The ERG explained that this forces the company to assume that overall survival and discontinuation rates were the same for both spleen and symptom responders. The ERG acknowledged that empirical justification was presented in the company's submission and assumptions of equivalence can be considered reasonable. However, the equivalence of these rates was subject to uncertainty not accounted for in the probabilistic analysis. The ERG highlighted that this may have some impact on the estimated ICER as overall survival is a key driver of the model. The ERG also highlighted that a further consequence of sourcing data from a source other than the COMFORT-II trial was that the probabilistic sensitivity analysis failed to fully acknowledge that the distribution across the 5 groups (spleen responders, symptom responders, non-responders, those discontinuing treatment and patients experiencing early death) were correlated, as the proportion of patients experiencing a symptom response was sampled independently. Correlation, between the remaining 4 groups was accounted for in the probabilistic sensitivity analysis.

5.28 The ERG considered the company's assumption of 0% mortality with ruxolitinib treatment to be implausible. During the clarification stage the company was requested to consider adding a strictly positive mortality rate for this phase of the model. In its response, the company reiterated the justification stated in its submission that as all deaths in the ruxolitinib group occurred after discontinuation a zero rate of death was assumed. However, the company acknowledged that this assumption may be optimistic. As such the company provided additional scenario analyses assuming either the same probability of death on discontinuation used for the BAT group (5.48%) or assuming a probability equal to 10%.

5.29 The ERG had concerns regarding the scenario analysis presented by the company in which separate overall survival curves were used for patients discontinuing ruxolitinib during the initial 24 week period and

for responders after the initial period. The ERG highlighted that the survival data for early discontinuers was very skewed, with patients either surviving for a short period of time or a long period of time. As a result, mean post discontinuation survival time was longer for ruxolitinib patients discontinuing early than those discontinuing following the initial 24 week period. It was unclear to the ERG how clinically plausible this was, as it implied that increasing the rate of early discontinuation lowers the generated ICER, which appears counter intuitive.

5.30 The ERG considered the assumption of no drug wastage for ruxolitinib to not accurately reflect drug usage in clinical practice. The ERG had concern about drug wastage given that most adverse events are managed by dose reduction or interruption, leading to additional costs.

5.31 The ERG expressed concern about the use of data from COMFORT-II to estimate the costs associated with BAT. The ERG stated that its clinical adviser suggested that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is rarely used in UK practice.

5.32 The ERG had concerns about the assumptions made using the data from the ROBUST study to estimate resource use in myelofibrosis. Patients treated with BAT/supportive care were expected to experience more complications compared with patients treated with ruxolitinib and therefore were likely to utilise more healthcare resources. In the ROBUST study, patients were treated with ruxolitinib and the resource used might not reflect the resource used by patients on BAT therapy. The rate of resource use used in the model for the BAT group may therefore be underestimated, resulting in an overestimation of the ICER. The ERG was not able to conduct further analysis because of a lack of alternative data.

Cost effectiveness results

5.33 The company presented cost effectiveness results with and without the patient access scheme (PAS). Only the cost effectiveness results with the PAS are included in this document. For details of the cost effectiveness results without the PAS, see pages 223-258 of the company's submission.

Table 9: Deterministic base case results for ruxolitinib compared with best available therapy –with PAS (from table 2, page 10 of company's patient access scheme submission)

	Best available therapy	**Ruxolitinib**
Total costs (£)	36,271	149,114
Total LYG	2.15	5.96
Total QALYs	1.476	3.989
Incremental costs (£)	-	112,843
Incremental LYG	-	3.81
Incremental QALYs	-	2.51
ICER (£/QALY) with PAS		44,905
LYG: Life years gained; QALYS: quality adjusted life years; ICER: incremental cost-effectiveness ratio; PAS: Patient access scheme		

5.34 The probabilistic ICER was £44,625 per QALY gained. The probability of ruxolitinib being cost effective using a threshold of £30,000, £40,000, £50,000 and £60,000 per QALY was 0.33%, 4.32%, 95.02% and 100% respectively with the PAS.

5.35 The company conducted a series of deterministic one-way sensitivity analyses. The majority of inputs had minimal impact on the ICER estimate with the exception of post-ruxolitinib discontinuation survival, and the overall survival estimate for BAT. However the estimated ICER did not exceed £50,000 per QALY gained in any of the sensitivity

analyses (for further details see Figure.72 on page 236 of the company submission).

Company scenario analyses

5.36 The company conducted a series of scenario analyses: Varying the model time horizon; assuming the BAT discontinuation rate followed an exponential, Weibull or log-normal distribution; varying the duration on BAT, using the ITT overall survival estimate from the COMFORT-II trial; post-BAT discontinuation survival (survival after BAT discontinuation) to follow a shape of 1 (as opposed to 0.63 in the base case); impact of different response criteria; discontinuation rate for patients on ruxolitinib achieving a spleen response was assumed to follow alternative distributions and assuming all patients to remain on treatment for a maximum duration of 3.5 years, 5 years, 7.5 and 10 years. None of these scenarios were found to significantly impact on the ICER.

ERG comments

5.37 The ERG stated that the extensive sensitivity and scenario analyses presented by the company showed the estimated ICER to be largely robust to a range of input values and assumptions made in the model.

5.38 The ERG commented that although the company had undertaken an extensive number of scenario analyses, it did not allow the joint uncertainty in the assumptions to be analysed and therefore there was uncertainty over the overall impact of these structural model assumptions.

ERG exploratory analyses

5.39 The ERG corrected 2 minor errors identified in the model.

5.40 The ERG undertook further exploratory analyses focusing on: assumptions around drug wastage (assuming a 5%, 10% and 15% wastage of ruxolitinib), lenolidomide replaced with hydroxycarbamide in the BAT basket, and assumptions around the mortality rate of people

whose disease responded to treatment with ruxolitinib. For further details of these analyses, see pages 116-119 of the ERG report.

5.41 The ERG undertook an analysis which combined all of its preferred assumptions:

- Adding a 5% wastage rate for ruxolitinib.
- Removing lenalidomide from the basket of therapies which made up best available care.
- Assuming that time on ruxolitinib was part of the time on treatment on BAT for non-responders.
- Assuming the BAT discontinuation rate was underestimated by 20%.

Table 10: ERG's alternative base case (deterministic with PAS, from table 33, page 120 of the ERG report)

	Ruxolitinib			**Best available therapy**			
	Life years	**QALYs**	**Costs**	**Life years**	**QALYs**	**Costs**	**ICER**
CS's Base-case (Corrected model)	5.96	3.989	£148,920	2.15	1.476	£36,238	£44,831
Alternative ERG base-case with CS mortality rate of 0.0%	5.90	3.948	£153,621	2.15	1.483	£35,435	£47,950
Alternative ERG base-case with ERG mortality rate of 7.06%	5.78	3.890	£153,097	2.15	1.483	£35,435	£48,894
QALY: quality adjusted life year; ICER: incremental cost effectiveness ratio; CS: company submission							

5.42 Ruxolitinib had a 0.0%, 0.3%, 66.2 % and 100% probability of being cost effective at a threshold of £30,000, £40,000, £50,000 and £60,000 respectively (with the PAS).

Innovation

5.43 Justifications for considering ruxolitinib to be innovative:

- The company stated that ruxolitinib is a first-in-class JAK inhibitor designed to target the critical step in the myelofibrosis disease process, over activation of the JAK/STAT signalling pathway.
- Results from the COMFORT trials conducted in the US and Europe, have demonstrated dramatic and early reductions in spleen size and symptom burden, 2 of the most debilitating aspects of myelofibrosis.
- The benefits of ruxolitinib therapy have been shown to be sustained during treatment, and long-term follow-up of the trials have demonstrated overall survival benefits for ruxolitinib over best available therapy.
- Ruxolitinib is generally well tolerated; the incidence of adverse events decreases over time and few patients discontinued therapy as a result of adverse events in the trials.
- Ruxolitinib addresses the unmet needs of patients with myelofibrosis and represents a step-change in the management of the condition.

6 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company submission reported that median survival using the various prognostic scoring systems varies from 1.3 to 15.4 years, depending on the system and the risk classification. Data from the Haematological Malignancy Research Network (HMRN) audit of 98 patients indicated that the median survival for the total cohort, regardless of risk classification, was 3.36 years (range 2.8 to 4.4). In the COMFORT-II trial, which included patients with intermediate-2 and high risk myelofibrosis, patients in the BAT group survived for 26 months (median 28 months). The company stated that the COMFORT-II trial population this is healthier than the population that will receive the drug in practice. This difference in populations is a result of the exclusion criteria used in the two registration trials. The company also stated that as a consequence, it is likely that the average life expectancy for patients will be below 24 months. The ERG reports the figures from the IPSS and DIPSS development studies. Using IPSS median overall survival is: low >10 years; intermediate-2 approximately 8 years; intermediate-2 approximately 4 years; and high risk approximately 2 years (27 months (95% CI: 23-31). Using DIPSS median survival was not reached in low-risk patients; it was 14.2 years in intermediate-1, 4 years in intermediate-2, and 1.5 years in high risk patients.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Because median overall survival was not reached in the ruxolitinib arm of the COMFORT-II trial it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT directly from the data. An indirect comparison using a subset of the ruxolitinib arm of COMFORT-II and the DIPSS cohort (Primary myelofibrosis patients only) generated a median survival of 5 years (95% CI: 2.9-7.8) on ruxolitinib compared with 3.5 years (95% CI: 3.0- 3.9) for the DIPSS cohort.
The treatment is licensed or otherwise indicated for small patient populations	The prevalence of myelofibrosis has been estimated to be 2.2 per 100,000 populations based on audit data for a region of England, thus 1185 patients in England and 70 patients in Wales are estimated to be living with the disease.

7 Equality issues

7.1 No potential equality issue were raised at the scoping workshop, or in the evidence submitted.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002464/WC500133226.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ruxolitinib within its marketing authorisation for treating myelofibrosis.

Background

Myelofibrosis is a cancer of the bone marrow in which the marrow is replaced by scar (fibrous) tissue. Myelofibrosis may be primary (known as chronic idiopathic myelofibrosis), or secondary to either polycythaemia vera (a disorder in which the bone marrow makes too many red blood cells) or essential thrombocythaemia (a disorder in which the bone marrow makes too many platelets).

The early stages of myelofibrosis may be asymptomatic in some people while others may have severe symptoms from the onset. 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. Enlargement of spleen (splenomegaly) may cause abdominal pain, dyspnoea (shortness of breath), early satiety (feeling full) and faecal incontinence, along with progressive anaemia. Splenomegaly can also lead to problems with blood circulation in the liver and spleen. Other symptoms include incurable itch, general malaise, weight loss, night sweats, low grade fever, anaemia, fatigue, and pallor. Between 10-20% of people with myelofibrosis develop acute myeloid leukaemia.

Many people with myelofibrosis have mutations in a gene known as Janus-associated kinase 2 (JAK2) gene. JAK signalling controls cytokines and growth factors that are important for blood cell production and immune function. Regardless of mutational status, loss of regulation of the JAK signalling pathway is thought to be the underlying mechanism of the disease in the myelofibrosis.

The annual incidence of myelofibrosis is approximately 0.75 per 100,000. The median survival is 5 years from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival. The peak incidence of primary myelofibrosis is between 50 and 70 years of age.

To guide treatment, myelofibrosis is classified into low, intermediate and high risk categories based on various prognostic factors such as age, presence of constitutional symptoms, haemoglobin level, white blood cell count, platelet

count, circulating blast cells, transfusion dependence, and presence of unfavourable karyotype.

Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, however, it is only suitable for people who are fit enough to undergo treatment. Other treatment options aim to relieve symptoms and improve quality of life. These include hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion. Ruxolitinib is available, through the Cancer Drug Fund, as a first or second line treatment for symptomatic splenomegaly in people with intermediate or high risk primary myelofibrosis, post polycythaemia myelofibrosis, and post essential thrombocytosis myelofibrosis when stem cell transplantation is not suitable. NICE Technology Appraisal Guidance 289 did not recommend ruxolitinib for treating symptomatic splenomegaly in people with myelofibrosis. Additional evidence on the effect of ruxolitinib on longer term survival and disease progression is now available which may help to address some of the key uncertainties identified during the appraisal.

The technology

Ruxolitinib (Jakavi, Novartis) is a protein kinase inhibitor that targets Janus-associated kinase(JAK) signalling. Ruxolitinib is administered orally.

Ruxolitinib has a UK marketing authorisation for 'the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis'.

Intervention(s)	Ruxolitinib with established clinical practice
Population(s)	Adults with disease-related splenomegaly or symptoms of • primary myelofibrosis (also known as chronic idiopathic myelofibrosis), • post polycythaemia vera myelofibrosis • post essential thrombocythaemia myelofibrosis
Comparators	Established clinical practice (including but not limited to hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion)

Outcomes	The outcome measures to be considered include: • symptom relief (including itch, pain and fatigue) • overall survival • progression-free survival • changes in spleen size • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows, consideration should be given to subgroups according to prognostic factors (age >65 years, haemoglobin <10 g/dL, leukocyte count >25 x 10^9/L, circulating blasts [immature blood cells] ≥ 1%, presence of constitutional symptoms).
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 289, June 2013, 'Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis' Proposed Technology Appraisal, ID 734, 'Ruxolitinib for treating polycythaemia vera that is resistant or intolerant to hydroxycarbamide'. Earliest anticipated date of publication: January 2016 Related Cancer Service Guidance: Guidance on Cancer Services, CSGHO, October 2003, 'Improving outcomes in haematological cancers' Related NICE Pathways: NICE Pathway: Blood and bone marrow cancers, Pathway last updated: March 2015, http://pathways.nice.org.uk/pathways/blood-and-bone-

	marrow-cancers
Related National Policy	Blood and marrow transplantation services (all ages), Chapter 29, Manual for Prescribed Specialised Services 2013/14 http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1 and 2. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) – [ID831]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Novartis Pharmaceuticals (ruxolitinib) Patient/carer groups • Afiya Trust • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer52 • Delete Blood cancer • Equalities National Council • Helen Rollason Cancer Charity • HAWC • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma Association • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • MPD Voice • Muslim Council of Britain • Muslim Health Network • Myeloma UK • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Professional groups • Association of Anaesthetists • Association of Cancer Physicians • Association of Surgeons of Great Britain and Ireland	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Alan Pharmaceuticals (thalidomide) • Bristol-Myers Squibb (hydroxycarbamide) • Celgene (lenalidomide, thalidomide) • Medac UK (hydroxycarbamide) • Nordic (hydoxycarbamide) Relevant research groups • Cochrane Haematological Malignancies Group • Elimination of Leukaemia Fund • Health Research Authority • Institute of Cancer Research • Leuka • Leukaemia & Lymphoma Research • Leukaemia Busters • MRC Clinical Trials Unit

• British Association for Surgical Oncology • British Committee for Standards in Haematology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society for Haematology • Cancer Network Pharmacists Forum • Cancer Research UK • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Health Forum • United Kingdom Clinical Pharmacy Association • United Kingdom Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Hammersmith and Fulham CCG • NHS South Norfolk CCG • Welsh Government	• National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • <u>Evidence Review Group</u> • NHS Centre for Reviews & Dissemination and Centre for Health Economics - York • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales NHS Trust

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

Appendix C

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology are invited to prepare a submission dossier, can respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to prepare a submission dossier respond to consultations on the draft scope, the Assessment Report and the Appraisal Consultation Document. They can nominate clinical specialists and/or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but are not asked to prepare a submission dossier. Commentators are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non- company commentator organisations can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Company evidence submission

June 2015

File name	Version	Contains confidential information	Date
		Yes/no	

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables

Figures

Abbreviations

AE	adverse event
AC	appraisal committee
AIC	Akaike information criterion
allo-SCT	allogeneic stem cell transplantation
AML	acute myeloid leukaemia
BAT	best available therapy
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criterion
BFI	Brief Fatigue Inventory
bid	twice daily
CALR	calreticulin
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COMFORT	COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment
COMP	Committee for Orphan Medicinal Products
CT	computed tomography
DIPSS	Dynamic International Prognostic Scoring System
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-Core 30
EQ-5D	5-dimension European Quality of Life questionnaire
ESA	erythropoiesis stimulating agent
ET	essential thrombocythaemia
EU	European Union
ERG	Evidence Review Group
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-An	Functional Assessment of Cancer Therapy – Anaemia
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FDA	Food and Drug Administration
GHS	Global Health Status
HAQ	Health Assessment Questionnaire
HC	hydroxycarbamide
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IMiD	immunomodulatory drugs

IPSS	International Prognostic Scoring System
ITT	intention-to-treat
IWG-MRT	International Working Group for MF Research and Treatment
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK/STAT	Janus kinase-signal transducers and activators of transcription
LCM	left costal margin
LFS	leukaemia-free survival
LT	leukaemic transformation
LymS	lymphoma subscale of the FACT-Lym
MF	myelofibrosis
MF-SAF	Myelofibrosis Symptom Assessment Form
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasms- Symptom Assessment Form
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	odds ratio
OS	overall survival
PAS	Patient Access Scheme
PET-MF	post- essential thrombocythaemia MF
PFS	progression-free survival
PGIC	Patient's Global Impression of Change
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
PPV-MF	post- polycythaemia vera MF
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PV	polycythaemia vera
QALY	quality-adjusted life years
qd	once a day
QoL	quality of life
RBC	red blood cell
RCT	randomised controlled trial
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SD	standard deviation
SF-6D	Short-Form Health Survey-6D

SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
SR	systematic review
SRM	standardised response mean
STA	single technology appraisal
TKI	tyrosine kinase inhibitor
TSS	total symptom score
TTO	time trade-off
WBC	white blood cell
WHO	World Health Organization

1 Executive summary

Ruxolitinib (Jakavi®) is a tyrosine kinase inhibitor (TKI) and, specifically, is a selective small molecule inhibitor of Janus kinase 1 (JAK1) and 2 (JAK2).[1] The JAK proteins are a family of molecules that mediate signalling through tyrosine kinase activity at receptors for cytokines, growth factors and hormones.[1] In healthy individuals, the JAK/STAT (signal transducer and activator of transcription) pathway is essential for normal haematopoiesis, inflammatory responses and immune function.[2] Dysregulated (overactive) signalling within the JAK/STAT pathway is a key pathophysiological feature of myelofibrosis (MF), leading to increased pro-inflammatory signalling and over-proliferation of haematopoietic cells.[3-6] Ruxolitinib inhibits the activity of JAK1 and 2 to suppress the activity of the JAK/STAT pathway, and thus targets the underlying pathogenic cause of MF.[1] (See section 2.1 for further details)

Ruxolitinib is the first disease-specific targeted treatment option for patients with MF, including primary MF, post-polycythaemia vera (PV) MF (PPV-MF) and post- essential thrombocythaemia (ET) MF (PET-MF) and is active regardless of the presence of JAK mutations.[7] As such ruxolitinib represents a step-change innovation for the treatment of MF as it is the first and only treatment to be proven effective, and licensed specifically for the treatment of patients with disease-related symptomatic splenomegaly or symptoms. The revised British Committee for Standards in Haematology (BCSH) guidelines recommend ruxolitinib as first-line therapy for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms and suggest that ruxolitinib can be considered for patients with hepatomegaly and portal hypertension.[8] In contrast, except for allogeneic stem cell transplantation (the only potentially curative option), other treatments, all of which except for busulphan are unlicensed, involve non-specific management of symptoms and confer limited benefit.[9] (See section 3.3 for further details)

Ruxolitinib thus addresses a clear unmet need. MF is a rare and life-threatening disease associated with a median survival for patients of all risk groups of approximately 69 months.[10] The disease is characterised by a severe and progressive constellation of symptoms, which include splenomegaly, night sweats, fever, weight loss, cachexia, pruritus, anaemia and fatigue.[11-13] Symptoms can be severely debilitating and have a major detrimental impact on a patient's health-related quality of life (HRQoL), and their ability to perform daily functions. The impact in terms of the deterioration in quality of life and diminished ability to perform daily functions is comparable to that observed in patients with metastatic cancer or acute myeloid leukaemia (AML).[11,14,15] Furthermore, up to 24% of patients are at risk of transformation to AML within the first decade after diagnosis, following which median overall survival is approximately 3 months.[16] (see section 3.1 and 3.2 for further details) Ruxolitinib provides clinically meaningful reductions in splenomegaly and improvements in disease-related symptoms and HRQoL (see section 1.3).

1.1 Statement of decision problem

Table 1 summarises the decision problem relating to this submission.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with disease-related splenomegaly or symptoms of • primary myelofibrosis (also known as chronic idiopathic myelofibrosis) • post polycythaemia vera myelofibrosis • post essential thrombocythaemia myelofibrosis	Adults with disease-related splenomegaly or symptoms of • primary myelofibrosis (also known as chronic idiopathic myelofibrosis) • post polycythaemia vera myelofibrosis • post essential thrombocythaemia myelofibrosis	
Intervention	Ruxolitinib with established clinical practice	Ruxolitinib with established clinical practice	
Comparator (s)	Established clinical practice without ruxolitinib	Established clinical practice without ruxolitinib, ie. best available treatment	
Outcomes	The outcome measures to be considered include: • symptom relief (including itch, pain and fatigue) • overall survival • progression-free survival • changes in spleen size • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • symptom relief (including itch, pain and fatigue) • overall survival • changes in spleen size • adverse effects of treatment • health-related quality of life	PFS has not been included as an outcome because it is not a measure that is generally applied in MF. There is no accepted definition of progression and therefore there is no accepted definition of PFS
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered	The cost-effectiveness evaluation estimates the cost per quality-adjusted life year (QALY). A patient lifetime horizon is used given the chronic nature of myelofibrosis and in order to capture all the relevant costs and benefits associated with the introduction of ruxolitinib in England and Wales. The perspective is that of the NHS and Personal Social Services (PSS).	

	from an NHS and Personal Social Services perspective.		
Subgroups to be considered	If evidence allows, consideration should be given to subgroups according to prognostic factors (age >65 years, haemoglobin <10 g/dL, leukocyte count >25 x 10^9/L, circulating blasts [immature blood cells] ≥ 1%, presence of constitutional symptoms).	Subgroup analyses were not carried out	The evidence did not allow consideration of subgroups because of the relatively small numbers of patients involved in pivotal trials and loss of statistical significance. In addition, previous analyses showed that all pre-specified subgroups benefitted from ruxolitinib treatment in terms of changes in spleen volume and total symptom score.[17]
Special considerations including issues related to equity or equality		Myelofibrosis presents primarily in the elderly with a median age at diagnosis of 65 years. Equity of treatment of the elderly is a concern, as evident from a report published by the House of Commons Committee of Public Accounts in March 2015.[18] MF is also a highly rare orphan disease.[19] The "Cancer Patient Experience Survey, 2010" found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer.[20] Therefore, access where appropriate to a treatment such as ruxolitinib should help to promote equality for both elderly patients and those with rarer forms of cancer.	

NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

1.2 Description of the technology being appraised

As summarised in Table 2, the licensed indication for ruxolitinib in the UK is: the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. Ruxolitinib is administered orally twice a day. Doses are based on platelet counts and may be titrated based on safety and efficacy. (see also sections 2.2 and 2.3)

Table 2 Technology being appraised

UK approved name and brand name	Approved name: ruxolitinib Brand name: Jakavi®
Marketing authorisation	Marketing authorisation in the European Union (EU) for ruxolitinib in the treatment of PMF, PPV-MF and PET-MF was received on 23 August 2012 and ruxolitinib was launched in the UK on 10 September 2012.
Indications and any restriction(s) as described in the summary of product characteristics	Ruxolitinib has a UK marketing authorisation for 'the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis'.[21] The contraindications for ruxolitinib are hypersensitivity to the active substance or to any of the excipients, pregnancy and lactation. Ruxolitinib is also indicated for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea. (EU marketing authorization was granted on 11 March 2015)
Method of administration and dosage	Oral The recommended starting dose for continuous treatment (based on platelet count) is: • 20 mg bid (patients with platelet count of > 200,000/mm^3) • 15 mg bid (patients with platelet count of 100,000 to 200,000/mm^3) • 5 mg bid and cautious titration (patients with platelet count of 50,000/mm^3 and < 100,000/mm^3) Doses may be titrated based on safety and efficacy. <u>Based on blood cell count:</u> Platelet count reduced to < 100,000/mm^3 during treatment: consider dose reduction with the aim of avoiding dose interruptions for thrombocytopenia. Platelet count reduced to < 50,000/mm^3 or absolute neutrophil count reduced to < 500/mm^3 during treatment: Interrupt treatment. When blood cells rise above these levels, restart treatment at 5 mg bid. Gradually increase dose as blood cell counts recover

	Based on response: If efficacy is insufficient and platelet and neutrophil count are adequate, doses may be increased by a maximum of 5 mg bid to a maximum of 25 mg bid. There should be no increase in the first 4 weeks of treatment and thereafter no more frequently than at 2-week intervals. The maximum dose is 25 mg bid

bid, twice daily; EU, European Union; PET-MF, post- essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post- polycythaemia vera myelofibrosis.PV, polycythaemia vera.

1.3 Summary of the clinical effectiveness analysis

There is a substantial body of evidence for the effects of ruxolitinib on splenomegaly and improvements in symptoms in patients with MF. Evidence for the safety and efficacy of ruxolitinib for the treatment of MF is based on the results of two phase 3 RCTs – COMFORT-I and COMFORT-II − which compared ruxolitinib with placebo and BAT, respectively, in patients with intermediate-2 or high-risk disease. [7,22-26] Further supportive evidence is provided by a phase 2 study, ROBUST, performed in the UK[27] and a phase 3b expanded access trial, JUMP,[28] both of which also included patients with intermediate-1 disease, as well as two studies which specifically involved patients with low platelet counts (a phase 2 study[29] and a dose-finding 1b study[30]) and reports of the efficacy and safety of ruxolitinib in patients with early disease (low risk).[31,32]

1.3.1 Efficacy demonstrated in COMFORT-I and COMFORT-II

The results for the COMFORT trials demonstrate that compared with placebo or BAT, ruxolitinib provides

- significant, clinically relevant and durable reductions in splenomegaly, (see section 4.7.1)
- clinically meaningful and durable improvements in disease-related symptoms and HRQoL (see sections 4.7.2 and 4.7.3), and
- benefits in terms of overall survival (see section 4.7.5).

Results for the primary analysis of both phase 3 studies have been reported for follow-up periods of 24 weeks (COMFORT-I) and 48 weeks (COMFORT-II) and demonstrated that a significantly greater proportion of patients achieved a reduction in spleen volume of at least 35% with ruxolitinib compared with placebo or best available therapy (BAT); thus the primary end point was met in both studies.[10,22] In COMFORT-I, at 24 weeks, 41.9% of ruxolitinib-treated patients compared with 0.7% of placebo-treated patients achieved a 35% or greater reduction in spleen volume (odds ratio [OR], 134.4; 95% CI 18.0 to 1004.9; $p < 0.001$). In COMFORT-II, at the primary analysis (48 weeks), this response was

achieved by 28% of patients in the ruxolitinib group versus 0% of patients in the BAT group (95% confidence interval [CI] 21% to 37%; p < 0.001). The effects of ruxolitinib therapy were rapid, were evident at the first assessment at 12 weeks compared with BAT, and improvements in splenomegaly and MF symptoms were durable. Long-term follow-up data for both studies (up to 3.5 years) indicate that reductions in spleen volume were sustained during treatment with ruxolitinib.[22-25] Both studies also identified that benefits of ruxolitinib were seen across all MF subtypes and in patients with intermediate-2 risk or high-risk disease. Furthermore treatment was effective regardless of *JAK* mutational status.

Effects on disease-related symptoms were assessed in COMFORT-I using the disease-specific MF-SAF which provides information on the effects of ruxolitinib versus placebo on a constellation of MF-associated symptoms. The individual symptoms of MF were present in over 70% of patients at baseline.[33,34] In total, 45.9% of ruxolitinib-treated patients achieved a 50% or greater improvement in modified MF-SAF total symptom score (TSS) at 24 weeks compared with 5.3% of patients in the placebo group, a difference that was highly statistically significant (OR, 15.3; 95% CI 6.9 to –33.7; p < 0.001).[26] At 24 weeks, ruxolitinib-treated patients had a 46.1% mean improvement in TSS, whereas placebo-treated patients had a 41.8% mean worsening in TSS (p < 0.001). The majority of responses occurred within 4 weeks after treatment initiation and the percentage of patients achieving a 50% or greater reduction in TSS was sustained from week 6 onwards.

Ruxolitinib treatment was shown to provide significant and sustained improvements in HRQoL compared with worsening HRQoL in placebo and BAT groups. [25,34,35] Even small reductions in spleen volume were associated with meaningful improvements in disease-related symptoms and HRQoL. At baseline, HRQoL scores in patients with MF were indicative of debilitating disease, but improvements in all HRQoL subscales of the EORTC QLQ-C30 were evident with ruxolitinib therapy in both phase 3 studies.

Despite both studies not being powered to detect differences in OS between ruxolitinib and the control group, both have demonstrated OS benefits for ruxolitinib over BAT or placebo. For COMFORT-II the most recent analysis, performed at a follow-up of 3.5 years, showed a statistically significant overall reduction in risk of death of 42% for ruxolitinib over BAT (HR, 0.58; 95% CI 0.36 to 0.93; p = 0.022).[22] In COMFORT-I, an analysis performed at a median follow-up of 51 weeks revealed a significant survival advantage for patients who received ruxolitinib, but a statistically significant benefit was no longer evident at 149 weeks.[25,26] The survival benefit from ruxolitinib in both trials is likely to be underestimated because a large number of patients in the comparator arms crossed over to ruxolitinib treatment. A pooled analysis of 3-year follow-up data for both studies found ruxolitinib was associated with a 35% reduction in the risk of death compared with control according to ITT analysis (HR 0.65; 95% CI 0.46 to 0.90; p = 0.01).[36]

1.3.2 Safety profile as demonstrated in COMFORT-I and COMFORT-II

The safety profile of ruxolitinib in MF has been established in the primary reports from the phase 3 studies COMFORT-I and COMFORT-II and indicates that ruxolitinib is generally well tolerated.[7,26] Anaemia was the most frequently reported grade 3 or 4 adverse event (AE) in both phase 3 trials (45% in COMFORT-I and 42% in COMFORT-II) and thrombocytopenia (13% in COMFORT-I and 8% in COMFORT-II) was the only other grade 3 or 4 AE reported in more than 8% of patients in both trials. These AEs rarely led to discontinuation and were generally managed by dose modifications and/or transfusions. These AEs were expected given the mechanism of action of ruxolitinib, and generally declined over time with continued therapy. For the primary analysis of both studies, the most frequently reported non-haematological AEs (any grade, reported in at least 20% of patients) were fatigue (COMFORT-I only), diarrhoea (both studies) and peripheral oedema (COMFORT-II only). These AEs were also the most frequently reported AEs in the placebo group in COMFORT-I, suggesting that they are likely to be manifestations of MF rather than of treatment. Grade 3 or 4 non-haematological AEs were infrequent overall and were generally more common in the control groups (placebo and BAT) than the ruxolitinib groups. In the primary analysis, abdominal pain (COMFORT-II) and fatigue (COMFORT-I only) were the only grade 3 or 4 AEs reported in at least 3% of patients receiving ruxolitinib. (see section 4.12 for further details)

During long-term follow-up over 3 years for patients in COMFORT-I and COMFORT-II, the incidence of AEs remained stable or decreased over time in patients receiving prolonged ruxolitinib therapy. There was no evidence that long-term treatment with ruxolitinib for 3 years or longer increased the risk of leukaemic transformation and AEs of special interest occurred at low rates.

1.3.3 Supporting efficacy evidence

Supporting evidence for the efficacy and safety of ruxolitinib in the treatment of patients with MF is provided by:

- the ROBUST study, a phase 2 study performed in the UK
- the phase 3b international expanded-access, JAK inhibitor ruxolitinib in MF patients (JUMP) trial
- Two studies and a subgroup analysis of data from the JUMP trial providing evidence in patients with low platelet counts (under 100 × 10^9/L),[29,30,37]
- Two studies in patients with early disease (low-risk),[32,38]
- A phase 1/2 study,[39] including long-term follow-up data, a further phase 2 study[40] and a number of expanded-access studies and reports of routine clinical use.[41-44]
  (see section 4.11 for further details)

The ROBUST study, a phase 2 study performed in the UK (n = 48), reported rapid and sustained improvements in symptoms and splenomegaly achieved with ruxolitinib in patients with MF.[27] This

study adds to the evidence reported for the COMFORT-I and –II studies in that, in addition to involving patients with intermediate-2 and high-risk disease, ROBUST also included patients with intermediate-1 risk disease and demonstrated benefits for ruxolitinib across all three risk subgroups. At week 48, 40% of patients achieved reductions in spleen length of at least 50% and 21% achieved a reduction in total symptom score (TSS) of at least 50% (as assessed using the Myelofibrosis Symptom Assessment Form, MF-SAF). Treatment success, defined as a 50% or greater decrease in spleen length and/or TSS at week 48, was achieved by 50.0% of the overall population and 57.1%, 38.5% and 52.4% of the intermediate-1 risk, intermediate-2 risk and high-risk disease groups, respectively. Consistent with findings from the COMFORT studies, the most common haematological AEs were anaemia (45.8% of patients) and thrombocytopenia (37.5%). The most common non-haematological AEs were abdominal pain (27.1%), epistaxis (27.1%), diarrhoea (25.0%), confusion (22.9%), fatigue (22.9%), headache (22.9%) and lethargy (20.8%), and were primarily grade 1/2.

The phase 3b expanded-access, JAK inhibitor rUxolitinib in MF Patients (JUMP) trial was also designed to assess the safety and efficacy of ruxolitinib in patients with high-risk, intermediate-2 risk or intermediate-1 risk disease. As of September 2014, 2138 patients had been enrolled in 25 countries and data have been reported for an analysis of 1144 patients who had received ruxolitinib for a median of 11.1 months.[28] At week 48, 61% of patients achieved at least a 50% reduction from baseline in palpable spleen length. Clinically meaningful improvements in symptoms were seen as early as week 4 and were maintained during the study. Ruxolitinib was generally well tolerated, with only 14% of patients discontinuing owing to AEs. The most common grade 3 or 4 haematological AEs were anaemia (33.0%), thrombocytopenia (12.5%) and neutropenia (3.9%); each of these rarely led to discontinuation of ruxolitinib. The incidences of grade 3 or 4 non-haematological AEs were low, with pneumonia being the only event reported in over 2% of patients (3.6%).

Two studies have specifically investigated the efficacy and safety of ruxolitinib in patients with a low platelet count (under 100×10^9/L), a group of patients excluded from the COMFORT trials but which accounts for approximately a quarter of patients with MF.[45-47] A phase 2 dose-finding study investigated the efficacy and safety of ruxolitinib in patients with low platelet counts (50 to 100×10^9/L) when initiated at a dose of 5 mg bid with the option to increase to 10 mg bid if platelet counts remained adequate.[29] An interim analysis reported that by week 24, 62% of patients achieved stable doses of at least 10 mg bid. At this time point, 20% of patients achieved a reduction in spleen volume of at least 35%, and the median percentage reduction from baseline in total symptom score (TSS) for those who completed 24 weeks of therapy was 43.8% and was 13.0% for patients receiving 5 mg once or bid (n = 8) and 63.5% for patients receiving 10 mg bid (n = 21). In the three patients who had their dose escalated to over 10 mg bid because of inadequate response, median percentage reduction from baseline in TSS at week 24 was 33.8%.[29] Thrombocytopenia was the most frequently reported grade 3 or 4 AE occurring in 56% of patients and grade 3 or 4 anaemia was reported in 42% of patients. Most other AEs were grade 1 or 2 and no other grade 3 or 4 AEs

were reported in more than 2 (4%) patients. Two patients discontinued owing to AEs: in one patient this was grade 4 thrombocytopenia.

In the JUMP trial, in patients with low platelet counts (50 to 100 × 10^9/L) ruxolitinib was initiated at a dose of 5 mg bid and could be increased to 10 mg bid at week 4 in patients with inadequate efficacy if platelet counts were at least 50 × 10^9/L and there had been no treatment-related toxicities that resulted in dose reduction, interruption or discontinuation during treatment at the 5 mg bid dose. Results for an interim analysis for 6 months of therapy in the first 50 patients with low platelet counts have been reported.[37] At week 24, 38.2% (13 of 34 evaluable patients) achieved a reduction of at least 50% from baseline in palpable spleen length. Clinically meaningful improvements in symptoms were seen as early as week 4 and were durable through week 12. The reduction in splenomegaly and improvements in symptoms observed in this subgroup of patients are however inferior to those achieved for the overall JUMP population. The most common grade 3 or 4 haematological AEs were thrombocytopenia (30%) and anaemia (28%): 3 patients (6%) discontinued owing to thrombocytopenia and 1 (2%) discontinued owing to anaemia. The results of this analysis, together with that of the phase 2 study described above, thus suggest that ruxolitinib doses of 5 to 10 mg bid are generally well tolerated and efficacious in patients with MF who have platelet counts of at least 50 to under 100 × 10^9/L but higher doses may be worth considering in such patients.

The open-label, phase 1b, dose-finding study (EXPAND) further investigates the optimum dose of ruxolitinib in patients with low baseline platelet counts. [30] Preliminary results have been reported and suggest that starting doses of 10 mg bid and 15 mg bid may be appropriate in patients with platelet counts of 50 to 74 × 10^9/L and 75 to 99 × 10^9/L, respectively.

Two studies have reported on the efficacy and safety of ruxolitinib in patients with early disease ie low or intermediate-1 risk disease. A retrospective real-world study in patients with low-risk (n = 25) or intermediate-1 risk (n = 83) reported that both groups experienced substantial reductions in splenomegaly during ruxolitinib treatment, and for most symptoms examined there was a shift towards a less severe profile as patients proceeded from diagnosis through to best response during treatment.[31] A second study reported a reduction in spleen size by palpation of 64% at 12 months, and a median reduction in the total symptom score assessed using the Myeloproliferative Neoplasms-Symptom Assessment Form (MPN-SAF) of 73% compared with baseline.[32] Grade 3 or 4 AEs included anaemia (28%) and thrombocytopenia (24%). Results from the JUMP study indicate that the safety and efficacy on ruxolitinib in intermediate-1 risk patients is consistent with that in the COMFORT trials. At 24 weeks, 64% (88/138) of intermediate-1 patients had achieved a ≥ 50% reduction from baseline in spleen length with a similar rate at week 48. From weeks 4 to 48, 30–40% of patients achieved a clinically meaningful response in the FACT-Lym score.[48]

The results of non-RCTs therefore provide further evidence for the safety profile of ruxolitinib and indicate that patients with low-risk or intermediate-1 risk disease, as well as those with intermediate-2

or high-risk disease (as demonstrated in the COMFORT trials), achieve clinically meaningful reductions in splenomegaly and symptoms with ruxolitinib. Furthermore, patients with low-platelet counts also benefit from ruxolitinib; in this subgroup, therapy should be initiated at 5 mg bid and should be titrated up to an effective dose. Therapy is generally well tolerated across all patient groups and few patients discontinue ruxolitinib therapy due to adverse events.

1.3.4 Strengths and limitations of the evidence base

Evidence for the efficacy and safety of ruxolitinib comes from a robust evidence based which includes data from two well-designed multicentre phase 3 studies with a follow-up of 3 to 3.5 years and supporting data from single-arm studies. Collectively, the COMFORT studies involved a total of 528 patients while the JUMP trial has reported data for 1144 patients with a median follow-up of 11 months. The evidence base is further strengthened by the fact that the similarity in design of the two COMFORT studies allows for assessment of the consistency of results for ruxolitinib which indeed was found to be the case across all endpoints. Patient characteristics in the studies are representative of patients who would be eligible to receive treatment with ruxolitinib in clinical practice in England and Wales; hence the data are directly relevant to the decision problem. Furthermore, both phase 3 studies employed the dosing regimen that would be used in the treatment of patients in England and Wales and the comparator in the COMFORT-II study, BAT, corresponds to the treatment options currently used in routine practice in England and Wales. The primary endpoint in both COMFORT studies - reduction in splenomegaly − is highly relevant to the treatment of MF as are the secondary endpoints, disease-related symptoms and impact on HRQoL. Furthermore, overall survival (OS) was included as a secondary endpoint in both trials. Although the studies were not powered to detect a statistically significant difference in OS given that a difference in OS would not be expected at the time of the primary analysis (ie at 6 months in COMFORT-I and 12 months in COMFORT-II), at a follow-up of 3 to 3.5 years, a statistically significant OS benefit for ruxolitinib over BAT was observed in COMFORT-II,[22] and in a pooled analysis of data from the two COMFORT studies.[36] The evidence base for ruxolitinib for the treatment of MF is thus very robust and has demonstrated significant clinical benefits which can be expected to be translated into clinical practice in England and Wales.

Limitations of the evidence base largely stem from some aspects of the design of the studies which in part reflect ethical considerations in the design of controlled trials. Thus results of COMFORT-II may be skewed by unequal (2:1) randomisation between treatments (ruxolitinib: BAT) which was chosen to facilitate recruitment and provide access to ruxolitinib for patients with no access to a clinically effective treatment for MF. Furthermore, both studies included a crossover design allowing non-responders in the control group to proceed to receive ruxolitinib. This crossover between treatment groups confounded assessment of OS and indeed neither study was powered to assess the impact of ruxolitinib on OS. However, as described above, despite the crossover, a statistically significant benefit for ruxolitinib over BAT was observed at a median follow-up of 3.5 years.[22] The wide array of

therapies used in the BAT arm of COMFORT-II and the high discontinuation rate in this treatment group impacts the value of results for the BAT group. However, this highlights that these treatment options have limited efficacy in patients with MF and BAT was considered to be representative of the real-world clinical options for the treatment of MF in England and Wales.

Thus despite a number of limitations the available evidence base provides a robust assessment of the likely benefits of ruxolitinib in routine clinical practice in England and Wales.

1.3.5 Conclusions

Results of the COMFORT-I and COMFORT-II trials conclusively demonstrate clinical benefits for ruxolitinib over current treatment options, BAT, or placebo, in the treatment of patients with MF and are supported by evidence from single-arm studies including a phase 2 study performed in the UK, an international open-access phase 3b study involving over 2000 patients, and studies in patients with low platelet counts or early stage disease. Across all patient groups, including those with low-risk or intermediate-1 disease (as well as intermediate-2 and high-risk disease) and patients with low platelet counts, ruxolitinib provides significant and clinically relevant reductions in splenomegaly and durable improvements in disease-related symptoms and HRQoL. There is also evidence for an improvement in the overall survival, as reported for the COMFORT-I and COMFORT-II trials. Ruxolitinib is generally well tolerated with few patients discontinuing therapy due to AEs, even in patients with low platelet counts. As such ruxolitinib provides a clinically meaningful alternative to current treatment options that could benefit many patients and their families.

1.4 Summary of the cost-effectiveness analysis

1.4.1 Outline of the model structure

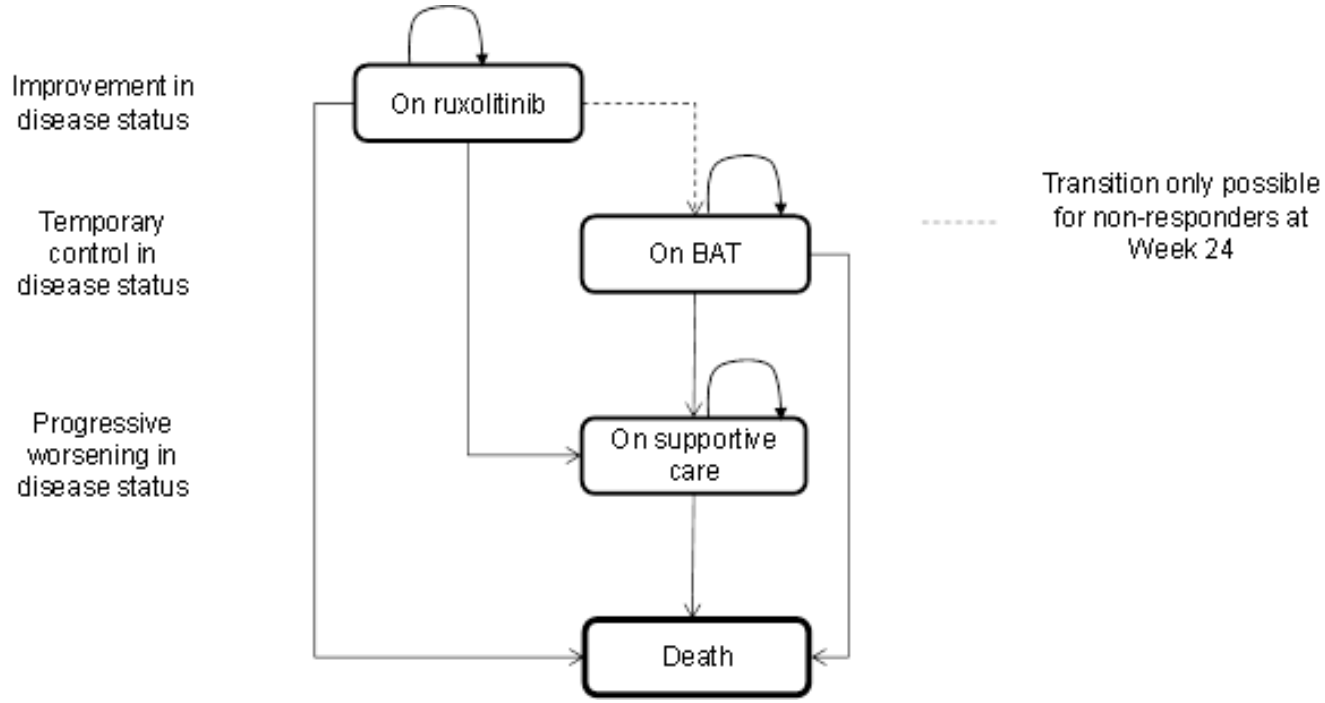
MF is a disease characterised by progressive worsening of symptoms, haematological parameters, splenomegaly, nutritional status (weight loss) and HRQoL. However, unlike most cancers, disease progression is not clearly defined in MF and there is a lack of clinical consensus regarding the definition of progressive disease. Standard therapies (referred to as best available treatment, BAT) provide some symptom relief but effects are short-lived and, following exhaustion of the various options including BAT, the patient's condition progressively worsens until death.

In the previous submission (TA289), key concerns raised included the fact that the model failed to capture the progressive nature of the disease or the impact of symptoms on HRQoL. Therefore in this submission the model structure, shown in Figure 1 below, was chosen to:

- represent the natural history of MF in sufficient detail to capture the impact of treatments on HRQoL and costs during the course of the disease

- make the best of use of data from the COMFORT-II trial which provided a direct comparison with the appropriate comparator, BAT.

Figure 1 Simplified schematic of the model structure



BAT, best available therapy

Given that the outcomes with respect to HRQoL and costs are considered to be largely defined by a patient's phase in the management of the condition, the health states in the model are defined by the therapy phases, namely:

- On ruxolitinib: receiving active therapy with ruxolitinib which provides improvements in symptoms, splenomegaly and HRQoL
- On BAT: receiving BAT which may provide some symptom relief and control of haematological parameters but little impact on HRQoL
- On supportive care.

The model is composed of two sub-models to estimate:

- the duration spent in each phase of the treatment pathway/disease, and
- the progression of HRQoL according to the phase of treatment/disease

The decision model is individual-patient based and uses a time-to-event approach; thus there are no time cycles. This approach was chosen over a cohort approach in order to model the progressive nature of MF and explore the impact of different structural assumptions.

Movement through the model

In the absence of ruxolitinib, patients enter the model initiating therapy on BAT (ie in the BAT health state). In this health state, patients typically receive a series of treatments that constitute BAT and achieve some transient control of symptoms and haematological parameters but not splenomegaly. Patients may continue to receive BAT until death or they may stop receiving BAT (after exhaustion of possible options) and progress to receive supportive care (in the Supportive Care health state). In this health state patients experience a gradual worsening of the disease (symptoms and haematological parameters) and HRQoL until death. No formal stopping rule is applied to patients receiving BAT.

Patients initiating ruxolitinib are categorised into five groups based on their outcomes at week 24.

- **Spleen responders:** patients who achieve a spleen response at week 24 (with or without a symptom response**)**
- **Symptom responders with no spleen response:** patients who achieve a symptom response at week 24 but who do not achieve the required level of spleen response.
- **Primary non-responders:** patients alive and on treatment but who achieve neither a spleen nor a symptom response at week 24. A treatment stopping rule, in line with the SmPC, is applied
- **The early discontinuation group:** patients who are alive at week 24 but who discontinue therapy prior to week 24
- **The early death:** patients who die prior to week 24

Patients who achieve a spleen response or a symptom response at week 24 remain on ruxolitinib therapy and hence in the ruxolitinib health state, subject to an ongoing risk of stopping ruxolitinib beyond week 24 due to a variety of reasons including loss of continuing efficacy and AEs. After stopping ruxolitinib treatment these patients move to supportive care and ultimately death.

At week 24 non-responders stop therapy with ruxolitinib and are then assumed to receive BAT (for the same duration as patients initiating BAT).

Patients who discontinue therapy prior to week 24 are assumed to move directly to receive supportive care and experience worsening in symptoms and haematological parameters until death.
Because there is no clear definition of response to treatment in clinical practice, the economic analysis used an adaptation of the clinical trial response definition developed by the IWG-MRT/ELN. The base case definition of response used to determine whether patients should continue on ruxolitinib therapy beyond week 24:

- **Spleen response**: non-palpable spleen in a patient who, at baseline, had splenomegaly that was palpable at 5–10 cm below the left costal margin (LCM), **or** spleen decreased by ≥ 50% in a patient with splenomegaly at baseline that was palpable at > 10 cm below the LCM, **or**
- **Symptom response**: a ≥ 50% reduction from baseline in the MF-SAF TSS

Outcomes included in the model

The economic model also tracks changes in HRQoL (on a continuous scale) and costs over time, according to different phases of the disease. These changes in HRQoL are modelled directly (rather than changes in symptoms and splenomegaly). The COMFORT-I and II trials[7,26] did not include a generic measure of HRQoL. However, the EORTC QLQ-C30 and modified MF-SAF v2 were used in COMFORT-I,[26] and COMFORT-II[7] included the EORTC QLQ-C30 and FACT-Lym. Although mapping algorithms are available between the EQ-5D and EORTC QLQ-C30, psychometric analyses indicated that the performance of these instruments in MF is of concern.[49,50] As a result, a condition-specific preference-based measure for MF, the MF-8D, was developed using appropriate existing measures, the MF-SAF and EORTC QLQ-C30.[51]

Patients with MF are at increased risk of complications such as transformation to leukaemia or thrombotic events and therefore the economic model sought to capture their impact. Haematological aspects of the disease are also important to capture because haematological progression is part of the natural course of MF and haematological events such as leucocytosis, thrombocytosis and anaemia can also be associated with MF treatments. As reflected in the economic model, these events are managed with dose modifications, temporary treatment interruptions, and, in the case of anaemia, by RBC transfusions.

Estimates of resource use due to the management of MF in the UK are scarce. Consequently, evidence from different sources was combined with assumptions to approximate the potential healthcare burden of MF in the UK and healthcare costs form a NHS perspective. The two key UK data sources that were identified were the Haematological Malignancies Research Network (HMRN) MF audit and the ROBUST clinical trial.[52,53] The HMRN audit provides information on the number of hospital nights, outpatient visits and laboratory tests among 98 patients in an area of England which provides a representative sample for the rest of the UK. ROBUST, the UK phase 2 study, provided data on resource use. Data from the JUMP international expanded access study[28] were used to represent the reduction in resource use associated with the use of ruxolitinib. These data were supplemented by information from the COMFORT trials and assumptions when appropriate.

1.4.2 Base case results

The model predicted that, over a lifetime, for patients initiating treatment on ruxolitinib, the discounted incremental QALYs were [redacted] and discounted incremental costs were £[redacted] compared to BAT. The ICER for ruxolitinib therapy was £[redacted].

Table 3 Incremental cost-effectiveness results

Technology (and comparators)	Total			Incremental			Incremental analysis
	Costs	Life years	QALYs	Costs	Life years	QALYs	
BAT	£36,271	2.15	1.476				
Ruxolitinib	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

1.4.3 Key drivers of CE results

A range of sensitivity and scenario analyses were conducted to test the robustness of the model input and structural assumptions. Overall, results were robust to most parameters and structural assumptions.

Reducing the time horizon to 10 years and over had little impact on the ICER. As expected, results were sensitive to the assumption used for the survival of patients initiating BAT as well as survival after ruxolitinib discontinuation. Experts indicated that survival adjustment for cross-over from the COMFORT trials provided a more clinically plausible estimate of survival compared to survival based on the ITT analysis (not corrected for cross-over).

Structural assumptions were also examined. Assuming a longer duration on BAT has limited impact on the ICER. Assuming that patients who do not achieve the required level of response at week 24 remain on BAT for a shorter duration compared with patients initiating BAT had limited impact on the ICER. Similarly, assuming all patients on ruxolitinib remained on treatment for a maximum duration of 3.5 years or alive for a maximum duration of 3.5 years following ruxolitinib discontinuation had a minimal impact on the ICER.

Different assumptions were explored for the progression of HRQoL. Most assumptions had limited impact on the ICER. We also examined changes in HRQoL measured using the MF-8D v2 and the EQ-5D which resulted in a minimal increase in the ICER.

A range of sensitivity analyses were conducted on costs and resource use. Varying these parameters had limited impact on the ICER.

1.4.4 Strengths and limitations of the analysis

The study has a number of strengths. The economic analysis is based on three and a half years of efficacy data from the COMFORT-II trial, supplemented with evidence from COMFORT-I trials and

two open label studies. Data on current management was taken, where possible, from UK sources, includingthe HMRN MF audit and the open label ROBUST study.

The model considered the important aspects of the nature and progression of the disease, including splenomegaly and symptoms and included important complications such as LT. Haematological aspects of the disease are captured through the requirement for RBC transfusions. The model included a stopping rule at 24 weeks to reflect the indication of ruxolitinib and expected clinical practice. Health-related quality of life (HRQoL) was measured using a condition specific measure, MF-8D as well as the EQ-5D.

As with any evaluation, the study has several limitations. These include the lack of a clear definition of response to treatment in clinical practice. The economic analysis therefore uses the definition by the recent International Working Group for MF Research and Treatment/ European LeukemiaNet (IWG-MRT/ELN) consensus-based definition of response criteria for use in clinical trials. However different definition were explored in scenario analyses and showed little impact on the ICER.

One key area of uncertainty is the OS for patients initiating BAT. In the COMFORT-II trial, patients on BAT were allowed to cross-over to ruxolitinib resulting in an overestimation of OS for patients initiating BAT. OS from the COMFORT-II trial corrected for cross-over using the RPSFTM method was considered to be the most appropriate source to use within the economic model.

Long term discontinuation and survival benefits following ruxolitinib discontinuation were also taken from the COMFORT-II study. The parametric distribution was fitted to the current data (3.5 years) and therefore, the extrapolation may be uncertain although scenario analyses were conducted assuming different distributions.

There were also some structural uncertainties in the method used to depict the treatment pathway and the natural course in MF such as estimating the survival post-BAT discontinuation or the survival following ruxolitinib discontinuation in patients not achieving a primary response at week 24. Scenario analyses were conducted to examine the impact of these structural assumptions and showed that the impact of these assumptions on the ICER was limited.

The economic analysis does not include the impact on carers and social services and productivity. This is likely to underestimate the benefit of ruxolitinib in England and Wales.

1.4.5 Other considerations

Impact on carers

The debilitating symptom burden, severe impact on quality of life and diminished ability to perform daily functions as a result of MF means than many patients are heavily reliant on informal carers and

formal care via social services. The costs of family carer time and social services are likely to be considerable. Studies from Spain and Italy have shown that 3-11 hours per day of informal care are provided to MF patients.[54,55] Based on the ONS estimate of £8.12 per hour,[56] the cost of providing informal care could amount to £8,900 - £32,000 per year. Between 18% and 28% of patients are medically disabled and these patients are likely to require formal care via social services.[11,57] Based on the median cost of a community care package for older people,[58] the annual cost would amount to £19,000. When patients respond to ruxolitinib, with a resultant improvement in symptom burden and quality of life, it is expected that carer requirements will reduce significantly although we currently do not have the data to quantify such reductions .

These studies have also shown that MF can have a considerable economic impact on patients and their carers. A third of patients (35%) included in the study in Italy were unable to continue in employment, resulting in a mean loss of income of €8,065 per year.[55] Only 19% of caregivers managed to maintain their normal level of work hours, resulting in an average loss of quantifiable income of €4,692 per year. The small study in Spain estimated that costs associated with work loss were €15,077 per patient.[54] While comparable information is not available for UK patients and carers, a similar loss of productivity is possible.

Since the economic analysis does not include the impact on carers and social services or the impact on productivity it is likely to underestimate the benefit of ruxolitinib in England and Wales.

End of life consideration

Our analysis indicates that, for patients treated with BAT, the mean survival is approximately 26 months (median 28 months). While this survival marginally exceeds the criterion of a life expectancy of normally less than 24 months, this trial population could be healthier than the general MF population because of clinical trial exclusion criteria such as uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. Importantly, the mean survival gain in the COMFORT-II trial is at least 21 months (median survival in the ruxolitinib arm has not yet been reached) which significantly exceeds the three month gain criterion.

The prevalence of primary MF has been estimated as 2.2 cases per 100,000 population.[59] Based on a population of 56,948,200 in mid-2013, it is estimated that 1,185 patients in England and 70 patients in Wales are living with MF. While the majority of patients with MF are symptomatic and have splenomegaly,[10] market research indicates that clinicians would treat about 50% patients,[60] based on risk classification and symptom burden.

Ruxolitinib is also licensed for the treatment of patients with polycythemia vera who are resistant to or intolerant of hydroxycarbamide. It is estimated that the eligible patient population in England and

Wales would be approximately 360 (see section 3.4.2), resulting in a total ruxolitinib eligible patient population of under 1,000.

Overall, it is plausible that patients with myelofibrosis who receive ruxolitinib are eligible for consideration under end of life criteria. The criteria of extension of life by at least three months and a small patient population are clearly met. Even with a life expectancy of approximately 26 months (which may be lower in the general MF population), the mean survival gain of at least 21 months is of such a magnitude greater than the 3 month gain suggested, that the health benefits of ruxolitinib should be given the additional weighting as set out in the end of life guidance.

1.5 Conclusions

MF is a rare, severe, debilitating and progressive disease with a profoundly negative impact on patients' HRQoL and ability to perform daily functions. There is a clear unmet need for effective treatments as, until the availability of ruxolitinib, treatments for MF were palliative only. The results from two multicentre, randomised, controlled trials demonstrate that ruxolitinib confers significant benefits in terms of spleen size reduction and improvement in symptom burden. Ruxolitinib therefore represents a step-change in the treatment of splenomegaly and associated symptoms of MF as it is the first and only effective, licensed treatment for this disease.

The estimate of cost-effectiveness indicates that, in the base case analysis for ruxolitinib vs BAT, the cost/QALY is £[redacted]

In summary, ruxolitinib represents a step-change in the treatment of MF as the first and only treatment to be effective and licensed for this indication.

2 The technology

2.1 Description of the technology

Ruxolitinib (Jakavi®) is a tyrosine kinase inhibitor (TKI), a member of the pharmacotherapeutic class: antineoplastic agents, protein kinase inhibitors; ATC code: L01XE18.[21]

Ruxolitinib is a TKI and, specifically, is a selective small molecule inhibitor of Janus kinase 1 (JAK1) and 2 (JAK2).[1] The JAK proteins are a family of molecules that mediate signalling through tyrosine kinase activity at receptors for cytokines, growth factors and hormones.[1] In healthy individuals, the JAK/STAT (signal transducer and activator of transcription) pathway is essential for normal haematopoiesis, inflammatory responses and immune function.[2] JAK1 is necessary for the formation of lymphocytes and the mediation of cytokine responses, in particular for inflammatory cytokines such as interleukin-6 and tumour necrosis factor-alpha, whereas JAK2 is required for the growth and differentiation of haematopoietic stem cells and progenitors (see section 2.1 for further details).[1,61,62]

Dysregulated (overactive) signalling within the JAK/STAT pathway is a common and key pathophysiological feature of the classic Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), a group of rare clonal haematopoietic stem cell disorders characterised by the abnormal amplification of one or more myeloid lineages.[2,3,61] In these neoplasms – primary myelofibrosis (PMF), polycythaemia vera (PV) and essential thrombocythaemia (ET) – genetic mutations in JAK1, JAK2 or other components of the JAK/STAT pathway result in constitutive activation of the pathway, leading to increased pro-inflammatory signalling and over-proliferation of haematopoietic cells (see section 3.1 for further details).[3-6]

Ruxolitinib inhibits the activity of JAK1 and 2 to suppress the activity of the JAK/STAT pathway, and thus targets the underlying pathogenic cause of myelofibrosis (MF).[1] Ruxolitinib is the first disease-specific treatment option for patients with MF, including post-PV MF (PPV-MF) and post-ET MF (PET-MF) and is active regardless of the presence of mutations in JAK1 or JAK2.[7] As such ruxolitinib represents a step-change innovation for the treatment MF as it is the first and only treatment to be proven effective, and licensed specifically for the treatment of patients with disease-related splenomegaly or symptoms thus addressing a hitherto unmet clinical need.

2.2 Marketing authorisation/CE marking and health technology assessment

This submission concerns the use of ruxolitinib for the treatment of PMF and MF secondary to PV or ET, ie PPV-MF and PET-MF.

The Committee for Orphan Medicinal Products (COMP) designated ruxolitinib an orphan drug for chronic idiopathic MF on 7 November 2008 and for MF secondary to polycythaemia vera (PV) or essential thrombocythaemia (ET) on 3 April 2009. [63] A European regulatory submission was made on 3 June 2010 to the Committee for Medicinal Products for Human Use (CHMP, European Medicines Agency [EMA]). A positive opinion was received on 19 April 2012. Marketing authorisation in the European Union (EU) for ruxolitinib in the treatment of PMF, PPV-MF and PET-MF was received on 23 August 2012 and ruxolitinib was launched in the UK on 10 September 2012.

Ruxolitinib is licensed for treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.[21] The contraindications for ruxolitinib are hypersensitivity to the active substance or to any of the excipients, pregnancy and lactation.

The main issue raised by the CHMP Assessment Report issued in 2012 was the lack of long-term safety data.[64] This is being addressed by annual efficacy and safety data updates from the pivotal trials, together with data from a registry study and other post-approval commitments. There are no conditions or restrictions with respect to the safe and effective use of ruxolitinib attached to the marketing authorisation.

EU regulatory approval for ruxolitinib for patients with PMF, PPV-MF and PET-MF was obtained in August 2012. Ruxolitinib has also been approved by the United States Food and Drug Administration (FDA) (November 2011) for the treatment of patients with intermediate-2 or high-risk MF, including PMF, PPV-MF and PET-MF. Ruxolitinib has marketing authorisation for treatment of MF in more than 80 countries including Canada, Australia and most countries in Europe.

Ruxolitinib has been recommended for use within NHS Scotland by the Scottish Medicines Consortium (SMC) for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF, PPV-MF or PET-MF.[65]

2.3 Administration and costs of the technology

Table 4 summarises details of treatment regimen, method of administration and relevant costs for ruxolitinib in the treatment of PMF, PPV-MF and PET-MF.

Table 4 Costs of the technology being appraised

	Details	**Source**
Pharmaceutical formulation	Tablet	SmPC[21]
Acquisition cost (excluding VAT)*	List price: 5 mg × 56 tablets: £1,680 10 mg × 56 tablets: £3,360 15 mg × 56 tablets: £3,360 20 mg × 56 tablets: £3,360	
Method of administration	Oral	SmPC[21]
Doses	Starting dose (based on platelet count): 20 mg bid (patients with platelet count of > 200,000/mm^3) 15 mg bid (patients with platelet count of 100,000 to 200,000/mm^3) 5 mg bid and cautious titration (patients with platelet count of 50,000/mm^3 and < 100,000/mm^3) **Maximum dose**: 25 mg twice daily	SmPC[21]
Dosing frequency	Twice daily (bid)	SmPC[21]
Average length of a course of treatment	The mean duration of treatment in the pivotal trial with a follow-up of 3.5 years is 2.4 years [22]	SmPC[21]
Average cost of a course of treatment	£674.30 per week	
Anticipated average interval between courses of treatments	Continuous treatment	
Anticipated number of repeat courses of treatments	N/A	
Dose adjustments	Doses may be titrated based on safety and efficacy Based on blood cell count: Platelet count reduced to < 100,000/mm^3 during treatment: consider dose reduction with the aim of avoiding dose interruptions for thrombocytopenia. Platelet count reduced to < 50,000/mm^3 or absolute neutrophil count reduced to < 500/mm^3 during treatment: Interrupt treatment. When blood cells rise above these levels, restart treatment at 5 mg bid.	SmPC[21]

	Details	**Source**
	Gradually increase dose as blood cell counts recover Based on response: If efficacy is insufficient and platelet and neutrophil count are adequate, doses may be increased by a maximum of 5 mg bid to a maximum of 25 mg bid. There should be no increase in the first 4 weeks of treatment and thereafter no more frequently than at 2-week intervals. The maximum dose is 25 mg bid.	
Anticipated care setting	Secondary	
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

bid, twice daily; N/A, not applicable; SmPC, Summary of Product Characteristics.

2.4 Changes in service provision and management

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with ruxolitinib.[21] It is anticipated that no other additional tests or investigations will be needed for selection of patients for treatment with ruxolitinib (see section 5.5.2 and 5.5.3). Assessment of prognostic risk is appropriate for all patients with MF when considering treatment options. Additional risk assessments are not required.

It is not anticipated that additional monitoring will be required and indeed use of ruxolitinib may require less monitoring than existing therapies. Complete blood counts, including a white blood cell (WBC) count differential, should be monitored every two to four weeks until ruxolitinib doses are stabilised, and then as clinically indicated.

Platelet transfusions and red blood cell (RBC) transfusions may be required to manage thrombocytopenia and anaemia, respectively. These events may reflect complications of the underlying disease and its progression as well as of treatment.

Ruxolitinib treatment should only be initiated by a physician experienced in the administration of anti-cancer agents. The setting of care is therefore secondary care but the technology does not require additional infrastructure in the National Health Service (NHS) to be put in place.

2.5 Innovation

MF is a rare and life-threatening disease associated with a median survival of approximately 69 months from the time of diagnosis.[10] MF is associated with a progressive constellation of symptoms, including splenomegaly (and splenomegaly-related symptoms such as abdominal pain, early satiety, diarrhoea and dyspnoea), night sweats, fever, weight loss, cachexia, pruritus, anaemia and fatigue.[11-13] Symptoms can be severely debilitating and have a major detrimental impact on a patient's health-related quality of life (HRQoL), and their ability to perform daily functions. There are currently no effective therapies approved for MF; conventional treatments provide limited or transient benefits and are associated with severe adverse events.[66] The only existing therapy with curative potential is allogeneic stem cell transplantation (allo-SCT), but patient eligibility has been found to be as low as 1.5%, and mortality as high as 30%.[67-69] There is therefore a significant unmet need for a therapy that: acts by targeting the underlying cause of the disease; can improve symptoms and HRQoL in patients with MF; is well tolerated; and is an option for all patients (unlike allo-SCT).

Ruxolitinib is a first-in-class JAK inhibitor designed to target the critical step in the MF disease process, overactivation of the JAK/STAT signalling pathway (as discussed in section 2.1). Results from two international, phase 3 trials conducted in the US and Europe, have demonstrated dramatic and early reductions in spleen size and symptom burden, two of the most debilitating aspects of MF.[7,26] The benefits of ruxolitinib therapy have been shown to be sustained during treatment, and long-term follow-up of the phase 3 trials have demonstrated overall survival (OS) benefits for ruxolitinib over best available therapy (BAT).[22,23,25] Furthermore, ruxolitinib is generally well tolerated; the incidence of adverse events (AEs) decreases over time and few patients discontinued therapy due to AEs in the phase 3 trials. Ruxolitinib thus addresses the unmet needs of patients with MF and represents a step-change in the management of the condition.

3 Health condition and position of the technology in the treatment pathway

3.1 Overview of disease

3.1.1 Disease overview

MF is a rare and debilitating disease in which normal bone marrow, the source of red and white blood cells, is replaced by fibrous scar tissue. The disorder is associated with substantial morbidity and early mortality, and patients experience a severe and progressive constellation of disease-related symptoms that contribute to a dramatic reduction in HRQoL and survival.[11,70]

MF is one of the MPN group of blood disorders which can develop *de novo* as a primary disease (PMF) or secondary to PV and ET, with these secondary disorders termed post-PV-MF and post-ET-MF (PPV-MF and PET-MF), respectively.[71 72]

MF is characterised by overproduction of multiple blood-cell lines and progressive replacement of the bone marrow with scar tissue, a process known as fibrosis. Over time, this progressive fibrosis eventually leads to bone marrow failure and to reduced blood cell production, manifesting as decreases in WBCs (leukopenia) and platelet counts (thrombocytopenia), and as anaemia. In addition, fibrosis leads to blood cells being produced outside the bone marrow, particularly in the spleen and liver. As a result, patients with MF commonly present with marked enlargement of the spleen (splenomegaly).[12,13]

As the disease progresses, patients may begin to experience a variety of life-affecting and debilitating MF-related symptoms. The cardinal symptom of splenomegaly is often accompanied by and associated with abdominal discomfort, pain under the ribs and a feeling of satiety that together contribute to disease-related cachexia. Patients also commonly experience severe night sweats, fever, fatigue, muscle and bone pain, severe and persistent itching (pruritis), and anaemia.[12,13] This constellation of symptoms has a considerable negative impact on the patient's HRQoL and their ability to perform daily functions (see section 3.2). Furthermore, life expectancy is substantially reduced (see section 3.4).

3.1.2 Aetiology and pathogenesis

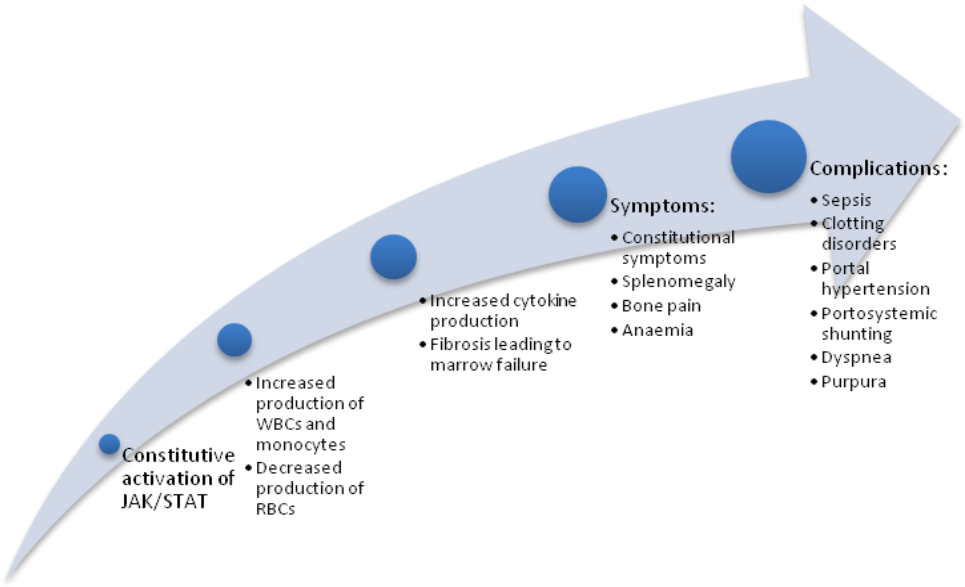
The conditions of PMF, PPV-MF and PET-MF are clinically distinct disorders that share molecular and pathological similarities. In PMF, all myeloid cell lineages over-proliferate, while in PV there is a particular accumulation of RBCs, and in ET there is an accumulation of platelets. [71]

This over-proliferation of blood cell precursors observed across all types of MF is a consequence of acquired genetic mutations, which result in dysregulation of key cell signalling pathways responsible for controlling cell proliferation, cell survival and production of inflammatory cytokines. Specifically, all forms of MF are associated with over-activation of the JAK/STAT signalling pathway.[2,73]

The most commonly observed mutated gene is that encoding the JAK2 protein. In one study, the *JAK2 V617F* mutation was observed in 55% of patients with PMF, 55% of patients with ET and 95% of patients with PV.[74] JAK2 mutations are therefore considered diagnostic for PV.[75] *MPL* is another gene frequently mutated in MF, and accumulating evidence is implicating the gene encoding the endoplasmic reticulum chaperone, calreticulin *(CALR)* in the pathogenesis of MF.[76,77] *CALR* mutations are exclusively seen in patients with PMF or ET who lack JAK2 and *MPL* mutations and are never observed in patients with PV or in patients with JAK2 and *MPL* mutations.[76,77] A proposed 2014 update to the World Health Organization (WHO) 2014 classification criteria for MPNs thus includes the presence of mutations in JAK2, *CALR* or *MPL* as a diagnostic criterion for PMF.[72]

The constitutive activation of the JAK/STAT pathway in all forms of MF results in over-production of cytokines and abnormal clonal haematopoietic stem cells. In the early stages of PMF this leads to overproduction of WBCs and platelets at the expense of RBCs (Figure 2). The overproduction of abnormal megakaryocytes and monocytes releases growth factors, which in turn stimulate the bone marrow fibroblasts to secrete collagen and reticulin.[78,79] Deposition of these two collagen components results in progressive bone marrow scarring (myelofibrosis) and ultimately causes failure of the bone marrow, effects that manifest as a deficiency of mature RBCs, WBCs and platelets.[70,80] To compensate for poor functioning of the bone marrow, blood cell production occurs in other organs such as the spleen and liver. This extramedullary haematopoiesis leads to splenomegaly and hepatomegaly.[81] Over time this JAK/STAT-derived pathology results in a constellation of MF-related symptoms.[81]

Figure 2 Role of constitutive activation of JAK/STAT signalling in the pathogenesis of MF



JAK/STAT, Janus kinase-signal transducers and activators of transcription; RBC, red blood cell, WBC, white blood cell

3.1.3 Course of disease and symptoms

The disease course of MF varies considerably among patients in terms of clinical presentation, severity and progression. In the majority of cases, MF is recognised and diagnosed only when patients become symptomatic, although approximately 30% of diagnoses are made on the basis of abnormal blood findings or the incidental discovery of morphological manifestations such as spleen enlargement.[12,82] The condition is most commonly seen in people aged over 60 years. For both men and women, the median age at diagnosis is 65 years, although it has been reported that a substantial number of patients with PMF are younger than 55 years at the time of diagnosis.[83-86]

Whilst the clinical course of disease can vary between individuals, MF typically progresses from an asymptomatic to a symptomatic condition with the development of complications. Overactive JAK signalling in PMF typically manifests initially at the cellular level, with an overproduction of mature WBCs (leukocytosis) and platelets (thrombocytosis) at the expense of mature RBCs, and patients often have borderline anaemia (haemoglobin under 10 g/dL) at diagnosis.[12,80,87] In patients with PV, RBC counts are increased, and in ET platelet counts are increased.[71] As the disease progresses beyond cellular manifestations, the symptoms and complications experienced are generally similar regardless of the underlying type of MF (PMF, PPV-MF, PET-MF). Management of patients focuses on treating the symptoms of the disease together with slowing progression to more advanced disease and avoiding the development of complications. As such, unlike other haematological malignancies,

patients with MF do not achieve remission and hence progression-free survival is not generally considered for this disease.

Symptoms

As the disease progresses, patients develop a range of debilitating symptoms (Table 5). Early signs and symptoms of MF include fatigue, weakness and shortness of breath.[12,13] [12,13]A recent survey involving 207 patients with MF has reported the five most severe symptoms to be fatigue, sexual desire problems, inactivity, concentration problems and difficulty sleeping.[57]

Fatigue may result from the effects of cachexia (a consequence of splenomegaly that also leads to abdominal compression and early satiety), elevated cytokine levels,[11] and anaemia.[70] Fatigue is regarded as one of the most challenging symptoms for patients to manage as it affects all aspects of their daily activities and is the most commonly reported symptom, occurring in around 85−90% of patients with MF.[11,15]

Table 5 Symptoms of myelofibrosis (MF) and their impact on patients

Symptoms	Frequency[a], %	Effect on patients	Cause
Fatigue	84%	Affects all aspects of daily life	Cachexia, elevated cytokine levels and decreased RBC production
Splenomegaly[83]	89%	Severe abdominal pain and discomfort, cachexia, weight loss	Extramedullary haematopoiesis
Constitutional symptoms			
Night sweats	56%	Sleep difficulties leading to increased fatigue	Hypercatabolism associated with MF
Fever	18%		
Weight loss	20%	Discomfort	Hypercatabolism and splenomegaly
Pruritus	50%	Severe discomfort, unable to take a bath or shower	Overproduction of cytokines
Bone pain	47%	Discomfort – unresponsive to narcotic medication	Increased haematopoiesis, periostitis and osteosclerosis

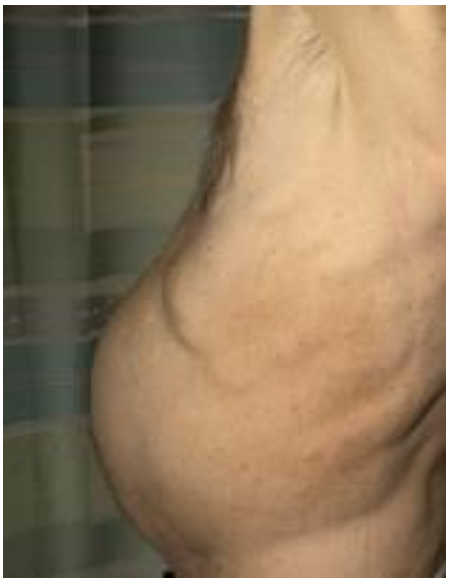
MF, myelofibrosis; RBC, red blood cell.

[a]Mesa et al 2007[11]

Spleen enlargement in MF, which results from extramedullary haematopoiesis, can be one of the most profound features of the condition. The splenomegaly can be massive, with spleen weight in

excess of 10 kg being not uncommon (Figure 3)[12,13,45] Such gross enlargement of the spleen is associated with compression of internal organs, pain under the left ribs, extreme discomfort and a plethora of debilitating symptoms that greatly affect patient well-being and HRQoL.[45] The additional bulk of an enlarged spleen goes hand in hand with symptoms of early satiety and abdominal pain, and is linked with disease-related cachexia.[88] Patients often experience profound weight loss, with one clinical database reporting that 49% of MF patients experienced weight loss.[15] The combination of emaciation and symptoms linked with splenomegaly can make even simple daily functions such as sitting uncomfortable.

Figure 3 Massive enlargement of spleen volume in a patient with MF



Photograph reproduced with permission from the MD Anderson Cancer Center, Houston, Texas , US

The constitutional symptoms of fever, night sweats and weight loss, believed to arise from the chronic state of hypercatabolism commonly associated with MF, can be intractable, and represent a major detriment to the HRQoL of patients with MF.[70] Furthermore the presence of constitutional symptoms is included in as one of the factors predictive of OS in the prognostic risk scoring systems developed for MF.[69,83,89] A survey of patients with classic MPNs found that 56% of MF patients had night sweats,[11] and a further survey reported that approximately 25% of patients experienced severe night sweats.[57] Anecdotal evidence suggests that these can be so severe that patients wake several times at night to change bed sheets. Night sweats reduce the quality of sleep and can further heighten the fatigue commonly experienced by MF patients.

Pruritis (severe itching) is another debilitating symptom, experienced by approximately 50% of patients with MF,[11,15] and was reported to be severe in approximately 25% of patients in one survey.[57] This is thought to be related to the increase in serum proinflammatory cytokine levels and constitutive

activation of the JAK/STAT pathway in basophils.[90] Pruritus is often aquagenic (ie triggered by contact with water), with patients experiencing severe post-bath itching that lasts for days. Aquagenic pruritus sometimes results in avoidance of taking showers, embarrassment from scratching one's body in public, and sleep deprivation.[91] Symptoms can be so severe that patients experience suicidal ideation.[92] The efficacy of conventional therapy in moderating constitutional symptoms is poor.[93] For example, a survey of UK physicians treating MF reported that a significant proportion of respondents considered there was currently no effective therapy for debilitating fatigue (40.7%), weight loss (34.6%), itching (27.2%),night sweats (25.9%) or fever (23.5%).[94]

The debilitating symptoms of MF are thought to be driven by the combined effects of massive splenomegaly and elevated levels of proinflammatory cytokines. Quality of life (QoL) scores for PMF patients have been reported to be equivalent to those for advanced metastatic cancer.[15] The efficacy of conventional therapy in moderating these symptoms is poor.[93]

In addition to the abdominal pain associated with splenomegaly, many patients also experience bone pain.[11] A recent survey reported bone pain to be severe in approximately 30% of patients with MF.[57] This is typically diffuse and localised to the metaphyses of the long bones, and is often unresponsive to narcotic medication. Bone pain is generally attributed to haematopoiesis, periostitis (ie inflammation of the periosteum or connective tissue that surrounds bone) and osteosclerosis (ie increase in bone density).[95]

Complications

As the condition progressively worsens, there is an increased likelihood of complications (Table 6) such as advanced fibrosis, extramedullary tumours, hepatomegaly, ascites, portal hypertension, portosystemic shunting and bone pain.[87,95] In addition, declining levels of WBCs, platelets and RBCs can result in sepsis, clotting disorders and transfusion dependence, respectively.

A significant number of complications are the result of splenomegaly, including gastric and intestinal disturbances, purpura and splenic infarction, as well as pulmonary and cardiovascular effects such as dyspnoea and portal hypertension.[84,87,88] These complications and associated morbidities, including gastrointestinal bleeding and accumulation of fluid in the abdomen, are severe and may be strong indications for splenectomy. In addition, sequestration of circulating blood cells by the enlarged spleen can cause a drastic reduction in RBCs, thereby increasing the burden of anaemia, significantly contributing to patient fatigue and reduced HRQoL, and resulting in transfusion dependence.[87,96] Approximately 50% of patients die from MF disease-related symptoms and complications such as portal hypertension, bleeding, infection, thrombosis and MF progression without acute transformation.[3,83,84,97,98] In addition to the detrimental impact on patients, many of these complications are costly to manage and the treatments/interventions themselves are associated with their own inherent risks.

As MF continues to advance, patients are at increased risk of evolution to acute myeloid leukaemia (AML), reported to occur in 8−23% of patients within 10 years from diagnosis.[16] Median OS following transformation to AML is approximately 3 months according to a study involving 91 cases of leukaemic transformation.[16] Approximately 20% of patients die following disease transformation to AML.[99]

Table 6 Complications of myelofibrosis (MF) and their impact on patients

Complications	Effect on patients	Cause
Sepsis	Can be life threatening	Neutropenia
Clotting disorders	Can be life threatening	Thrombocytopenia
Debilitating fatigue	Affects all aspects of daily life	Constitutional symptoms and anaemia
Transfusion dependence		Anaemia
Portal hypertension	Complications such as GI bleeding, accumulation of fluid in the abdomen	Splenomegaly
Dyspnoea	Shortness of breath making activities difficult	Splenomegaly
Purpura	Skin discolouration	Splenomegaly
Portosystemic shunting		Hepatomegaly
Transformation to AML	Major impact on overall survival	

AML, acute myeloid leukaemia; GI, gastrointestinal; MF, myelofibrosis.

Cervantes 1998; Rupoli 1994; Tefferi 2000[84,87,88]

3.2 Effects of disease on patients, carers and society

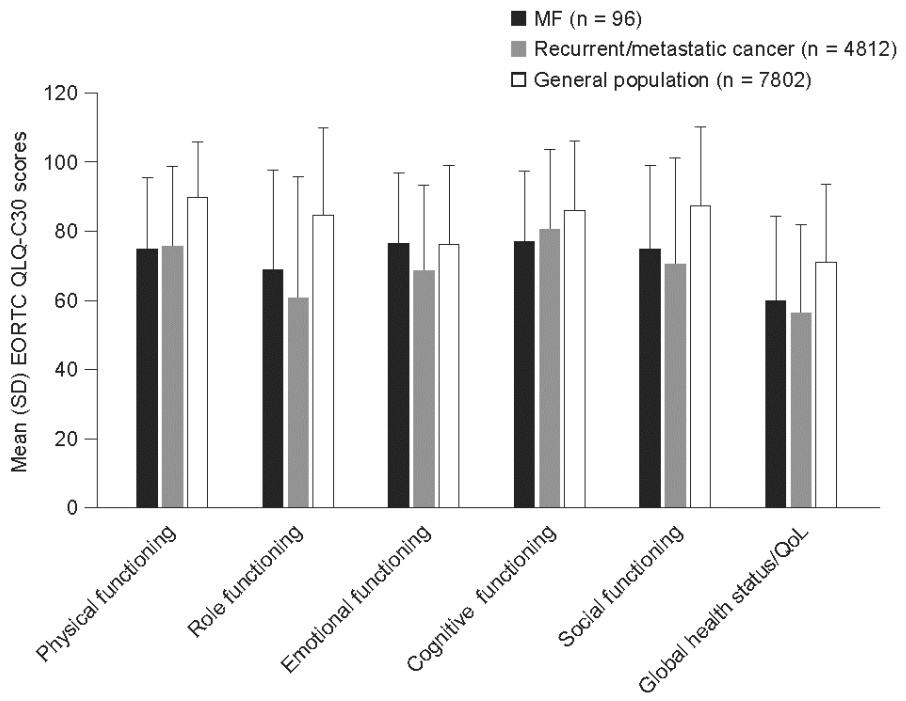
3.2.1 Impact of symptoms on HRQoL

MF has a considerable impact on HRQoL as evident from a number of studies in patients with MPNs and reporting data specifically for patients with MF.

One study used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [100] to assess the HRQoL of 96 patients with MF together with 161 patients with ET and 145 patients with PV.[15] The average duration of disease from diagnosis was 7.8 years and two thirds of patients were receiving cytoreductive therapy at the time of assessment. Scores for all subscales except emotional functioning were at least 10 points lower for patients with MF compared with the general population and Global Health Status/QoL was found to be comparable to that reported for patients with recurrent or metastatic cancer in a previous study (Figure 4).[15] Scores for individual symptom scales indicated that MF was associated in particular with

fatigue, dyspnoea, insomnia, appetite loss, constipation and diarrhoea. Overall, EORTC scores for MF closely matched those previously reported for patients with recurrent/metastatic cancer or AML.[15]

Figure 4 Impact of MF on HRQoL, according to the EORTC QLQ-C30 questionnaire



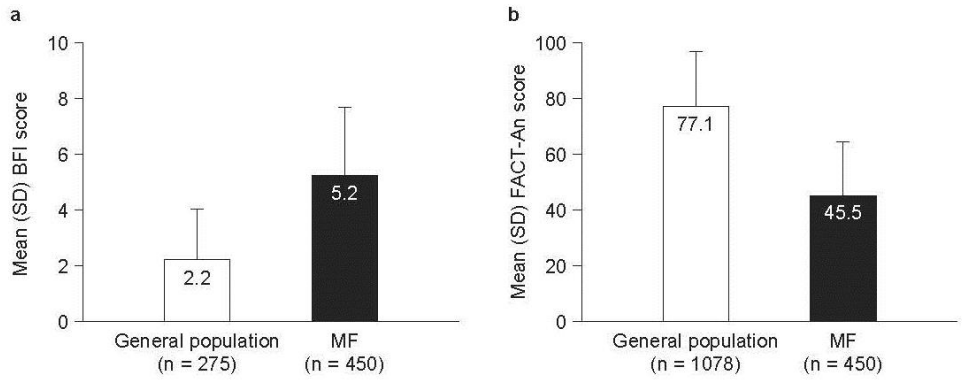
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; HRQoL, health-related quality of life; MF, myelofibrosis.
Scherber et al. 2011.[15]

A further study of HRQoL in patients with newly-diagnosed MPNs including 22 patients with PMF also reported worse HRQoL in patients with PMF than in the general population.[101] In patients with PMF, EORTC QLQ-C30 scores for all items of the functional scale, including Global Health Status (GHS), were worse than in the general population aged 60 to 69 years. Comparison of newly diagnosed patients with a cohort of patients with long-term PMF (mean disease duration of 7.8 years) showed significantly more fatigue, abdominal pain and discomfort, insomnia, fever, weight loss and lower overall QoL in patients with long-term PMF, suggesting that HRQoL deteriorates over time in patients with PMF.

Results of a Spanish study in 33 patients diagnosed with MF for an average of 51.4 months suggest that the impact of symptoms on HRQoL can be greater than that reported for schizophrenia, anxiety or mental health.[54] The study asked patients to rate symptoms and HRQoL. Mean QoL values on a scale from 0 (worst imaginable) to 100 (best imaginable) were 80.3 (standard deviation [SD]: 20.2) before the disease and 39.1 (SD: 23.0) at the worst moment of disease, corresponding to a worse QoL than that reported for the worst stage of schizophrenia, anxiety or depression in Spain.

A further study assessed the burden of fatigue in 1179 patients with myeloproliferative disorders, including 456 individuals with MF.[11] Mean scores for fatigue according to the Brief Fatigue Inventory (BFI) and the Functional Assessment of Cancer Therapy−Anaemia (FACT-An) indicated that patients with MF experience fatigue to a far greater degree than published norms (Figure 5). Indeed, scores for fatigue indicated that fatigue in patients with MF is similar to or worse than that in patients receiving chemotherapy for haematological malignancies, is equivalent to that in patients with non-Hodgkin's lymphoma, and is only slightly less than that in patients with overt leukaemia. This study also reported that 18% of patients were medically disabled because of MF and 34.5% of patients with myeloproliferative disorders, including MF, needed assistance with activities of daily living.[11]

Figure 5 Fatigue scores in patients with MF compared with the general population according to a) BFI and b) FACT-An



BFI, Brief Fatigue Inventory, scored from 0 (no fatigue/does not interfere with activity) to 10 (as bad as you can imagine/completely interferes with activity). FACT-An, Functional Assessment of Cancer Therapy−Anaemia, scored from 0 (poor QoL) to 100 (high QoL).
MF, myelofibrosis, SD, standard deviation.
Mesa et al. 2007.[11]

Another large study involving a US cohort of 813 patients with MPNs including 207 patients with MF has reported on symptom burden, QoL, activities of daily living and work/productivity.[57] Approximately 80% of patients with MF reported that MPN-related symptoms reduced their HRQoL. MF was reported to interfere with daily activities in 53% of patients, and 18% of patients reported spending 1 to 3 days in bed over the previous month (Table 7). Of responding patients, 59% reported working reduced hours, 28% reported having a medical disability and 30% reported retiring early.

Table 7 Impact of MF symptoms on activities of daily living

Activity	**Interference, n (%)**					
	Any interference[a]			**Considerable interference[2b]**		
Interfered with daily activities (ever)	110 (53)			43 (21)		
Interfered with family or social life (ever)	163 (79)			35 (17)		
Activities limited by pain/discomfort (ever)	127 (61)			25 (12)		
Days affected						
	1−3	4−6	7−9	10−12	13−15	≥ 16
Days cancelling planned activities in the past 30 days	44 (21)	22 (11)	2 (1)	7 (3)	3 (1)	8 (4)
Days spent in bed (all or most of the day) in the past 30 days	38 (18)	13 (6)	1 (<1)	4 (2)	4 (2)	7 (3)

MF, myelofibrosis.[a]A score >1 on a scale of 1 (not at all) to 5 (a great deal).

[b]A score of 5 on a scale of 1 (not at all) to 5 (a great deal).

Mesa et al 2014[57]

Together these studies indicate that the symptoms related to MF can have a significant impact on HRQoL, including affecting activities of daily living and work/productivity.

3.2.2 Economic impact on patients and carers

MF can also have a considerable economic impact on patients and their caregivers as revealed in an Italian study involving 287 patients with primary or secondary MF receiving ruxolitinib or other therapies, and 98 caregivers.[55] A third of patients (35%) were unable to continue in employment, resulting in a mean loss of income of €8065 per year. Approximately half of caregivers reported spending at least 3 hours a day taking care of their relative. Only 19% of caregivers managed to maintain their normal pace of work, and as a result the average loss of quantifiable revenue was estimated at €4692 per year. Ruxolitinib was reported to improve symptoms in 92% of patients (compared with 59% if on other therapies) and to improve pace of work in 87% of cases (compared with 44% of patients receiving other therapies).

The Spanish study involving 33 patients with MF (described above), also reported an impact on the ability to work and on the economic cost of MF.[54] Of the 33 patients, 15 were in employment and six of these (40%) reported problems with working. Costs associated with work loss were estimated at €15,077 per patient, while informal care costs were estimated to be €71,259 per patient. This resulted in total indirect and non-medical costs of €86,315, corresponding to annual costs of €15,142 per patient (assuming an expected survival of 5.7 years).

3.3 Clinical pathway of care

At present ruxolitinib is the only approved pharmacological treatment for patients with MF.

Prior to the approval of ruxolitinib for the management of MF there were no approved treatments for this indication and available treatments were palliative in nature, generally targeting only one or two of the symptoms, and providing limited alleviation. For example, a survey of UK physicians treating patients with MF reported that erythropoiesis stimulating agent (ESA) and thalidomide were principally used to treat anaemia, hydroxycarbamide for leucocytosis, thrombocytopenia, splenomegaly, night sweats and fever, and steroids for weight loss.[94] Furthermore, an analysis of treatment patterns for 98 patients with MF diagnosed between September 2004 and August 2010 in England reported the first-line treatments to include observation (41%), blood products (22%), hydroxycarbamide (13%), aspirin (7%), allograft (5%), prednisolone (4%), erythropoietin (2%), danazol (2%) and thalidomide (1%).[52] Thus, while there is no clear standard therapy, treatments such as hydroxycarbamide, steroids and thalidomide are commonly used in the UK and are recommended for use by the BCSH guidelines. Nevertheless, most of these treatments fail to address either the known mechanisms of disease progression or the underlying pathology of dysregulated JAK/STAT signalling, while the severe side effects associated with treatment options may in fact decrease patient HRQoL. Indeed, as described in section 4.7.4, clinical outcomes for BAT corresponding to a selection of these agents as chosen by the investigator in the COMFORT-II ruxolitinib trial were found to be similar to those of placebo.[102]

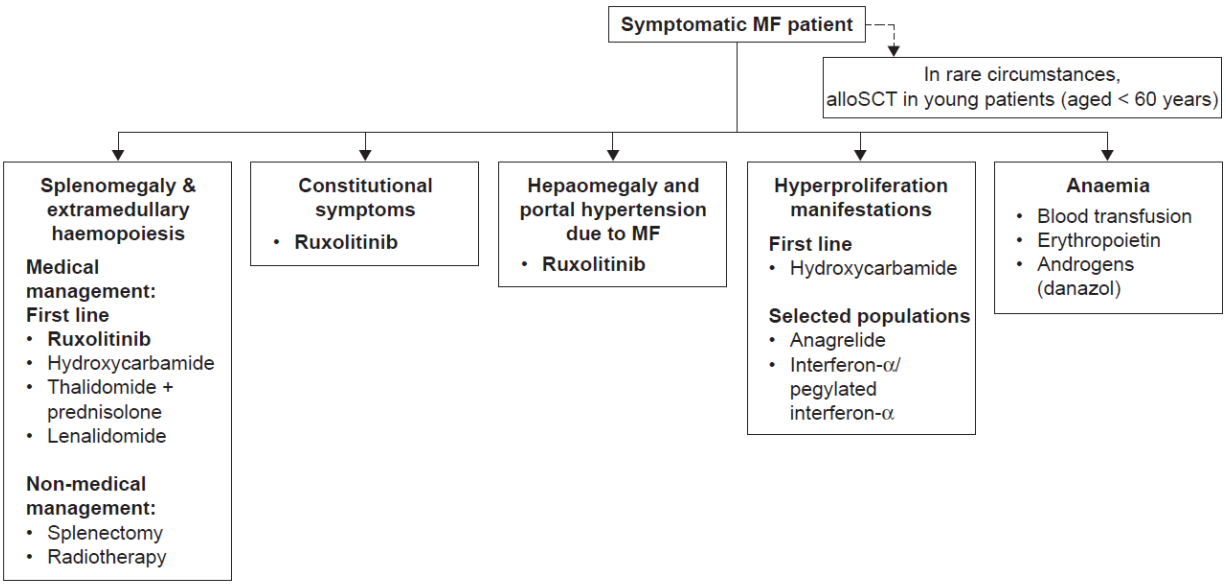
BCSH guidelines − ruxolitinib

In 2012, the British Committee for Standards in Haematology (BCSH) produced guidelines for the diagnosis and management of MF based on a detailed review of the published literature.[93] These guidelines provided direction on the investigation and management of primary MF, PPV-MF and PET-MF. They were published before the approval of ruxolitinib for the treatment of MF and made recommendations based on the available therapies while including a comment of the emerging data for JAK inhibitors. Following the approval of ruxolitinib the BCSH provided an update of their guidelines to recommend ruxolitinib as first-line therapy for this indication (the update only concerns the role of ruxolitinib and does not review other treatment recommendations).[8]

BCSH guidelines recommend ruxolitinib as first line therapy for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms

According to the updated guidelines, ruxolitinib is recommended as first line therapy for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms regardless of *JAK2* V617F mutation status and can be considered for patients with hepatomegaly and portal hypertension (Figure 6).

Figure 6 Algorithm for management of symptomatic MF based on BCSH guidelines



allo-SCT, allogeneic haematopoietic stem cell transplantation; BCSH, British Committee for Standards in Haematology; JAK, Janus kinase; MF, myelofibrosis.
Reilly et al., 2012 [93]; Reilly et al. 2014[8]

BCSH guidelines recommend that in patients with an inadequate response, the ruxolitinib dose should be modified to the maximum tolerated dose and continued for 24 weeks before deciding whether to discontinue

The BCSH also gives guidance on modifying the dose of ruxolitinib and deciding if treatment should be discontinued.[8] They recommend that where the response is inadequate the dose should be modified to the maximum tolerated dose and that treatment should be continued for 24 weeks. The decision to stop ruxolitinib therapy should be dependent upon a combination of different factors including the beneficial effect of treatment on splenomegaly and/or symptoms and presence or absence of toxicity. These recommendations are in agreement with a recent review of management of patients with MF which recommends that in responding patients, ruxolitinib should be continued as long as the symptoms of disease are better than at baseline and comments that responses are

usually seen within 3 to 6 months of starting therapy.[10] If no reduction in spleen size or symptoms is seen over this time period, alternative therapies should be considered.

Alternative medical treatments

The 2012 BCSH guidelines make the following recommendations regarding alternative medical treatments:

- Hydroxycarbamide is recommended for patients with symptomatic splenomegaly in the absence of cytopenias, although published data supporting its efficacy are limited. Complete responses are rare and doses of more than 1.5 g/day may be required to achieve a clinical effect. These high doses typically lead to problematic side effects, most notably significant cytopenias.
- Thalidomide plus prednisolone, or lenalidomide (for patients with anaemia and platelets over 100×10^9/L), is recommended as an alternative to hydroxycarbamide for patients with symptomatic splenomegaly and cytopenias.
- Recombinant erythropoietin and androgens, particularly danazol, are recommended as therapeutic options for the treatment of anaemia.

However, as described in section 4.7.4, the outcomes for

All conventional treatments except busulphan have not been approved for the treatment of MF

None of these conventional treatments (summarised in Table 8) has been evaluated for use in MF in a randomised controlled trial (RCT) and, with the exception of busulphan, none of them has FDA or EMA approval for the specific treatment of MF. Most conventional agents have only limited benefits for short periods of time (median 4 to 5 months), and many are associated with debilitating side effects which often lead to treatment discontinuation, or are associated with an increased risk of transformation to AML.[66] As a result, it is important that treatment is discontinued soon after patients become unresponsive.

Table 8 Summary of drugs used to treat myelofibrosis

Drug	Target symptom	Limitations
Hydroxycarbamide (hydroxyurea)	Control leucocytosis, thrombocytosis and splenomegaly	Modest response rates[68] and rarely induces complete resolution of splenomegaly[45] Resistance or intolerance is common and limits the feasibility of dose escalation[103] Can lead to leg ulcers[45,103] Can cause or exacerbate cytopenias preventing effective dose escalation[103] Gastrointestinal disturbances noted[104] May increase risk of transformation to AML[105]
Oral alkylators, busulphan and melphalan	Control leucocytosis, thrombocytosis and splenomegaly	May increase risk of transformation to AML[66,106]
Immunomodulators, thalidomide, lenalidomide and interferon-alpha	Cytopenias, splenomegaly and constitutional symptoms	Reduced RBC transfusion dependence and splenomegaly[107,108] AEs lead to frequent treatment discontinuation[3,109]
Erythroid-stimulating agents, erythropoietin and danazol (androgen therapy)	Anaemia	May increase risk of AML transformation[110]

AEs, adverse events; AML, acute myeloid leukaemia; RBC, red blood cell.

Allogeneic stem cell transplantation, splenectomy, splenic irradiation or observation

Allo-SCT is the only curative treatment but is generally reserved for patients under 45 years of age

The only treatment with curative potential for MF is allo-SCT. However, because transplant-related morbidity and mortality are high – the one-year transplant-related mortality rate is estimated to be around 30%[67,68] – allo-SCT is generally reserved for patients aged younger than 45 years[70,93] who are considered to have a poor prognosis if left untreated (ie intermediate-2 or high risk).[68] Thus, the majority of MF patients are unsuitable for transplantation and for most the aim of treatment is symptom-oriented palliation and improvement in HRQoL.[6,68,70]

Only limited benefit is achieved with splenic irradiation and splenectomy can be associated with complications

Other non-medical options include observation (or “watch and wait”), splenectomy or splenic irradiation[6,111] No significant survival benefit has been demonstrated following splenectomy in patients with MF and the potential benefits of such an intervention should be weighed against the complications.[6] Splenic irradiation can be used to decrease symptomatic splenomegaly but provides only transient reductions in spleen size and haematopoietic toxicity is common. Radiation therapy is considered a temporary measure to be employed in patients who are too ill to tolerate chemotherapy or splenectomy.[66,87]

Other guidelines and guidance

The only other guidelines relating to the treatment of MF are the 2011 European LeukemiaNet (ELN) recommendations, which address treatment of the major clinical issues in PMF including treatment of anaemia, splenomegaly and constitutional symptoms, and do not include the management of PPV-MF or PET-MF.[68] There are no relevant National Institute for Health and care Excellence (NICE) guidelines relating to management of MF. Previously, NICE assessed ruxolitinib in this indication and did not recommend ruxolitinib based on the available evidence. However, additional evidence is now available and the SMC has recently recommended ruxolitinib for management of disease-related splenomegaly or symptoms in patients with PMF, PPV-MF or PET-MF.

3.4 Life expectancy and number of people with the disease

3.4.1 Life expectancy

MF is a progressive disease which substantially reduces patient life expectancy. Approximately half of patients with MF die from MF disease-related symptoms and complications,[3,83,97,98] while a further 20% die following disease transformation to AML.[99] Historical data show that, for patients with PMF, median survival following diagnosis is 4.0 to 5.7 years overall,[83,99] while for patients with secondary MF, median survival following diagnosis is 5.7 to 7.5 years. [112,113] However, within each of these groups survival varies considerably and various prognostic systems have been devised with the aim of assisting therapeutic decision making.[69,83,89] Median survival using the various prognostic scoring systems varies from 1.3 years to 15.4 years, depending on the system and the risk classification.

Perhaps of more relevance to the UK, data from the HMRN audit of 98 patients indicated that the median survival for the total cohort, regardless of risk classification, was 3.36 (range 2.80–4.40) years.[52]

The COMFORT-II trial population is more representative of current treatment and the patients who would be eligible for ruxolitinib treatment than historical controls. Our analysis showed that BAT patients survived for only 26 months (median 28 months). The mean survival gain in the COMFORT-II trial was at least 21 months (ruxolitinib arm has not yet reached the median).

3.4.2 Patient population

The prevalence of MF is estimated to be 2.2 per 100,000 based on audit data for a region of England.[59] Thus 1,185 patients in England and 70 patients in Wales are estimated to be living with MF. Of these, approximately 50% are considered to be eligible to receive ruxolitinib corresponding to 630 patients,[60] given that a proportion of patients is asymptomatic or does not have splenomegaly at diagnosis and therefore would not be eligible for treatment at this stage.

Ruxolitinib is also licensed for treatment of patients with PV who are resistant or intolerant to hydroxycarbamide (HC).[21] The prevalence of PV is estimated to be 6.05 per 100 000 inhabitants.[114] Of these, 80% are assumed to receive HC and 13.4% are assumed to become resistant to or intolerant of HC (based on data from the HMRN audit).[115] Thus the number of PV patients who would be eligible to receive ruxolitinib is estimated to be 358 in England and Wales. The overall patient population eligible for ruxolitinib treatment is thus estimated to be below 1,000.

3.5 NICE guidance, pathways and commissioning guides

There are no relevant NICE guidance or guidelines for management of MF. See section 3.3 for relevant guidelines and recommendations. Previously NICE assessed ruxolitinib in this indication and did not recommend ruxolitinib based on the available evidence[116]. However additional evidence is now available and SMC has recently recommended ruxolitinib for management of disease-related splenomegaly or symptoms in patients with PMF, PPV-MF and PET-MF.[65]

3.6 Clinical guidelines and national policies

See section 3.3 for relevant guidelines and recommendations.

3.7 Issues relating to current clinical practice

Despite the publication of the BCSH guidelines for the management of MF,[8,93] there are a number of issues relating to current clinical practice for the management of these patients.

Firstly, although the BCSH guidelines recommend ruxolitinib as first-line therapy for symptomatic splenomegaly and/or MF-related constitutional symptoms, a recent survey of 75 UK physicians regarding management of 1994 patients with MF has reported that only half (51%) of patients were receiving drug therapy; a third had never received drug therapy and 16% had discontinued drug therapy.[117] Of those receiving drug therapy, only 45% were receiving ruxolitinib. A third (32%) were receiving hydroxycarbamide, 15% were receiving immunomodulatory drugs (IMiDs) and 2% were receiving androgens. Thus patients still receive a range of different therapies and many do not receive

active treatment. This is reflective of the situation prior to the approval of ruxolitinib. For example, a UK audit reported that seven different first-line treatments were used in 60 patients with MF who received active treatment within a 6 year period to 2010,[52] and in COMFORT-II, one of the pivotal phase 3 trials for ruxolitinib, the control treatment, BAT as chosen by the investigator included a range of different therapies such as hydroxycarbamide, glucocorticoids, epoetin alpha, IMiDs and purine analogues (see section 4.3 for details).[7]

Secondly, it is important to monitor response to treatment, especially so that therapy can be discontinued in patients who fail to respond, thereby allowing alternative treatments to be considered. Reductions in spleen size and resolution of disease-related symptoms such as constitutional symptoms, together with normalisation of peripheral blood counts, are key criteria used by the International Working Group for MF Research and Treatment (IWG-MRT) to define clinical improvement (see section 4.3 outcomes) for use in clinical trials.[107] The ELN guidelines also recognise spleen size, blood cell count and bone marrow morphology as appropriate criteria for assessment of response, but do not give details of possible definitions for response.[68] Thus there are no clear clinical recommendations for how to define a response to treatment and when to discontinue treatment. The BCSH guidelines make recommendations regarding when to discontinue therapies for anaemia,[93] and the revised BCSH guidelines provide recommendations for when to consider dose modification or discontinuation of ruxolitinib (see section 3.3).[8]

3.8 Equality

MF is generally diagnosed in individuals over 60 years of age; the median age at diagnosis is 65 years.[83-86] In 2011, a UK Department of Health strategy document expressed concerns over the under-treatment of the elderly, and found that age was a major factor in determining treatment,[118] and the following year a Department of Health consultation document defined, as one of the care objectives for the newly-created NHS Commissioning Board and Clinical Commissioning Groups, the need to comply with legislation about age discrimination in the provision of services, and noted that the elderly have been historically under-served by the health service.[119] Equity issues regarding the elderly still remain, as evident from a report published by the House of Commons Committee of Public Accounts in March 2015 stating that the inequalities and variations that were highlighted in 2011 still persist and that survival rates and access to treatment are unjustifiably poor for older people in particular.[18]

MF is also a highly rare orphan disease.[19] The 2010 Department of Health “Cancer Patient Experience Survey” found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer.[20] The 2014 report also states the need to focus on improving care and survival for patients with rarer cancers, indicating that this is still an important concern.[120]

Patients with MF may therefore be less likely to receive extensive cancer treatment because of their age, and may also be at risk of receiving poorer treatment because of the rarity of their disease. Equality of access may be achieved by ensuring that the benefits of newer treatments reach these patients.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Overview and methodology

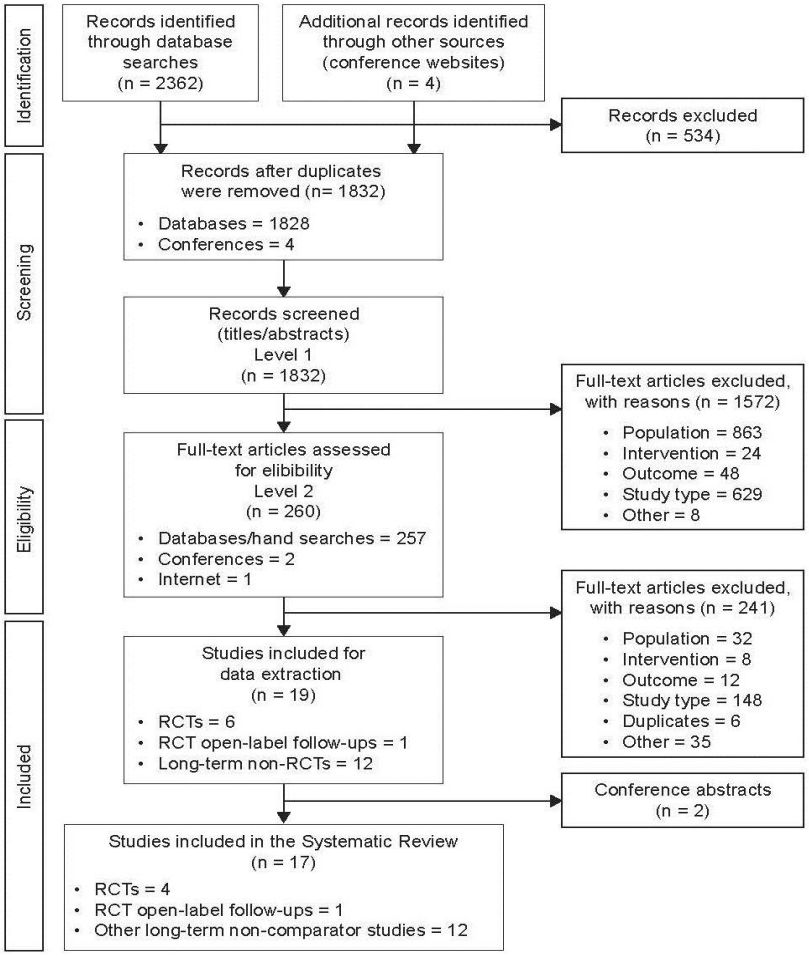
An initial systematic review (SR) was performed on 27 July 2011 to identify all clinical and observational studies of interventions in patients with MF, including studies comparing ruxolitinib with other treatments that are commonly used to treat MF or placebo and non-comparative studies. The initial SR was updated on 19 March 2012. Two further updates were then performed using a similar strategy but slightly different methodology; these were performed on 9 December 2013 and on 10 December 2014. A broad search strategy was employed to capture all studies which reported clinical evidence for ruxolitinib and other therapeutic agents available in the UK for the treatment of disease-related splenomegaly or symptoms in adult patients with primary MF, PPV-MF or PET-MF Specific inclusion and exclusion criteria were utilised to identify relevant references. Data pertaining to key efficacy, effectiveness and safety outcomes were assessed. After full-text screening of selected articles, studies investigating ruxolitinib were selected. Details of the methodology for the 2011/12 and 2013/14 reviews are provided in Section 8 (appendices), including details of the search strings, data sources, inclusion and exclusion criteria and abstraction methodology.

4.1.2 Search results

2011/12 review

Searches of the electronic databases for the period 1 January 1960 to 19 March 2012 identified a total of 2362 studies and searches of conference websites yielded a total of four articles. Of these, 1832 titles or abstracts entered the first step of screening and 260 titles or abstracts advanced to the second step of full text review. After full-text review, four RCTs met the inclusion criteria, of which two studies were of ruxolitinib in patients with MF and two were of other treatments. The review also identified one open-label follow-up of an RCT (not in ruxolitinib), and 12 other long-term non-RCT studies, one of which investigated ruxolitinib. A flow diagram of the article selection process is shown in Figure 7.

Figure 7 PRISMA diagram of included and excluded studies in the systematic review

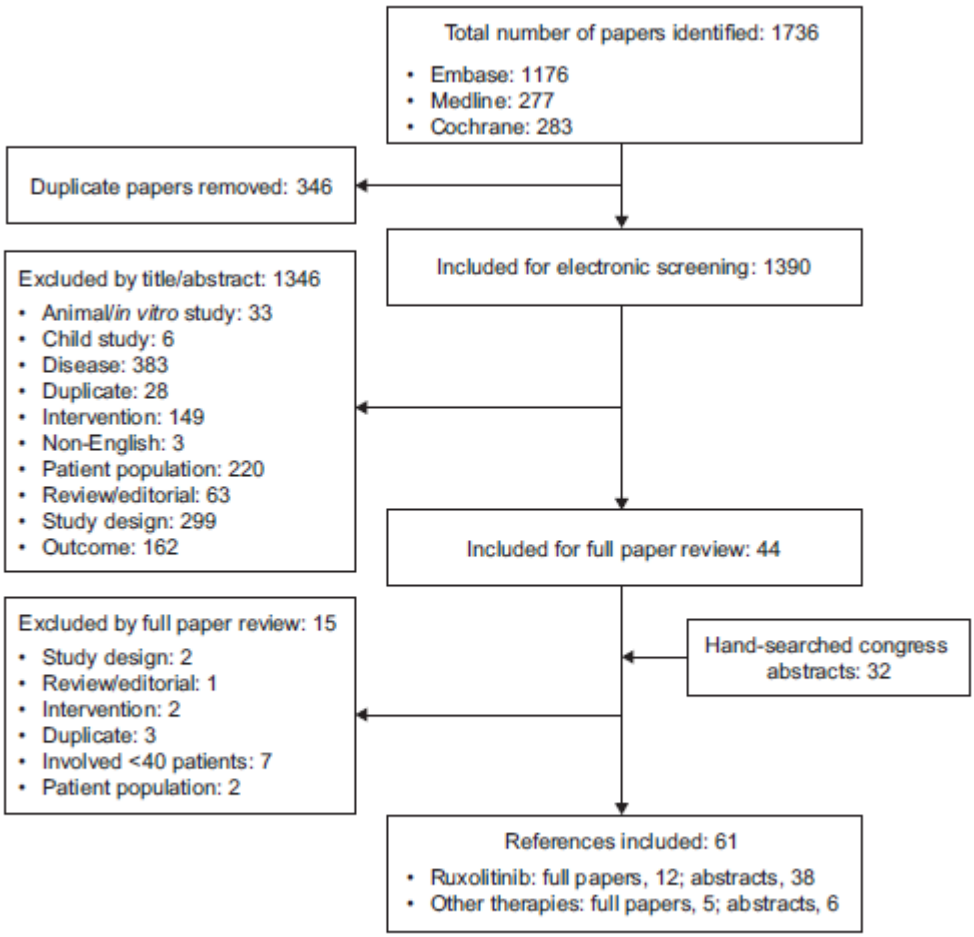


PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

2013/14 review

Taken together, the two searches identified 1736 articles, 346 of which were duplicates and were removed, resulting in 1390 articles being included for electronic screening (Figure 8). After applying inclusion and exclusion criteria, 1346 articles were excluded and 44 articles were ordered for a full reference review. Hand-searching of congress abstracts identified 32 further relevant abstracts. Of the 76 references, 15 were excluded on full review, leaving 61 references from which data were extracted into summary tables. Of these 50 concern ruxolitinib.

Figure 8 PRISMA diagram of studies in the clinical systematic review of treatments for MF



MF, myelofibrosis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

4.2 List of relevant randomised controlled trials

The systematic search identified two relevant RCTs of ruxolitinib in patients with MF: COMFORT-I[25,26] and COMFORT-II (see Table 9). (The full publication of the 3-year data from COMFORT-II was published after the search data for the 2014 SR and hence was not identified in the SR but is included in this submission.) Both studies were multicentre, parallel-group, phase 3 studies that were designed to assess the efficacy and tolerability of different doses of ruxolitinib in patients with PMF, PPV-MF and PET-MF.

The COMFORT-II trial evaluated the efficacy and safety of ruxolitinib versus BAT in patients with PMF, PPV-MF and PET-MF. BAT included a wide range of different treatments including observation only (see Table 11 for further details), thus highlighting that there is no standard of care and no

clinical consensus regarding the best treatments for MF.[7,121] This RCT evaluates ruxolitinib against current real-world clinical options for the treatment of MF, and is therefore relevant to the decision problem. The COMFORT-II study was not blinded as treatment in the control group, BAT, was chosen by the investigator. The open label design allowed the clinician to adjust doses and manage patients with the chosen therapy. COMFORT-I was double-blinded and therefore provides valuable supportive data.

Both RCTs are discussed in full in this dossier. COMFORT-II is used as the primary source of data for the health economic analysis because it provides data on the relevant comparators. COMFORT-I provides key data on symptoms.

Table 9 List of relevant randomised control trials of ruxolitinib in MF

Trial	Intervention	Comparator	Population	Primary study reference
COMFORT-I (NCT00952289) (INCB 18424-351)	Rux (15 mg or 20 mg bid)	Placebo	Subjects with PMF, PPV-MF or PET-MF	Verstovsek et al. *N Engl J Med* 2012;366:799–807[26]
COMFORT-II (NCT00934544) (INC424A2532)[7]	Rux (15 mg or 20 mg bid)	BAT	Subjects with PMF, PPV-MF or PET-MF	Harrison *e*t al. *N Engl J Med* 2012;366:787–98[7]

BAT, best available therapy; bid, twice daily; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; MF, myelofibrosis; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis; Rux, ruxolitinib.

4.3 Summary of methodology of the relevant randomised controlled trials: Phase 3 studies COMFORT-I and COMFORT-II

Study design

A summary of the comparative methodology of the COMFORT-I and COMFORT-II studies is shown in Table 10.[7,26] The phase 3 studies were designed with some similarities to allow for assessment of reproducibility of results, but differ significantly in their design. COMFORT-I was a 24-week randomised, double-blind, placebo-controlled study and COMFORT-II was a 48-week open-label randomised study comparing ruxolitinib and BAT. COMFORT-I was conducted at 89 sites in the USA, Canada and Australia and COMFORT-II was conducted at 57 sites in Europe, including centres in the UK. Both studies assessed oral ruxolitinib 15 mg or 20 mg twice daily (bid) versus matched placebo (COMFORT-I) or versus BAT (COMFORT-II) and included a number of both clinical and HRQoL outcomes together with assessments of safety.

Table 10 Comparative summary of methodology of the randomised control trials for ruxolitinib in MF

Trial number (acronym)	**COMFORT-I**[24-26] 26,122	**COMFORT-II**[7,23] 7,121
Location	Conducted at 112 sites in the United States, Canada, Australia	Conducted at 61 sites in Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, United Kingdom
Trial design	Randomised, double-blind, placebo controlled trial	Open-label, randomised, active-controlled trial
Eligibility criteria for participants	Inclusion criteria: Age ≥ 18 years Diagnosis of PMF, PPV-MF or PET-MF according to WHO criteria (2008) Life expectancy of ≥ 6 months An IPSS score of 2 (intermediate-2 risk level) or ≥ 3 (high risk) ECOG performance status of ≤ 3 (scale of 0 to 5) Palpable spleen measuring ≥ 5 cm below the left costal margin Peripheral blood blast count of < 10% Absolute peripheral blood CD34+ cell count > 20 × 106/L Disease that was resistant or refractory to available treatment or to be intolerant of or not candidates for such therapy. Disease that required treatment defined by any of the following: IPSS prognostic score ≥ 3, palpable spleen length ≥ 10 cm, score of > 3 on at least 2 items or score of 5 on 1 item on the MF-SAF v2.0 diary Exclusion criteria: Absolute neutrophil count ≤1 × 109/L or platelet count < 100 × 109/L) Direct bilirubin ≥ 2 × ULN; alanine aminotransferase ≥ 2.5 × ULN; creatinine > 2.0 mg/L) History of malignancy within the	Inclusion criteria: Age ≥ 18 years Diagnosis of PMF, PPV-MF or PET-MF Life expectancy of > 6 months An IPSS score of 2 (intermediate-2 risk level) or ≥ 3 (high risk) ECOG performance status of ≤ 3 (scale of 0 to 5) Palpable spleen measuring ≥ 5 cm below the costal margin Peripheral blood blast count of < 10% Platelet count ≥ 100 × 109/L without assistance of growth or thrombopoietic factors, or platelet transfusions Absolute neutrophil count ≥ 1 × 109/L Exclusion criteria: History of ANC ≤ 0.5 × 109/L or platelet count < 50 × 109/L except during treatment for myeloproliferative neoplasm or cytotoxic therapy Inadequate liver or renal function as demonstrated by direct bilirubin > 2.0 × ULN,

	previous 5 years Splenic irradiation within 12 months prior to randomisation Prior treatment with any JAK inhibitor or concurrent treatment with other prohibited medications	alanine aminotransferase > 2.5 × ULN, creatinine > 2.0 mg/L History of malignancy in past 5 years Splenic irradiation within 12 months prior to screening Previous treatment with JAK inhibitor Pregnant or breastfeeding
Settings and locations where the data were collected	112 sites in the United States, Canada, Australia	61 sites in Europe
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication	<u>Intervention(s) and comparator(s)</u> Oral rux tablet 15 mg or 20 mg bid (n = 155) Matched placebo (n = 154) <u>Criteria for crossover from control to rux</u> Up to week 24: required both symptom worsening and ≥ 25% spleen volume increase from baseline After week 24: required ≥ 25% spleen volume increase from baseline <u>Criteria for continuing treatment/extension phase</u> Up to week 24, patients randomised to rux who were unblinded for symptomatic spleen growth had to withdraw from the study After week 24, patients randomised to rux who were unblinded for spleen growth could remain in the study if the investigator determined they were receiving benefit	<u>Intervention(s) and comparator(s)</u> Oral rux tablet 15 mg or 20 mg bid (n = 146) BAT (n = 73) <u>Criteria for crossover from control to rux</u> At any time if progression occurred defined as ≥ 25% increase in spleen volume from on-study nadir (including baseline) or splenectomy <u>Criteria for continuing treatment/extension phase</u> If a qualifying progression event occurred: patients randomly assigned to receive BAT could receive rux patients randomly assigned to rux could continue to receive rux if they were still deriving a clinical benefit
Primary outcomes (including scoring methods and timings of assessments)	Proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 24, assessed by MRI or CT scan	Proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume at week 48, assessed by MRI or CT scan
Secondary outcomes (including scoring methods and timings of	Duration of maintenance of reduction in spleen volume in patients initially randomised to	Proportion of patients achieving a ≥ 35% reduction in spleen volume at week 24, assessed

assessments)	receive rux, assessed by MRI or CT scan Proportion of patients who had a ≥ 50% reduction from baseline in week 24 TSS, measured by the modified MF-SAF v2.0 diary Change from baseline in week 24 TSS, measured by the modified MF-SAF v2.0 diary Overall survival HRQoL assessments using EORTC QLQ-C30 and PROMIS Fatigue scale (exploratory endpoints)	by MRI or CT Duration of maintenance of spleen volume reduction ≥ 35% reduction from baseline and 25% above the on-study nadir Time to achieve a first ≥ 35% reduction in spleen volume from baseline Progression-free survival Leukaemia-free survival Overall survival Transfusion dependency/independency Change in BM histomorphology HRQoL assessments using EORTC QLQ-C30 and FACT-Lym (exploratory endpoints)
Pre-planned subgroups	MF subtype	MF subtype, sex and prognostic category

ANC, absolute neutrophil count; BAT, best available therapy; bid, twice daily; BM, bone marrow; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; CT, computerised tomography; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; HRQoL, health-related quality of life; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; MF-SAF v2.0, Myelofibrosis Symptom Assessment Form version 2.0; MRI, magnetic resonance imaging; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis; PROMIS, Patient Reported Outcomes Measurement Information System; rux, ruxolitinib; TSS, total symptom score; ULN, upper limit of normal; WHO, World Health Organization.
Verstovsek *et al.* 2012, 2013, 2015;[24-26] Harrison *et al.* 2012[7]; Cervantes et al 2013[23]; Verstovsek et al. 2012;[26,122] Harrison et al. 2012.[7,121]; Clinical study reports[123,124]

4.3.1 Similarities and differences in design

Similarities

In both studies, the starting dose of ruxolitinib for each individual patient was determined according to baseline platelet counts: patients with a platelet count of 100 to 200 × 10^9/L received 15 mg bid, and patients with a count exceeding 200 × 10^9/L received 20 mg bid. The dose could be increased by 5 mg bid up to a maximum of 25 mg bid to increase efficacy and could be decreased for reasons of safety (for example, dosage was reduced if neutropenia or thrombocytopenia developed).

For both studies, the primary endpoint was the proportion of patients achieving a 35% or greater reduction in spleen volume (at 48 weeks in COMFORT-II and at 24 weeks in COMFORT-I). This degree of response (ie 35% or greater reduction in spleen volume measured by magnetic resonance

imaging [MRI]) corresponds to a 50% reduction in palpable spleen length (as established in the phase 1/2 study of ruxolitinib in patients with MF; see appendix 8.18).[73] Spleen volume was assessed by MRI or by computed tomography (CT) (for patients who were not suitable candidates for MRI) at baseline and at 12-week intervals and was independently reviewed. Images were read centrally by a reader unaware of the treatment. Both studies also included assessment of spleen length at study visits (4-week intervals).

Both studies also included assessments of symptoms and HRQoL (detailed in appendix 8.17). In COMFORT-I, MF symptoms were assessed using the modified Myelofibrosis Symptom Assessment Form (MF-SAF) v2.0 diary; assessments were performed daily for 7 days prior to starting the study drug and up to week 24 (see section 4.3.2 for further details). Patient-reported outcome assessments in COMFORT-I, including Patient's Global Impression of Change (PGIC) questionnaire, EORTC QLQ-C30 and Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire, were performed at each scheduled visit. In COMFORT-II, HRQoL assessments (EORTC QLC-C30 and Functional Assessment of Cancer Therapy – Lymphoma [FACT-Lym] questionnaire) were performed at baseline and weeks 8, 16, 24 and 48.

Differences

In both studies, patients in the control group could cross over to receive ruxolitinib under specified conditions, but the criteria for early crossover to ruxolitinib were less stringent in COMFORT-II than in COMFORT-I. In COMFORT-I, patients were eligible for early unblinding if they had a 25% or greater increase in spleen volume from baseline, and those receiving placebo could cross over to ruxolitinib treatment. For early unblinding to occur before week 24, patients also had to demonstrate worsening early satiety accompanied by weight loss or worsening splenic pain accompanied by increased narcotic requirements. After completion of the primary analysis (when all patients had completed the week 24 evaluation or discontinued treatment and 50% of patients had completed the week 36 visit), the study was unblinded and all patients randomised to receive placebo could cross over to receive ruxolitinib. Patients who crossed over early were not included in any analyses except for OS.

In COMFORT-II, patients with disease progression (defined according to the study protocol as either 25% or greater increase in spleen volume from on-study nadir, including baseline, or a splenectomy) could discontinue from the randomised phase of the study and enter the extension phase at any time. In the extension phase, patients previously in the BAT group could receive ruxolitinib (if they met safety criteria) and patients previously in the ruxolitinib group could continue to receive ruxolitinib if they were still deriving a clinical benefit.

In COMFORT-II, patients in the control group received BAT, which included any commercially available agents (as monotherapy or in combination) or no therapy at all, and could be changed or combined with another therapy at any time during the study (Table 11). During the study, 49 patients

(67% of those in the BAT group) received at least one active therapy and 24 (33%) received no active treatment. The most commonly used therapies were antineoplastic agents (51%; n = 37) – of which hydroxycarbamide comprised 92% (n = 34 patients) – and glucocorticoids (16%; n = 12) (Table 11). The only other therapies used in five or more patients were prednisone/prednisolone (n = 9) and epoetin-alpha (n = 5).

Table 11 Treatments received in COMFORT-II in patients randomised to BAT and who received active treatment

Treatment	Frequency, n (%)
Antineoplastic agents	37 (51)
Hydroxycarbamide	34 (47)
Glucocorticoids	12 (16)
Epoetin alpha	5 (7)
Immunomodulators	5 (7)
Purine analogues	4 (6)
Androgens	3 (4)
Interferons	3 (4)
Nitrogen mustard analogues	2 (3)
Pyrimidine analogues	2 (3)

BAT, best available therapy

4.3.2 Patients

A summary of the inclusion and exclusion criteria for COMFORT-I and COMFORT-II are shown in Table 10.

In both COMFORT trials, patients aged 18 years and older with intermediate-2 risk or high-risk (according to the International Prognostic Scoring System [IPSS] – see Appendix 8.17 for details) PMF, PPV-MF or PET-MF, and a palpable spleen length of 5 cm or greater below the left costal margin, were eligible for enrolment.[7,26,121,122] Both studies enrolled patients with MF irrespective of their *JAK2V617F* mutation status – *JAK2V617F* is one of several mutations that have been associated with MF in some but not all patients.[3,70]

In addition, eligibility for COMFORT-I required patients to be resistant or refractory to, intolerant of, or not suitable candidates for BAT, and to be indicated for the treatment of MF. These patients must have discontinued other investigational agents for MF 14 days or 6 half-lives prior to the first baseline visit. In COMFORT-II, patients who were not candidates for stem cell transplantation were also eligible for enrolment. Both studies excluded patients who had received prior treatment with a JAK inhibitor.

4.3.3 Outcomes

The primary and secondary outcomes of the COMFORT-I and II studies are described in Table 10.[7,26,121,122] For both studies, the primary and key secondary endpoints are highly reproducible, not subject to investigator bias, and correspond to the IWG-MRT definition of clinical improvement for nearly all patients with splenomegaly.

Reduction in spleen volume and length

In both studies, the primary outcome was the proportion of patients achieving a reduction in spleen volume (measured by MRI or CT) from baseline of 35% or greater at week 24 (COMFORT-I) or week 48 (COMFORT-II). This degree of response (ie 35% or greater reduction in spleen volume measured by MRI) corresponds to a 50% reduction in palpable spleen length (as established in the phase 1/2 study of ruxolitinib in patients with MF; see Appendix 8.18).[73] It also corresponds to the definition of a spleen response defined in the recent IWG-MRT and ELN consensus report which makes recommendations regarding response criteria for use in clinical trials (see Table 12).[125] Assessment of change in spleen volume rather than length was chosen for the assessment of spleen response in the clinical trial setting because it is a more robust and objective measurement of spleen size than physical examination by palpation. Independent central review of spleen volume by MRI or CT was considered by the regulatory authorities for trial registration to be an appropriate endpoint analysis for these clinical trials.

Table 12 Revised IWG-MRT and ELN response criteria for MF

Response categories	Required criteria (for all response categories, benefit must last for ≥ 12 weeks to qualify as a response)
CR	Bone marrow: Age-adjusted normocellularity; < 5% blasts; ≤ grade 1 MF and Peripheral blood: haemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; Platelet count ≥ 100 × 10^9/L and < UNL;< 2% immature myeloid cells and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EHM
PR	Peripheral blood: haemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; platelet count ≥ 100 × 10^9/L and < UNL;< 2% immature myeloid cells and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EHM or Bone marrow: Age-adjusted normocellularity; < 5% blasts; ≤ grade 1 MF and peripheral blood: haemoglobin ≥ 85 but < 100 g/L and < UNL; neutrophil count ≥ 1 × 10^9/L and < UNL; platelet count ≥ 50, but < 100 × 10^9/L and < UNL;< 2% immature myeloid cells and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EHM
Clinical improvement (CI)	The achievement of anaemia, spleen or symptoms response without progressive disease or increase in severity of anaemia, thrombocytopenia, or neutropenia

Response categories	**Required criteria (for all response categories, benefit must last for ≥ 12 weeks to qualify as a response)**
Anaemia response	Transfusion-independent patients: a ≥ 20 g/L increase in haemoglobin level Transfusion-dependent patients: becoming transfusion-independent
Spleen response	A baseline splenomegaly that is palpable at 5 to 10 cm, below the LCM, becomes not palpable or A baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50% A baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not eligible for spleen response A spleen response requires confirmation by MRI or computed tomography showing ≤ 35% spleen volume reduction
Symptoms response	A ≥ 50% reduction in the MPN-SAF TSS
Progressive disease	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5 to 10 cm or A ≥ 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or Leukaemic transformation confirmed by a bone marrow blast count of ≥ 20% or A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1×10^9/L that last for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anaemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month
	Recommendations for assessing treatment-induced cytogenetic and molecular changes
Cytogenetic remission	A least 10 metaphases must be analysed for cytogenetic response evaluation and requires confirmation by repeat testing within 6 months window CR: eradication of a pre-existing abnormality PR: ≥ 50% reduction in abnormal metaphases (partial response applies only to patients with at least ten abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analysed in peripheral blood granulocytes and requires confirmation by repeat testing within 6 months window CR: eradication of a pre-existing abnormality PR: ≥ 50% decrease in allele burden (partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

CI, clinical improvement; CR, complete response; ELN, European LeukemiaNet; EMH, extramedullary haematopoiesis; IWG-MRT, International Working Group for MF Research and Treatment; LCM; left costal

margin; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; MRI, magnetic resonance imaging; PR, partial response; TSS, total symptom score; UNL, upper normal limit
Tefferi el al. 2013.[125]

In routine clinical practice, spleen length, assessed by manual palpation, is generally assessed rather than spleen volume. Spleen length has been shown to correspond well with spleen volume demonstrated by imaging techniques and the COMFORT studies also included assessment of spleen length at study visits (4-week intervals).

In COMFORT-I, a secondary outcome was duration of reduction in spleen volume. In COMFORT-II, secondary outcomes included the proportion of patients achieving a 35% or greater reduction in spleen volume measured by MRI at week 24, duration of maintenance of spleen volume reduction and time to first reduction in spleen volume of at least 35% from baseline.

Symptoms

The COMFORT-I study included, as a key secondary endpoint, the proportion of patients who had a 50% or greater reduction from baseline in total symptom score (TSS) at week 24.[26] (This endpoint was not assessed in the extension study.)[24] A 50% reduction in TSS was chosen as an endpoint for this trial because a reduction of this magnitude correlated with a significant improvement in disease symptoms in the phase 1/2 trial.[73] This definition of symptom response is now endorsed by the revised IWG-MRT and ELN consensus report, which includes at least a 50% reduction in TSS as a clinical response criterion for demonstrating clinical improvement.[125] This highlights the importance of quantifying drug activity in terms of improving symptom burden. TSS was assessed using the modified MF-SAF v2.0. The MF-SAF (detailed in Appendix 8.17) is a disease-specific tool that has been developed and validated (in consultation with the FDA) for use specifically in patients with MF to measure the burden of disease symptoms.[14] The tool includes seven questions that assess night sweats, itching (pruritus), abdominal discomfort, pain under the ribs on the left side, feeling of fullness (early satiety), muscle or bone pain and inactivity on a scale of 0 (absent) to 10 (worst imaginable). The TSS is the sum of the scores for the first six of these seven symptoms and excludes inactivity, giving a total value out of 60. Change in body weight from baseline was included as an exploratory endpoint in this study.

Fatigue is also a major symptom associated with MF which is not captured in the MF-SAF. However, this is assessed by the EORTC QLQ-C30 and PROMIS as described below.

HRQoL

Effects on HRQoL were assessed in COMFORT-I and COMFORT-II using the disease-specific EORTC QLQ-C30 and FACT-Lym scale, and the more general PGIC questionnaire and PROMIS Fatigue scale (see Appendix 8.17 for details of these tools).[7,26,34,35] Data for all measures were

collected during the core study and the EORTC QLQ-C30 was administered during long-term follow-up.

Overall survival

Both studies and their long-term extension follow-ups have assessed OS.[7,25,26] A pooled analysis of data from COMFORT-I and COMFORT-II provides data on 3-year survival from these studies, adjusted for baseline characteristics and for crossover.[36] and an analysis of 3-year survival from COMFORT-I adjusted from crossover has also been reported [25]

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Details of the statistical analyses used in both COMFORT trials are described in Table 13. For both COMFORT-I and COMFORT-II, the primary efficacy variable was the proportion of patients with a 35% or greater reduction in spleen volume. Both studies were designed to have a 90% or greater power to detect a treatment difference in the primary endpoint at the two-sided alpha level of 0.05 using the chi-squared test.[7,26,121,122] The studies were not powered to detect significant differences in survival outcomes.

Patients were analysed on an intention-to-treat (ITT) basis for all efficacy endpoints. Patients who discontinued drug or crossed over before 24 weeks (in COMFORT-I) or did not have a 48-week assessment of spleen volume (in COMFORT-II because of discontinuation and entering the open-label extension phase) were counted as non-responders (for change in spleen volume and symptom score). In COMFORT-I, the primary endpoint was analysed using the Fisher exact test because there were so few responders in the placebo group. In COMFORT-II, the two groups were compared using the exact Cochran–Mantel–Haenszel test, stratified according to prognostic risk category. In both studies, comparative secondary efficacy variables were tested in a fixed sequence-testing procedure and time-to-event data were analysed using the Kaplan–Meier method.

Table 13 Summary of statistical analyses in RCTs for ruxolitinib in MF

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
COMFORT-I[26]	To evaluate the efficacy, safety and tolerability of rux bid compared with placebo for patients with intermediate-2 or high-risk MF	Primary endpoint (proportion achieving ≥ 35% reduction in spleen volume from baseline to week 24) was analysed using Fisher's Exact test. Secondary endpoints were analysed at an alpha level of 0.05 using χ^2 test (proportion with ≥ 50% TSS reduction from baseline in week 24), Wilcoxon signed rank-sum test and analysis of covariance (change in TSS from baseline to week 24) log-rank test (overall survival), and Kaplan–Meier (durability of spleen response and survival time)	It was assumed that at least 30% of patients in the rux group would achieve a ≥ 35% reduction from baseline to week 24, and that the rate for the patients receiving the placebo would be no more than 10%. Under this assumption, a sample size of 240 people (120 per group) would provide sufficient statistical power (97%) to detect a treatment difference in the primary endpoint at the two-sided alpha level of 0.05 using the χ^2 test.	All patients with missing baseline values were excluded from the analysis of that variable. People who discontinued or crossed over before 24 weeks were counted as non-responders in analyses of change in spleen volume and TSS
COMFORT-II[7]	To compare efficacy and safety of rux with BAT in patients with PMF, PPV-MF, or PET-MF	Primary endpoint (the proportion achieving a ≥ 35% reduction in spleen volume from baseline at week 48) was analysed by using the CHM test. The key secondary endpoint was to be tested only if the primary endpoint showed significance at the two-sided alpha level of 0.05 Survival curves for leukaemia-free survival, overall survival and progression-free survival were estimated using the Kaplan–Meier method Hazard ratios and the corresponding 95% confidence intervals were estimated using the Cox proportional hazards model, stratified according to baseline prognostic category; the between-group treatment difference was tested with the use of a stratified two-sided log-rank test	Assuming at least 35% of patients receiving the active treatment would achieve a 35% reduction from baseline to week 48, and that rate for the control participants would be no more than 10%, a sample size of 150 people (100 in active treatment group and 50 in control) would provide statistical power of at least 90% to detect a treatment difference in the primary endpoint at the 2-sided alpha level of 0.05 using the χ^2 test	Patients were required to have a baseline spleen volume measurement to be included in the primary analysis. People with a missing week 48 spleen volume measurement was counted as a non-responder

BAT, best available therapy; bid, twice daily; CHM, Cochran–Mantel–Haenszel; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; MF, myelofibrosis; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis; RCT, randomised controlled trial; TSS, total symptom score.

Verstovsek et al. 2012;[26] Harrison et al. 2012.[7]

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Patient disposition

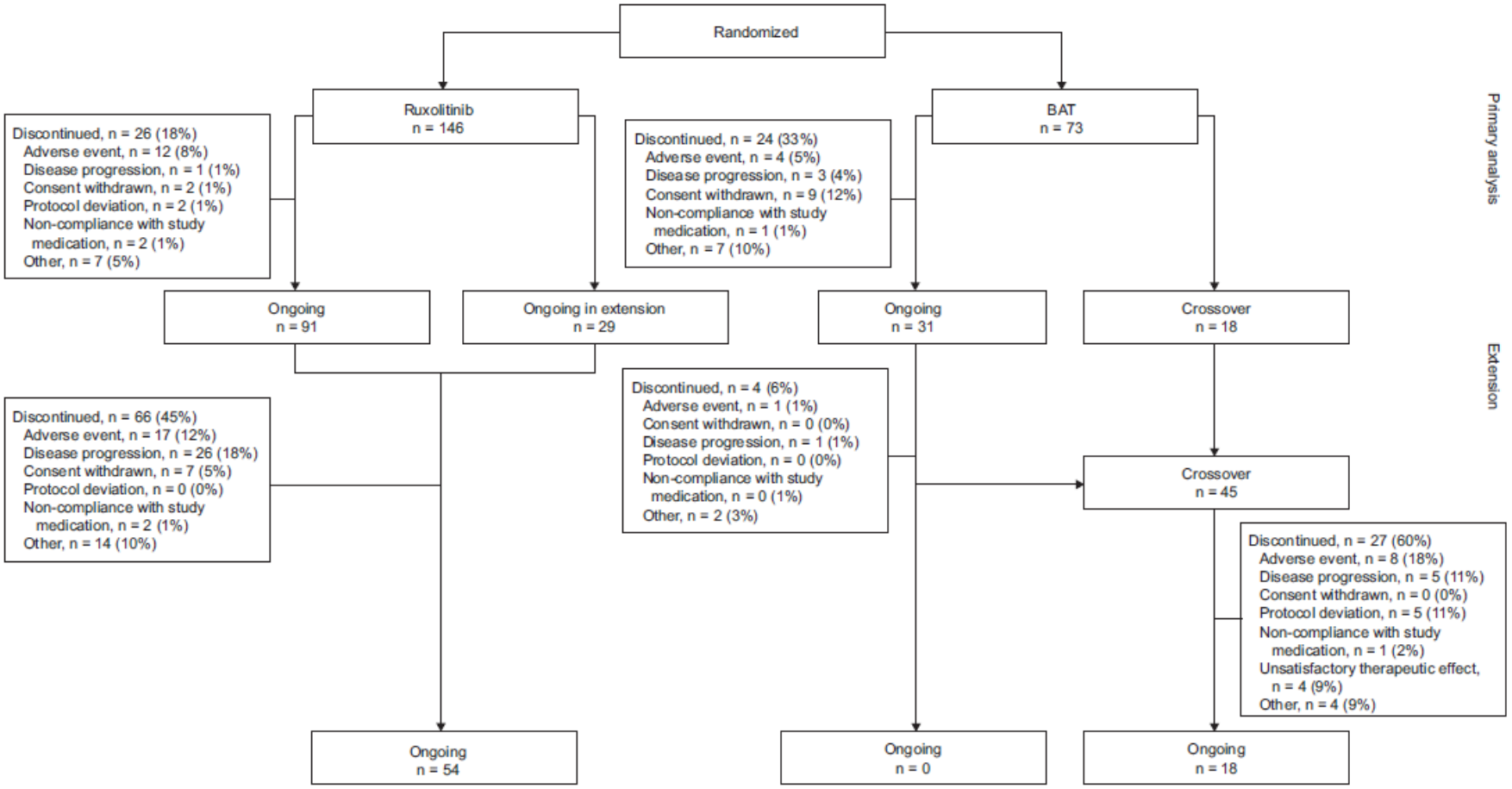
In the two studies, at the last reported follow- up (COMFORT-II, 3.5 years and COMFORT-I, 3 years) one third to a half of all patients randomised to ruxolitinib remained on treatment (COMFORT-II, 37% and COMFORT-I, 50%) as did 40% to 51% of patients who crossed over to ruxolitinib, indicating continued benefit for active treatment.[22,25]

COMFORT-II

The patient disposition for the COMFORT-II study, including the primary reasons for treatment discontinuation, is shown in Figure 9.[7,23,121] From July 2009 to January 2010, a total of 219 patients were enrolled, with 146 randomised to ruxolitinib and 73 to BAT. At the time of primary analysis data cut-off (when the last patient had completed the 48-week visit), 91 (62.3%) patients in the ruxolitinib group and 31 (42.5%) patients in the BAT group were ongoing in the randomised treatment phase. In the ruxolitinib group, 29 (19.9%) patients entered the extension phase because they were still receiving some clinical benefit and 26 (17.8%) discontinued treatment; the main reason for discontinuation was AEs (8.2%). Of the BAT group, 18 (24.7%) patients crossed over to receive ruxolitinib in the extension study and 24 (32.9%) discontinued treatment; the main reason was withdrawal of consent (12.3%).

In total, 120 of 146 (82.2%) patients randomised to ruxolitinib entered the extension phase and 54 (37.0%) remained on treatment at the 3.5-year follow-up. The main reasons for discontinuing over the 3.5-year period were AEs (19.9%) and disease progression (18.5%). Of the BAT group, 45 (61.6%) patients crossed over to receive ruxolitinib (median time to crossover was 66 weeks) in the extension study and 18 (40.0% of those who crossed over) remained on treatment at the 3.5-year follow-up. The main reasons for discontinuing from ruxolitinib therapy in the BAT crossover group were AEs (17.8%), disease progression (11.1%) and protocol deviation (11.1%). No patients remained on BAT at 3.5 years.

Figure 9 CONSORT flow diagram for COMFORT-II



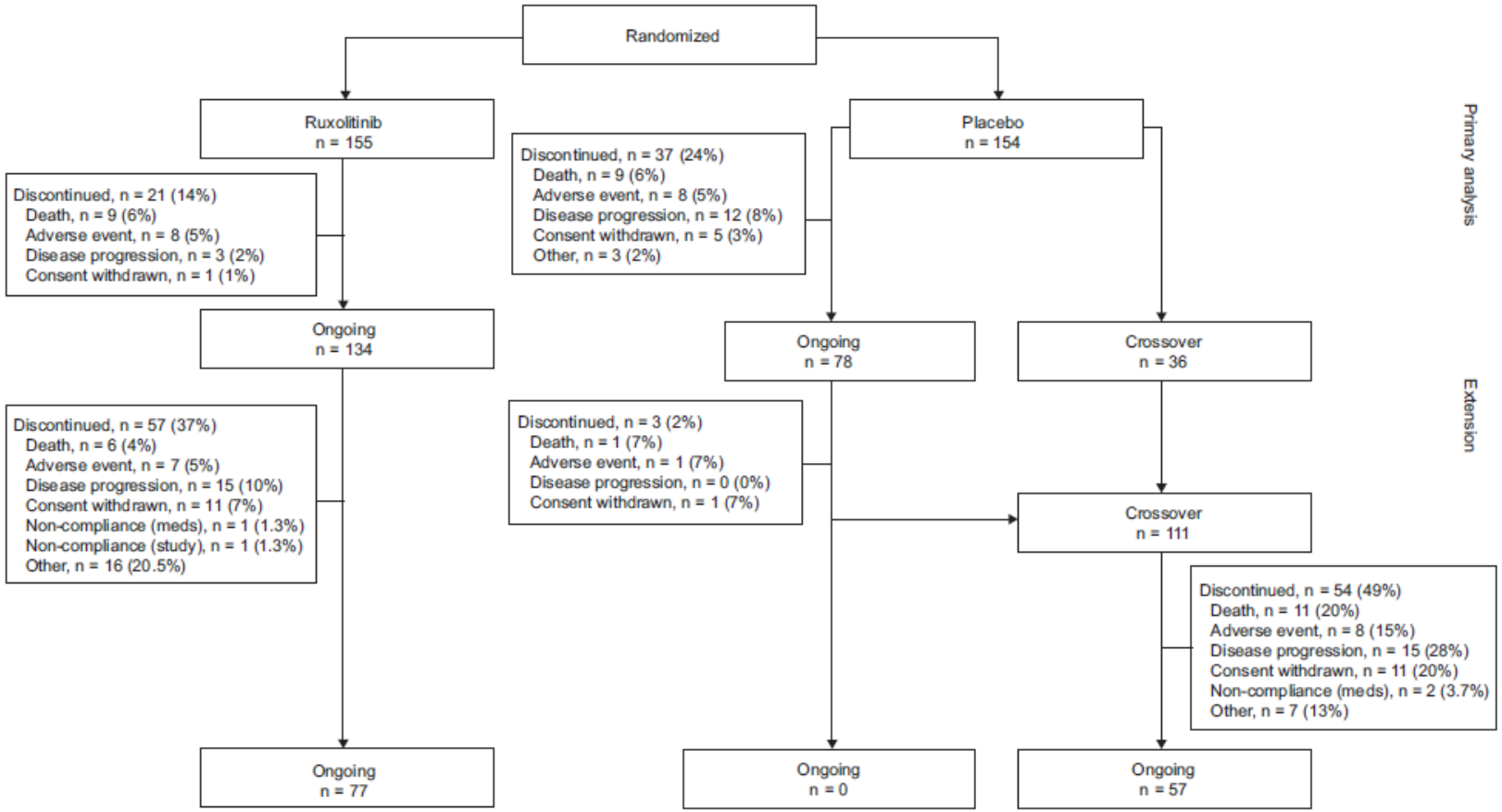
BAT, best available therapy; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; CONSORT, Consolidated Standards of Reporting Trials Harrison et al. 2012, [7,121] Cervantes et al.[23]

COMFORT-I

The patient disposition for the COMFORT-I study, including the primary reasons for treatment discontinuation, is shown in Figure 10.[26,122] From September 2009 to April 2010, a total of 309 patients were enrolled and randomised to ruxolitinib (n = 155) or placebo (n = 154). As prospectively defined, data cut-off occurred when all patients enrolled had completed week 24 or discontinued and half of the patients remaining in the study had completed the week 36 visit (median follow-up, 32 weeks). At this date, 134 (86.5%) patients in the ruxolitinib group and 78 (50.6%) patients in the placebo group were receiving randomised treatment. In the ruxolitinib group, the main reasons for discontinuing were death (5.8%) and AEs (5.2%). In the placebo group, 36 (23.4%) patients crossed over to receive ruxolitinib and 37 (24.0%) discontinued from the study. The main reasons for discontinuation were disease progression (7.8%), death (5.8%) and AEs (10.6%).

Patients were followed up at 2 years and at 3 years.[24,25] At 3 years, 77 of 155 (49.7%) patients originally assigned to ruxolitinib remained on treatment (median follow-up of 149 weeks). Of the 154 patients randomised to placebo, none remained on placebo at 3 years; 40 (26.0%) discontinued from the study and 111 (72.1%) crossed over to ruxolitinib. Of the 111 patients who crossed over to ruxolitinib (at a median time to crossover of 41 weeks), 57 (51.4%) remained on treatment at the 3-year follow-up (median exposure 105 weeks) and the remaining 54 (48.6%) discontinued the treatment. In all groups, disease progression was the primary reason for discontinuation of treatment (23.1% of patients in the ruxolitinib group, 32.5% in the placebo and 27.8% in the crossover group).[24,25,34]

Figure 10 CONSORT flow diagram for COMFORT-I



COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; CONSORT, Consolidated Standards of Reporting Trials.

Mesa et al. 2013,[34] Verstovsek et al. 2012, [26,126] Verstovsek et al. 2013. [127]

4.5.2 Patient baseline characteristics

Patient demographics and baseline disease characteristics for the 309 patients enrolled in COMFORT-I and the 219 patients included in COMFORT-II are shown in Table 14.[7,26] The baseline patient demographics and disease characteristics were similar in the two studies. In both studies, there were no significant differences between the two treatment groups in any of the baseline characteristics, with the exception of age in COMFORT-I ($p < 0.05$). The proportion of patients who had received prior therapy with hydroxycarbamide was higher in COMFORT-II (73% versus 61%).

Table 14 Characteristics of participants in the RCTs of ruxolitinib in MF across randomised groups

Characteristic	**COMFORT-I [26] (n = 309)**		**COMFORT-II [7] (n = 219)**	
	Ruxolitinib (n = 155)	**Placebo (n = 154)**	**Ruxolitinib (n = 146)**	**BAT (n = 73)**
Median age (range), years	66 (43 to 91)	70 (40 to 86)	67 (35 to 83)	66 (35 to 85)
Male, %	51.0	57.1	57	58
Disease type, %				
PMF	45.2	54.5	53	53
PPV-MF	32.3	30.5	33	27
PET-MF	22.6	14.3	14	19
IPSS risk status, %				
High	58.1	64.3	60	59
Intermediate-2	41.3	35.1	40	40
Prior hydroxy-carbamide use, %	67.1	56.5	75	68
Palpable spleen length, median (range), cm	16 (0 to 33)[a]	16 (5 to 34)	14 (5 to 30)	15 (5 to 37)
Spleen volume, median (range), cm^3	2598 (478 to 7462)	2566 (521 to 8881)	2408 (451 to 7766)	2318 (728 to 7701)
Platelet count, median (range), × 10^9/L	262 (81 to 984)	238 (100 to 887)	244 (–)	228 (–)

Characteristic	**COMFORT-I [26] (n = 309)**		**COMFORT-II [7] (n = 219)**	
Haemoglobin Median (range), g/dL < 10 g/dL, %	10.5 (6.6 to 17.0) –	10.5 (3.5 to 17.3) –	– 45	– 52
JAK2V617F mutation positive,%	72.9	79.9	75	67
[a]One patient had a baseline spleen length recorded as non-palpable in error but had a prior measurement of 16 cm and a baseline spleen volume of 2450 cm^3				

BAT, best available therapy; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis; RCT, randomised controlled trial.
Verstovsek et al. 2012;[26] Harrison et al. 2012.[7]

4.6 Quality assessment of the relevant randomised controlled trials

The quality of evidence assessment is presented in Table 15.[7,26,121,122] In both studies, randomisation was carried out appropriately using a validated interactive voice response system. In COMFORT-I, treatment allocation was concealed adequately with the use of matched placebo tablets. Prognostic factors were similar between treatment groups at the outset in both studies. More patients discontinued in the placebo and BAT groups than in the ruxolitinib groups, as might be expected given the limitations of these treatments and the option to cross over to receive ruxolitinib. The studies used an intention-to-treat analysis for all efficacy endpoints. The primary manuscripts report the results of the primary endpoints and all secondary endpoints.

The primary endpoint in COMFORT-II, ie reduction in spleen volume of at least 35%, is an objective measure of response which was assessed using MRI or CT. As such, there is limited risk of bias.

Table 15 Quality assessment results for RCTs for ruxolitinib in MF

	COMFORT-I[26]	**COMFORT-II**[7]
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes, the study remained blinded until completion of the primary analysis	No, this was an open-label study
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No, this was an open-label study
Were there any unexpected imbalances in drop-outs between groups?	More patients discontinued from the placebo group, as would be expected when compared with active treatment and given the option to cross over to receive ruxolitinib	More patients in the BAT group discontinued compared with the ruxolitinib group. This might be expected given the limitations of BAT and given the option to cross over to receive ruxolitinib.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Patients were analysed according to treatment group. Change from baseline was only calculated for patients with baseline data.	Patients were analysed according to treatment group. Change from baseline was only calculated for patients with baseline data

BAT, best available therapy; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; MF, myelofibrosis; RCT, randomised controlled trial.

Harrison et al. 2012;[7,121] Verstovsek et al. 2012[26,122]

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Both phase 3 studies (COMFORT-I and COMFORT-II) have reported their primary outcomes,[7,26] and long-term follow-up data for up to 3.5 years have also been reported for both studies[22-25]. The two phase 3 studies met their primary endpoint with significantly more ruxolitinib-treated patients obtaining a 35% or greater reduction in spleen volume compared with BAT-treated patients at week 48 in COMFORT-II,[7] and compared with placebo-treated patients at 24 weeks in COMFORT-I.[26] Reductions in splenomegaly were rapid and were sustained over time in patients receiving ruxolitinib for up to 3 years in COMFORT-I and 3.5 years in COMFORT-II studies.[22,23,25] Improvements in disease-specific symptoms were observed in COMFORT-I, and improvements in HRQoL were

reported in both studies. Furthermore, both studies reported improvements in OS with ruxolitinib compared with BAT or placebo.

A summary of the primary analysis results, including reductions in splenomegaly, for COMFORT-I and COMFORT-II is provided in Table 16.

Table 16 Summary of the primary analysis results for COMFORT-I and II

Outcome	COMFORT-II [7]	COMFORT-I [26]
Spleen volume		
Patients achieving ≥ 35% spleen volume reduction		
at week 12	29.5% vs 1.4%	39.4% vs 0%
at week 24	32% vs 0%, p < 0.001	41.9% vs 0.7%, p < 0.0001[a]
at week 48	28% vs 0%, p < 0.001[a]	–
Mean change in spleen volume		
at week 24	−29.2% vs +2.7%, p < 0.001	−31.6% vs +8.1%
at week 48	−30.1% vs +7.3%, p < 0.001	–
Symptoms		
Patients achieving ≥ 50% reduction in TSS at week 24	–	45.9% vs 5.3%, p < 0.001
Mean change from baseline in TSS at week 24	–	46.1% vs −41.8%, p < 0.001
PGIC: patients rating condition much/very much improved at week 24, %	–	66.9% vs 11.2%
HRQoL		
Mean change from baseline in Global Health Status/QoL (EORTC QLQ-C30)	+9.1 vs +3.4[b]	+12.3 vs −3.4, p < 0.0001[c]
Mean change from baseline in FACT-Lym score	+ 11.3 vs −0.9[b]	–
Survival		
Overall survival	92.0% vs 95.0%, (HR, 1.01, 95% CI 0.32 to 3.24)[d,e]	91.6% vs 84.4%, (HR, 0.50; 95% CI 0.25 to 0.98; p = 0.04)[f]
Progression-free survival	69.9% vs 74.0%, (HR, 0.81, 95% CI 0.47 to 1.39)[b]	–

[a]Primary endpoint; [b]at 48 weeks; [c]at 24 weeks; [d]at median follow-up of 61 weeks; [e]at median follow-up of 51 weeks

CI, confidence interval; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; HR, hazard ratio; HRQoL, health-related quality of life; PGIC, Patient's Global Impression of Change; TSS, total symptom score.

Harrison et al. 2012;[7] Verstovsek et al. 2012;[26] Clinical study report.[123,124]

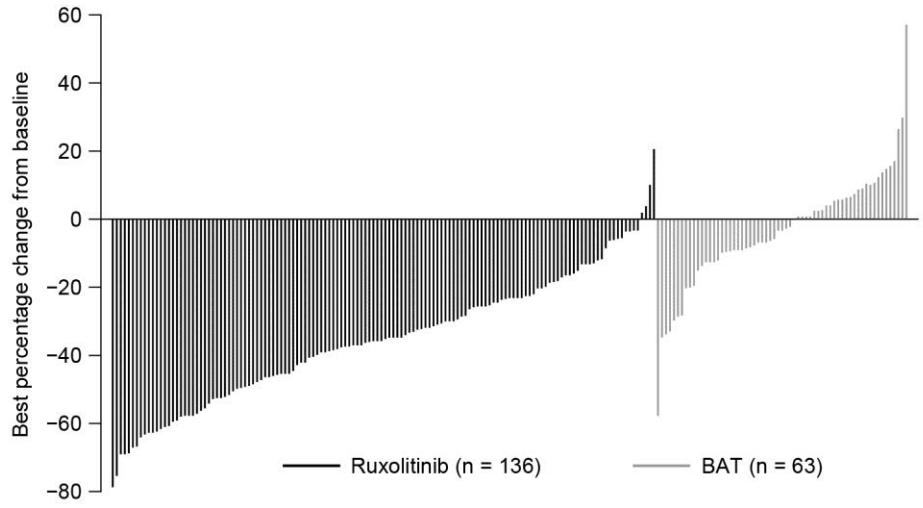
4.7.1 Spleen response

Ruxolitinib provides significant reductions in splenomegaly compared with BAT or placebo

In COMFORT-II the primary endpoint was met, with significantly more ruxolitinib-treated patients obtaining a 35% or greater reduction in spleen volume at week 48 than BAT-treated patients.[7] At the primary analysis (48 weeks), this response was achieved by 28% of patients in the ruxolitinib group versus 0% of patients in the BAT group (95% confidence interval [CI] 21% to 37%; $p < 0.001$). During 48 weeks of study, a measurable reduction in spleen volume from baseline at any time during the study (best response) was experienced by almost all patients in the ruxolitinib group (97%) compared with 56% of patients in the BAT group (Figure 11). Among the patients with available baseline data and at least one subsequent measurement, only 4 patients (3%) in the ruxolitinib group compared with almost half of patients (n = 28, 44%) in the BAT group had an increase in spleen volume. At week 48, the mean percentage change in spleen volume in the ruxolitinib group was −30.1% versus +7.3% in the BAT group ($p < 0.001$).

The proportion of patients achieving a 35% or greater reduction in spleen volume at week 24 was a key secondary endpoint of the COMFORT-II trial and was also met; significantly more ruxolitinib-treated patients had a response at week 24 than patients in the BAT group (32% versus 0%, respectively; $p < 0.001$).[7] In addition, the mean percentage change from baseline in spleen volume at 24 weeks was −29.2% for ruxolitinib-treated patients compared with +2.7% for BAT-treated patients ($p < 0.001$).

Figure 11 Waterfall plot of the best percentage change from baseline in spleen volume at 48 weeks for COMFORT-II

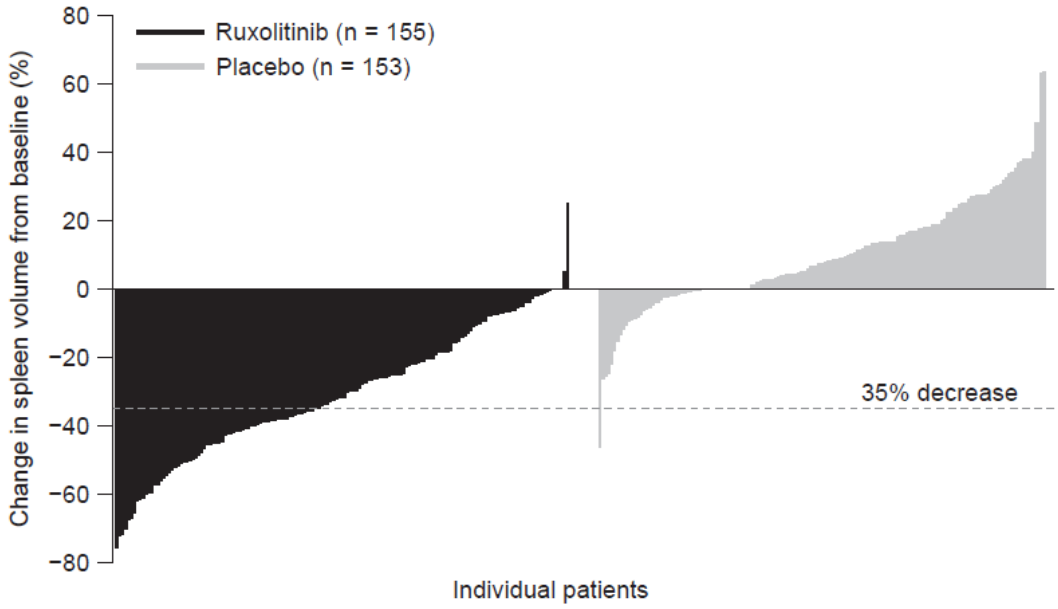


	Ruxolitinib	BAT
Decreased spleen volume as best percentage change from baseline	132 (97%)	35 (56%)
Increased spleen volume as best percentage change from baseline	4 (3%)	28 (44%)

Best percentage change from baseline in spleen volume, as assessed by magnetic resonance imaging or computerised tomography, at any time within the first 48 weeks of treatment, among patients with a baseline assessment and at least one subsequent assessment. Data are shown for individual patients.
BAT, best available therapy.
Harrison et al. 2012.[7]

The primary endpoint in COMFORT-I was also met, with significantly more patients receiving ruxolitinib obtaining a 35% or greater reduction in spleen volume at 24 weeks than patients receiving placebo.[26] At 24 weeks, 41.9% of ruxolitinib-treated patients compared with 0.7% of placebo-treated patients achieved a 35% or greater reduction in spleen volume (odds ratio [OR], 134.4; 95% CI 18.0 to 1004.9; $p < 0.001$). In the primary analysis of COMFORT-I, 96.8% of ruxolitinib-treated patients achieved a reduction in spleen volume at any time during the study, whereas approximately three-quarters of patients in the placebo group had either an increase in spleen volume (66.7%) or no change (9.8%) (Figure 12). For patients with available baseline and week 24 data, the mean reduction in spleen volume in ruxolitinib-treated patients (n = 139) was 31.6% − comparable to that reported for ruxolitinib in COMFORT-II at the equivalent time point − whereas placebo-treated patients (n = 106) had a mean increase in spleen volume of +8.1%.

Figure 12 Waterfall plot of percentage change from baseline in spleen volume at 24 weeks in COMFORT-I



Percentage change from baseline in spleen volume at week 24 (139 patients in the ruxolitinib group and 106 in the placebo group) or at the last evaluation before week 24 (16 patients in the ruxolitinib group and 47 in the placebo group). Data for 1 patient with a missing baseline value are not included on the graph.
Verstovsek et al. 2012.[26]

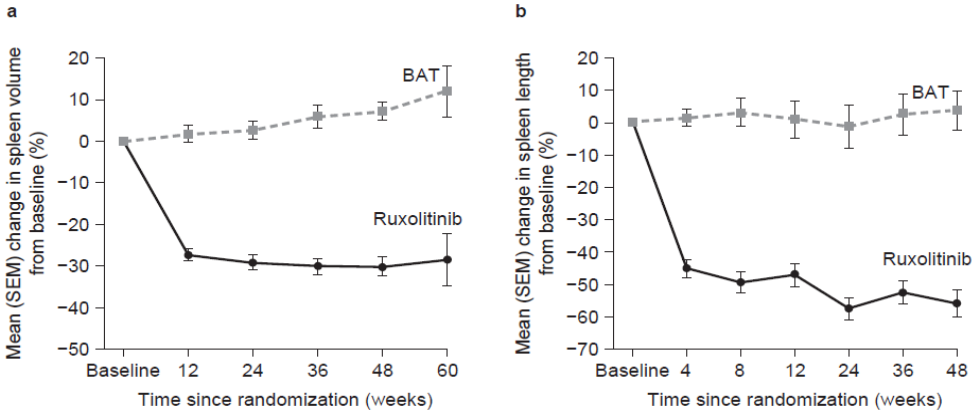
Ruxolitinib provides more rapid reductions in splenomegaly than BAT or placebo

In both COMFORT-II and COMFORT-I, the reductions in splenomegaly were rapid and sustained over time in patients receiving ruxolitinib.

Many ruxolitinib-treated patients in COMFORT-II achieved a reduction in spleen volume of 35% or greater by the first MRI or CT assessment at week 12.[7] Of the 69 ruxolitinib-treated patients who achieved a 35% or greater reduction in spleen volume during the 48-week primary study period, 64% (n = 44, 30% of the total ruxolitinib group) achieved this response by week 12. In comparison, only one patient in the BAT group achieved a 35% or greater reduction in spleen volume at week 12. The median time to achieving a 35% or greater spleen volume reduction (as assessed by MRI) was 12.3 weeks in the ruxolitinib group. The mean change in spleen volume in the ruxolitinib group at week 12 was approximately 30% (Figure 13).[128]

As shown in Figure 13, the rapid spleen response was evident as reductions in both spleen volume and spleen length.[7,128] At the first assessment (week 4), the mean palpable spleen length had decreased by approximately 45% in ruxolitinib-treated patients, whereas the mean palpable spleen length had increased in BAT-treated patients.

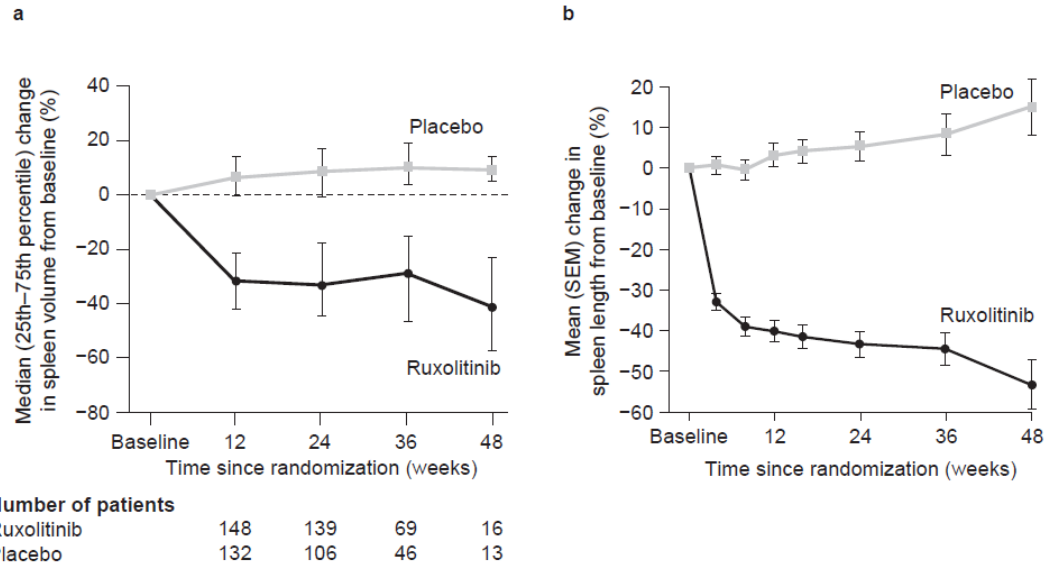
Figure 13 Mean percentage change in a) spleen volume and b) in palpable spleen length from baseline over time in COMFORT-II: core study



BAT, best available therapy; BL, baseline; SEM, standard error of the mean.
Harrison et al. 2011;[128] 2012.[7]

The reductions in spleen volume in the ruxolitinib group in COMFORT-I were also rapid. By the first assessment at week 12, 39.4% of patients in the ruxolitinib group had achieved a 35% or greater reduction in spleen volume compared with no patients in the placebo group. The median change in spleen volume at 12 weeks was approximately 30% (Figure 14).[26] As in COMFORT-II, changes in spleen volume were found to correspond to changes in spleen length, as assessed by palpation by the investigator, which were also evident early and seen within 4 weeks of initiation of ruxolitinib therapy. At 12 weeks, a reduction in mean length of approximately 33% was seen in patients receiving ruxolitinib, while no reductions were evident in the placebo group (Figure 14).[129]

Figure 14 a) Median percentage change from baseline in spleen volume over time and b) Mean percentage change from baseline in spleen length over time in COMFORT-I: core study



Number of patients				
Ruxolitinib	148	139	69	16
Placebo	132	106	46	13

a: Verstovsek et al. 2012[26] b: Verstovsek et al. 2011[129]

Ruxolitinib provides durable reductions in splenomegaly (volume and length)

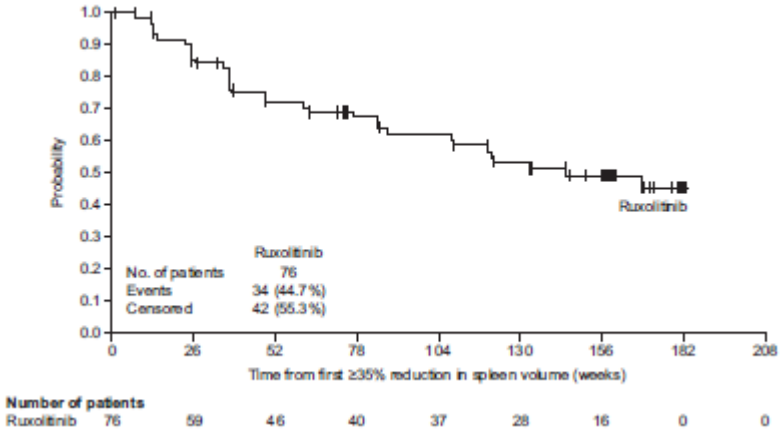
The COMFORT-II primary analysis demonstrated that reductions in spleen volume were durable over 48 weeks.[7,128] The mean percentage reduction in spleen volume from baseline was maintained from week 12 onwards in the ruxolitinib group, whilst spleen volume increased gradually over the 48 weeks of the core study in the BAT group (Figure 13). In the primary analysis, the median duration of spleen volume response was not reached, with 80% of patients in the ruxolitinib group still having a response at a median follow-up of 12 months. Similar durable results were observed for changes in palpable spleen length over 48 weeks (Figure 13). At week 48, the mean reduction in palpable spleen length was 56% in the ruxolitinib group compared with a mean increase of 4% in the BAT group.

In COMFORT-I the reduction in spleen volume was also shown to be durable with continued therapy, and among patients who had a reduction of 35% or more in spleen volume, 67% had this reduction in spleen volume maintained for 48 weeks or more.[26] The median reduction in spleen volume at week 48 was approximately 32% (Figure 14). Reductions in mean palpable spleen length from baseline were evident from week 4 and maintained in the ruxolitinib group, whereas a gradual increase from baseline was observed in the placebo group. At 48 weeks, the mean reduction in spleen length in the ruxolitinib group in COMFORT-I was approximately 43% (Figure 14).[129]

Reductions in splenomegaly (volume and length) achieved with ruxolitinib are durable over more than 3 years

Over the 3.5-year follow-up of COMFORT-II, 52.1% of patients (n = 76) receiving ruxolitinib achieved a 35% or greater reduction in spleen volume.[22] In the ruxolitinib arm, the Kaplan–Meier estimated probabilities of maintaining the spleen response (ie a 35% reduction in spleen volume) at 1, 2, and 3 years were 72%, 62%, and 49% respectively, in patients achieving such a degree of response (Figure 15). The median duration of maintenance of spleen volume reduction was 2.76 years in the ruxolitinib arm.[22]

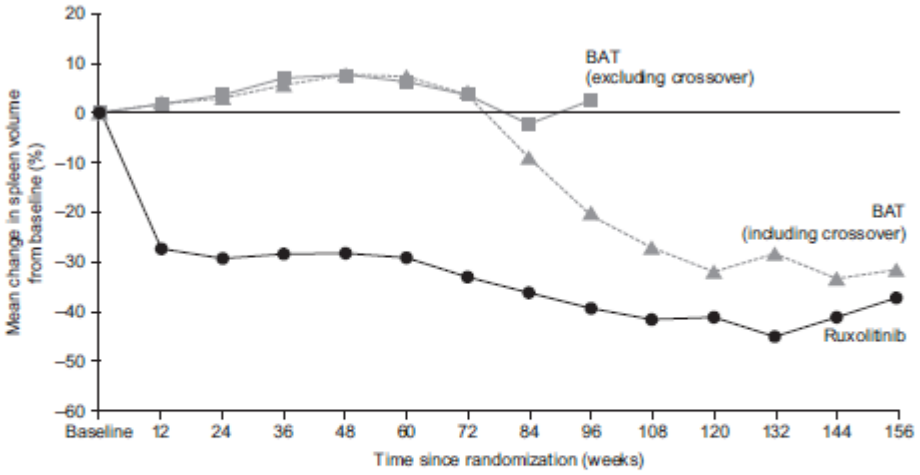
Figure 15 Duration of spleen response in COMFORT-II: extension



Harrison et al. 2014.[22]

The mean reduction in spleen volume at week 156 in the ruxolitinib group was approximately 35% (Figure 16).[23]

Figure 16 Mean change in spleen volume from baseline over time for COMFORT-II: extension



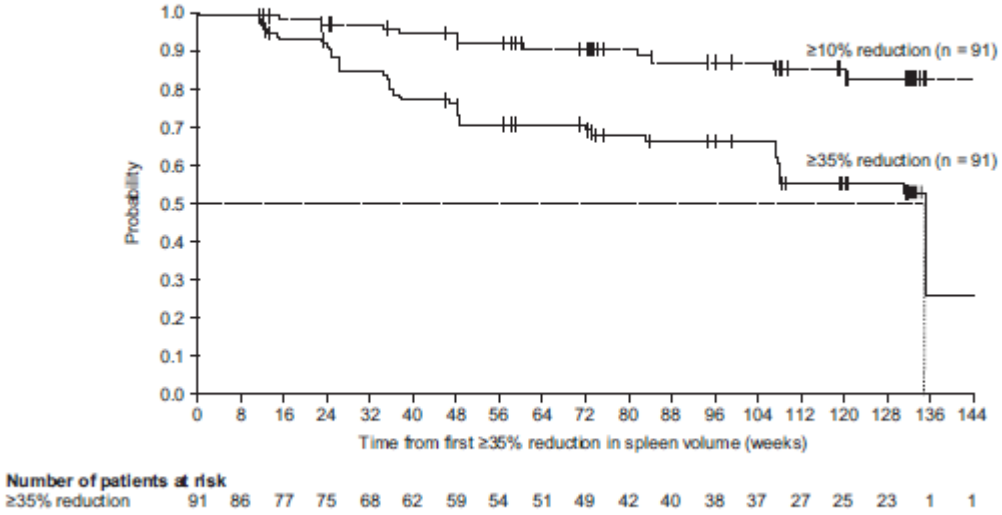
Number of patients

Ruxolitinib	146	136	125	118	113	102	93	79	61	49	58	46	50	16
BAT (excluding patients who crossed over to ruxolitinib)	73	60	44	39	34	24	16	6	2	0	0	0	0	0
BAT (including patients who crossed over to ruxolitinib)	73	60	46	41	38	29	23	20	16	16	14	15	13	6

BAT, best available therapy.
Cervantes et al. 2013.[23]

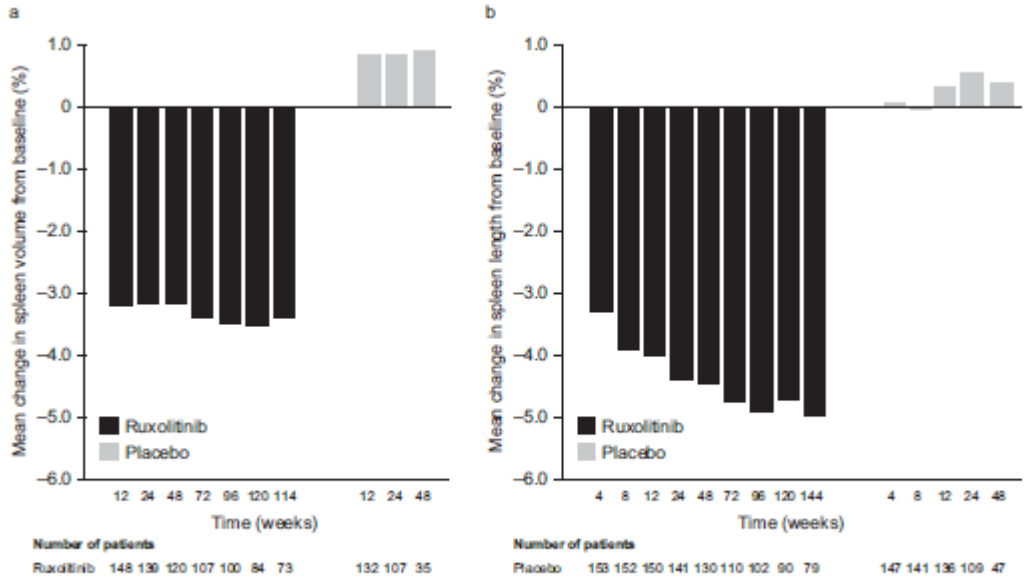
In COMFORT-I, reductions in splenomegaly were also shown to be sustained during the 3-year follow-up period.[25] At 3-year follow-up, 91 patients (59%) randomised to ruxolitinib achieved a 35% or greater reduction in spleen volume at any time in the study. The probability of maintaining this response for more than 132 weeks from the time of their initial response was 53%. Furthermore, the probability of maintaining a reduction in spleen volume of at least 10% in those achieving a 35% reduction at any time was approximately 90% Figure 17). Mean reductions in spleen volume were similar at 6 months (31.6%), 2 years (34.9%)[24] and at a median follow-up of 144 weeks (34.1%), and reductions in spleen volume corresponded with reductions in spleen length; the mean percentage change from baseline in palpable spleen length was −43.4% at week 24 (median −41.2%) and −49.4% at week 144 (median −50.0%) (Figure 18).[25]

Figure 17 Durability of spleen volume reduction in COMFORT-I: long-term follow-up



Verstovsek et al. 2015.[25]

Figure 18 Change in spleen size in COMFORT- I: long-term follow-up



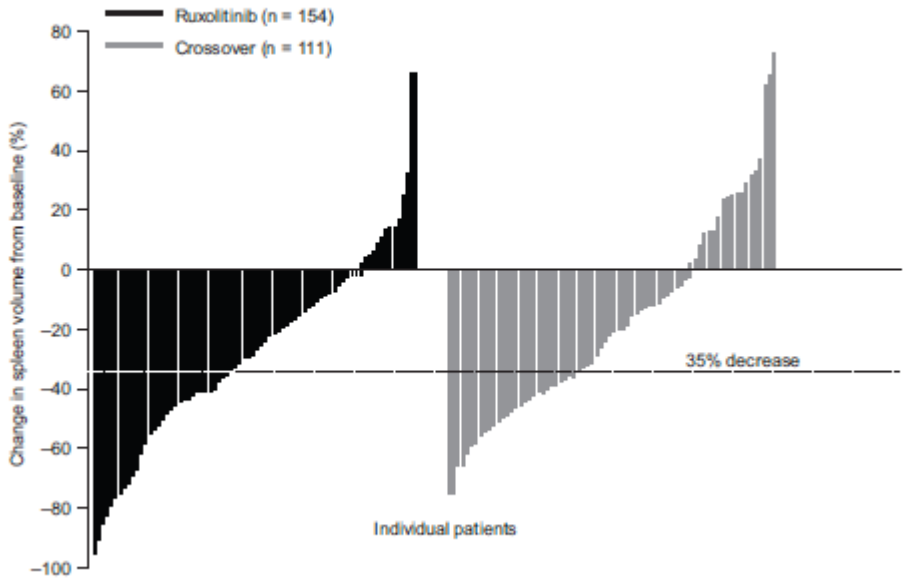
Verstovsek et al. 2015.[25]

Patients crossing over to ruxolitinib from BAT show reductions in splenomegaly

In both COMFORT-II and COMFORT-I, improvements in splenomegaly were observed in the control group when patients crossed over to receive ruxolitinib. In COMFORT-II, assessments of change in spleen volume in the BAT arm were determined based on the patient's original baseline spleen volume and not from the time of crossover. Patients crossed over from the BAT arm to receive ruxolitinib over the course of approximately 6 to 8 months. From week 84 onwards reductions in spleen volume from baseline were observed and the mean reduction from baseline in the BAT group reached approximately 30% at 144 weeks (Figure 16).[23]

In COMFORT-I (2-year follow-up), at a median follow-up of 14 months from crossover, patients who crossed over from placebo experienced a mean 30.0% reduction in spleen volume from the time of crossover (Figure 19). This equated to a mean reduction of 18% from baseline and compared with a mean reduction of 27.5% achieved in the ruxolitinib group.[24]

Figure 19 Waterfall plot of percentage change from baseline in spleen volume at a median follow-up of 24 months for patients randomised to ruxolitinib and patients who crossed over from BAT to ruxolitinib in COMFORT-I: long-term follow-up



BAT, best available therapy.
Verstovsek et al. 2013.[24]

4.7.2 MF-associated symptoms and HRQoL

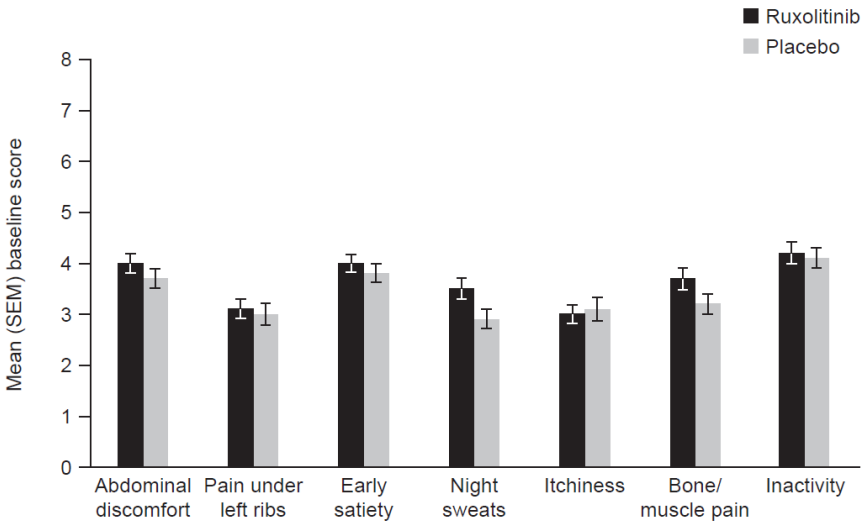
MF-associated symptoms: COMFORT-I

The COMFORT-I study provides information on the effects of ruxolitinib versus placebo on a constellation of MF-associated symptoms. To assess the impact of treatment on MF-related symptoms, patients completed a modified version of the MF-SAF in the form of an electronic diary each night over the first 24 weeks of the study and completed a PGIC questionnaire at each scheduled study visit.

Symptom scores at baseline were indicative of debilitating disease

According to the modified MF-SAF v2, the individual symptoms of MF were present in over 70% of patients at baseline.[33,34] The most prevalent of the individual symptoms, abdominal discomfort, early satiety and inactivity, were present in more than 90% of patients at baseline. Individual symptom scores at baseline were similar for both treatment groups, with most symptoms being rated as 3 to 4 in severity (on a scale of 0 [absent] to 10 [worst imaginable]) (Figure 20). The mean TSS at baseline was 18.2 for ruxolitinib-treated patients and 16.9 for placebo-treated patients (out of a potential maximum score of 60 indicating worst possible symptoms).

Figure 20 Modified Myelofibrosis Symptom Assessment Form version 2.0 individual symptom scores at baseline in COMFORT-I



Patients with symptoms at baseline (%):

Ruxolitinib	95.3	83.9	94.0	80.5	75.8	81.9	91.9
Placebo	94.1	80.9	91.4	83.6	74.3	82.9	92.8

Scale range: 0 = absent to 10 = worst imaginable.

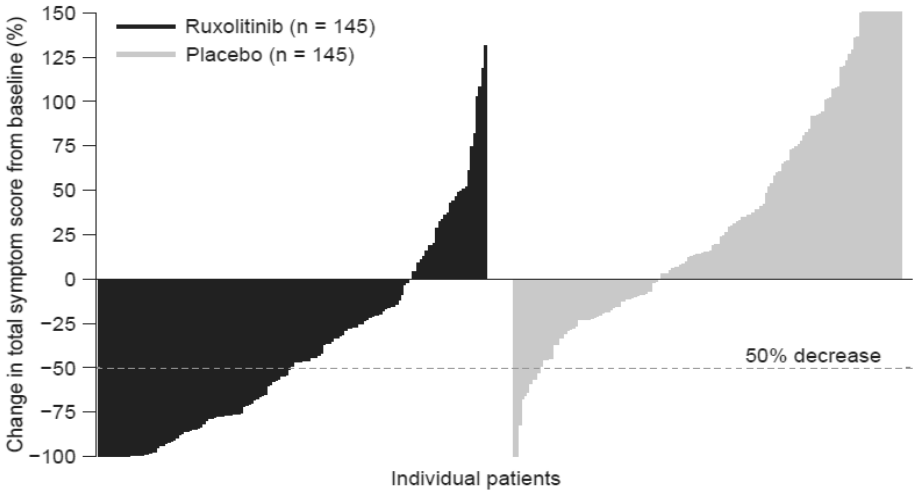
SEM, standard error of the mean.

Mesa et al. 2013.[34]

Ruxolitinib provides clinically significant improvements in disease-related symptoms

In total, 45.9% of ruxolitinib-treated patients achieved a 50% or greater improvement in modified MF-SAF TSS at 24 weeks compared with 5.3% of patients in the placebo group, a difference that was highly statistically significant (OR, 15.3; 95% CI 6.9 to –33.7; p < 0.001) (Figure 21).[26] At 24 weeks, ruxolitinib-treated patients had a 46.1% mean improvement in TSS, whereas placebo-treated patients had a 41.8% mean worsening in TSS (p < 0.001).

Figure 21 Waterfall plot of percentage change from baseline in total symptom scores at 24 weeks in COMFORT-I

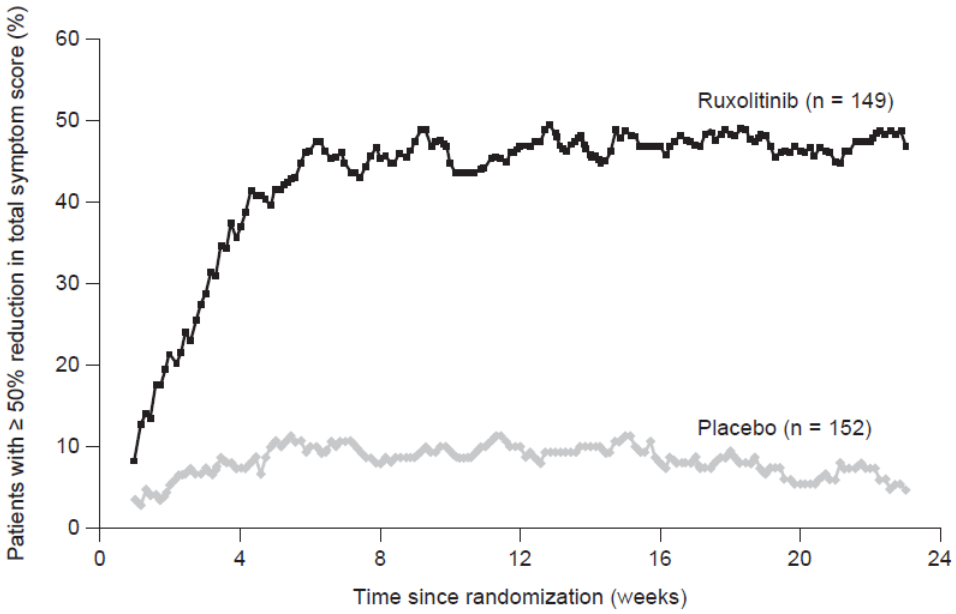


Percentage change from baseline in total symptom score at week 24 (129 patients in the ruxolitinib group and 103 in the placebo group) or at the last evaluation before week 24 (16 patients in the ruxolitinib group and 42 in the placebo group). Five patients with a baseline score of 0, 8 patients with missing baseline values, and 6 patients with insufficient data after baseline are not included.
Verstovsek et al. 2012.[26]

Improvements in disease-related symptoms achieved with ruxolitinib were rapid and durable

Improvements in TSS in the ruxolitinib group were rapid and were maintained over the 24-week primary analysis period.[26] The majority of responses occurred within 4 weeks after treatment initiation and the percentage of patients achieving a 50% or greater reduction in TSS was sustained from week 6 onwards (Figure 22).

Figure 22 Percentage of patients with 50% or greater reduction in total symptom score over time in COMFORT-I

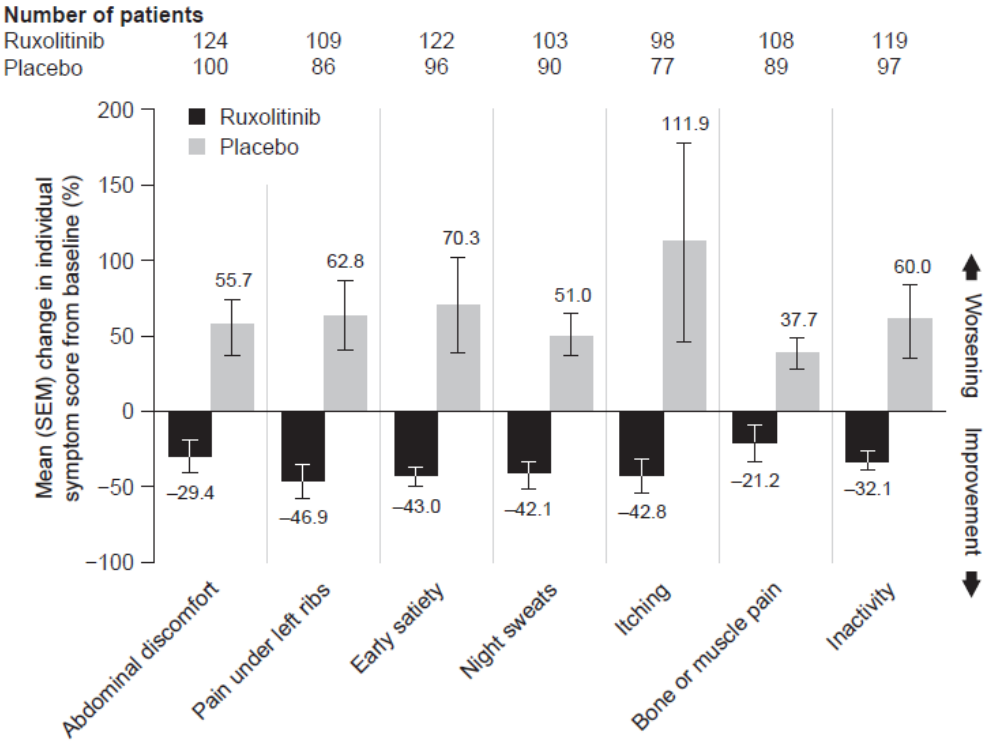


Each value plotted represents the moving average for the previous 7 days.
Verstovsek et al. 2012.[26]

Ruxolitinib showed significant improvements in all MF-SAF individual symptom scores

Ruxolitinib showed significant improvements in all MF-SAF individual symptom scores at the primary analysis time point of 24 weeks, while all scores in placebo-treated patients worsened ($p < 0.01$).[26] An approximately linear worsening of symptom scores was observed for patients receiving placebo over the entire 24 weeks (Figure 23). Differences between ruxolitinib and placebo were statistically significant at all time points ($p < 0.001$).[34]

Figure 23 Mean percentage change in Myelofibrosis Symptom Assessment Form individual symptom scores at 24 weeks



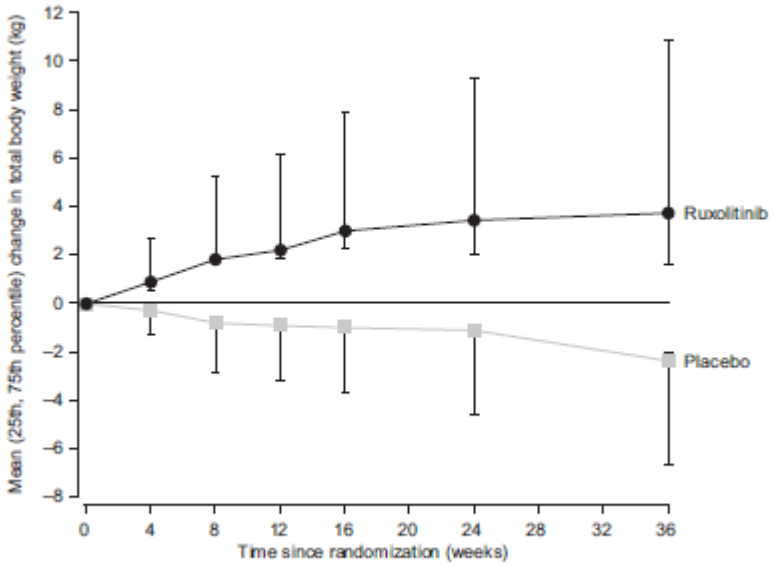
SEM, standard error of the mean.

Verstovsek et al. 2012.[26]

Ruxolitinib increased weight gain compared with placebo in patients with MF

Consistent with the improvement in spleen volume and symptoms, ruxolitinib-treated patients experienced an increase in body weight over time, whereas those receiving placebo lost weight. Ruxolitinib-associated weight gain was observed as early as after 1 month of treatment (Figure 24).[122]

Figure 24 Change in weight over time in COMFORT-I



Verstovsek et al. 2012.[122]

Ruxolitinib-treated patients rated their condition as improved after 24 weeks of therapy

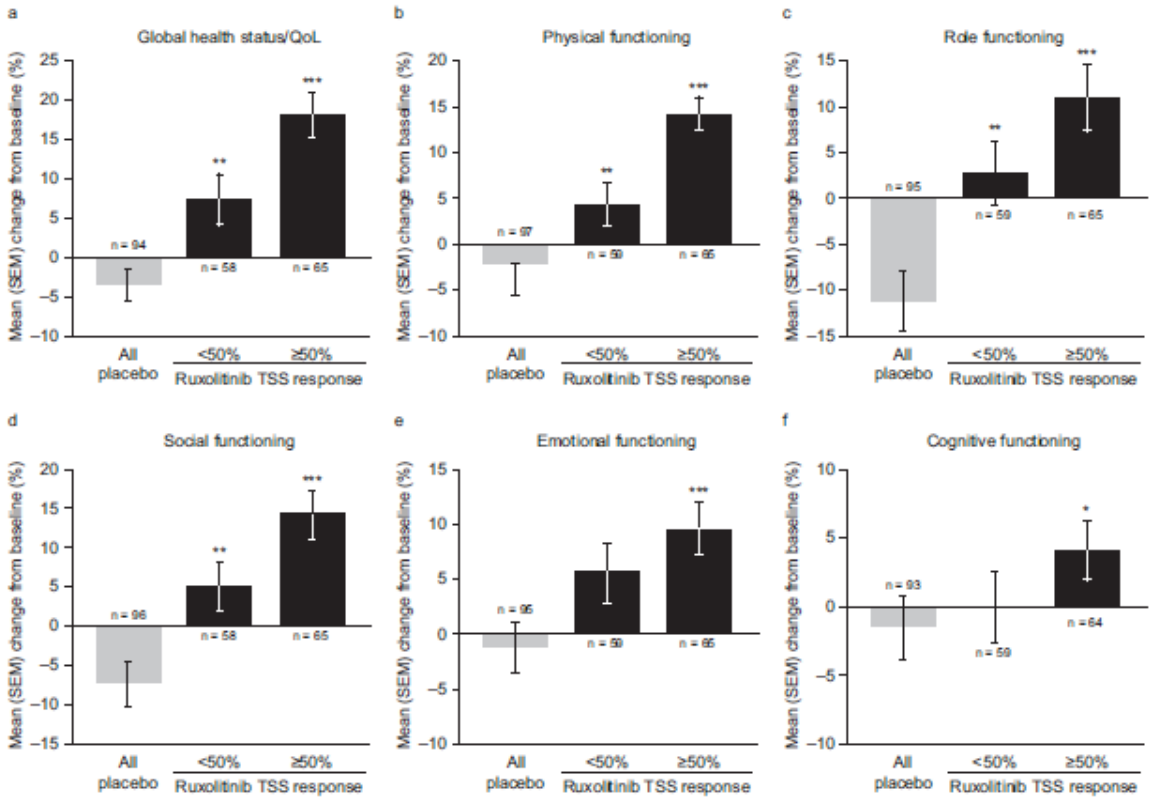
Improvements in MF symptoms with ruxolitinib treatment were also evident when symptoms were measured using the PGIC questionnaire. At week 24, the majority of ruxolitinib-treated patients (67%) rated their condition as “much improved” or “very much improved”, whereas most (70%) placebo-treated patients rated their condition as “unchanged” or “worse”.[122] Few patients in the placebo-treated group rated their condition as improved at week 24. Furthermore, almost all (91.2%) patients randomised to ruxolitinib who achieved an improvement in TSS of at least 50% characterised their condition as “much improved” or “very much improved”, suggesting the TSS provides an assessment of clinical benefit as perceived by the patient.[34]

Improvements in TSS achieved with ruxolitinib appear to correlate with improvements in HRQoL

A further analysis of data from COMFORT-I indicated that patients treated with ruxolitinib who achieved an improvement in TSS of at least 50% achieved greater improvements in HRQoL (GHS and the five functional domains of the EORTC QLQ-C30) than did patients who achieved an improvement of less than 50%, suggesting that TSS response correlates with HRQoL (Figure 25).[34] In addition, the improvement in HRQoL achieved in ruxolitinib-treated patients with a TSS improvement

of at least 50% was significantly greater than in placebo-treated patients for GHS and four of the five functional domains.

Figure 25 Relationship between TSS response with ruxolitinib and HRQoL in COMFORT-I



*p ≤ 0.05; ** p ≤ 0.001; *** p < 0.0001

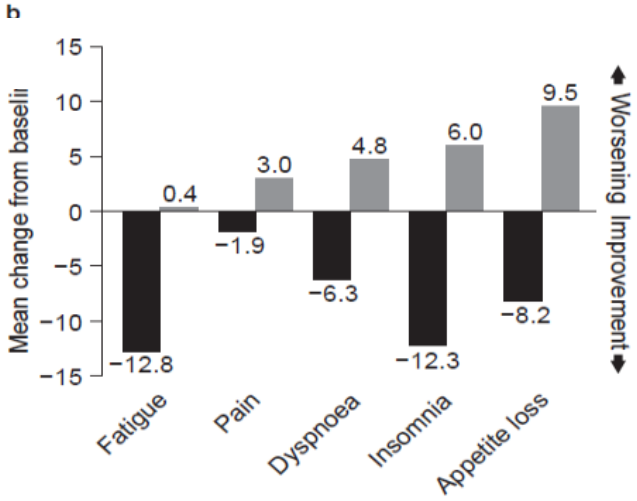
Relationship between symptoms as assessed by the modified MF-SAF, with QoL as assessed by EORTC QLQ-C30 at baseline. Patients receiving ruxolitinib who were categorised as at least 50% Total Symptom Score (TSS) responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients in the placebo group.

Mesa et al. 2013.[34]

Ruxolitinib showed significant improvements in MF-associated symptoms compared with BAT

In COMFORT-II, *post hoc* exploratory analysis of HRQoL and symptom analyses have been performed on the primary analysis data set and provide insights into the effects of ruxolitinib versus BAT on MF-associated symptoms at 48 weeks.[35] Of the nine symptom scores assessed by the EORTC QLQ-C30, six (appetite loss, dyspnoea, fatigue, insomnia, pain and diarrhoea) were significantly improved in the ruxolitinib group compared with the BAT group. Mean change from baseline in symptoms scores at week 48 are shown in Figure 26.[7]

Figure 26 Overall adjusted mean change from baseline to week 48 in EORTC QLQ-C30 Symptom Scores in COMFORT-II



EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30.
Harrison et al. 2012.[7]

4.7.3 HRQoL

In both COMFORT-I and COMFORT-II, HRQoL assessments were included in the primary analysis and during long-term follow-up (section 4.3).

Baseline HRQoL scores were indicative of patients having debilitating disease and reduced HRQoL

At baseline, scores for EORTC QLQ-C30 subscales (COMFORT-I and COMFORT-II) and PROMIS Fatigue (COMFORT-I) were indicative of patients having debilitating disease and reduced HRQoL (Table 17).[34,35] Symptom scores at baseline were similar between treatment groups and there was good agreement between the two studies.

Table 17 Baseline scores on the EORTC QLQ-C30 and PROMIS fatigue

Patient-reported outcome	**COMFORT-II**		**COMFORT-I**	
	Ruxolitinib group (mean)	**BAT group (mean)**	**Ruxolitinib group (mean)**	**Placebo group (mean)**
EORTC QLQ-C30 subscales				
GHS	55.5	50.1	52.7	52.9
Physical Functioning	69.5	65.1	69.7	67.2
Role Functioning	67.0	64.4	64.5	63.2
Emotional Functioning	75.3	70.2	73.3	75.5
Cognitive Functioning	80.2	75.3	80.7	80.1
Social Functioning	80.4	73.5	68.0	66.1
PROMIS				
PROMIS Fatigue	NA	NA	43.7	43.3
Maximum score is 100 for both scales and is indicative of best possible status for EORTC QLQ-C30 subscales and worst possible status for PROMIS Fatigue scale.				

BAT, best available therapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; GHS, Global health status; NA, not assessed; PROMIS, Patient Reported Outcomes Measurement Information System.

Mesa et al. 2013,[34] Harrison et al. 2013.[35]

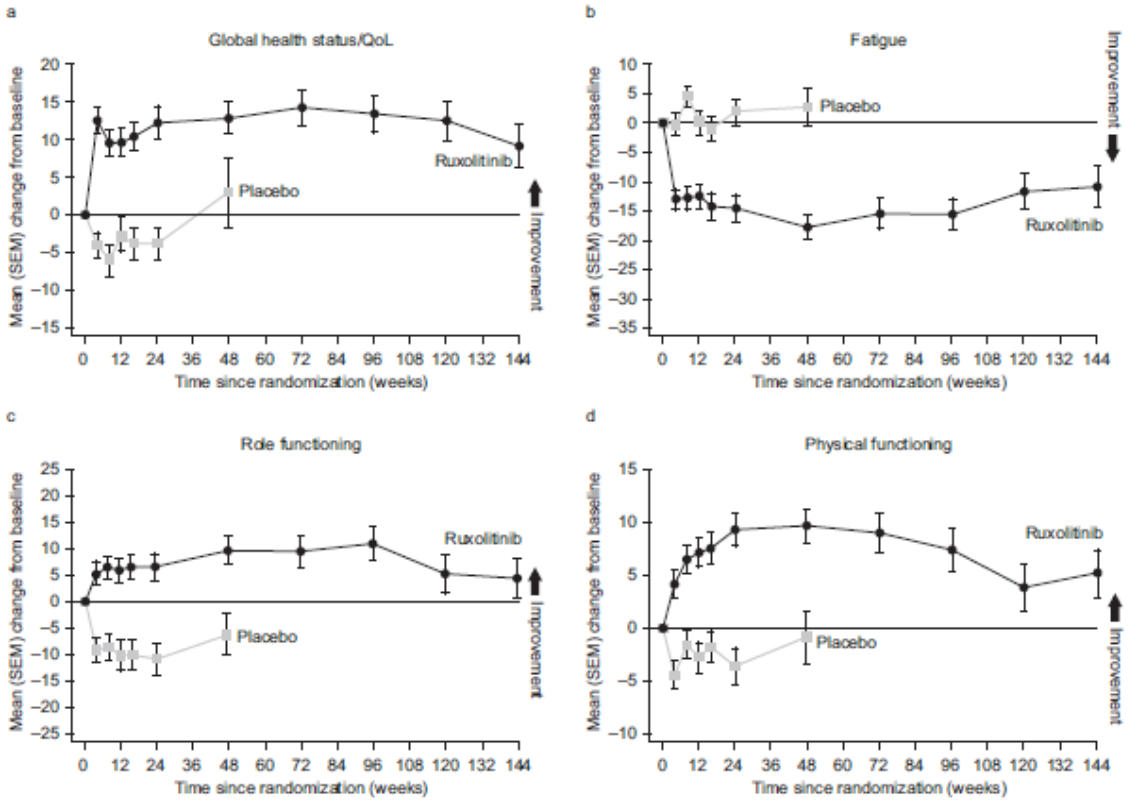
Ruxolitinib provides significant and sustained improvements in HRQoL compared with worsening of HRQoL with placebo or BAT

Both studies included assessments of HRQoL using the EORTC QLQ-C30. In COMFORT-II, improvements from baseline in GHS and QoL and the Role Functioning HRQoL domain of the EORTC QLQ-C30 were observed in the ruxolitinib group at 48 weeks; in contrast, in the BAT group, only a small increase in GHS was observed and there was a decrease in the Role Functioning score.[7] Average adjusted mean treatment differences between ruxolitinib and BAT over the 48 weeks were statistically significant for GHS (8.8), Physical Functioning (8.0) and Role Functioning (12.6) ($p < 0.001$ for all three comparisons) in favour of ruxolitinib.[35] In COMFORT-I increases from baseline in GHS, Physical Functioning and Role Functioning scores were observed at the first assessment in patients receiving ruxolitinib and were sustained during the 3-year follow-up; in contrast, decreases in scores from baseline were observed with placebo and remained during the first 24 weeks prior to crossing over to receive ruxolitinib (Figure 27).[25]

In COMFORT-II, effects of treatment on HRQoL were also assessed using the FACT-Lym scale. FACT-Lym scores were similarly indicative of substantial improvements in MF-associated symptoms in the ruxolitinib group at 48 weeks and worsening symptoms in the BAT group. Adjusted mean treatment differences were statistically significant and in favour of ruxolitinib over BAT for all four summary scores at all time points.[35]

In COMFORT-I, effects on fatigue were assessed using the EORTC QLQ-C30 and PROMIS Fatigue scale. Improvements in fatigue were observed from the first assessment and were sustained throughout the 3-year follow-up, while no improvement was observed in the placebo group (EORTC QLQ-C30 results presented in Figure 27).[25] At week 24, patients receiving ruxolitinib reported a significantly greater mean percentage improvement from baseline in fatigue according to the PROMIS Fatigue scale, compared with the placebo group (15.6% improvement versus 9.1% worsening, respectively; $p < 0.0001$).[122]

Figure 27 Improvements in EORTC QLQ-C30 over time in COMFORT-I



EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; QoL, quality of life; SEM, standard error of the mean.

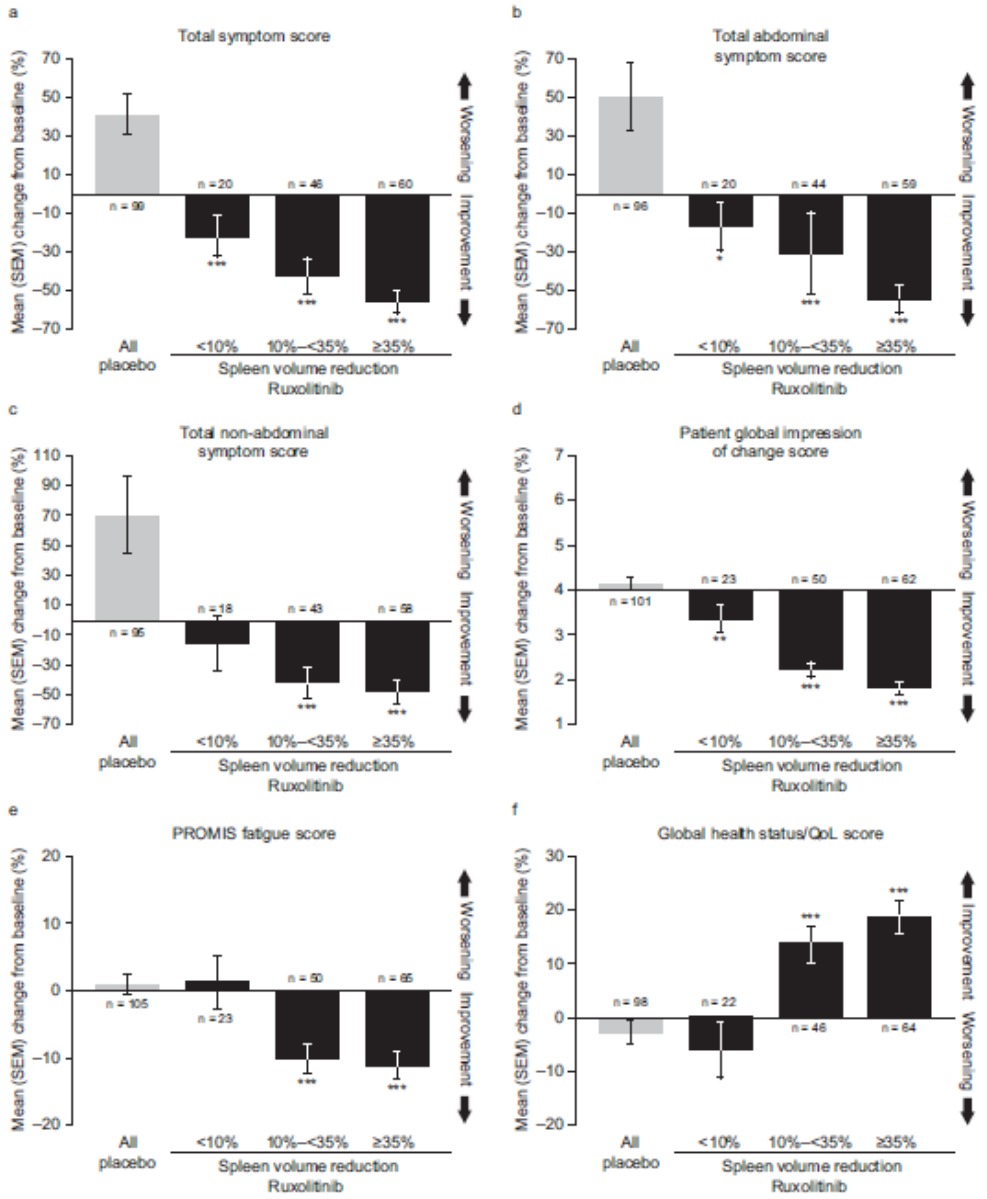
Verstovsek et al. 2015.[25]

Even small reductions in spleen volume with ruxolitinib are associated with meaningful improvements in disease-related symptoms and HRQoL (COMFORT-I)

A further analysis of data from COMFORT-I investigated the relationship between the reduction in spleen volume achieved with treatment and the improvement in symptoms and HRQoL.[34] For all measures of HRQoL and symptoms considered (TSS, total abdominal symptom score, total non-abdominal symptom score, PGIC, PROMIS and EORTC QLQ-C30 GHS patients receiving ruxolitinib who achieved a reduction in spleen volume of at least 35% reported a significantly greater improvement in HRQoL and symptom score from baseline than patients receiving placebo (Figure 28). A significant improvement in HRQoL and symptom score from baseline was also reported for patients receiving ruxolitinib who achieved a reduction in spleen volume of 10% to 35% indicating that patients achieving at least a 10% reduction in spleen volume benefit from treatment. Indeed, patients with a reduction in spleen volume of less than 10% also reported a significant improvement in TTS, total abdominal symptom score and PGIC scale score compared with placebo. These results suggest that even small reductions in spleen volume with ruxolitinib are associated with meaningful

improvements in disease-related symptoms and HRQoL It should also be noted that treatment was effective in patients who had symptoms but no splenomegaly, as well as patients with splenomegaly but no symptoms.[10]

Figure 28 Relationship between spleen volume reduction with ruxolitinib and symptoms and HRQoL in COMFORT-I



*p ≤ 0.05; ** p ≤ 0.001; *** p < 0.0001.

Relationship between symptoms as assessed by the modified Myelofibrosis Symptom Assessment Form v2.0, with quality of life (QoL) as assessed by EORTC QLQ-C30 at baseline. Patients receiving ruxolitinib who were categorised as ≥ 50% Total Symptom Score (TSS) responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients in the placebo group.

Mesa et al. 2013.[34]

4.7.4 Comparison of BAT and placebo

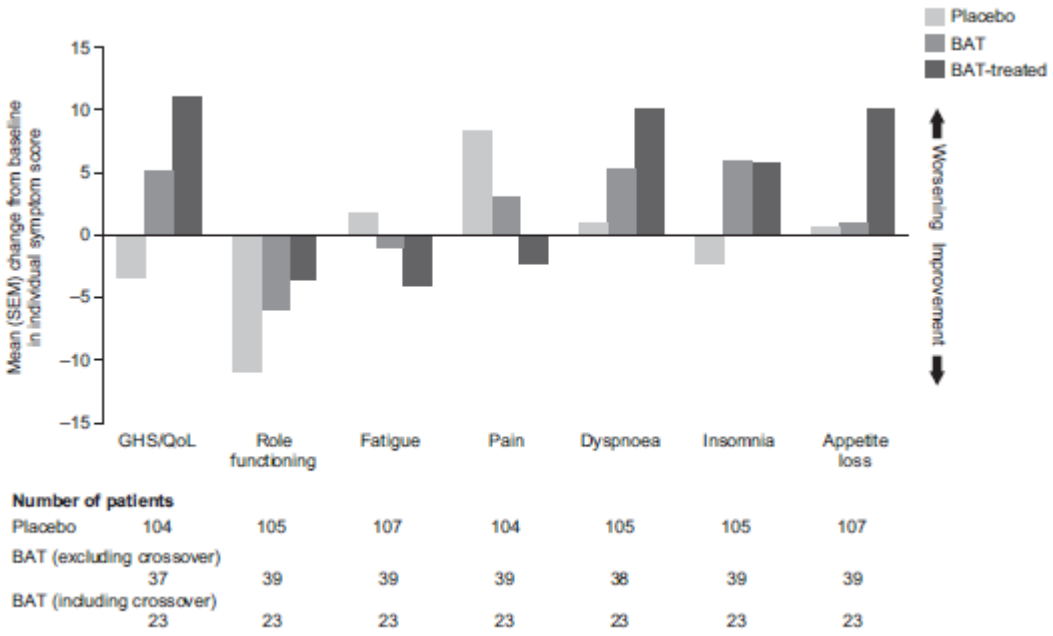
Effects of BAT on splenomegaly and HRQoL are similar to those observed with placebo

The relative efficacy of BAT compared with placebo has been assessed in a comparison of the data for the control groups from COMFORT-II (n = 73) and COMFORT-I (n = 154).[102] The demographic and baseline characteristics were generally similar between the control arms of the two studies, although patients who received placebo were older, and a higher proportion had high-risk disease and were *JAK2V617F*-positive. Of the BAT group in COMFORT-II, 49 (67%) patients received any BAT and 24 (33%) received no treatment. At the data cut-off, 24% of patients in both studies had crossed over to receive ruxolitinib.

During the 24-week study period, most patients in both groups (BAT, 69%; placebo, 75%) had measurable increases in spleen volume. Only one patient (0.7%) who received placebo, and no patients who received BAT, achieved a 35% or greater reduction in spleen volume from baseline at week 24. At 24 weeks, neither group had clinically meaningful improvements from baseline (10 points) in any of the EORTC QLQ-C30 function or symptom scores (Figure 29). When considering the subgroup of BAT patients who received treatment (rather than observation), an improvement of over 10 points was achieved for GHS, dyspnoea and appetite loss.

This *post hoc* analysis suggests that current therapies for MF provide little improvement in spleen size, symptoms or HRQoL and have a similar efficacy to placebo for the treatment of MF.

Figure 29 Mean change in EORTC QLQ-C30 GHS and subscales at week 24 in the placebo arm of COMFORT-I and BAT arm of COMFORT-II



Positive values indicate improvement in GHS/QoL; negative scores indicate improvement in fatigue, pain, dyspnoea, insomnia and appetite loss.
BAT, best available therapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS, global health status; QoL, quality of life; SD, standard deviation.
Mesa et al. 2007.[102]

4.7.5 OS

Neither COMFORT-I nor COMFORT-II were powered to detect differences in OS between ruxolitinib and the control group. Furthermore, in both studies patients were permitted to cross over from the placebo (COMFORT-I) or the BAT (COMFORT-II) arm to ruxolitinib (see section 4.3). In both studies the possible survival benefits of ruxolitinib are likely to be underestimated as in both studies, all patients in the control groups discontinued therapy or crossed over to receive ruxolitinib over the 3-year follow-up.

COMFORT-II

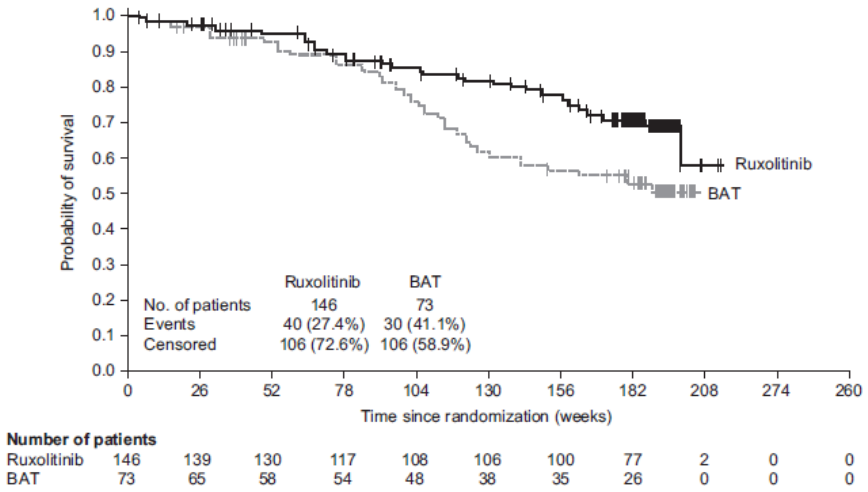
At the 3.5-year follow-up, ruxolitinib was associated with a 42% risk reduction of death compared with BAT in COMFORT-II

OS has been analyses for patients in COMFORT-II at median durations of follow-up of 12 months, 14 months, 3 years and 3.5 years. At the time of the first two assessments, few patients had died and differences in OS between the two treatment groups were not statistically significant. At a median

follow-up of 12 months, there were 10 deaths, 6 (4%) in the ruxolitinib group and 4 (5%) in the BAT group; differences in OS and leukaemia-free survival between groups were not statistically significant (leukaemia-free survival: hazard ratio [HR], 0.65; 95% CI 0.18 to 2.31; OS: HR, 0.70; 95% CI 0.20 to 2.49).[7] A second analysis performed for a planned safety update with approximately 2 months of additional follow-up (median, 61.1 weeks) also showed no significant difference in OS (HR, 1.01; 95% CI 0.32 to 3.24). A statistically significant difference was however evident at the third analysis at a median follow-up of 3 years. At this time point here were 29 deaths in the ruxolitinib group (19.9%) compared with 22 deaths in patients randomised to receive BAT (30.1%), such that the Kaplan–Meier estimated probability of survival at week 144 was 81% for patients originally randomised to ruxolitinib versus 61% for those originally randomised to BAT. These data suggest a relative reduction of 52% in the risk of death with ruxolitinib compared with BAT (HR, 0.48; 95% CI 0.28 to 0.85; p = 0.009) and an absolute risk reduction of 20%.[23]

A further analysis was performed at a follow-up of 3.5 years.[22] This analysis included additional survival information for 15 of 41 patients who were previously deemed lost to follow-up (ruxolitinib, n = 5; BAT, n = 10). In the earlier analyses these patients were censored and hence considered to be alive prior to 48 weeks hence providing a conservative estimate of the difference between treatments over the first year. At 3.5 years there were 40 deaths in the ruxolitinib group (27%) compared with 30 deaths in patients randomised to receive BAT (41%). A statistically significant overall reduction in risk of death of 42% was observed with ruxolitinib compared with BAT (HR, 0.58; 95% CI 0.36 to 0.93; p = 0.022), and the estimated probability of being alive at 3.5 years was 71% in the ruxolitinib arm and 54% in the BAT arm. Given that a majority of patients randomised to BAT crossover to receive ruxolitinib (at a median of 66 weeks), this analysis is likely to underestimate the survival benefit of ruxolitinib. Compared with previous analyses, an earlier separation of the OS curves is seen at approximately week 72 (versus week 96) as a results of inclusion of the additional survival information (Figure 30).

Figure 30 Overall survival in COMFORT-II: median follow-up of 3.5 years



BAT, best available therapy

Harrison et al. 2014.[22]

COMFORT-I

Ruxolitinib prolonged OS compared with placebo in patients with MF in COMFORT-I

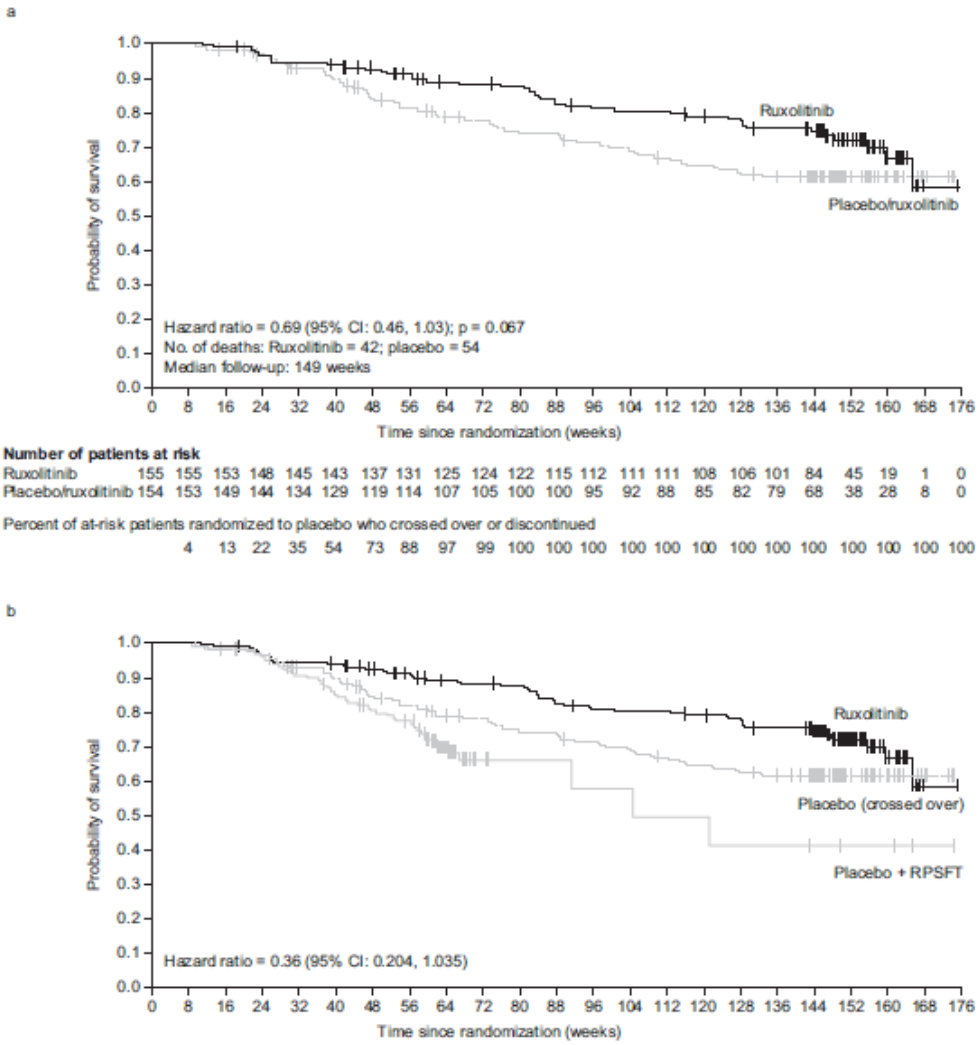
In COMFORT-I, in the planned analysis performed at the time of primary data cut-off, fewer deaths were reported in the ruxolitinib group (n = 10; 6.5%) than in the placebo group (n = 14; 9.1%), but the difference was not statistically significant (HR, 0.67; 95% CI 0.30 to 1.50; p = 0.33).[26] A further analysis performed at a median follow-up of 51 weeks (4 additional months of follow-up) revealed a significant survival advantage for patients who received ruxolitinib, with 13 deaths in the ruxolitinib group (8.4%) and 24 deaths in the placebo group (15.6%) (HR, 0.5; 95% CI 0.25 to 0.98; p = 0.04). This survival benefit was achieved despite the fact that at the time of analysis, most patients in the placebo group had crossed over to ruxolitinib (n = 111, 72.1%) or discontinued from the study (n = 37, 24.0%) (median time to crossover, 41.1 weeks).[24,122] Furthermore, the study was not powered to demonstrate differences in OS between treatment groups, and the fact that patients could cross over from placebo to ruxolitinib means that effects on survival are likely to be underestimated.

OS analysis was also performed at 149 weeks' (3 years) follow-up. At this time point the HR for OS favoured patients originally randomised to ruxolitinib over those originally randomised to placebo (the majority of whom crossed over to ruxolitinib) although results did not reach statistical significance (Figure 31).[25] There were 42 deaths in the ruxolitinib group and 54 in the placebo group; HR 0.69 (95%CI 0. 46 to 1.03; p = 0.067). However, by week 80, all patients originally randomised to placebo had either discontinued from the study or had crossed over to ruxolitinib.[130] Thus the survival analyses after week 80 are comparing patients who received ruxolitinib since randomisation with patients who started receiving ruxolitinib later in the study and received ruxolitinib for a median of 105 weeks. As

more patients in the placebo arm crossed over to receive ruxolitinib, the risk of death for this group decreased, approaching that for patients originally randomised to receive ruxolitinib.

To estimate the true effect or ruxolitinib on OS, adjusting for crossover, a rank-preserving structural failure time (RPSFT) analysis was performed. The OS HR was 0.36 (95% CI 0.204 to 1.035), a value consistent with the hypothesis that the ITT analysis underestimates the survival benefit of ruxolitinib relative to 'true' placebo therapy (Figure 31).[25]

Figure 31 Overall survival in COMFORT-I: a) Overall survival according to ITT analysis, b) rank-preserving structural failure time (RPSFT) analysis of overall survival



CI, confidence interval; ITT, intent-to-treat; RPSFT, rank-preserving structural failure time.
Verstovsek et al. 2015.[25]

According to a pooled analysis, ruxolitinib was associated with a 71% reduction in the risk of death compared with control treatment (BAT or placebo) when correcting for crossover

A pooled analysis of 3-year follow-up data from COMFORT-I and COMFORT-II found that treatment with ruxolitinib was associated with significantly improved survival compared with control (placebo or BAT) (Table 18).[36] Over the 3-year follow-up there were 71 (24%) deaths in patients randomised to ruxolitinib (n = 301) and 76 (33%) deaths in patients randomised to control. Survival was consistent across both studies (COMFORT-I versus COMFORT-II; HR, 1.1; 95% CI 0.8 to 1.6; p = 0.54) and ruxolitinib was associated with a 35% reduction in the risk of death compared with control according to ITT analysis (HR 0.65; 95% CI 0.46 to 0.90; p = 0.01). Using a RPSFT modelling to correct for crossover, the ruxolitinib versus control HR was 0.29 (95% CI 0.13 to 0.63; p = 0.01) suggesting a 71% reduction in the risk of death for ruxolitinib compared with control. Ruxolitinib was associated with improved OS in both intermediate-2 risk and high-risk disease groups.

Table 18 Summary of OS hazard ratios for pooled analysis at 3-year follow-up of COMFORT-I and II

Comparison	**Hazard ratio**
Overall	
HR for ruxolitinib versus control	0.65; 95% CI 0.46 to 0.90; p = 0.01
HR for ruxolitinib versus control adjusting for crossover (RPSFT)	0.29; 95% CI 0.13 to 0.63; p = 0.01
Effect of baseline spleen size	
Risk for each 5 dL increase in spleen volume	1.09; 95% CI 1.03 to 1.15; p = 0.003
Adjusted risk for each 5 dL increase in spleen volume (adjusted)[a]	1.14; 95% CI 1.07 to 1.21
Comparison between studies	
(COMFORT-I versus COMFORT-II)	1.1; 95% CI 0.8 to 1.6; p = 0.54
Comparison between risk groups	
IPSS (Int-2 versus High Risk)	0.47; 95% CI 0.33 to 0.67; p < 0.0001
[a]Adjusted for baseline characteristics and treatment	

HR, hazard ratio; IPSS, International Prognostic Scoring System; RPSFT, rank-preserving structural failure time
Vannucchi et al. 2013.[36]

Post-hoc analysis

The risk of death was found to increase with increasing baseline spleen volume

An assessment of survival based on baseline prognostic covariates including baseline haemoglobin, WBC count, age, MF subtype and spleen volume identified that larger spleen volume, higher baseline WBC and increased age correlated with incremental increases in the risk of death, irrespective of treatment. After adjustment for prognostic baseline characteristics and treatment, the risk of death increased by 9% for each additional 5 dL increase in spleen volume at baseline (HR, 1.09; 95% CI 1.03 to 1.15; p = 0.003).[36]

A greater reduction in spleen volume with ruxolitinib was associated with greater reductions in the risk of death

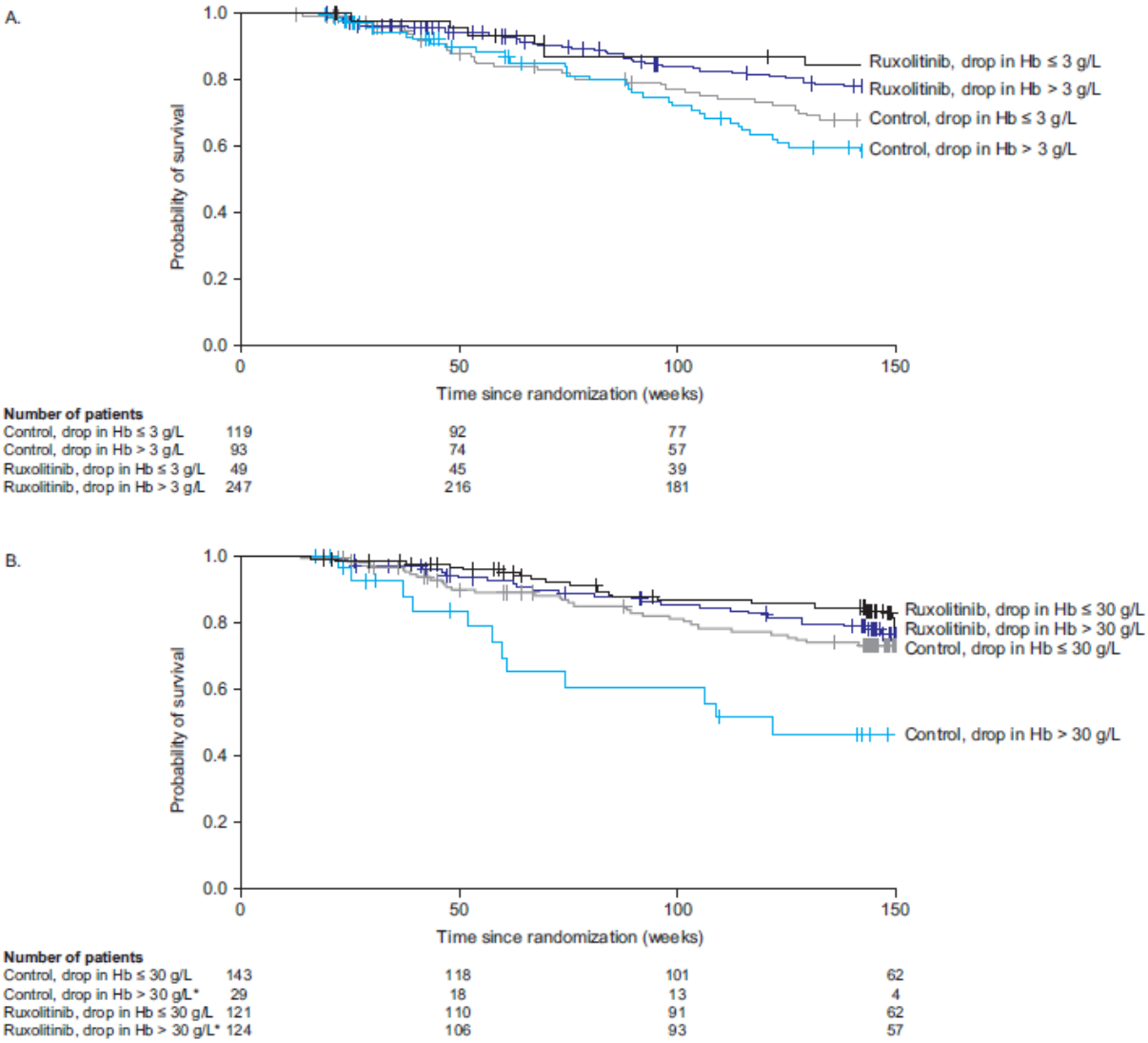
An analysis of OS according to spleen volume reductions at week 24 revealed a positive correlation between the extent of spleen volume reduction achieved on treatment with ruxolitinib and a reduced risk of death. The HR for patients who achieved at least a 50% spleen response compared with patients who achieved less than a 10% reduction from baseline or had no assessment at week 24 was 0.18 (0.07 to 0.47). No such association between spleen response and survival was seen with placebo or BAT.[36]

Ruxolitinib overcomes the adverse prognostic effect of anaemia

Previous studies have shown that haemoglobin levels in patients with MF are prognostic for OS, with low haemoglobin levels being associated with worse outcomes. An analysis of 3-year pooled data from COMFORT-I and COMFORT-II revealed that baseline haemoglobin levels were predictive of OS in the control group (HR, 0.73; 95% CI 0.61 to 0.87) but not in the ruxolitinib group (HR, 0.90; 95% CI 0.77 to 1.07).[131,132] Further analyses have investigated the possible impact of transient reductions in haemoglobin levels observed following initiation of therapy with ruxolitinib. In the COMFORT studies, at week 12, 82% of patients receiving ruxolitinib had a decrease in haemoglobin level of at least 3 g/L from baseline and 41% of patients had a decrease of at least 30 g/L. In contrast, haemoglobin level remained stable in the control group. Analysis of OS according to the decrease in haemoglobin level at week 12 found that a decrease of 3 g/L or less compared with a decrease of over 3 g/L was not significantly associated with OS in either the ruxolitinib or control group (ruxolitinib: HR, 0.85; 95% CI 0.27 to 2.69; control: HR, 0.72; 95% CI 0.34 to 1.49) and the same was observed for a decrease of 30 g/L or less versus over 30 g/L (ruxolitinib: HR, 0.84; 95% CI 0.47 to 1.52; control: HR, 0.76; 95% CI 0.36 to 1.59). Thus the transitory decrease in haemoglobin levels observed on initiation of treatment with ruxolitinib does not adversely affect OS. Furthermore, patients receiving ruxolitinib who had a haemoglobin level decrease of over 3 g/L or over 30 g/L had a survival benefit compared with patients in the control group, who had a haemoglobin level decrease of 3 g/L or less, or 30 g/L or less. Thus the transient decrease in haemoglobin levels observed on initiation of ruxolitinib treatment does not bear the same prognostic implications as haemoglobin level changes that occur as a consequence of

MF pathology and indeed, ruxolitinib appears to dilute the negative prognostic effect of lower haemoglobin levels on OS. Transient haemoglobin level changes during ruxolitinib treatment initiation should not lead to premature interruption or discontinuation.

Figure 32 Kaplan–Meier plot of overall survival by haemoglobin level decrease relative to a) 3 g/L and (b) 30 g/L at week 12 (landmark at week 12)



Hb, haemoglobin

Ruxolitinib prolonged OS in COMFORT-II compared with that observed for conventional therapy in a historical cohort of patients with PMF

A further study has compared survival from diagnosis for patients with primary MF who were enrolled in COMFORT-II and received ruxolitinib (either following the initial randomisation or who crossed over from placebo, n = 100) with a comparable cohort of patients from the multicentre DIPSS database

who received conventional treatments (n = 350).[133] OS was found to be significantly better for patients receiving ruxolitinib: estimated median survival was 3.5 years for the DIPPS cohort compared with 5 years for ruxolitinib-treated patients (HR, 0.61; 95% CI 0.41 to 0.91; p = 0.0148). The 8-year cumulative survival probability from initial diagnosis was 32.2% (95% CI 16.5 to 49.1) in the COMFORT-II cohort and 15.9% (95% CI 11.6 to 20.8) in the DIPSS cohort. After adjusting for age at diagnosis and IPSS risk at the time of entering the analysis, a significant survival benefit was still evident (HR, 0.64; 95% CI 0.4 to 0.96; p = 0.034). The study observations suggest that ruxolitinib may modify the natural history of MF.

4.7.6 Progression-free survival and leukaemia-free survival

At a follow-up of 3.5 years, ruxolitinib was associated with a 20% reduction in the risk of disease progression

In COMFORT-II, at a follow-up of 3.5 years, patients who received ruxolitinib had a reduced risk of disease progression (HR, 0.80; 95% CI 0.54 to 1.19) compared with that of patients who received BAT. The Kaplan–Meier estimate PFS at 3.5 years was 0.27 for the ruxolitinib arm (95% CI 0.18 to 0.35) and 0.23 for the BAT arm (95% CI 0.1 to 0.37) (Table 19).[22] Furthermore, the risk of leukaemia or death was reduced by 39% in patients treated with ruxolitinib (HR, 0.61; 95% CI 0.30 to 0.88).

Table 19 Progression-free survival results in COMFORT-II

Response categories	Patients treated with ruxolitinib (n = 146)	Patients treated with BAT (n = 73)
Events, n (%)	86 (58.9)	34 (46.6)
Censored, n (%)	60 (41.1)	39 (53.4)
Median PFS (95% CI), y	1.6 (1.2 to 2.3)	1.4 (1.1 to 1.9)
Hazard ratio (95% CI)[a]	0.80 (0.54 to 1.19)	
Kaplan–Meier estimate (95% CI)	0.27 (0.18 to 0.35)	0.23 (0.11 to 0.37)
Summary of first events, n (%)		
Total	86 (58.9)	34 (46.6)
Increase in spleen volume of ≥ 25% from on-study nadir	77 (52.7)	26 (35.6)
Splenic irradiation	0	1 (1.4)
Splenectomy	1 (0.7)	3 (4.1)
Leukaemic transformation	0	0
Death	8 (5.5)	4 (5.5)

[a]HR < 1 denotes benefit to ruxolitinib arm. HR > 1 denotes benefit to BAT arm.

PFS was defined as the interval between randomisation and the occurrence of the first event.

BAT, best available therapy; PFS, progression-free survival

Harrison et al. 2014.[22]

4.8 Subgroup analysis

A number of subgroup analyses of COMFORT-I and COMFORT-II data have been undertaken and generally show that the benefits of ruxolitinib over placebo or BAT are consistent in all subgroups considered.

In COMFORT-I, subgroup analyses were performed for the primary outcome (proportion of patients with a 35% or greater reduction in spleen volume from baseline to week 24) and change in TSS from baseline to week 24 for MF subtype (pre-planned) and presence/absence of *JAK2V617F* mutation (*post hoc*).[26,122] In COMFORT-II, subgroup analyses were performed for the primary outcome (proportion of patients with a 35% or greater reduction in spleen volume from baseline to week 48) for MF subtype, sex and prognostic category (all pre-planned) and presence/absence of *JAK2V617F* mutation (*post hoc*).[7,121]

Further reported analyses from COMFORT-I include a subgroup analysis according to MF subtype, age, IPSS risk group, Eastern Cooperative Oncology Group (ECOG) performance status, *JAK* mutational status and other baseline factors,[17] *post hoc* analysis of outcomes according to degree of splenomegaly and symptom severity,[134] a *post hoc* analysis looking at associations between ruxolitinib-induced changes in weight, cholesterol and survival,[135] and evaluation of dose effects.[136,137]

Reported analyses from COMFORT-II include assessment of reduction in *JAK2V617F* allele burden,[138] multivariate and logistic regression analyses looking at cytokine levels and associations with spleen and symptom changes,[139-141] and assessment of the prognostic impact of mutational status on outcomes.[142,143]

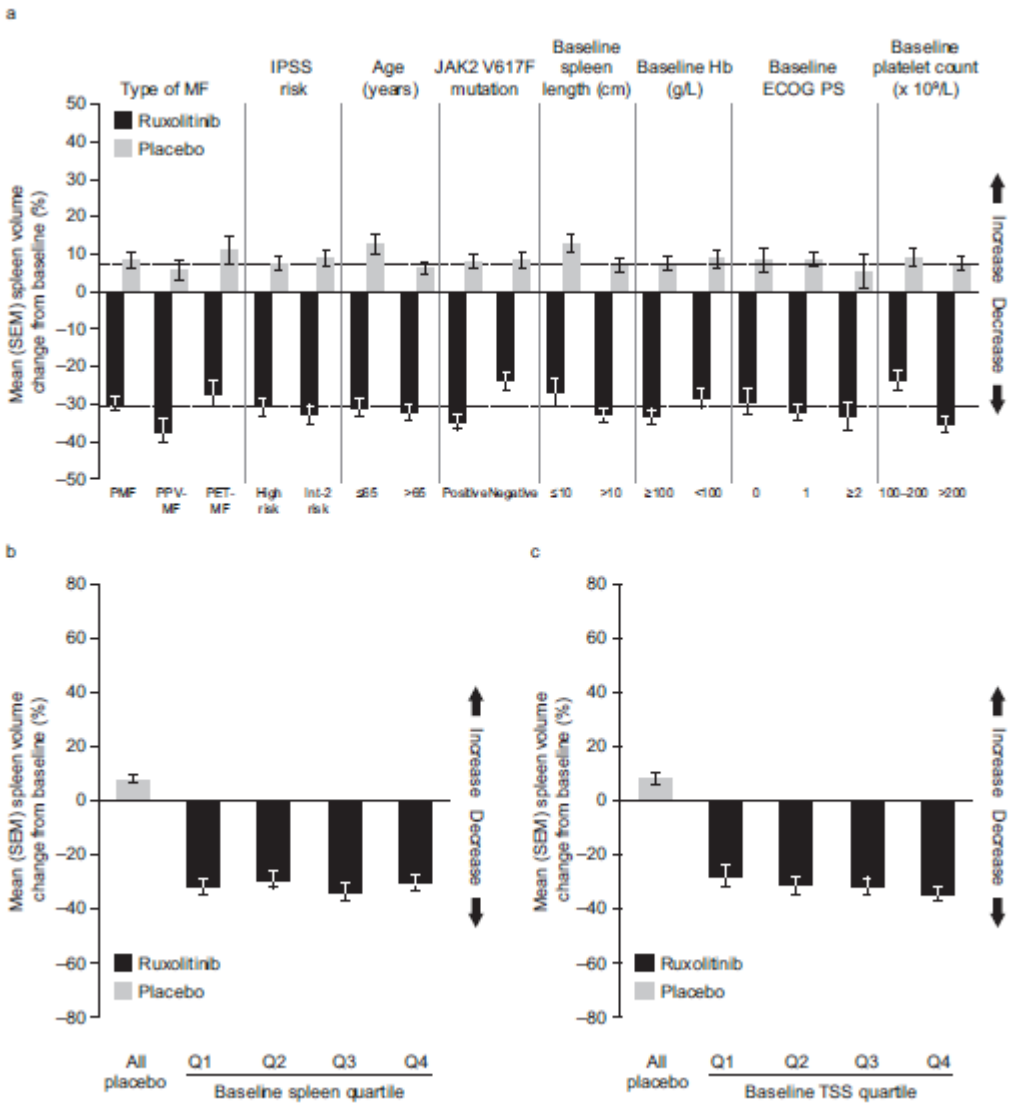
Ruxolitinib is effective in reducing spleen volume regardless of baseline spleen size and across all patient severity subgroups

Analyses of COMFORT-I identified that ruxolitinib is effective in reducing spleen volume regardless of baseline spleen size and across all patient severity subgroups.[17] The mean reduction in spleen volume from baseline to week 24 achieved with ruxolitinib was found to be similar in all subgroups considered (including MF subtype, patient age, IPSS risk group, ECOG performance status, *JAK2V617F* mutational status, and baseline values for haemoglobin, platelet count and spleen length) (Figure 33). A further analysis according to baseline spleen volume quartile or baseline TSS quartile showed a consistent reduction in spleen volume regardless of baseline spleen volume or TSS.

Ruxolitinib reduces spleen volume irrespective of mutational status

Analyses of both COMFORT-I and COMFORT-II indicate that the benefits of ruxolitinib over placebo or BAT are observed in patients with or without the *JAK2V617F* allele as shown in Figure 33.[7,24,26,144]

Figure 33 Percentage change in spleen volume from baseline to week 24 by patient subgroup in COMFORT-I: a) MF subtype, patient age, IPSS risk group, ECOG performance status and JAK2 V617F mutational status; and baseline values for haemoglobin, platelet count and spleen length, b) baseline spleen volume quartile and c) baseline total symptom score (TSS) quartile



Verstovsek et al. 2013.[17]

4.9 Meta-analysis

A meta-analysis has not been performed. Although some of the efficacy outcomes are the same for COMFORT-I and II, there are considerable differences between studies with regard to the patient population, treatments, and study duration. A meta-analysis was therefore not undertaken.

4.10 Indirect and mixed treatment comparisons

The relevant comparator for the economic assessment is BAT. Comparative data for the efficacy and safety of ruxolitinib versus BAT is available in the COMFORT-II trial. A comparison of efficacy data for the control groups of COMFORT-I and COMFORT-II suggest that the effects of BAT on splenomegaly and HRQoL are similar to those observed with placebo (see section 4.7.4). Thus data from COMFORT-I provides further supporting data regarding the relative efficacy of ruxolitinib versus BAT. An indirect treatment comparison was therefore not performed.

4.11 Non-randomised and non-controlled evidence

The systematic review identified 12 non-RCTs of ruxolitinib in patients with MF, as described in this section 4.1.2 and in Section 8 appendices. The UK ROBUST study was identified as an abstract and has since been published as a full paper. The full paper is included in this submission.

The findings of non-RCTs provide supporting data on the efficacy and safety of ruxolitinib in the treatment of patients with MF. The ROBUST study was a phase 2 study performed in the UK and is described below,[27] as is the JUMP trial, a phase 3b expanded-access trial which has reported data for 1144 patients to date.[28] Two further studies plus a subgroup analysis of data from the JUMP trial provide information on the efficacy and safety of ruxolitinib in patients with low platelet counts (under 100×10^9/L),[29,30,37] and two further reports give data on the efficacy of ruxolitinib in patients with early disease (low-risk);[32,38] these are also described in this section. Results for the phase 1/2 study,[39] including long-term follow-up data, a further phase 2 study[40] and a number of expanded-access studies and reports of routine clinical use,[41-44] have also been published and are summarised in Appendix 8.18.

4.11.1 The ROBUST study: a UK phase 2 study

The ROBUST study is an open-label, 48-week, phase 2 study which has recently reported a final analysis.[53] Patients eligible for inclusion in ROBUST were those with PMF, PPV-MF or PET-MF, with or without prior therapy, who had intermediate-1 risk, intermediate-2 risk or high-risk disease and were recruited from ten UK centres.

The study presented data for 48 patients with a mean age of 69.9 (43.0–89.9) years, of whom 14 had intermediate-1 risk, 13 had intermediate-2 risk and 21 had high-risk disease. Patients' mean baseline spleen length was 13.3 cm and mean TSS was 16.3.

Results from the UK ROBUST study support those of COMFORT-I and COMFORT-II demonstrating benefit for ruxolitinib in patients with MF across all risk groups involved (intermediate-1 risk, intermediate-2 risk and high risk)

At week 48, 39.6% of patients receiving ruxolitinib achieved reductions in spleen length of at least 50% and all risk groups were shown to benefit equally (responses of at least 50% were found in 50.0%, 15.4% and 47.6% of patients with intermediate-1 risk, intermediate-2 risk and high-risk disease, respectively). Mean spleen length decreased to 6.6 ± 7.2 cm, a mean reduction of 46.7%, and reductions were similar across all risk groups (mean percentage reduction: intermediate-1 risk, 51.6%; intermediate-2 risk, 37.0%; high-risk, 48.6%, Figure 34). Reductions were rapid and were observed as early as week 4 (the first assessment) in the overall population and all risk groups, and were sustained to week 48.

The ROBUST data also show improvements in MF-associated symptoms at 48 weeks. Mean TSS improved from 15.4 at baseline to 7.6 at week 48, a mean reduction of 50.6%. Improvements were achieved in all risk groups (intermediate-1, improved by 6.4; intermediate-2, improved by 8.0; high, improved by 9.1). A reduction of at least 50% in TSS from baseline to week 48 was seen in 21.4% of patients in intermediate-1 risk, 23.1% in intermediate-2 risk and 19.0% in high-risk disease groups. Reductions in MF-SAF TSS were rapid and were observed as early as week 4 and sustained for the duration of treatment to week 48. Additionally, reductions in individual MF-SAF symptom scores from baseline to week 48 were achieved for all symptoms across the overall population and all three of the risk groups, except for a slight increase in bone/muscle pain in patients with high-risk disease.

This study also included a composite primary endpoint of treatment success, defined as a 50% or greater decrease in spleen length and/or TSS at week 48. Using this measure, 50.0% of the overall population and 57.1%, 38.5% and 52.4% of the intermediate-1 risk, intermediate-2 risk and high-risk disease groups, respectively, achieved treatment success on ruxolitinib.

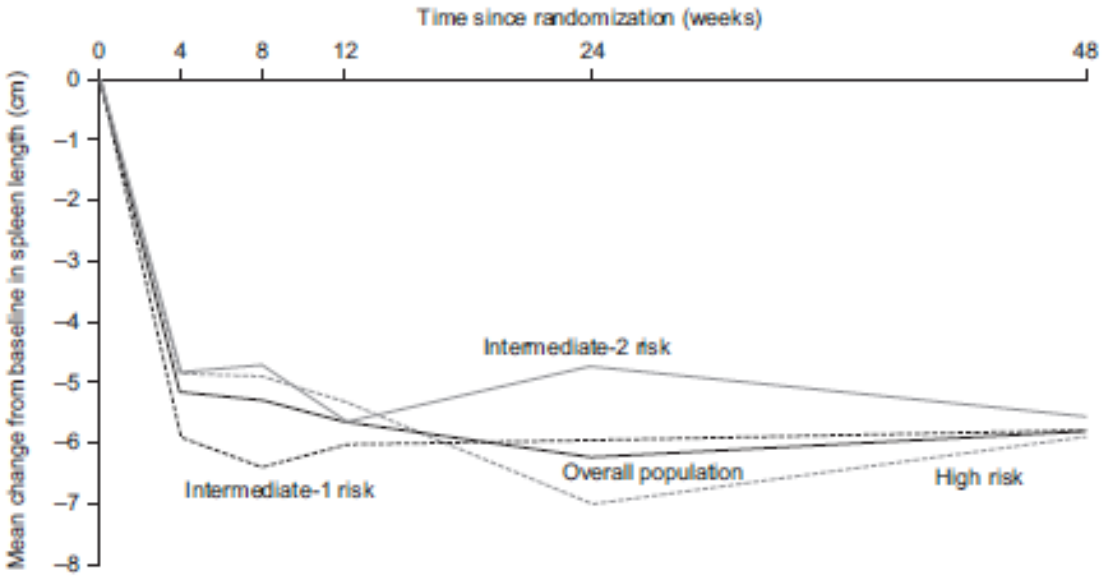
Five-dimension European Quality of Life questionnaire (EQ-5D) data were also reported for the first time in patients with MF. Mean EQ-5D score was 0.72 at baseline (n = 43), and at 4 weeks a statistically significant increase in EQ-5D score to 0.78 was observed for evaluable patients (n = 40, p = 0.036). This numerical improvement was maintained until week 48.

Consistent with findings from the COMFORT studies, the most common haematological AEs were anaemia (45.8% of patients) and thrombocytopenia (37.5%). Overall, mean platelet levels decreased by approximately 40% from baseline to week 4 and then stabilized. Haemoglobin levels dropped by

10% from baseline to week 12, then recovered toward baseline levels by week 48 (5% lower than baseline). In some cases (n = 6, 12.5%), the recovery of haemoglobin levels required concomitant treatment with erythropoiesis-stimulating agents or transfusions of packed red blood cells. Of six patients who were known to be transfusion-dependent at baseline, one became transfusion-independent by the end of the study; transfusion status was unavailable for the remaining 42 patients. The most common non-haematological AEs were abdominal pain (27.1%), epistaxis (27.1%), diarrhoea (25.0%), contusion (22.9%), fatigue (22.9%), headache (22.9%) and lethargy (20.8%), and were primarily grade 1/2.

Two patients developed AML on study. One patient (intermediate-1 risk) had a bone marrow blast count > 20% that was sustained for at least 8 weeks (LFS criteria); blast counts for the second patient (intermediate-2 risk) were not available throughout the study to confirm a sustained increase. A third patient (intermediate-1 risk) developed AML about 8 months following the end of the study and while still receiving treatment with ruxolitinib. There was one death during the study (first patient above) reported as being due to AML; this death occurred after treatment discontinuation.

Figure 34 Mean change in spleen length from baseline to week 48 in ROBUST



Mead et al. 2014.[27]

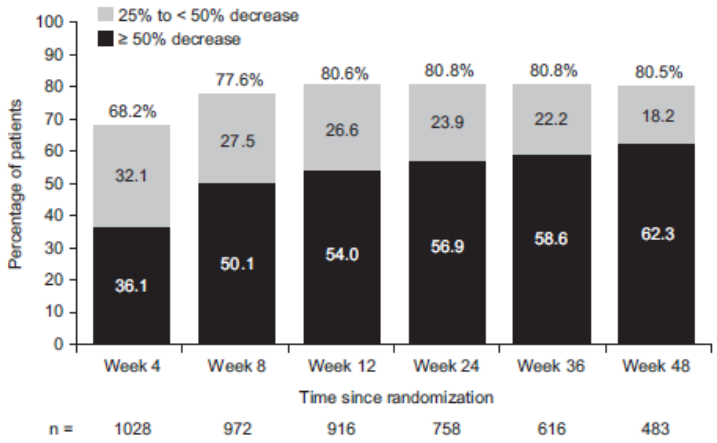
4.11.2 The JUMP trial: a phase 3b extended access trial in 25 countries

An extended-access phase 3b study reported results consistent with the phase 3 COMFORT studies including meaningful improvements in HRQoL from week 4

The phase 3b expanded-access, JAK inhibitor ruxolitinib in MF patients (JUMP) trial was designed to assess the safety and efficacy of ruxolitinib in patients with PMF, PPV-MF or PET-MF with high-risk, intermediate-2 risk or intermediate-1 risk disease with a palpable spleen who were treatment naive, had progressed or were intolerant of prior therapy. As of September 2014, 2138 patients had been enrolled in 25 countries. Data have been reported for an analysis of 1144 patients who had received ruxolitinib for a median of 11.1 months.[28] At this time point approximately two-thirds of patients had either remained on treatment (36%) or transitioned to commercial drug (34%). Each patient's starting dose of ruxolitinib was determined by baseline platelet levels. At follow-up, the median daily dose was 37.2 mg for patients who initiated therapy at a dose of 20 mg bid and 23.4 mg for patients who initiated therapy at a dose of 15 mg bid.

At weeks 24 and 48, 55% and 61% of patients, respectively, achieved at least a 50% reduction from baseline in palpable spleen length, and the majority of patients (69%) had experienced at least a 50% reduction in spleen length from baseline at any time by week 48 (Figure 35). Furthermore, 81% of patients achieved a reduction of ≥25% from baseline from week 12 onwards. Responses were rapid and durable; the median time to the first reduction in spleen length of 50% was 5.1 weeks (range, 0.1 to 53.1 weeks), and the Kaplan–Meier estimated probability of maintaining a spleen response for 24 weeks was 93% (95% CI 91% to 95%) and for 48 weeks was 72% (95% CI 54% to 84%).

Figure 35 Proportion of patients achieving a reduction in spleen length from baseline of at least 50%.



Martino et al. 2014.[28]

Clinically meaningful improvements in symptoms were seen as early as week 4, as evaluated by the FACT-Lym total score and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and were maintained during the study. At each time point (weeks 4, 12, 24 and 48) approximately 45% to 50% of patients achieved a clinically significant improvement (ie minimally important difference) in both the FACT-Lym total score and the FACIT-Fatigue scale. PFS, leukaemia-free survival and OS at 48 weeks were estimated at 0.89 (95% CI 0.86 to 0.90), 0.91 (0.89 to 0.93) and 0.92 (0.90 to 0.94), respectively.

Ruxolitinib was generally well tolerated, with only 14% of patients discontinuing owing to AEs. The most common grade 3 or 4 haematological AEs (grade 3 or higher) were anaemia (33.0%), thrombocytopenia (12.5%) and neutropenia (3.9%); each of these rarely led to discontinuation of ruxolitinib. The incidences of grade 3 or 4 non-haematological AEs were low, with pneumonia being the only event reported in over 2% of patients (3.6%). Grade 3 or 4 infections occurring in over 5 patients included pneumonia (3.6%; n = 41), nasopharyngitis (1.1%; n = 13), sepsis (0.9%; n = 10), gastroenteritis (0.5%; n = 6), lung infection (0.5%; n = 6) and septic shock (0.5%; n = 6), and tuberculosis was reported in 3 patients (0.3%; no grade 3 or 4). There were no reports of progressive multifocal leukoencephalopathy. Overall, safety and efficacy of ruxolitinib in JUMP are consistent with those in the phase 3 COMFORT studies.

4.11.3 Efficacy and safety in patients with low platelet counts

Approximately a quarter of patients with PMF have low platelet counts (under 100 × 10^9/L) as a consequence of disease,[45-47] and such patients were excluded from the COMFORT-I and COMFORT-II studies. Results from three studies, however, suggest that ruxolitinib is also efficacious in patients with low platelet counts, and the optimal starting dose in such patients is being investigated in an ongoing phase 1b dose-finding study.

Phase 2 trial, study 258

A phase 2 dose-finding study investigated the efficacy and safety of ruxolitinib in patients with low platelet counts (50 to 100 × 10^9/L) when initiated at a dose of 5 mg bid with the option to increase to 10 mg bid if platelet counts remained adequate.[29] An interim analysis of data from this study reported that by week 24, 62% of patients achieved stable doses of at least 10 mg bid. A median percentage reduction in spleen volume of 24.2% was achieved at 24 weeks and 20% of patients achieved a reduction in spleen volume of at least 35%. When evaluated by titrated dose (average dose over the last 4 weeks of the study, up to week 24), median percentage reductions from baseline in spleen volume at week 24 were 16.7% for patients who received 5 mg once or bid (n = 7) and 28.5% for patients who received 10 mg bid (n = 20). Decreases in TSS were also observed in patients who completed 24 weeks of therapy (n = 32). The median percentage reduction from baseline in TSS for those who completed 24 weeks of therapy was 43.8% and was 13.0% for patients receiving 5 mg

once or bid (n = 8) and 63.5% for patients receiving 10 mg bid (n = 21). In the three patients who had their dose escalated to over 10 mg bid because of inadequate response, median percentage reduction from baseline in TSS at week 24 was 33.8%.[29] The study reported a mean change in EORTC QLQ-C30 GHS score from baseline of approximately 13 at week 24.

As expected for this patient population, thrombocytopenia was the most frequently reported grade 3 or 4 AE occurring in 56% of patients and grade 3 or 4 anaemia was reported in 42% of patients. Most other AEs were grade 1 or 2 and no other grade 3 or 4 AEs were reported in more than 2 (4%) patients. Non-haematological AEs (any grade) reported in over 10% of patients were diarrhoea (28%), peripheral oedema (26%), nausea (24%), abdominal pain (24%) and fatigue (22%). Thrombocytopenia necessitating dose reductions and dose interruptions occurred in 12 (24%) and 8 (16%) patients, respectively, and occurred mainly in patients with baseline platelet counts of 75×10^9/L or less. Two patients discontinued owing to AEs: in one patient this was grade 4 thrombocytopenia. The results of this study therefore indicate ruxolitinib, initiated at a dose of 5 mg bid, can benefit patients with low platelet counts.

JUMP

The phase 3b extended access trial, JUMP, described above, included patients with low platelet counts (at least 50 to under 100×10^9/L). In this patient population ruxolitinib was initiated at a dose of 5 mg bid and could be increased to 10 mg bid at week 4 in patients with inadequate efficacy if platelet counts were at least 50×10^9/L and there had been no treatment-related toxicities that resulted in dose reduction, interruption, or discontinuation during treatment at the 5 mg bid dose. Results for an interim analysis for 6 months of therapy in the first 50 patients with low platelet counts have been reported.[37] At this time point, 82% of patients (31 of 38 patients starting therapy on 5 mg bid) remained on the 5 mg bid dose and 18% had undergone dose escalation to 10 mg bid..

At week 24, 38.2% (13 of 34 evaluable patients) achieved a reduction of at least 50% from baseline in palpable spleen length; overall, 44.7% of patients (21/47) achieved at least a 50% reduction from baseline in spleen length at any time. Clinically meaningful improvements in symptoms, as assessed using the FACT-Lym total score, were seen as early as week 4 (mean change from baseline, 8.2) and were durable through week 12 (change from baseline, 9.6). The reduction in splenomegaly and improvements in symptoms observed in this subgroup of patients are however inferior to those achieved for the overall JUMP population.

Overall, the adverse effect profile was consistent with previous studies in patients with platelet counts under 100×10^9/L. The most common grade 3 or 4 haematological AEs were thrombocytopenia (30%) and anaemia (28%): 3 patients (6%) discontinued owing to thrombocytopenia and 1 (2%) discontinued owing to anaemia. Grade 1/2 haemorrhages were reported in 4 (8%) patients and grade 3 or 4 haemorrhages in 2 (4%) patients. Rates of grade 3 or 4 non-haematological AEs were low, with

only the following occurring in more than one patient: pyrexia (6.0%); septic shock (4.0%); and arthralgia (4.0%). Nine patients (18%) discontinued therapy owing to AEs. The results of this analysis thus suggest that ruxolitinib doses of 5 to 10 mg bid are generally well tolerated and efficacious in patients with MF who have platelet counts of at least 50 to under 100 × 10^9/L but higher doses may be worth considering in such patients.

EXPAND

The open-label, phase 1b, dose-finding study (EXPAND) further investigates the optimum dose of ruxolitinib in patients with low baseline platelet counts. [30] Preliminary results have been reported for this study and suggest that starting doses of 10 mg bid and 15 mg bid may be appropriate in patients with platelet counts of 50 to 74 × 10^9/L and 75 to 99 × 10^9/L, respectively.

This on-going study is investigating doses of 5 mg bid to 15 mg bid in two groups of patients, those with platelet counts of 50 to 74 × 10^9/L (stratum 2) and those with platelet counts of 75 to 99 × 10^9/L (stratum 1). Doses of up to 15 mg bid have been investigated in patients with platelet counts of 75 to 99 × 10^9/L and doses of up to 10 mg bid have been investigated in patients with the lower platelet levels. Results for a preliminary analysis of data for 34 patients have shown that most (97%) patients achieved reductions in palpable spleen length and 50% of patients achieved a reduction in spleen length of at least 50% as their best response. Improvements in symptoms, as assessed using the MF-SAF TSS, were also observed; a reduction from baseline of at least 50% at any time in TSS was achieved by 43% (6/14) of patients with platelet counts of 75 to 99 × 10^9/L and 66.7% (8/12) of patients with platelet counts of 50 to 74 × 10^9/L.

The reported adverse effects were consistent with the known safety profile of ruxolitinib. In this analysis, 24% of patients in stratum 1 (n = 5) and 31% of patients in stratum 2 (n = 4) permanently discontinued drug owing to an AE. Two patients in stratum 2 discontinued owing to grade 3 or 4 thrombocytopenia; other AEs leading to discontinuation were reported in only one patient in either stratum. Thrombocytopenia (stratum 1, 67%; stratum 2, 85%) and anaemia (stratum 1, 43%; stratum 2, 23%) were the most frequently reported grade 3 or 4 AEs in both strata. Three patients in stratum 1 and one patient in stratum 2 reported grade 3 or 4 haemorrhagic events. Other grade 3 or 4 AEs were reported in up to 10% of patients in either stratum. Data for further patients enrolled in the expansion phase of this study are required to confirm the optimum starting dose for ruxolitinib in patients with low platelet counts, but these results suggest that doses higher than those investigated in this patient population in the phase 2 study and JUMP trial are well tolerated and could be appropriate starting doses for this subgroup of patients.

4.11.4 Efficacy and safety in early disease (low-risk)

Both the COMFORT trials involved only patients with intermediate-2 or high-risk disease, as did a phase 2 study in Asian patients,[40] while most other studies report data for patients with intermediate-1, intermediate-2 or high-risk disease (eg ROBUST, JUMP, EXPAND and various real-world studies.[27,30,42-44,145] Evidence is now emerging for a benefit for ruxolitinib in patients with low-risk disease, as reported for a retrospective review of real-world data for 108 patients with low- or intermediate-1 risk disease treated with ruxolitinib at centres in the USA[38] and a report regarding 25 patients with low- or intermediate-1 risk disease treated at a single US centre.[32]

A retrospective real-world study has reported on the impact of ruxolitinib on splenomegaly and symptoms in a cohort of patients with low-risk (n = 25) or intermediate-1 risk (n = 83) disease.[31] Both low- and intermediate-1 risk MF patients experienced substantial reductions in splenomegaly during ruxolitinib treatment; the proportion of patients with moderate or severe splenomegaly (at least 10 cm palpated spleen) decreased from 64% at MF diagnosis to 16% at best response during ruxolitinib treatment in patients with low-risk disease and from 53% at MF diagnosis to 10% at best response in patients with intermediate-1 risk disease. For most symptoms examined, there was a shift toward a less severe profile as patients proceeded from diagnosis through to best response during treatment.

A second study reported on clinical responses in 25 patients with low- or intermediate-1 risk disease treated with ruxolitinib at a single US centre for a median of 12 months.[32] The percentage of reduction in spleen size by palpation increased during the course of follow-up from 49% at 3 months to 57% and 64% and 6 and 12 months, respectively, and a median reduction of 73% in the TSS assessed using the MPN-SAF compared with baseline was achieved ($p < 0.001$), together with improvements in each of the parameters of the TSS. Grade 3 or 4 AEs included anaemia (28%) and thrombocytopenia (24%).

The findings from these two studies indicate that patients with low-risk and intermediate-1 risk disease, as well as those with more advanced disease, benefit from ruxolitinib treatment.

4.12 Adverse reactions

4.12.1 Overview of studies

The safety profile of ruxolitinib in MF has been established in the primary reports from the phase 3 studies COMFORT-I and COMFORT-II and long-term follow-up of these studies, and is complemented by data from the phase 1/2 study (see Appendix 8.18), the UK phase 2 trial, ROBUST (see section 4.11), the expanded access JUMP trial (see section 4.11), as well as for in patients with low platelet counts (see section 4.11).

The COMFORT-I and COMFORT-II studies indicate that ruxolitinib is generally well tolerated.[7,26] Anaemia was reported as the most frequent grade 3 or 4 AE in both phase 3 trials and thrombocytopenia was the only other grade 3 or 4 AE reported in more than 8% of patients in both trials. These AEs were generally manageable by dose modifications and/or transfusions, improved over time, and rarely led to treatment discontinuation (1% and 3.6% of patients). Indeed, the updated BCSH guidelines recommend that anaemia is managed by dose reductions or concomitant use of erythropoiesis-stimulating agents, and/or anabolic steroids (See section 3.3).[8] The incidences of non-haematological AEs were low in both studies and most were grade 1 or 2 in severity. Results from COMFORT-I and COMFORT-II long-term extension studies, with follow-up of treatment given for at least 3 years, suggest that the AEs of anaemia, thrombocytopenia, bleeding events and infections generally decreased over time. Data from non-RCTs confirm that ruxolitinib is generally well tolerated, with few patients experiencing grade 3 or 4 non-haematological AEs. Additionally, data from studies in healthy volunteers and in other indications such as refractory/relapsed acute leukaemia, PV and ET are consistent with those reported for patients with MF.

4.12.2 Phase 3 trials: COMFORT-I and COMFORT-II

Safety data from the two phase 3 studies provide a comprehensive assessment of the safety profile of ruxolitinib in patients with MF. The data give an indication of the AEs that may be associated with ruxolitinib in this patient population and the need for dose reductions and other strategies to manage AEs. The results of both COMFORT-I and COMFORT-II are relevant to the decision problem.

The primary analysis results for COMFORT-II give details of the safety profile of ruxolitinib in 146 patients over 48 weeks and provide an indication of how the safety profile of ruxolitinib compares with that of BAT.[7,121] Three-year and 3.5-year safety data are also available.[22,23,146]

Results for the primary analysis of COMFORT-I report on the incidence of AEs, dose reductions and treatment discontinuations for 155 patients who received ruxolitinib compared with 154 patients who received placebo, followed for a median of 32 weeks.[26] Two-year and 3-year safety data are also available from COMFORT-I providing further information on the long-term safety profile of ruxolitinib.[25]

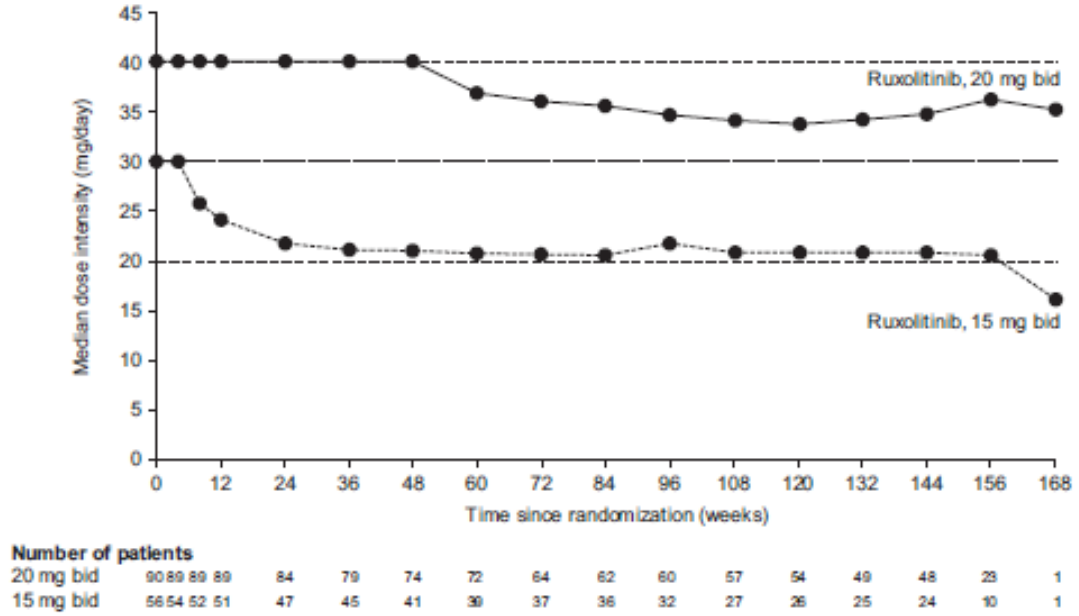
4.12.3 Dose titration

Following initial dose titration, the dose intensity for ruxolitinib remained stable over time in both studies; patients randomised to 15 mg bid and 20 mg bid were titrated to a mean dose of 10 mg bid and 15 mg bid respectively

In COMFORT-II the reported mean dose intensity of ruxolitinib at the primary analysis was 30 mg/day (range: 10 to 49 mg/day).[7] Long-term follow-up of patients in the extension study of COMFORT-II, which includes patients who have received over 3 years of ruxolitinib treatment, has shown that in the

group of patients receiving ruxolitinib at a starting dose of 20 mg bid, the median daily dose remained stable to week 48 (39.7 mg) during the double-blind, primary analysis period, and then decreased slightly over time to 34.3 mg/day at week 144. In the group that received a starting dose of ruxolitinib 15 mg bid, the median dose intensity decreased over the first 24 weeks of therapy and stabilised at approximately 20 mg/day (20.8 mg/day at week 144) (Figure 36)[23,146]

Figure 36 Dose intensity of ruxolitinib over time for COMFORT-II: 3-year follow-up

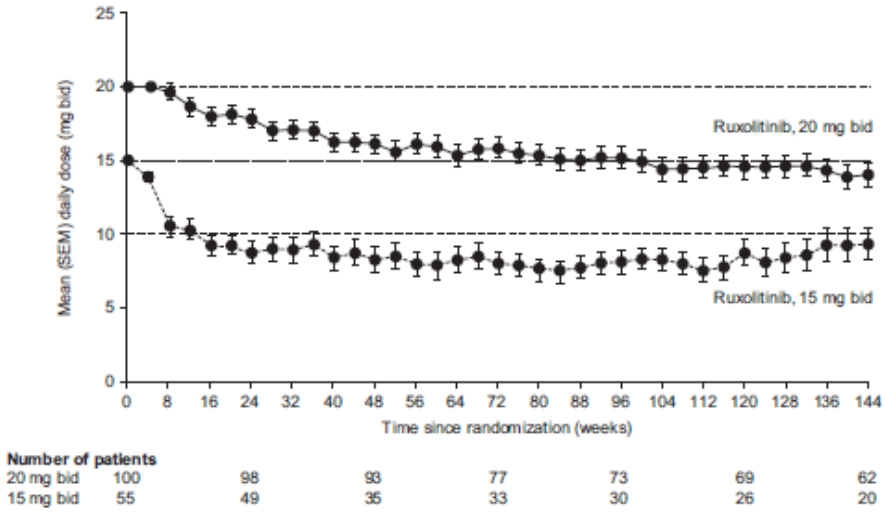


bid, twice daily.

Cervantes et al. 2013.[146]

In COMFORT-I, approximately 70% of patients had dose adjustments during the first 12 weeks of therapy and by week 24,[130] patients originally randomised to ruxolitinib 15 mg bid were titrated to a mean dose of approximately 20 mg/day and those originally randomised to 20 mg bid dosing were titrated to doses of between 30 and 40 mg/day. Figure 37 shows how the doses of ruxolitinib then remained stable over 144 weeks of treatment.[25]

Figure 37 Mean daily dose of ruxolitinib over time in COMFORT-I: 3-year follow-up



bid, twice daily.

Verstovsek et al. 2015.[25]

4.12.4 Primary analysis

A summary of the AEs at primary analyses for both the COMFORT-II and COMFORT-I studies is provided in Table 20.

Table 20 Adverse events across randomised groups in COMFORT-I and COMFORT-II: primary analysis

System organ/ class/ adverse events	COMFORT-I (24 weeks) [26,122,123]			System organ/ class/ adverse events	COMFORT-II (48 weeks) [7,121,124]		
	Ruxolitinib % of patients (n = 155)	Placebo % of patients (n = 151)	Relative risk (95% CI)		Ruxolitinib % of patients (n = 146)	BAT % of patients (n = 73)	Relative risk (95% CI)
Death[a], n (%)	9 (5.8)	11 (7.3)		Death[b], n (%)	6 (4.1)	4 (5.5)	
SAEs, n (%)	43 (27.7)	53 (35.1)		SAEs, n (%)	44 (30.1)	21 (28.8)	
Grade 3 or 4 AEs, n (%)	73 (47.1)	67 (44.4)		Grade 3 or 4 AEs, n (%)	61 (41.8)	18 (24.7)	
Withdrawal due to AEs, n (%)	17 (11.0)	16 (10.6)		Withdrawal due to AEs, n (%)	12 (8.2)	4 (5.5)	
Any AEs, n (%)	151 (97.4)	148 (98.0)		Any AEs, n (%)	145 (99.3)	66 (90.4)	
Non-haematological adverse events (≥ 10% of ruxolitinib-treated patients), % any grade/grade 3 or 4							
Fatigue	25/5	34/7		Diarrhoea	23/1	12/0	
Diarrhoea	23/2	21/0		Peripheral oedema	22/0	26/0	
Peripheral oedema	19/0	23/1		Asthenia	18/1	10/1	
Ecchymosis	19/0	9/0		Dyspnoea	16/1	18/4	
Dyspnoea	17/1	17/4		Nasopharyngitis	16/0	14/0	
Dizziness	15/1	7/0		Pyrexia	14/2	10/0	
Nausea	15/0	19/1		Cough	14/0	15/1	
Headache	15/0	5/0		Nausea	13/1	7/0	
Constipation	13/0	12/0		Arthralgia	12/1	7/0	
Vomiting	12/1	10/1		Fatigue	12/1	8/0	
Pain in extremity	12/1	10/0		Pain in extremity	12/1	4/0	
Insomnia	12/0	10/0		Abdominal pain	11/3	14/3	

System organ/ class/ adverse events	**COMFORT-I (24 weeks)** [26,122,123]			**System organ/ class/ adverse events**	**COMFORT-II (48 weeks)** [7,121,124]		
	Ruxolitinib % of patients (n = 155)	**Placebo % of patients (n = 151)**	**Relative risk (95% CI)**		**Ruxolitinib % of patients (n = 146)**	**BAT % of patients (n = 73)**	**Relative risk (95% CI)**
Arthralgia	11/2	9/1		Back pain	10/2	11/0	
Pyrexia	11/1	7/1		Headache	10/1	4/0	
Abdominal pain	10/3	41/11		Pruritus	5/0	12/0	
Haematology laboratory values[c]							
Anaemia (grade 3 or 4)	45.2	19.2		Haemoglobin (grade 3 or 4)	42	31	
Thrombocytopenia (grade 3 or 4)	12.9	1.3		Platelets (grade 3 or 4)	8	7	
Neutropenia	7.1	2.0					

[a]Deaths during study or within 28 days of last dose. Principal causes of death in the ruxolitinib group were muscle weakness and general deterioration, subdural haematoma, renal failure, non-small cell lung cancer, acute myeloid leukaemia (AML), pneumonia (in 2 patients), and sepsis (in 2 patients). Principal causes of death in the placebo group were staphylococcal infection, gastrointestinal haemorrhage, intestinal perforation, multi-organ failure, pneumonia, sepsis (in 2 patients), and disease progression (in 4 patients).One patient in the placebo group died after crossover to ruxolitinib therapy.

[b]The causes of death in the ruxolitinib group were hepatic failure, cerebral haemorrhage, and portal-vein thrombosis after surgery for metastatic squamous-cell carcinoma of the head and neck (in 1 patient); pulmonary oedema and cardiac arrhythmia (1); retroperitoneal haemorrhage after an orthopaedic procedure (1); intestinal perforation associated with terminal ileitis (1); respiratory infection (1); cardiac arrest and myelofibrosis (1); cardiac failure (1); pulmonary extramedullary haematopoiesis and pulmonary failure (1); post-transplantation lymphoproliferative disorder and multiorgan failure (1); and myelofibrosis (2). The causes of death in the BAT group were pneumonia, septic shock, multisystem organ failure, and acute myeloid leukaemia (in 1 patient); post-splenectomy *Klebsiella pneumoniae* sepsis (1); splenectomy, peritoneal haemorrhage, and respiratory failure (1); and renal failure and acute myeloid leukaemia (1).

[c]Worst laboratory value occurring on the randomised treatment phase only

AE, adverse event; BAT, best available therapy; CI, confidence interval; SAE, serious adverse event.

Verstovsek et al. 2012,[26,122] Harrison et al. 2012,[7,121] Clinical study reports.[123,124]

Few patients discontinued ruxolitinib due to AEs

In COMFORT-II, primary analysis safety data were reported for 146 patients randomised to receive ruxolitinib and 73 patients randomised to receive BAT.[7,121] Of the latter, 33% received no treatment. At the primary analysis data cut-off, 58% of the BAT group had discontinued from the randomised treatment phase, compared with 38% of the ruxolitinib group. Thus, exposure to randomised treatment was greater in the ruxolitinib group. In both groups, few patients discontinued treatment because of AEs (ruxolitinib, 8%; BAT, 6%). However, dose reductions or interruptions due to AEs (of any grade) occurred more frequently in the ruxolitinib group than in the BAT group (63% versus 15%, respectively).

The safety population of COMFORT-I included 155 patients who received ruxolitinib and 151 patients randomised to placebo.[26,122] The number of patient-years exposure was 105 in the ruxolitinib group and 87 in the placebo group. The lower exposure in the placebo group was due to study discontinuation and crossover to ruxolitinib. At the primary analysis, 11% of patients in each treatment group had withdrawn from the study due to AEs.

The incidence of SAEs was similar in the ruxolitinib and BAT groups

In COMFORT-II, the incidence of serious adverse events (SAEs) was similar in the two treatment groups (ruxolitinib, 30%; BAT, 29%).[123] Anaemia was the most frequently reported SAE in both treatment groups, with an incidence of 5% in the ruxolitinib group and 4% in the BAT group.[7] Pneumonia was the only other SAE reported in 5% or more of patients in either group and this occurred more frequently in the BAT group. The only other SAEs reported in more than 2% of patients in either group were: abdominal pain, pyrexia and oesophageal varices for ruxolitinib; and dyspnoea, pneumonia, actinic keratosis, ascites, peritoneal haemorrhage and respiratory failure for BAT. In COMFORT-I, the only SAEs reported in more than 2% of patients were pneumonia, anaemia and fatigue for the ruxolitinib group; and pneumonia, splenic infarction, and abdominal pain for the placebo group.[123]

Most non-haematological AEs experienced with ruxolitinib were grade 1 or 2 in severity

For the primary analysis of both studies, the most frequently reported non-haematological AEs (any grade, reported in at least 20% of patients) were fatigue (COMFORT-I only), diarrhoea (both studies) and peripheral oedema (COMFORT-II only). These AEs were also the most frequently reported AEs in the placebo group in COMFORT-I, suggesting that they are likely to be manifestations of MF rather than of treatment. In COMFORT-II, diarrhoea was the only AE (any grade) for which the difference in incidence between ruxolitinib and BAT was greater than 10% (23% versus 12%, respectively for diarrhoea of any grade). However, grade 3 or 4 diarrhoea was reported in only two patients in the ruxolitinib group. In COMFORT-I, the most frequent AE (any grade) in the placebo group was

abdominal pain and its incidence was 4-fold higher in the placebo group than the ruxolitinib group (41.1% versus 10.3%), suggesting that ruxolitinib helps relieve abdominal pain associated with MF.

Few grade 3 or 4 non-haematological AEs were reported for ruxolitinib in either study. Abdominal pain (COMFORT-II) and fatigue (COMFORT-I only) were the only grade 3 or 4 AEs reported in at least 3% of patients. Grade 3 or 4 abdominal pain was also reported in 3% of patients receiving BAT in COMFORT-II and 11% of patients receiving placebo in COMFORT-I. The other grade 3 or 4 AEs reported in at least 3% of patients receiving placebo (in COMFORT-I) were fatigue and dyspnoea.

Grade 3 or 4 anaemia occurred in approximately 45% of patients receiving ruxolitinib, but was generally transient and rarely led to treatment discontinuation

In COMFORT-I, the overall incidence of grade 3 or 4 anaemia was approximately 2-fold higher in the ruxolitinib group than in the placebo group (45% versus 19%, respectively). The high incidence of anaemia in the placebo group suggests that this may be a manifestation of the disease itself. Approximately half of all cases of grade 3 or 4 anaemia occurred within the first 8 weeks of therapy, after which the monthly incidence declined. By 6 months, the proportion of patients with grade 3 or 4 anaemia was similar for the two treatment groups. Only one patient in each treatment group discontinued therapy because of grade 3 or 4 anaemia. The mean number of RBC transfusions required per month was similar for the ruxolitinib and placebo groups (1.7% and 2.2%, respectively). During the primary study period, almost half of the patients in both groups who were transfusion dependent at baseline became transfusion independent (according to the IWG-MRT criteria) (41.2% in the ruxolitinib group versus 46.9% in the placebo group).

Analysis of treatment response according to the presence of grade 3 or 4 anaemia showed that this AE did not adversely affect the efficacy of ruxolitinib. In the ruxolitinib group, patients with new onset grade 3 or 4 anaemia had similar improvements in splenomegaly and MF symptoms (TSS) to those seen in the ruxolitinib-treated patients without anaemia. By contrast, placebo-treated patients with anaemia had a worse TSS than those without this AE.

In COMFORT-II, at baseline, approximately two-thirds of patients had grade 1 or 2 anaemia. During the primary analysis period, the incidence of grade 3 or 4 anaemia was similar to that reported for COMFORT-I and was somewhat higher in ruxolitinib-treated patients than in BAT-treated patients (42% versus 31%). However, this event rarely led to treatment discontinuation and was generally manageable with dose modifications and/or RBC transfusions. The mean number of transfusions per month was similar in the ruxolitinib and BAT groups (0.86 versus 0.91, respectively). In the ruxolitinib group, a higher number of transfusions was required in patients who started on the 20 mg dose than in those who started on the 15 mg dose (58% versus 41%). Only 5% of patients receiving ruxolitinib required dose interruptions or reductions due to anaemia (1% in the BAT group).

Grade 3 or 4 thrombocytopenia occurred in a similar proportion of patients receiving ruxolitinib or BAT

In COMFORT-I, grade 3 or 4 thrombocytopenia was reported in 13% of the ruxolitinib group compared with 1% in the placebo group (Table 20).[26] Approximately half of all cases of grade 3 or 4 thrombocytopenia in ruxolitinib-treated patients occurred during the first 8 weeks of therapy, and led to dose adjustments or brief interruptions to therapy. Only five patients experienced more than one episode of grade 3 or 4 thrombocytopenia, and only one patient in each group discontinued due to grade 3 or 4 thrombocytopenia. The incidence of grade 3 or 4 episodes of bleeding was low in both treatment groups (ruxolitinib 2.6% versus placebo 2.0%).

In COMFORT-II, the incidence of grade 3 or 4 thrombocytopenia was similar in the ruxolitinib and BAT groups (8% versus 7%, respectively) and thrombocytopenia was the most common reason for dose modifications in both groups (41% of patients in the ruxolitinib group and 1% in the BAT group). However, only one patient in each group discontinued during the randomised phase due to grade 3 or 4 thrombocytopenia.

4.12.5 Long-term follow-up

There was no change in the rate, distribution or severity of non-haematological AEs during ruxolitinib therapy with longer-term treatment

Two-year and 3-year data are available from the long-term extension to COMFORT-I.[24,25] Data regarding non-haematological AEs are reported for patients randomised to ruxolitinib and are compared for each 12-month period up to 36 months or more; 77 of the 155 patients randomised to ruxolitinib remained on study at 36 months or more. The incidence of new onset non-haematological AEs (any grade or grade 3 or 4) remained stable or decreased over time and most AEs were grade 1 or 2 (Table 21 and Table 22). Fatigue, pneumonia and abdominal pain were the only grade 3 or 4 AEs reported in at least 3% of patients during each 12-month period from month 12 onwards.

Table 21 Incidence (%) of new-onset non-haematological adverse events (any grade): COMFORT-I 2-year and 3-year long-term follow-up data

Adverse event	≤ 6 months (Placebo)	Duration of ruxolitinib treatment					
		≤6 months	6 to 12 months	12 to 18 months	18 to 24 months	24 to 36 months[a]	≥ 36 months[a]
Fatigue	31.9	25.7	5.8	7.9	8.4	15.3	7.7
Diarrhoea	22.9	23.2	5.7	5.7	3.4	10.8	3.9
Ecchymosis	9.2	18.1	5.5	4.3	1.6	5.7	0
Dyspnoea	16.1	16.8	4.5	6.4	4.8	2.9	3.3
Peripheral oedema	23.2	16.7	5.3	6.3	4.8	12.6	0
Headache	5.0	15.5	0.9	2.1	1.5	2.7	0
Dizziness	6.5	14.2	5.3	6.5	3.2	3.0	3.5
Nausea	17.0	12.8	5.2	3.0	0	5.1	5.9
Constipation	12.1	12.0	4.2	5.9	4.3	10.1	9.0
Vomiting	10.8	12.0	2.5	1.0	0	2.4	5.5
Pain in extremities	10.7	11.4	8.5	4.3	1.6	4.2	3.3
Pyrexia	6.4	11.3	2.4	3.7	6.7	8.5	2.9
Insomnia	10.7	10.7	4.2	2.0	2.8	3.7	0
Abdominal pain	40.7	10.1	5.0	4.9	0	3.6	0
Arthralgia	7.9	10.1	2.5	5.0	0	6.6	6.3

Verstovsek et al. 2013.[24]

Verstovsek et al 2015.[25]

Table 22 Incidence of new onset grade 3 or 4 non-haematological adverse events regardless of causality: COMFORT-I 3-year long-term follow-up data

Incidence (%)	Ruxolitinib			
	0 to < 12 months (n = 155)	12 to < 24 months (n = 130)	24 to < 36 months (n = 103)	≥ 36 months (n = 82)
Fatigue	6.2	0.9	3.3	0
Pneumonia	5.6	3.6	3.5	0
Abdominal pain	4.2	0	3.2	0
Arthralgia	2.1	0	0	0
Diarrhoea	2.1	0	0	0
Dyspnoea	2.1	0.9	2.2	2.5
Pain in extremity	2.1	0	1.1	0
Hyperuricaemia	1.4	0.9	0	2.5
Fall	1.4	0.9	0	0
GI haemorrhage	1.4	0.9	0	0
Septic shock	1.4	0	0	0
Muscular weakness	1.4	0	1.1	0
Hypoxia	1.4	0	2.2	0
Sepsis	0.7	1.7	2.2	0
Epistaxis	0.7	1.7	0	0
Renal failure acute	0.7	0.9	2.2	2.4
Abdominal pain upper	0.7	0	2.2	0
Myocardial infarction	0	0.9	0	4.8

Percentage of patients for each event was based on the effective sample size of the time interval (number of patients at risk at the beginning of the interval minus half the censored patients during the time interval). Adverse events is included if the incidence was ≥ 2 patients at any yearly interval.

Verstovsek et al. 2015.[25]

Three-year data (and some additional 3.5 year data) regarding non-haematological AEs are also available from the long-term extension to COMFORT-II and rates adjusted for patient-year exposures are compared for: patients randomised to ruxolitinib for treatment in the core study (n = 146); patients randomised to ruxolitinib for treatment during the core and extension study (n = 146); patients randomised to BAT (n = 73); and patients randomised to BAT who crossed over to receive ruxolitinib (n = 45).[23] The incidence of all AEs (any grade) was lower during the extension than in the core study

in patients randomised to ruxolitinib and the incidence of grade 3 or 4 AEs remained low in the extension study in this patient group (Table 23). Analysis of the incidence of events of special interest over time (by 6-month interval) also showed no increase in incidence with continued treatment (Table 24). Results for the 3.5 year follow-up were consistent with those for the 3 year follow-up.[22]

The incidences of AEs in patients who crossed over from BAT to receive ruxolitinib were generally similar to or lower than those in patients initially randomised to ruxolitinib, with the exception of dyspnoea (20.0% versus 14.1%) and pain in extremity (20.0% versus 10.0%); however, the incidences of grade 3 or 4 dyspnoea and pain in extremity were low (Table 23).

Table 23 Adjusted incidence (%) of non-haematological AEs (regardless of study drug): COMFORT-II 3-year follow-up

Adjusted rate per 100 patient-year exposure[a]	Ruxolitinib randomised (n = 146)	Ruxolitinib randomised + extension (n = 146)	BAT randomised (n = 73)	Ruxolitinib crossover (n = 45)
Peripheral edema	20.0/0	17.4/0	31.4/1.5	17.8/2.2
Diarrhoea	22.3/1.2	15.4/0.7	19.4/0	20.0/0
Asthenia	16.5/2.4	11.5/1.6	13.4/1.5	17.8/2.2
Dyspnoea	14.1/1.2	11.2/1.3	22.4/4.5	20.0/2.2
Pyrexia	12.9/1.8	11.5/1.3	10.5/0	13.3/0
Fatigue	13.5/0.6	11.2/0.7	11.9/0	13.3/2.2
Nasopharyngitis	15.9/0	11.8/0	14.9/0	8.9/0
Bronchitis	10.6/1.2	11.5/1.3	9.0/1.5	6.7/0
Cough	12.9/0	10.5/0	17.9/1.5	11.1/2.2
Arthralgia	11.2/1.2	8.9/0.7	10.5/0	13.3/2.2
Weight gain	13.5/1.8	9.5/1.0	1.5/0	8.9/0
Nausea	12.3/0.6	8.9/0.3	10.5/0	8.9/0
Pain in extremity	10.0/0.6	7.2/0.3	6.0/0	20.0/0
Headache	10.6/1.2	6.9/0.7	6.0/0	15.6/0
Back pain	10.6/1.8	7.5/1.3	14.9/0	6.7/0
Insomnia	5.3/0	3.9/0	10.5/0	8.9/0
Abdominal pain	10.0/2.9	6.6/1.6	19.4/4.5	6.7/2.2
Epistaxis	7.6/0	5.2/0.7	7.5/0	11.1/0
Pruritus	5.3/0	5.2/0	19.4/0	8.9/0

[a]Incidence given as any grade/grade 3 or 4

AE, adverse event ; BAT, best available therapy

Cervantes et al. 2013,[23] Harrison et al. 2014.[22]

Table 24 Incidence (%) of AEs (any grade) of special interest during treatment with ruxolitinib: COMFORT-II 3-year follow-up

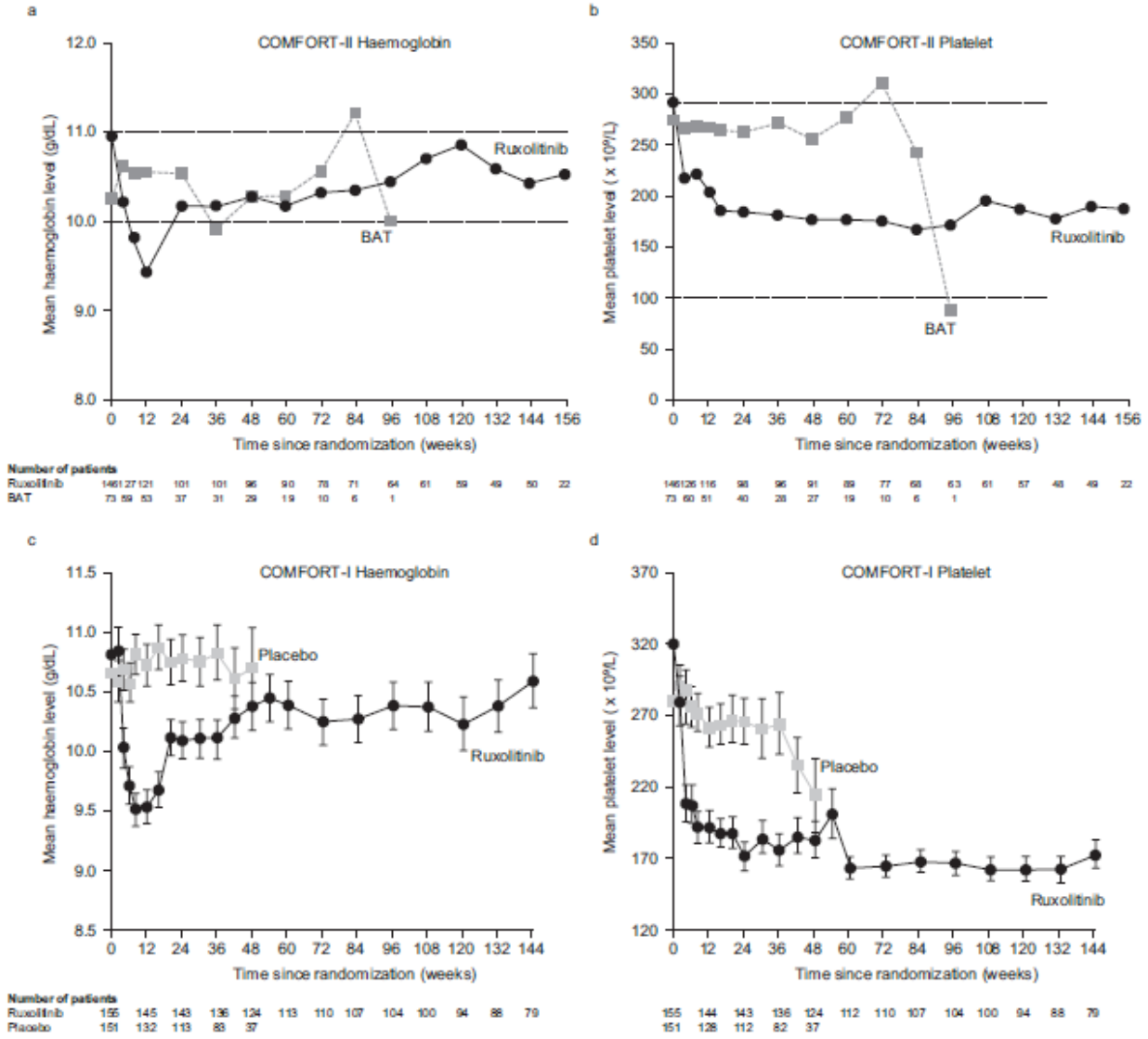
Adverse event	Duration of ruxolitinib treatment						
	0 to 24 weeks (n = 146)	24 to 48 weeks (n = 134)	48 to 72 weeks (n = 116)	72 to 96 weeks (n = 101)	96 to 120 weeks (n = 93)	120 to 144 weeks (n = 81)	144 to 168 weeks (n = 72)
Anaemia	34.9	12.7	8.6	13.9	8.6	7.4	8.3
Thrombocytopenia	43.2	22.4	15.5	12.9	10.8	12.3	2.8
Bleeding	17.1	14.2	9.5	11.9	7.5	9.9	6.9
Epistaxis	6.8	1.5	0.9	4.0	0	1.2	1.4
Haematoma	5.5	4.5	3.4	1.0	0	2.5	1.4
Infections	50.0	35.1	37.9	25.7	43.0	33.3	25.0
Bronchitis	3.4	6.7	8.6	3.0	10.8	4.9	4.2
Gastroenteritis	5.5	3.0	0.9	1.0	2.2	1.2	0
Nasopharyngitis	13.7	5.2	7.8	4.0	10.8	3.7	4.2
Urinary tract infection	4.8	2.2	5.2	4.0	5.4	3.7	2.8
Weight gain	8.2	8.2	5.2	5.0	2.2	0	0

Cervantes et al. 2013.[23]

Rates of anaemia and the need for RBC transfusions decreased over time during treatment with ruxolitinib

In both studies, haemoglobin levels initially decreased following initiation of therapy with ruxolitinib, reaching a nadir at approximately 12 weeks and then increased and remained above 10 g/dL from week 24 onwards (Figure 38).[23,25] The incidence of grade or 4 anaemia was therefore greatest during the first 6 months on therapy and declined considerably over months 6 to 24. In COMFORT-II, rates of anaemia (any grade) decreased from 35% during the first 6 months to less than 14% for subsequent 6-month periods (Table 24). A similar decline in the incidence of anaemia was observed in COMFORT-I (Figure 39).

Figure 38 (a) Haemoglobin and (b) platelet levels in COMFORT-II over time: 3-year follow-up and c)Haemoglobin and (d) platelet levels in COMFORT-I over time: 3-year follow-up

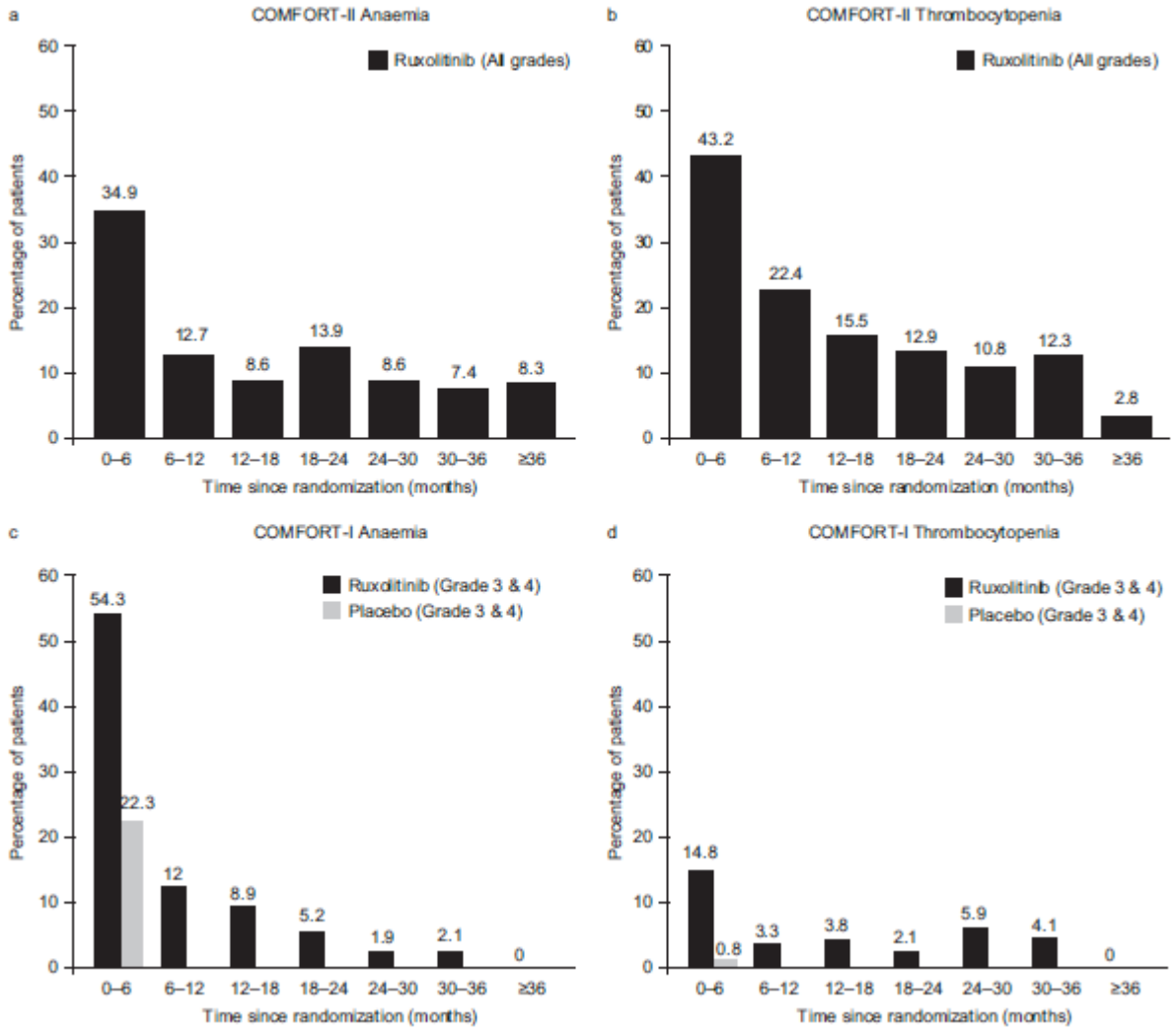


BAT, best available therapy.

Cervantes et al. 2013, Verstovsek et al. 2015.[23,25,146]

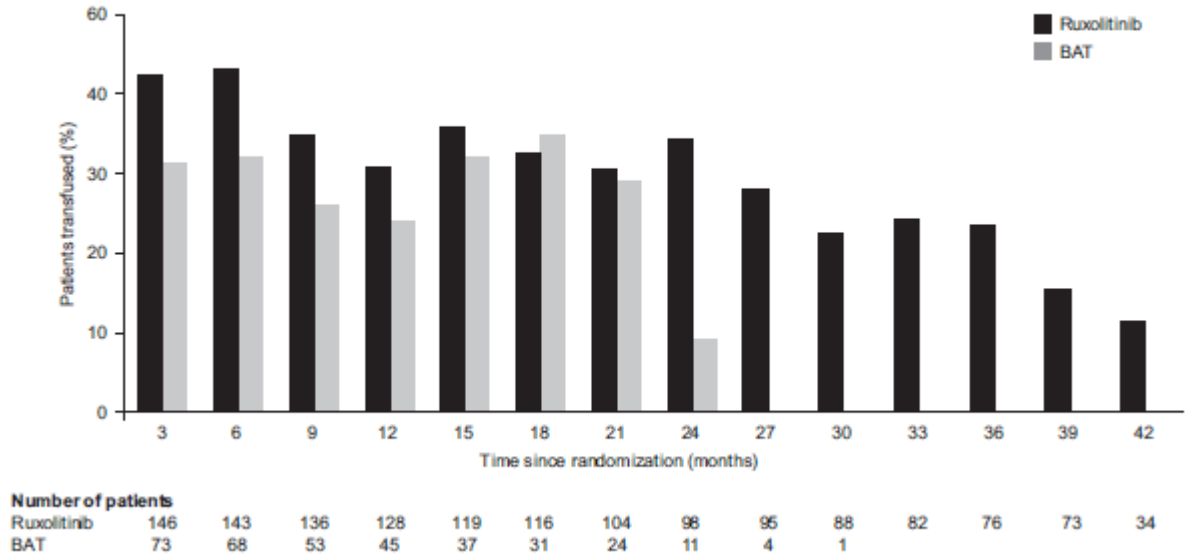
Anaemia was generally manageable with dose modifications, RBC transfusions, or both. Three-year data from COMFORT-II show that while the transfusion rate was slightly higher in the ruxolitinib group than in the BAT group over the first 24 weeks of therapy, this declined thereafter to a similar rate to that in the BAT group during long-term therapy (Figure 40). Only two (1%) patients receiving ruxolitinib in COMFORT-II and one receiving ruxolitinib in COMFORT-I discontinued therapy due to anaemia or a decrease in haemoglobin levels.

Figure 39 Incidence of new onset (a) anaemia and (b) thrombocytopenia of any grades in COMFORT-II over time and incidence of new onset (c) anaemia and (d) thrombocytopenia of grade 3 or 4 in COMFORT-I over time: 3-year follow-up



Verstovsek et al. 2015,[25] Cervantes et al. 2013.[23,146]

Figure 40 Percentage of people receiving RBCs in COMFORT-II: 3-year follow-up



Transfusions after crossover from BAT to ruxolitinib are excluded

BAT, best available therapy.

Cervantes et al. 2013.[23,146]

Thrombocytopenia generally decreased over time and long-term treatment was not associated with serious new or worsening platelet abnormalities

Data from COMFORT-II and COMFORT-I show that platelet levels decreased over the first 3 weeks of therapy and then stabilised in patients receiving ruxolitinib (Figure 38).[23,25,130] In COMFORT-II, the incidence of thrombocytopenia (any grade) decreased from 43% during the first 6 months to 22% for the second 6 months and was less than 15% for subsequent 6-month periods (Table 24). In addition, most (80%) events reported during the study extension were grade 1 or 2 in severity. A similar decline in the incidence of grade 3 or 4 thrombocytopenia was observed in COMFORT-I during 6-month periods following the first 6 months on treatment. In COMFORT-II, seven patients discontinued therapy over the 3-year follow-up owing to thrombocytopenia.

There was no evidence of risk of increased leukaemic transformation associated with ruxolitinib treatment

No evidence of an increased risk of leukaemic transformation with ruxolitinib therapy was observed in the 3-year follow-up of COMFORT-I or 3.5-year follow-up of COMFORT-II. At the 3-year follow-up of COMFORT-II, eight cases of leukaemic transformation (defined as a peripheral blood blast count of 20% or greater, sustained for 8 weeks, or a bone marrow blast count of 20% or greater) were observed: 5 cases (3.4%) in the group of patients originally randomised to ruxolitinib (median duration

of follow-up 151 weeks) and 3 cases (4.1%) in the group of patients originally randomised to BAT (median follow-up 122 weeks). An additional event of leukaemia was reported in the safety database as a serious AE in the BAT arm. At a median follow-up of 191 weeks (3.5 years), 6 patients in each treatment group had developed leukaemia (ruxolitinib, 4.1%; BAT, 8.2%); analysis of the time to leukaemic transformation revealed a reduction in risk of 70% for the ruxolitinib group compared with the BAT group (HR, 30, 95% CI 0.08 to 1.09). Furthermore, the risk of leukemia or death was reduced by 39% in patients treated with ruxolitinib (HR, 0.61; 95% CI 0.30 to 0.88). The Kaplan–Meier estimate of leukaemia-free survival (LFS) at 3.5 years was 0.69 for the ruxolitinib arm (95% CI 0.60 to 0.76) and 0.54 for the BAT arm (95% CI 0.41 to 0.65). However these results should be interpreted cautiously given the small patient numbers.[22]

In the 3-year follow-up of COMFORT-I an additional 4 cases of AML were reported in addition to the 4 cases reported at 2 years. Four of the cases were in patients originally assigned to ruxolitinib and 4 in patients originally assigned to placebo. The rate of leukaemic transformation per person per year of ruxolitinib exposure was 0.0121/person-year in patients originally randomised to ruxolitinib and 0.0233/person-year in patients originally randomised to placebo.[25] These values compare with historical control rates of 0.038/person-year and 0.036/person-year for the phase 1/2study of ruxolitinib.[39]

4.12.6 AEs of special interest

As of February 2015, 13,273 individuals have received ruxolitinib as part of clinical trials and post-marketing exposure corresponds to 21,029.3 patient-treatment years. Data from this exposure provides the current evidence base for the safety profile of ruxolitinib. Because of the potential immunosuppressive effect of JAK inhibition, AEs of special interest include progressive multifocal leukoencephalopathy (PML) and infections such as tuberculosis.[21]

A single case of PML has been reported in the ROBUST study.[147] PML is a rare and usually fatal viral disease characterised by progressive demyelination or inflammation of the subcortical white matter of the brain at multiple locations. It occurs almost exclusively in individuals with severe immune deficiency and is caused by infection by the John Cunningham virus which is present in approximately 40% to 60% of the general population but becomes active only under conditions of severe immunosuppression. The case reported in a patient receiving ruxolitinib involved a 75-year-old man with intermediate-2 risk MF treated with ruxolitinib 20 mg bid. Ten weeks after initiation of ruxolitinib therapy he reported minor symptoms consistent with cognitive impairment and expressive dysphasia. A brain biopsy identified histology consistent with PML. It is not clear whether the PML was directly related to ruxolitinib treatment. An extensive review of the global safety database for ruxolitinib has confirmed that no other cases of PML have been reported in patients receiving ruxolitinib.

Tuberculosis has been reported in patients receiving ruxolitinib for MF.[21];[23,145,148,149] In COMFORT-II, over the 3 years of follow-up, two patients (1.4%) in the ruxolitinib arm had tuberculosis,[23] and in JUMP, tuberculosis was reported in three patients (0.3%).[145] Although this is an uncommon AE, having been reported in only 0.3% of patients receiving ruxolitinib in COMFORT-I and COMFORT-II and in JUMP, it is recommended that physicians should evaluate patients for active or inactive tuberculosis before starting treatment, carefully observe patients receiving ruxolitinib for signs and symptoms of infections and initiate appropriate treatment promptly.[21]

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Overview of efficacy and safety evidence for ruxolitinib in MF

There is a substantial body of evidence for the effects of ruxolitinib on splenomegaly and improvements in symptoms in patients with MF. Evidence for the safety and efficacy of ruxolitinib for the treatment of MF is based on the results of two phase 3 RCTs – COMFORT-I and COMFORT-II − which compared ruxolitinib with placebo and BAT, respectively, in patients with intermediate-2 or high-risk disease.[7,23,25,26] Further supportive evidence is provided by a phase 2 study, ROBUST, performed in the UK[27] and a phase 3b expanded access trial, JUMP, [28] both of which also included patients with intermediate-1 disease, as well as two studies which specifically involved patients with low platelet counts (a phase 2 study[29] and a dose-finding 1b study[30]) and reports of the efficacy and safety of ruxolitinib in patients with early disease (low risk).[31,32]

Efficacy

Ruxolitinib provided significant and clinically relevant reductions in splenomegaly

Results for the primary analysis of both phase 3 studies have been reported for follow-ups of 24 weeks (COMFORT-I) and 48 weeks (COMFORT-II) and demonstrated that a significantly greater proportion of patients achieved a reduction in spleen volume of at least 35% with ruxolitinib compared with placebo or BAT. The effects of ruxolitinib therapy were rapid, were evident at the first assessment at 12 weeks compared with BAT, and improvements in splenomegaly and MF symptoms were durable. Long-term follow-up data for both studies (up to 3.5 years) indicate that reductions in spleen volume were sustained during treatment with ruxolitinib and further, suggest that ruxolitinib provides an OS advantage compared with BAT. The phase 3 studies identify that benefits of ruxolitinib were seen across all MF subtypes and in patients with intermediate-2 risk or high-risk disease. Furthermore treatment was effective regardless of *JAK* mutational status.

Ruxolitinib therapy achieved clinically meaningful and durable improvements in disease-related symptoms and HRQoL

Ruxolitinib treatment was shown to provide significant and sustained improvements in MF-associated symptoms and HRQoL compared with worsening HRQoL in placebo and BAT groups. Even small reductions in spleen volume were associated with meaningful improvements in disease-related symptoms and HRQoL. At baseline, HRQoL scores in patients with MF were indicative of debilitating disease, but improvements in all HRQoL subscales of the EORTC QLQ-C30 were evident with ruxolitinib therapy in both phase 3 studies.

Ruxolitinib improved overall survival

Despite both studies not being powered to detect differences in OS between ruxolitinib and the control group, both have also demonstrated OS benefits for ruxolitinib over BAT or placebo. For COMFORT-II the most recent analysis, performed at a follow-up of 3.5 years showed a statistically significant overall reduction in risk of death of 42% for ruxolitinib over BAT (HR, 0.58; 95% CI 0.36 to 0.93; p = 0.022). In COMFORT-I, an analysis performed at a median follow-up of 51 weeks revealed a significant survival advantage for patients who received ruxolitinib (HR, 0.5; 95% CI 0.25 to 0.98; p = 0.04) but a statistically significant benefit was no longer evident at 149 weeks probably reflecting the impact of crossover of patients from placebo to ruxolitinib. A pooled analysis of 3-year follow-up data for both studies found ruxolitinib was associated with a 35% reduction in the risk of death compared with control according to ITT analysis (HR 0.65; 95% CI 0.46 to 0.90; p = 0.01).

Safety

Ruxolitinib is generally well tolerated with few patients discontinuing therapy due to AEs

The safety profile of ruxolitinib in MF has been established in the primary reports from the phase 3 studies COMFORT-I and COMFORT-II and indicates that ruxolitinib is generally well tolerated.[7,26] Anaemia was the most frequently reported grade 3 or 4 AE in both phase 3 trials and thrombocytopenia was the only other grade 3 or 4 AE reported in more than 8% of patients in both trials. These AEs rarely led to discontinuation and were generally managed by dose modifications and/or transfusions. These AEs were expected given the mechanism of action of ruxolitinib, and generally declined over time with continued therapy. Grade 3 or 4 non-haematological AEs were infrequent overall and were generally more common in the control groups (placebo and BAT) than the ruxolitinib groups.

During long-term follow-up over 3 years for patients in COMFORT-I and COMFORT-II, the incidence of AEs remained stable or decreased over time in patients receiving prolonged ruxolitinib therapy. There was no evidence that long-term treatment with ruxolitinib for 3 years or longer increased the risk of leukaemic transformation and AEs of special interest occurred at low rates.

Data from non-RCTs and observational studies confirm that ruxolitinib is generally well tolerated, with few patients experiencing grade 3 or 4 non-haematological AEs, and are consistent with those reported for COMFORT-I and COMFORT-II.

Ruxolitinib is well tolerated in patients with low platelet counts

Three studies have extended the investigation of ruxolitinib to patients with low platelet counts. Two studies (a phase 2 study[29] and the phase 3b JUMP study[37]) have involved initiation of therapy at a dose of 5 mg bid followed by dose escalation if platelet counts remained adequate. In both studies thrombocytopenia was the most frequently reported grade 3 or 4 AE, but few patients discontinued therapy owing to thrombocytopenia or other AEs, indicating that therapy was generally well tolerated. Results of an ongoing dose-escalation study in patients with low platelet counts suggest that therapy in such patients can be initiated at a dose of 10 mg bid or 15 mg bid.[30] Thus ruxolitinib appears to be well tolerated in this group of patients who were excluded from the phase 3 COMFORT studies.

4.13.2 Strengths and limitations of the clinical evidence base

Strengths

Evidence for the benefits of ruxolitinib comes from two robust multicentre phase 3 studies with a follow-up of 3 to 3.5 years and supporting data from single-arm studies

The primary evidence in support of ruxolitinib in patients with MF comes from two robust multicentre phase 3 studies. Collectively, these studies involved a total of 528 patients with MF. In both phase 3 studies, median follow-up was approximately 1 year for the primary analysis and further data have been reported for a follow-up of 3 years in COMFORT-I and 3.5 years in COMFORT-II.[22,23,25] Further data are available from a number of non-RCTs including a UK phase 2 trial, ROBUST, involving 50 patients, and from a phase 3b study, JUMP, for which data have been reported for 1144 patients with a median follow-up of 11 months. [28]

Similarities in the design of the phase 3 studies allows for assessment of the consistency of results for ruxolitinib

Similar response rates (35% or greater reduction in spleen volume) and reductions from baseline in spleen volume at week 24 were achieved in both phase 3 studies, and both demonstrated rapid and sustained reductions in palpable spleen length. Improvements in HRQoL and the safety profile for ruxolitinib were also consistent across the two studies.

Patient characteristics in the studies are representative of patients who would be eligible to receive symptomatic treatment with ruxolitinib in clinical practice in England and Wales

The demographic and clinical characteristics of patients in COMFORT-I, COMFORT-II, the UK ROBUST trial and JUMP are representative of patients who would be eligible to receive symptomatic treatment with ruxolitinib in clinical practice in England and Wales. The two phase 3 studies enrolled adult patients with the three MF disease types and with intermediate-2 risk or high-risk disease. Such patients would be expected to have splenomegaly or symptoms, and hence correspond to the approved indication for ruxolitinib. The phase 2 UK ROBUST trial and JUMP again enrolled adult patients diagnosed with PMF, PPV-MF or PET-MF who had or had not received previous treatment and with intermediate-1 risk, intermediate-2 risk or high-risk disease. Furthermore, clinical data gathered at four UK study sites were included in the analysis for the COMFORT-II trial, and the ROBUST trial recruited patients from centres in the UK. Therefore, the patients in these trials can be expected to be representative of the patient population with MF in England and Wales.

Both phase 3 studies employed the dosing regimen that would be used in the treatment of patients in England and Wales

Both COMFORT-I and COMFORT-II, together with ROBUST and JUMP, employed the licensed starting dose of ruxolitinib and thus again closely reflect routine clinical practice for the treatment of MF in England and Wales.

The comparators used in both studies correspond to the current treatment options used in routine practice in England and Wales

Currently available treatment for MF in England and Wales (hydroxycarbamide, anagrelide, prednisolone/prednisone, erythropoietin-alpha, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, interferon-alpha, melphalan, cytarabine) is comparable with the BAT strategy used in COMFORT-II. For example, an analysis of treatment patterns for 98 patients with MF diagnosed between September 2004 and August 2010 in England reported first-line treatments to include observation (43%), blood products (22%), hydroxycarbamide (13%), aspirin (7%), allograft (5%), prednisolone (4%), erythropoietin (2%), danazol (2%) and thalidomide (1%),[52] and an recent survey of UK physicians managing approximately 2000 patients with MF found that of those receiving drug treatment, therapies other than ruxolitinib included hydroxycarbamide, IMiDs and androgens.[117] Therefore, it may be assumed that the positive clinical benefits associated with ruxolitinib therapy versus BAT reported in the COMFORT-II trial would apply to the UK population.

The primary endpoint for both phase 3 studies – reduction in splenomegaly − is highly relevant to the treatment of MF

Reduction in splenomegaly was the primary endpoint in both phase 3 studies and is highly relevant to the treatment of MF. A reduction in spleen size represents a reversal of extramedullary haematopoiesis and, as such, is well recognised as an objective measure of a clinically meaningful response. The IWG-MRT defines clinical improvement as achieving a reduction in palpable spleen length of 50% or greater.[107] This corresponds to a reduction in spleen volume of approximately 35%.[73]

However, there is evidence to suggest that patients who achieve a reduction in spleen volume of less than 35% also achieve significant benefit in terms of reduced symptoms. Analysis of data from COMFORT-I according to the extent of spleen reduction achieved revealed that patients who had a reduction in spleen volume of 10% to 35% or even a reduction of less than 10% achieved clinically meaningful improvements in symptoms.[34] These data thus suggest that the primary endpoint for both studies probably underestimates the benefit of ruxolitinib therapy.

Secondary endpoints used in the phase 3 studies are highly relevant for assessment of the clinical benefit of ruxolitinib therapy

Secondary endpoints in both trials included assessment of disease-related symptoms and HRQoL, which are also highly relevant for assessment of the clinical benefit of ruxolitinib therapy. The COMFORT-I trial monitored changes in MF-specific symptom scores, evaluated using the validated MF-SAF which provides a direct measure of the impact of the treatment on the patient, and are further reflected in improvements in HRQoL. COMFORT-I also employed the PROMIS questionnaire to measure the frequency and impact of fatigue and the PGIC questionnaire to evaluate a patient's overall sense of whether a treatment has been beneficial by improving their symptoms. Effects on HRQoL were assessed in both studies using the EORTC QLQ-C30, an established cancer-specific HRQoL instrument, and COMFORT-II also included assessments using the FACT-Lym scale, which provides a summary index of a patient's physical, functional and symptom outcomes. These endpoints thus provide a measure of the benefit experienced by the patient. ROBUST and JUMP trials also include assessment of the impact of ruxolitinib on MF-specific symptoms as well as splenomegaly.

OS is a relevant outcome measure but generally requires longer follow-up than is currently available

OS is highly relevant for the treatment of MF and was included as a further secondary endpoint in both studies. Neither study was powered to detect statistically significant differences in OS, reflecting the fact that the median OS for patients with high- or intermediate-2 risk disease (as included in these studies) is 2−4 years and hence a meaningful impact on OS was not expected at the time of the primary analysis (ie at 6 months in COMFORT-I and 12 months in COMFORT-II). Furthermore,

patients with a life expectancy of less than 6 months were excluded from the studies. However, by a median follow-up of 3 to 3.5 years, corresponding to the median OS expected for the patients included in these studies, a statistically significant OS benefit for ruxolitinib over BAT was observed in COMFORT-II,[22] and ina pooled analysis of data from the two COMFORT studies.[36]

The incidence and severity of AEs and the need for RBC transfusions were assessed in both phase 3 studies

Both COMFORT-I and COMFORT-II collected data on the incidence and severity of AEs throughout the 3-year follow-up period for treatment with ruxolitinib. Furthermore, haemoglobin levels and platelets were also assessed regularly throughout treatment, as was the need for RBC transfusions and the incidence of bleeding events. These provide an assessment of the impact of the most frequently reported grade 3 or 4 AEs, anaemia and thrombocytopenia, and are highly relevant to clinical practice.

Limitations

Evidence for ruxolitinib versus the active comparator BAT is based on the COMFORT-II trial. Evidence for the efficacy (including the impact on symptoms) and safety of ruxolitinib are also provided by the placebo-controlled COMFORT-I trial, and a comparison of efficacy outcomes for the control groups of both studies suggest that BAT provides no clinical benefits over placebo. Possible limitations from both COMFORT-I and COMFORT-II are therefore discussed here.

Results of COMFORT-II may be skewed by unequal randomisation between treatments

In COMFORT-II, patients were randomised in a 2:1 ratio to ruxolitinib or BAT, respectively. The unequal randomisation between treatments may have skewed the comparisons between these two patient groups. A 2:1 randomisation ratio of ruxolitinib to BAT was chosen to facilitate recruitment and provide access to ruxolitinib for patients with no access to a clinically effective treatment for MF.

Crossover between treatment groups confounded assessment of OS

While both trials included OS as a secondary endpoint, neither study was powered to detect differences in OS, and both studies included a crossover design allowing non-responders in the control group to proceed to receive ruxolitinib. The fact that many patients in the control group crossed over or discontinued therapy means that the possible survival benefits of ruxolitinib in either study are likely to be underestimated. This is particularly the case for COMFORT-II, as patients were permitted to cross over to receive ruxolitinib at any time if they had an increase in spleen size from baseline of at least 25%. However, in an analysis at a follow-up of 3.5 years, a statistically significant overall reduction in risk of death of 42% was observed with ruxolitinib compared with BAT (HR, 0.58; 95% CI 0.36 to 0.93; p = 0.022), and the estimated probability of being alive at 3.5 years was 71% in

the ruxolitinib arm and 54% in the BAT arm.[22] A statistically significant OS benefit was also reported for COMFORT-I for a median follow-up of 51 weeks (HR, 0.5; 95% CI 0.25 to 0.98; p = 0.04), and at 3 years' follow-up for COMFORT-I, the HR for OS still favoured patients originally randomised to ruxolitinib over those originally randomised to placebo (the majority of whom crossed over to ruxolitinib), although the difference was no longer statistically significant (HR, 0.69; 95% CI 0.46 to 1.03; p = 0.067).[25] A RPSFT analysis was also performed to estimate the HR after adjustment for crossover. According to this analysis the OS HR was 0.36 (95% CI 0.204 to 1.035), a value consistent with the hypothesis that the ITT analysis underestimates the survival benefit of ruxolitinib relative to 'true' placebo therapy.

The duration of follow-up for the COMFORT studies is insufficient to assess a possible impact on the risk of transformation to AML

The risk of transformation to AML could not be assessed because the duration of follow-up in the COMFORT studies is not long enough. Patients with MF are at risk of transformation to AML, which is generally fatal within approximately 3 months. In the 3-year follow-up of COMFORT-I, eight cases of AML were reported. Four of the cases were in patients originally assigned to ruxolitinib and four in those who started on placebo. Leukaemic transformation rates per person per year were comparable both between ruxolitinib and placebo groups (0.0121 and 0.0233/person-year respectively)[25] and to rates for historical controls (0.038/person-year).[39] In the 3.5-year follow-up of COMFORT-II, 6 patients in each treatment group had developed leukaemia (ruxolitinib, 4.1%; BAT, 8.2%); analysis of the time to leukaemic transformation revealed a reduction in risk of 70% for the ruxolitinib group compared with the BAT group (HR, 30, 95% CI 0.08 to 1.09).[22] Furthermore, the risk of leukemia or death was reduced by 39% in patients treated with ruxolitinib (HR, 0.61; 95% CI 0.30 to 0.88)

The open-label design of COMFORT-II may have biased the results of patient-reported outcome measures

Bias may have been introduced into the results of patient-reported outcome measures due to the open-label design of COMFORT-II. To accommodate the potentially wide variety of therapies chosen by physicians for the BAT arm, as well as the possible need for dose adjustments and treatment changes, COMFORT-II employed an open-label design. This design may have led to bias in the results of patient-reported outcomes. However, the improvements in symptoms and HRQoL reported for ruxolitinib-treated patients in COMFORT-II were similar to those reported for the double-blind COMFORT-I study, suggesting that this was not the case.

The wide array of therapies used in the BAT arm of COMFORT-II and the high discontinuation rate limits the value of results for the comparator group

The value of the results for the comparator group is limited by the wide array of therapies used in the BAT arm of COMFORT-II and the high discontinuation rate for BAT. In COMFORT-II, one-third of

patients in the BAT group received no treatment and the remaining two-thirds received various different therapies, with hydroxycarbamide (47%) and prednisone (12%) being the only agents used in more than 10% of patients in the BAT group. This, together with the high discontinuation rate for the BAT group (58% at the data cut-off point for the primary analysis and no patients remained on BAT at the 3-year follow-up [38% discontinued and 62% crossed over to ruxolitinib]), makes it difficult to assess the response to individual therapies or their tolerability, and limits the value of assessments of efficacy and safety in the BAT group. However, this highlights that these treatment options have limited efficacy in patients with MF. BAT was considered to be the most appropriate active comparator to evaluate the efficacy of ruxolitinib and is representative of the real-world clinical options for the treatment of MF in England and Wales. The long list of therapies used in the trial highlights the need for an effective therapy for MF.

4.13.3 End of life criteria

In order to be considered as a 'life extending treatment at the end of life', all the following criteria must be met:[150]

- Treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The technology is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

Whilst the trial-based evidence shows a mean life expectancy of approximately 26 months (median 28 months), this is in a trial population that is healthier than the population that will receive the drug in practice. This difference in populations is due to the exclusion criteria used in the two registration trials, for example, those with uncontrolled hypertension, unstable angina, low platelet counts or a life expectancy of less than 6 months were excluded. As a consequence, it is likely that the average life expectancy for patients will be below 24 months. The mean survival gain in the COMFORT-II trial (of at least 21 months given the ruxolitinib arm has not yest reached the median –

Figure 41), is substantially greater than the 3 month gain suggested in the end of life guidance.

Figure 41 Overall survival probability in COMFORT-II

Furthermore, in the consideration of other technologies, althoughthe three criteria are commonly used (survival **normally less** than 24 months, survival gain of **at least** 3 months and population **not exceeding** 7,000 patients), the committee recognised in ID680 the importance of judging each case on its own merits.[151] Indeed, during the appraisal of paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer (ID680) the criteria for end of life were accepted as met by the committee despite a survival gain of less than 3 months as it was considered particularly significant relative to the average survival of people with this condition.

As evidenced in ID680, we believe that the additional weighting given to end of life QALYs can be applied if one threshold is missed but more than compensated for by exceeding another threshold by a considerable margin. So even with a life expectancy of approximately 26 months (which we consider would be lower in the general MF population), the mean survival gain is of such a magnitude (of at least 21 months – median in ruxolitinib arm not reached) greater than the 3 month gain suggested, that the health benefits of ruxolitinib should be given the additional weighting as set out in the end of life guidance.

4.14 Ongoing studies

Ruxolitinib continues to be investigated in MF. COMFORT-I and COMFORT-II continue to report long-term follow-up results; final results for a follow-up of 5 years are expected at the end of 2015. Further follow-up is also expected for the ongoing JUMP trial. Other ongoing trials which may report data within the next 12 months are summarised in Table 25.

Table 25 Ongoing studies of ruxolitinib in patients with PMF, PPV-MF and PET-MF

Trial (NCT no)	Therapy	Phase	Expected (primary) completion date
NCT01317875	Ruxolitinib	Phase 1	December 2015
NCT00509899	Ruxolitinib	Phase 1/2	December 2007
NCT01392443	Ruxolitinib	Phase 2	February 2016
NCT00952289 (COMFORT-I)	Ruxolitinib versus placebo	Phase 3	November 2010
NCT00934544 (COMFORT-II)	Ruxolitinib versus BAT	Phase 3	January 2011
NCT01969838	Momelotinib versus Ruxolitinib	Phase 3	June 2016

AML, acute myeloid leukaemia; BAT, best available therapy; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF,primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

A systematic review (SR) of the literature was performed to identify evidence regarding the economic burden associated with MF (including PMF, PPV-MF and PET-MF). The first literature review was performed to support a previous NICE single technology appraisal (STA), and searches were performed on 27 July 2011, with an update search conducted on 19 March 2012. A second SR performed to support this submission aimed to replicate these original search strings to identify the most recent economic evidence for the use of ruxolitinib as a treatment for MF. Studies of interest included those reporting on the economic burden of MF from both payer and societal perspective. A date limit from January 2012 to December 2014 was applied. Details of the electronic searches performed and the resulting hits for both SRs are provided in Section 8 Appendix 11.

The 2011/2012 SR did not identify any relevant economic assessments.

The 2012/2014 SR identified two relevant cost–utility analyses for ruxolitinib versus BAT.[116,152,153] These are summarised in Table 26.

5.1.1 Evaluation for England and Wales

A paper, Wade et al,[152] provided a summary of the ruxolitinib NICE single technology appraisal (STA) submitted in 2013.[116] Table 26 provides an overview of the submission including the cost-effectiveness modelling presented by Novartis, and the revised analysis developed by the Evidence Review Group (ERG). This submission describes a revised economic assessment which makes use of additional data which have become available since the previous submission and aims to address the issues raised by the ERG (see section 5.6.3 for further details).

5.1.2 Canadian evaluation

One abstract reported the results of a cost–utility study that compared ruxolitinib with BAT for treatment of MF from a Canadian societal perspective.[153] The investigators employed a four-health-state Markov model, using 12-week cycles to simulate a hypothetical cohort of patients with MF. Clinical data inputs were taken from the COMFORT-II randomised controlled trial, which enrolled patients with intermediate-2- or high-risk PMF, PPV-MF or PET-MF. Survival assumptions were derived from a historical comparison of patients in the phase 1/2 study.[39] A lifetime time horizon was employed. Drug, indirect and other medical costs, as well as those linked to the management of adverse events, were considered. The outcomes of the Markov model included costs over the time horizon, life-years, quality-adjusted life-years (QALYs) and time spent as a responder to treatment. A

one-way sensitivity analysis and probabilistic sensitivity analysis were conducted, using estimated ranges and probability distributions for each input parameter.

The estimated total mean lifetime costs were CAD494,859 for treatment with ruxolitinib, compared with CAD421,755 for treatment with BAT.[153] Ruxolitinib was estimated to provide a QALY gain of 4.01 QALYs per patient, compared with 2.82 QALYs per patient for BAT, yielding an incremental cost-effectiveness ratio (ICER) of CAD61,444 per QALY for ruxolitinib compared with BAT. Deterministic sensitivity analysis identified key model drivers as the resource cost for non-responders and improved survival in the intermediate-2-risk group. Probabilistic sensitivity analysis found that, for a willingness-to-pay threshold of CAD100,000 per QALY, ruxolitinib has a 100% probability of being cost-effective compared with BAT.

Table 26 Summary of cost-effectiveness evaluations identified

Reference	**Year**	**Country(ies) where study was performed**	**Summary of model**	**Patient population (average age, years)**	**QALYs (intervention, comparator)**	**Costs (currency) Intervention, comparator**	**ICER (per QALY gained)**	**Sensitivity analysis**
El Ouagari et al[153] [abstract]	2012	Model: Canada Data: Europe	Markov model (ruxolitinib vs best available therapy (BAT)), Canadian societal perspective, 12 weeks per cycle, lifetime time horizon, simulated progression in 4 different health states	Data were derived from patients enrolled in the COMFORT-II study and included high-risk or intermediate-2-risk patients with MF	Ruxolitinib: 4.01 BAT: 2.82	<u>Total average lifetime costs</u> Ruxolitinib: CAD494,859 BAT:CAD421,755 <u>Drug costs</u> Ruxolitinib: CAD205,484 BAT: CAD59,289 <u>Other medical costs</u> Ruxolitinib: CAD217,527 (majority are resource costs) BAT: CAD266,008 <u>Indirect costs</u> Ruxolitinib: CAD71,848 BAT: CAD96,458	Overall (deterministic average): CAD61,444 Mean ICER from stimulations; CAD59,216 Ruxolitinib therapy cost-effective vs BAT	NR
Wade et al[152]	2013	Model: UK Data: Europe,	State-transition	The main clinical	<u>Base case:</u> Ruxolitinib: 1.15	<u>Incremental cost</u> <u>Base case</u>	<u>Base case</u> £73,980	A range of

[Full paper] Supplementary data from NICE technology appraisal guidance 289		US, Australia and Canada	Markov model designed to simulate the natural course of MF, 12 weeks per cycle, 35-year time horizon, costs and benefits were both discounted at 3.5%, the manufacturer's model consisted of 4 mutually exclusive health states	effectiveness data were derived from two RCTs: COMFORT-II and COMFORT-I and included patients who had intermediate-2 risk or high risk MF		Ruxolitinib: £85,027		sensitivity analyses were carried out
					Manufacturer's revised economic analysis			
					<u>Revised base case</u> Ruxolitinib vs BAT: 1.36	<u>Revised base case</u> Ruxolitinib vs BAT: £77,437	<u>Revised base case</u> Ruxolitinib vs BAT: £56,963	
					ERG's revised economic analysis			
							<u>Revised base case</u> Ruxolitinib vs BAT: Range £73,980 to £148,867	

BAT, best available therapy; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MF, myelofibrosis; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY, quality-adjusted life-year; RCT, randomised controlled trial; UK, United Kingdom; US, United States.

5.2 De novo analysis

5.2.1 Patient population

Ruxolitinib is licensed for the treatment of disease-related splenomegaly or symptoms in patients with PMF or PPV-MF or PET-MF.[21] The patient population described in the decision problem matches that of the licensed indication.

The economic evaluation is conducted in accordance with the COMFORT-II trial population.[7] All patients on the trial had intermediate-2 risk or high-risk MF (defined using IPSS criteria), and a palpable spleen length of at least 5 cm (see 4.3.1 and 4.3.2). Evidence from the COMFORT-II trial is supplemented by evidence from the COMFORT-I trial[26] which compared ruxolitinib with placebo in patients with MF. Inclusion criteria in COMFORT-I were the same as for COMFORT-II with the exception that patients in COMFORT-I had to be resistant or refractory to, intolerant of, or, in the investigator's opinion, not candidates for BAT, and for whom treatment of MF was indicated (see 4.3.1 and 4.3.2).

It should be noted that the licensed population and population included in the final NICE scope is broader than the population included in the COMFORT trials[7,26] as it is not restricted by risk group defined using the IPSS or baseline palpable spleen length. Although the patients included in the COMFORT trials may represent only a subset of the licensed population, an analysis of data from COMFORT-I suggests that similar benefits are achieved in patients irrespective of risk categories or baseline palpable spleen length (see section 4.8).[17] This is further confirmed by the ROBUST UK phase II trial and the JUMP expanded access study.[48,53,145]

The final NICE scope stipulates that subgroups should be explored if evidence allows. Analysis of COMFORT-II trial data revealed that the benefit of ruxolitinib over BAT was observed across all pre-specified patient subgroups investigated, including subgroups defined according to gender, MF subtype, IPSS risk category, prior exposure to hydroxyurea (HU) and *JAK2 V617F* mutation.[154] Similar findings were observed in COMFORT-I over placebo.[17] Analysis for specific subgroups was therefore not explored.

5.2.2 Model structure

The conceptual model was developed with the aid of an Advisory Group, composed of three haematologists through a series of interactive meetings, teleconferences and email exchanges, supplemented by a review of the evidence available. The Advisory group provided clinical input and opinion on topics such as:

- Application of a stopping rule

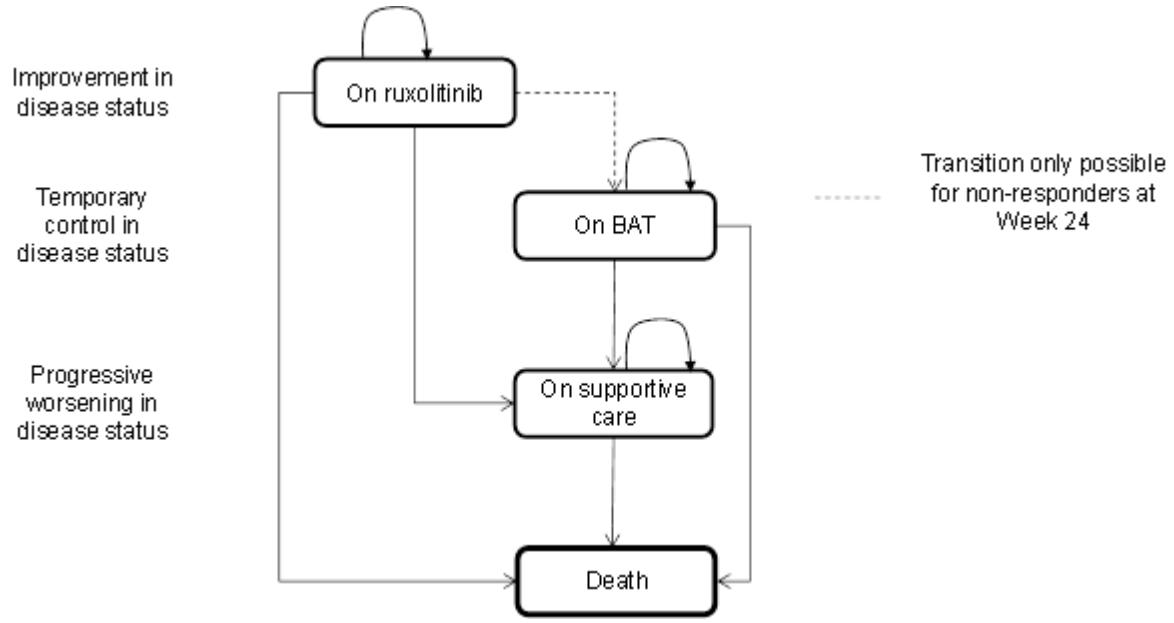
- Definition of response criteria
- Possible treatment strategies after discontinuation of ruxolitinib and BAT
- Resource utilisation
- Appropriate data and analyses for OS estimates

The model structure, shown in Figure 42 was chosen to:

- represent the natural history of MF in sufficient detail to capture the impact of treatments on HRQoL and costs during the course of the disease
- make the best of use of data from the COMFORT-II trial which provided a direct comparison with the appropriate comparator.

This structure also addresses some of the comments raised by the ERG and Appraisal Committee (AC) during the previous appraisal of ruxolitinib for MF (see Table 49).[155,156]

Figure 42 Simplified schematic of the model structure



BAT, best available therapy.

Structure and health states

The model is composed of two sub-models to:

- Estimate the duration spent in each phase of the treatment pathway/disease, and
- Estimate the progression of HRQoL according to the phase of treatment/disease.

In contrast to most cancers, disease progression is not clearly defined in MF and there is a lack of clinical consensus regarding the definition for progressive disease. The disease is characterised by a progressive worsening of symptoms, haematological parameters, splenomegaly, nutritional status

(weight loss) and HRQoL (see section 3.1.1 and 3.1.2). BAT provides some symptom relief (including haematological parameters) but effects are short-lived (as evident from COMFORT-II), and following exhaustion of the various options included in BAT, the patient's condition progressively worsens. Patients may then receive supportive care, considered to consist of RBC transfusions and palliative management/monitoring of the disease progression, until death. Given that the outcomes with respect to HRQoL and costs are considered to be largely defined by a patient's phase in the management of the condition, the health states in the model are defined by the therapy phases, namely:

- **On ruxolitinib**: receiving active therapy with ruxolitinib which provides improvements in symptoms, splenomegaly and HRQoL
- **On BAT**: receiving BAT which may provide some symptom relief and control of haematological parameters but have limited impact on HRQoL
- **On supportive care**: receiving supportive care which is associated with a progressive worsening of the condition until death.

Patients can move to the Death health state from each of the three treatment health states (if appropriate).

In practice, approximately 5% of patients with MF may be considered for allo-SCT[52] as an alternative to BAT or ruxolitinib, but because of the small number of patients involved and lack of relevant data, this option was not included in the economic analysis. Patients with MF with an enlarged spleen may also undergo splenic irradiation and splenectomy (see section 3.3) in practice. However, splenectomy and splenic irradiation are rarely used in the UK[52] due to the associated morbidity and mortality and were therefore not included in the model.

Type of model

The decision model is constructed in Visual Basic for Excel. In contrast to many oncology models submitted to NICE, the model is individual-patient based and uses a time-to-event approach; thus there are no time cycles. This approach was chosen over a cohort approach in order to model the progressive nature of MF (worsening in HRQoL in the supportive care health state) and explore the impact of different structural assumptions. Given that HRQoL is expected to be non-linear (i.e progressive worsening once a patient has exhausted the options included in BAT), the individual-based approach is believed to be more flexible and transparent compared with a cohort approach, which would require the use of tunnel states and lead to the model being convoluted. Furthermore, this approach provides additional flexibility to explore the impact of different structural assumptions and increased transparency. However, the model is not a true patient-level model in the sense that many of the functions are programmed to estimate the average, rather than the heterogeneity between individuals. For simplicity and to speed up calculation, time is rounded to the nearest week (with the minimum sampled time possible being a week).

Movement through the model

Patients enter the model initiating treatment with ruxolitinib or BAT. Clinical advisors considered ruxolitinib versus BAT (including no treatment) to be the most appropriate comparison.

Patients initiating therapy on BAT

In the absence of ruxolitinib, patients enter the model initiating therapy on BAT (ie in the BAT health state). In this health state, patients typically receive a series of treatments that constitute BAT and achieve some control of symptoms, haematological parameters and HRQoL but not splenomegaly. Patients may continue to receive BAT until death and therefore remain in the BAT health state and then move to Death directly. Alternatively, patients may stop receiving BAT (after exhaustion of possible options) and progress to receive supportive care (in the Supportive Care health state). In this health state patients experience a gradual worsening of the disease (symptoms and haematological parameters) and HRQoL until death.

Prior to death patients have increased requirements for transfusion and management of thrombotic complications, and may require pain control, antibiotics, cytotoxic drugs, surgical options, blood analyses and other tests. This is not included in the economic model as a separate health state due to the lack of evidence and given that it is unclear whether the introduction of ruxolitinib would affect the time patients spend in this phase. For simplicity, a one-time cost is included in the economic analysis prior to death (see section 5.5.6).

It should be noted that formal response criteria for therapies others than ruxolitinib are not used in clinical practice since the impact of BAT on symptoms is usually transient and the agents included in BAT are relatively inexpensive and well tolerated.[8,93] Thus, no stopping rule is applied and no formal response criteria are considered for patients receiving BAT in the model.

Patients initiating therapy on ruxolitinib

Patients initiating ruxolitinib are categorised into five groups based on their outcomes at week 24 (criteria for spleen and symptom response are described in section 5.2.4.)

- **Spleen responders** (Group 1) are patients who achieve a spleen response at week 24 (with or without a symptom response**)**
- **Symptom responders** (Group 2) are patients who achieve a symptom response at week 24 but who do not achieve the required level of spleen response.
- **Primary non-responders** (Group 3) are patients alive and on treatment but who achieve neither a spleen nor a symptom response at week 24**.**
- **The early discontinuation group** (Group 4) constitutes patients who are alive at week 24 but who discontinue therapy prior to week 24
- **The early death** (Group 5) group is patients who die prior to week 24

Primary responders (Groups 1 and 2)

Patients who achieve a spleen response (Group 1) or a symptom response (Group 2) at week 24 (criteria for spleen and symptom response are described in section 5.2.4) remain on ruxolitinib therapy and hence in the ruxolitinib health state.

Thereafter there is an ongoing risk of stopping ruxolitinib beyond week 24 due to a variety of reasons including loss of continuing efficacy and AEs. There is no clear guideline or accepted consensus on when to stop treatment following primary response to ruxolitinib. For example, Harrison et al (2014)[10] recommend that ruxolitinib therapy should be continued as long as the symptoms of disease are better than at baseline in patients achieving initial primary response. The SmPC[21] states that "*it is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms*."

In the extension phase of COMFORT-II, patients were able to remain on ruxolitinib until the clinician believed patients were no longer deriving a benefit. The discontinuation rate from COMFORT-II is therefore likely to reflect what would happen in clinical practice. Consequently, in the model, the discontinuation rate from the COMFORT-II trial was used as a proxy for discontinuation of ruxolitinib (see section 5.3.6)

In the economic model, primary responders (Groups 1 and 2) who discontinue ruxolitinib (due to lack of efficacy or AEs) then move directly to the Supportive Care health state and experience a worsening in symptoms and haematological parameters until death. This assumption, included in the base case, was made as the COMFORT-II trial did not collect data on treatments received after discontinuing ruxolitinib therapy. In clinical practice a proportion of patients receiving ruxolitinib are likely to receive BAT following ruxolitinib discontinuation. However, it is unclear for how long these patients would receive BAT and experience symptom control. Assuming that patients receiving ruxolitinib move directly to the Supportive Care health state is probably a conservative assumption which favours the BAT arm. A proportion of patients may die whilst on ruxolitinib and would not proceed to the next treatment phase.

Primary non-responders (Group 3)

At week 24, primary non-responders stop therapy with ruxolitinib. Thus a treatment stopping rule is included at week 24 for patients initiating ruxolitinib (as described in section 5.2.4).

In the absence of evidence, primary non-responders are assumed to receive BAT and supportive care following ruxolitinib discontinuation for the same duration as patients initiating BAT. Hence, these patients are assumed to live an additional 24 weeks compared with patients initiating therapy with

BAT. According to clinical advisors, this assumption is considered to be conservative with respect to the benefits of ruxolitinib, as even though they do not achieve a spleen response or symptom response by week 24, these patients may experience an improvement compared with patients commencing therapy with BAT. This possible benefit is not fully reflected in the base case.

Early discontinuation and early death groups (Groups 4 and 5)

Patients may die before week 24 (Group 5). Patients who discontinue therapy prior to week 24 for other reasons (Group 4) are assumed to move directly to receive supportive care and experience a worsening in symptoms and haematological parameters until death.

Outcomes included in the model

The economic model tracks changes in HRQoL (on a continuous scale) and costs over time, according to different phases of the disease. The advantage of this approach is that the assumption of constant HRQoL within health states is not required, when appropriate. This approach is based on the methodology used to model other chronic diseases such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis[157-159] where the progression of a disease measure (typically scores obtained using the Health Assessment Questionnaire [HAQ]) is modelled in order to estimate HRQoL. In this economic analysis, changes in HRQoL are modelled directly (rather than changes in symptoms and splenomegaly which could then link to HRQoL) given that the COMFORT-trials did not collect data on symptoms measured using the MF-SAF after week 24 and in patients receiving BAT.

In addition, patients with MF are at increased risk of complications such as transformation to leukaemia or thrombotic events (see section 3.1.3). Leukaemic transformation (LT) is an important aspect of the progression in MF (see section 3.1.3). Therefore the economic model sought to capture its impact (see section 5.3.8). Evidence is available from the COMFORT trials. However, it should be noted that there is uncertainty regarding the long-term impact of ruxolitinib on LT.

Evidence for the impact of ruxolitinib on the risk of thrombosis is not available; therefore this was not included in the economic analysis. This approach was considered acceptable given that thrombosis is a rare clinical event. It is also difficult to differentiate thrombosis due to the disease itself and thrombosis due to other factors especially in this older patient population. Preliminary evidence suggests that ruxolitinib can lead to an improvement in pulmonary hypertension.[160]

Haematological aspects of the disease are important to capture because haematological progression is part of the natural course of MF and, in the short-term, treatments for MF, such as ruxolitinib, may be associated with haematological events such as leucocytosis, thrombocytosis and anaemia (see section 4.12.4). These events are managed effectively with dose modifications, temporary treatment interruptions, and, in the case of anaemia, by RBC transfusions (see section 4.12.4). In the economic model, the management of haematological events is considered as follows:

- management of anaemia (due to treatment) includes monitoring and the requirement for RBC transfusions,
- thrombocytopenia and neutropenia (due to treatment) are assumed to be managed with dose reductions/interruptions,
- management of haematological events related to the natural course of MF is included in the economic model through the requirement for RBC transfusions

5.2.3 Features of the de novo analysis

The key features of the de novo analysis are summarised in Table 27.

The model estimates the cost per QALY which is in line with the NICE methods guide.[150] The decision model employs a lifetime patient horizon and uses a direct NHS and personal social services (PSS) perspective (using 2013–2014 as the price year) as recommended by the NICE methods guide.[150] A patient lifetime horizon was used given the chronic nature of the disease and in order to capture all the relevant costs and benefits associated with the introduction of ruxolitinib in England and Wales. However, given the uncertainty in the long-term extrapolation, a time horizon of 5, 10, 15 and 20 years are considered in scenario analyses (see Table 55). The decision model uses a discount rate of 3.5% per annum for both costs and benefits as recommended in the NICE methods guide for economic evaluation.[150] This is also explored in scenario analyses (Table 77).

Table 27 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (assumed to be 35 years)	NICE reference case[150] Sufficient to capture all meaningful differences in technologies compared
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[150]
Discount of 3.5% for utilities and costs	3.5% discounting per annum applied for both costs and benefits	NICE reference case[150]
Perspective (NHS/PSS)	NHS/PSS	NICE reference case[150]

NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years.

Data sources used in the model

The economic model is primarily based on data from COMFORT-II. However, when necessary, data from COMFORT-I, two open label studies of ruxolitinib (ROBUST UK and JUMP), audit data (HMRN) or assumptions were used.

Table 28 summarises the source of data used for the main inputs parameters used in the base case.

Table 28 Sources of data used in the base case

	COMFORT-II	COMFORT-I	ROBUST	JUMP	HMRN	Derived	Assumptions	Comments
BAT discontinuation	✓							
Proportion of BAT patients dying upon discontinuation	✓							
BAT OS	✓							
BAT post-discontinuation survival						✓		
Outcomes of patients on ruxolitinib at week 24	✓	✓						Proportion of symptom responders taken from COMFORT-I
Ruxolitinib discontinuation rate	✓							
Proportion of patients dying upon ruxolitinib cessation	✓							
Ruxolitinib post-discontinuation survival	✓							
Rate of LT	✓							
Baseline quality of life (QoL)		✓						
Change in QoL		✓					✓	Assumption made for BAT
Dose intensity for ruxolitinib	✓							
BAT received	✓							
Monitoring whilst on BAT (outpatient visits and laboratory tests)					✓			
Other resource utilisation whilst on BAT (excluding transfusion)			✓		✓			Assumed to be same between BAT and supportive care
RBC transfusion whilst on BAT							✓	Fewer RBC assumed in BAT compared with supportive care

	COMFORT-II	COMFORT-I	ROBUST	JUMP	HMRN	Derived	Assumptions	Comments
Monitoring whilst on supportive care (outpatient visits and laboratory tests)							✓	Less monitoring assumed in supportive care compared with BAT
Other resource utilisation whilst on supportive care (excluding transfusion)			✓		✓			Assumed to be same for BAT and supportive care
RBC transfusion units whilst on supportive care		✓						
Monitoring whilst on ruxolitinib (outpatient visits and laboratory tests)							✓	Assumption for monitoring based on guidelines
Impact of ruxolitinib on other resource use (excluding transfusion)				✓				
Impact of ruxolitinib on RBC transfusion	✓							
Rate of AEs	✓							

AE, adverse event; BAT, best available therapy; LT, leukaemic transformation; OS, overall survival; QoL, quality of life; RBC, red blood cell.

5.2.4 Intervention technology and comparators

Intervention: ruxolitinib

The economic analysis uses evidence from the COMFORT trials in which ruxolitinib was prescribed in accordance with the license (see Table 4 and section 2.3).

Stopping rule

The economic analysis incorporates a stopping rule at week 24 for patients initiating ruxolitinib who do not achieve a spleen response and/or a symptom response. The stopping rule was applied at this time point to reflect the licensed treatment discontinuation recommendations and the BCSH guidelines, which state that the treatment should be discontinued after 6 months if there has been no reduction in splenomegaly or improvement in symptoms since initiation of therapy.[8,21] However, neither the SmPC nor the BCSH guidelines specify what would be considered a clinically meaningful improvement in splenomegaly and/or symptoms and hence do not provide clear guidance on the conditions that should be met to warrant continuing ruxolitinib therapy. In clinical practice there is no consensus about the definition of response and the decision to discontinue treatment is usually taken on a case-by-case basis.[8,93,161] An appropriate definition of response was therefore required for use with the stopping rule.

Definition of response

The definition of response used for the stopping rule was chosen based on consideration of the consensus-based definition of response criteria for use in clinical trials set out in the recent IWG-MRT/ELN guidelines[125], together with recognition that in clinical practice measurement of response is typically based on an improvement in spleen length and/or symptom reduction. The IWG-MRT/ELN[125] consensus definition of response defines clinical improvement as “the achievement of **anaemia, spleen or symptoms response** without progressive disease or increase in severity of anaemia, thrombocytopenia, or neutropenia” (see Table 12). For the stopping rule, response was therefore defined in terms of either a spleen response or a symptom response.

In the IWG-MRT/ELN guidelines a **spleen response** is defined as:

- a ≥ 50% reduction in spleen length in patients with a baseline splenomegaly that is palpable at > 10 cm below the LCM, or
- non-palpable spleen in patients with a baseline splenomegaly that is palpable at 5–10 cm below the LCM.

This is a stringent definition of spleen response as in clinical practice patients achieving a smaller reduction in spleen size may experience clinically meaningful improvements (see section 4.7.2). Thus a scenario analysis is conducted assuming a lower threshold (≥ 25% reduction in spleen length) as

the definition for spleen response in patients with a baseline splenomegaly that is palpable at > 10 cm below the LCM.

The IWG-MRT/ELN guidelines define a **symptom response** as:

- a ≥ 50% reduction in the MPN-SAF TSS.

The modified MF-SAF v2 (a similar instrument to the MPN-SAF) was used in the COMFORT-I trial and therefore provides information on symptom response to ruxolitinib. As with the spleen response, this is a stringent definition of symptom response and Mesa et al (2011) have reported that the majority of patients with improvements in TSS of at least 25% (measured using the MF-SAF) rated their disease as much or very much improved using the Patient Global Impression of Change (PGIC) Scale.[162] Thus, a scenario analysis is conducted using a lower threshold (≥ 25% reduction in MF-SAF TSS) as the definition for symptom response.

The FACT-Lym, a validated instrument providing information on particular symptoms, was used in the COMFORT-II trial. Results for the FACT-Lym from COMFORT-II therefore provide an alternative option for informing the stopping rule based on symptom response in the economic model. This instrument is not specific for MF and is less sensitive compared with the modified MF-SAF v2, but includes a cancer site-specific questionnaire, LymS, with questions about specific symptoms such as fatigue, itching, night sweats and pain, which are relevant to MF. The minimally important difference (MID) score for the LymS has been defined in the published literature (including values for the lower and upper bound).[163] Using attainment of an improvement of at least the MID as a definition of response, symptom response rates can be determined from LymS scores. Harrison et al (2013)[35] reported symptom response rates over time in the COMFORT-II trial using this definition. Scenario analyses are conducted using symptom responses based on the lower or upper bound of the MID for the LymS as reported by Harrison et al (2013).

In the base-case the following definitions of response were used to determine whether patients should continue on ruxolitinib therapy beyond week 24:

- **Spleen response**:
  non-palpable spleen in a patient with splenomegaly at baseline that is palpable at 5–10 cm below the left costal margin (LCM), **or** spleen decreases by ≥ 50% in a patient with splenomegaly at baseline that is palpable at > 10 cm below the LCM, **or**
- **Symptom response**: a ≥ 50% reduction from baseline in the MF-SAF TSS.

Alternative definitions for spleen or symptom response used in the economic model are summarised in Table 29.

Table 29 Alternative definitions for spleen response and symptom response used for the stopping rule in the economic model

Scenario	Spleen response in patient with spleen palpable at 5–10 cm below LCM at baseline	Spleen response in patient with spleen palpable at > 10 cm below the LCM at baseline	Symptom response
Base case	Non-palpable spleen	**≥ 50%** decrease from baseline	**≥ 50%** reduction from baseline in MF-SAF TSS
Scenario 1	As for base case	**≥ 50%** decrease from baseline	**≥ 25%** reduction from baseline in MF-SAF TSS
Scenario 2	As for base case	**≥ 25%** decrease from baseline	**≥ 50%** reduction from baseline in MF-SAF TSS
Scenario 3	As for base case	**≥ 25%** decrease from baseline	**≥ 25%** reduction from baseline in MF-SAF TSS
Scenario 4	As for base case	**≥ 50%** decrease from baseline	Achievement of **upper** bound of MID for LymS
Scenario 5	As for base case	**≥ 50%** decrease from baseline	Achievement of **lower** bound of MID for LymS
Scenario 6	As for base case	**≥ 25%** decrease from baseline	Achievement of **upper** bound of MID for LymS
Scenario 7	As for base case	**≥ 25%** decrease from baseline	Achievement of **lower** bound of MID for LymS
[a]In patients with baseline splenomegaly palpable at > 10 cm below the LCM			

LCM, left costal margin; LymS, lymphoma subscale of the FACT-Lym; MF-SAF, Myelofibrosis Symptom Assessment Form; MID, minimal important difference.

Comparator: BAT

The NICE scope defined the comparator of interest to be established clinical practice without ruxolitinib.[164] BAT, as used in the COMFORT-II trial, is considered by clinical experts to correspond to established clinical practice in England and Wales (see section 4.13.2). In COMFORT-II,[7] the most frequently used therapies were hydroxycarbamide (hydroxyurea), prednisone/prednisolone and epoetin alfa. Other treatments used as BAT included lenalidomide and thalidomide (see Table 11). A proportion of patients also received no treatment (observation only). The range of treatments and the proportion of patients receiving each agent is similar to that reported in the HMRN audit[52] (see section 4.13.2). Although lenalidomide has been rarely used in the UK to date, the recent UK clinical guideline[93] recommends its use in patients with platelets count over 100,000/mm^3.

Other possible therapies for management of MF are allo-SCT and splenectomy or splenic irradiation. However these are not considered to be included in current established clinical practice in England and Wales and there is a lack of appropriate data to reliably inform such a comparison. Therefore no analysis is conducted against allo-SCT or against splenectomy or splenic irradiation.

As previously noted in section 5.2.2, no stopping rule was assumed for patients initiating BAT. Since the impact of BAT on symptoms and splenomegaly is transient, and BAT therapies are relatively cheap, formal response criteria at week 24 are not used in clinical practice.[8,93]

5.3 Clinical parameters and variables

Clinical data used within the model included:

- OS for patients initiating BAT and not previously exposed to ruxolitinib
- the duration on BAT
- the proportion of patients dying while on BAT
- the time to death from discontinuing BAT (derived parameter)
- the proportion of patients on ruxolitinib according to their outcomes at week 24 (ie spleen responders, symptom responders, non-responders, early discontinuation and early death)
- the time to discontinuing ruxolitinib
- the proportion of patients dying on ruxolitinib
- the time to death following discontinuation from ruxolitinib
- the probability of leukaemic transformation

These parameters are discussed in turn.

5.3.1 Overall survival for patients initiating BAT and not previously exposed to ruxolitinib

The ITT analysis (not corrected for crossover) is likely to be biased and overestimate OS in the BAT arm as patients were allowed to cross over to ruxolitinib treatment and the majority (61.6%) did so.[161] It is therefore not a true reflection of the survival of patients treated under current practice (ie in the absence of ruxolitinib). The ITT analysis corrected for crossover is therefore considered to provide the most reliable representation of the survival for patients treated under current practice.[161]

Adjustment for cross-over

The NICE methods guide stipulates in section 5.7.8 that:
"In RCTs, participants randomised to the control group are sometimes allowed to switch treatment group and receive the active intervention. In these circumstances, when intention-to-treat analysis is considered inappropriate, statistical methods that adjust for treatment switching can also be presented….The relative merits and limitations of the methods chosen to explore the impact of switching treatments should be explored and justified with respect to the method chosen and in relation to the specific characteristics of the data set in question. These characteristics include the mechanism of crossover used in the trial, the availability of data on baseline and time-dependent

characteristics, and expectations around the treatment effect if the patients had remained on the treatment to which they were allocated."

Several approaches could be used to adjust for cross-over, with the common approach being

- **The rank-preserving structural failure time models (RPSFTM).** This method uses a counterfactual framework that utilizes survival times that would have been observed if no treatment had been given to estimate the casual effect of treatment. It is assumed that counterfactual survival times are independent of treatment group, and g-estimation is used to determine a value for the treatment effect, which satisfies this constraint. The RPSFTM identifies the treatment effect using only the randomization of the trial, observed survival and observed treatment history. The standard one-parameter version of the model assumes that the treatment effect ("time ratio") is equal (relative to the time for which the treatment is taken) for all patients no matter when the treatment is received (the "common treatment effect" assumption). The RPSFTM method is known to be sensitive to the "common treatment effect" assumption, but the importance of this sensitivity depends on the size of the treatment effect observed in the trial in question.
- **The iterative parameter estimation (IPE).** This method is an extension of the RPSFTM method, using parametric methods. The same accelerated failure time model is used, but a parametric failure time model is fitted to the original unadjusted intention-to-treat (ITT) data to obtain an initial estimate of the treatment effect. The failure times of switching patients are then re-estimated using this model, and this iterative procedure continues until the new estimate is very close to the previous one, at which the point is said to have converged. An additional assumption is that survival times follow a parametric distribution, and thus it is important to identify suitable parametric models, which in itself can be problematic. However, using a parametric model may result in quicker convergence, provided a suitable parametric distribution can be identified. Like the RPSFTM method, the IPE method is sensitive to the "common treatment effect" assumption
- **The inverse probability of censoring weights (IPCW).** This method is an approach for adjusting estimates of a treatment effect in the presence of any type of informative censoring. Patients are artificially censored at the time of switch, and remaining observations are weighted based upon covariate values and a model of the probability of being censored. This allows patients who have not been artificially censored to be weighted in order to reflect their similarities to patients who have been censored in an attempt to remove the selection bias caused by the censoring—patients who did not switch and have characteristics similar to patients who did switch receive higher weights. The IPCW method assumes "no unmeasured confounders", which requires data to be available on all baseline and time-dependent prognostic factors of mortality that independently predict informative censoring (switch).[165] The IPCW method is known to be highly prone to error when a very large proportion of control

patients (greater than approximately 90% in the trial with sample size 500) switch onto the experimental treatment.

- **The two-stage approach**. This method effectively recognizes that the clinical trial is randomized up until a specific disease-related time point (i.e., disease progression), but beyond that point, the study is essentially an observational one. First, a treatment effect specific to switching patients is estimated and the survival times of these patients are adjusted, subsequently allowing the treatment effect specific to experimental group patients to be estimated. A structural nested failure time model (SNM) with g-estimation approach has been used to estimate the treatment effect in switchers. Like RPSFTM (a derivative form of SNM), counterfactual survival is used; however, SNM makes the assumption of "no unmeasured confounders" rather than basing estimation of the randomization of the trial. A simplified approach, which does not rely upon g-estimation, has been developed to analyze the type of switching often observed in oncology randomized clinical controlled trials. Both approaches rely on the ability to identify a secondary baseline where all patients are assumed to be at the same disease-related time point.

All switching adjustment methods are subject to important limitations. In some circumstances some methods are likely to be appropriate, whereas others are likely to be inappropriate. While no method may be perfect, each should be assessed in order to establish the most appropriate adjusted estimate of the OS treatment effect in the COMFORT-II trial.

Assessment of the validity of the approaches used to adjust for cross-over

Analyses are based on the 3 years follow-up data. The two-stage method requires that there be a "secondary baseline" within the trial, after which treatment switching becomes possible. This secondary baseline must be related to the disease, such that the prognosis of patients can be classified as similar at this time point. An example of such a time point in the context of the COMFORT-II trial is disease progression. If treatment switching was allowed only after disease recurrence, and if we wished to adjust for switching that occurred after disease progression, we could use the time of disease recurrence as a secondary baseline for each patient. However, in the COMFORT-II trial, we wish to adjust for treatment switching, and nearly half (42%) of such switching occurred before disease progression. Therefore, a suitable secondary baseline required by the two-stage method does not exist and, the two-stage method is not considered appropriate for this study.

The IPCW method assumes no unmeasured confounders. During the course of the COMFORT-II study, a set of covariates was collected periodically. However, some were measured less frequently than others and some were available only for up to 48 weeks. For example, (1) spleen length was assessed at baseline; at weeks 4, 8, 12, 16, 24, 36, and 48; and every 12 weeks thereafter; (2) spleen volume was assessed at baseline; at weeks 12, 24, 36, and 48; and every 12 weeks thereafter; (3) Eastern Cooperative Oncology Group (ECOG) performance status was assessed at baseline; at weeks 4, 8,16, 24, and 48; and every 24 weeks thereafter; and (4) the EORTC (European

Organisation for Research and Treatment of Cancer) QLQ-C30[a] and FACT-Lym (Functional Assessment of Cancer Therapy–Lymphoma) symptom scores were assessed at baseline and at weeks 8, 16, 24, and 48, with no further assessment after week 48. Therefore, the no-unmeasured-confounders assumption may not hold. Furthermore, 15 patients in the BAT arm and 21 patients in ruxolitinib arm had missing data at baseline for the covariates that could be used for the analysis. Hence, the IPCW method was not considered appropriate for this study.

The RPSFTM and IPE methods are potentially appropriate for this study. These methods maintain the original randomized group definitions and thus preserve the validity of between-group comparisons. The ITT analysis showed a > 40% reduction in risk of death in the ruxolitinib arm compared to the BAT arm. There is no suggestion that the treatment effect varies depending on when the treatment is received. The IPE method is an extension of the RPSFTM, but requires an additional parametric assumption for the survival times. Therefore, we chose RPSFTM over IPE. The RPSFTM method relates observed failure times and treatment histories to failure times that would have been observed if never treated (counterfactual) through an acceleration factor (e^{ψ}).[166] The acceleration factor is the ratio of survival time when the patient is off treatment versus the survival time when the patient is on treatment. An acceleration factor that is less than 1 (or $\psi < 0$) indicates that treatment is beneficial. This acceleration factor is estimated using a grid of hypothetical values of ψ (g-estimation) and then used to calculate the corrected survival time for patients who switched treatment. Then, the corrected treatment effect (HR) is calculated using the corrected survival time.

OS adjusted for cross-over using the RPSFTM

Data from the COMFORT-II cohort corrected for crossover (based on the 3 years follow-up data) were used in the base case (Figure 43). Scenario analyses are conducted using the OS from the ITT population not corrected for crossover (Table 59).[7]

[a] QLQ-C30 = questionnaire developed to assess the quality of life of cancer patients.

Figure 43 Overall survival in COMFORT-II (ITT and corrected for crossover)

CII, COMFORT-II trial; ITT, intention-to-treat; RPSFT, rank preserving structured failure time.
ITT analysis: Harrison et al. 2014;[22] Corrected for crossover: Data on file

Individual patient-level data were obtained for the ITT population (based on 3.5 years follow-up data) and the crossover-adjusted population in COMFORT-II (based on 3 years follow-up data). A range of parametric survival models (Weibull, exponential, Gompertz, log-normal) was considered for the COMFORT-II cohort corrected for crossover (Figure 44). Different parametric models incorporate different hazard functions. Exponential models are only suitable if the observed hazard is approximately constant and positive. Weibull and Gompertz models incorporate monotonic hazards, while the logged model (log-normal) can incorporate non-monotonic hazards but typically has a long tail due to a reducing hazard as time increases beyond a certain point.

Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were calculated. The results suggest that the Gompertz distribution provides the best fit to the data (Table 30). However, goodness of fit criteria only provides an indication of the goodness of fit to the observed period and do not categorically indicate that one distribution should be preferred to the remaining distributions. The observed KM was plotted against the four fitted parametric distributions (exponential, Weibull, Gompertz and log-normal). The Gompertz distribution provided the best fit to the observed data (and had the lowest AIC/BIC) and a plausible extrapolation (Figure 44) and was therefore used in the base case. Other distributions were examined in scenario analysis (Table 58). The Weibull distribution

provided a plausible fit to the observed data up to week 110. The log-normal and exponential distributions provided neither a plausible fit to the observed data nor a plausible extrapolation.

Table 30 Assessment of parametric survival models for overall survival in patients receiving BAT corrected for crossover (taken from COMFORT-II)

Model	Obs	df	AIC	BIC	Predicted mean (in weeks)
Exponential	73	1	92.76	95.05	[redacted]
Weibull	73	2	83.19	87.77	[redacted]
Gompertz	73	2	76.82	81.40	[redacted]
Log-normal	73	2	92.79	97.37	[redacted]

AIC, Akaike information criterion, BAT, best available therapy; BIC, Bayesian information criterion; df, degree of freedom; Obs, observations.

Figure 44 Kaplan–Meier curve for overall survival in patients initiating BAT (corrected for crossover) and fit of selected parametric distributions (taken from COMFORT-II)

BAT, best available therapy; KM, Kaplan–Meier; LCI, lower confidence interval; Obs, observations; UCI, upper confidence interval

5.3.2 Duration on BAT

The duration on BAT (used as a proxy for the period of time patients experience a temporary control of the disease) in patients not previously exposed to ruxolitinib is taken directly from the COMFORT-II trial. All patients originally randomised to the control arm of the COMFORT-II trial discontinued BAT. The median duration of exposure to BAT was 45.1 weeks.[7] Reasons for stopping BAT were:

- discontinuation due to AEs, withdrawal of consent, disease progression or other reasons (38.4% of patients),
- cross-over to ruxolitinib (61.6% of patients).

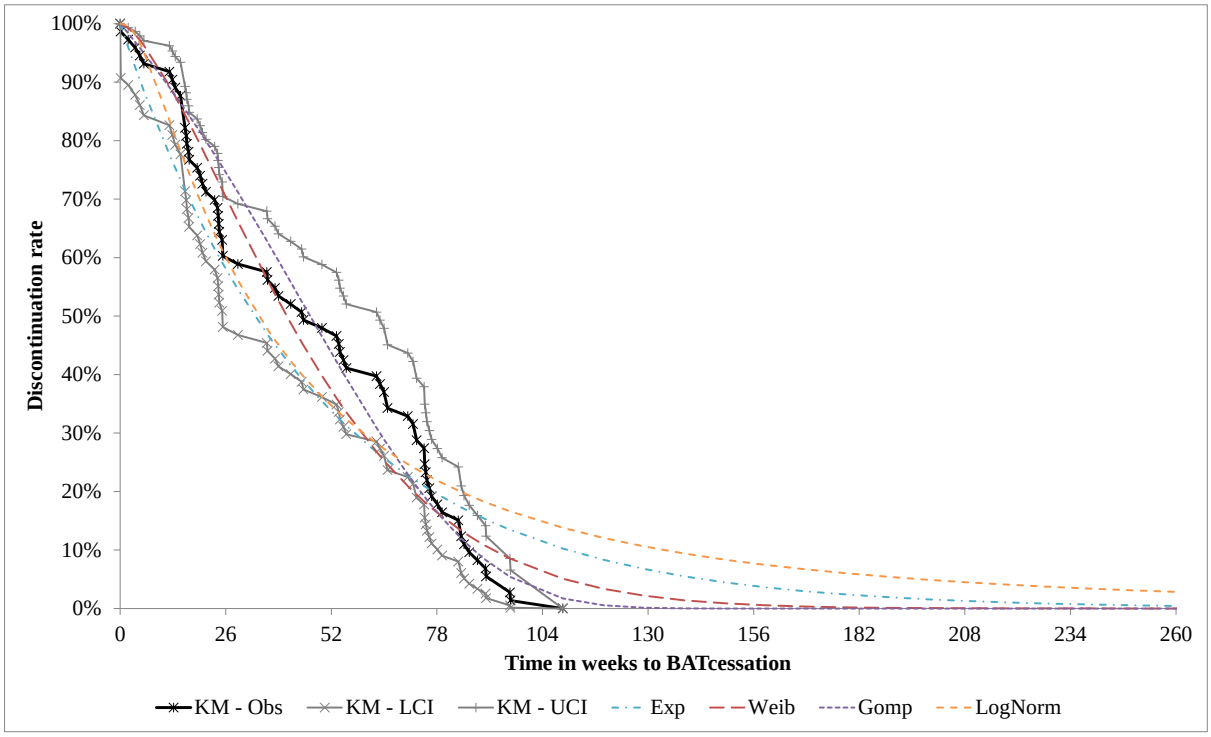
Individual patient level data from the COMFORT-II trial were analysed for patients enrolled in the control arm (n = 73) to generate a Kaplan–Meier curve for BAT exposure. Although the KM was complete and thus could be used directly, a range of parametric survival models (Weibull, exponential, Gompertz, log-normal) was considered (Figure 45) in order to facilitate the conduct of the PSA and sensitivity/scenario analyses. The Gompertz distribution provided the best visual fit to the observed data and fit in terms of both the AIC and BIC and was thus used in the base case (Table 31). Scenario analyses were conducted using other distributions (Table 56). The Weibull distribution provided a less reasonable fit compared with the Gompertz distribution but was considered plausible. The exponential and log-normal distributions did not provide a good fit to the data.

Table 31 Assessment of parametric survival models for exposure to BAT (taken from COMFORT-II)

Model	Obs	df	AIC	BIC	Predicted mean (in weeks)
Exponential	73	1	197.27	199.56	47.87
Weibull	73	2	185.15	189.73	47.42
Gompertz	73	2	173.96	178.54	48.35
Log-normal	73	2	220.42	225.00	60.26

AIC, Akaike information criterion, BAT, best available therapy; BIC, Bayesian information criterion; df, degree of freedom; Obs, observations.

Figure 45 Kaplan–Meier curve for time to stopping BAT and fit of selected parametric distributions (taken from COMFORT-II)



BAT, best available therapy; KM, Kaplan–Meier; LCI, lower confidence interval ; Obs, observations; UCI, upper confidence interval .

It may be possible that the discontinuation rate in the COMFORT-II trial is an overestimate of what would be expected in clinical practice given the open-label trial design. To reflect the uncertainty in this parameter, a series of scenario analyses was conducted assuming the exposure duration on BAT from the COMFORT-II trial to be underestimated by a factor of 10% to 40% (Table 57).

5.3.3 Proportion of patients dying on BAT

Out of the 73 patients who stopped BAT in COMFORT-II (due to discontinuation or crossover to ruxolitinib), 4 patients died upon discontinuation. To reflect this, in the economic model we assumed that 5.48% (n = 4/73) of patients would die while receiving BAT.

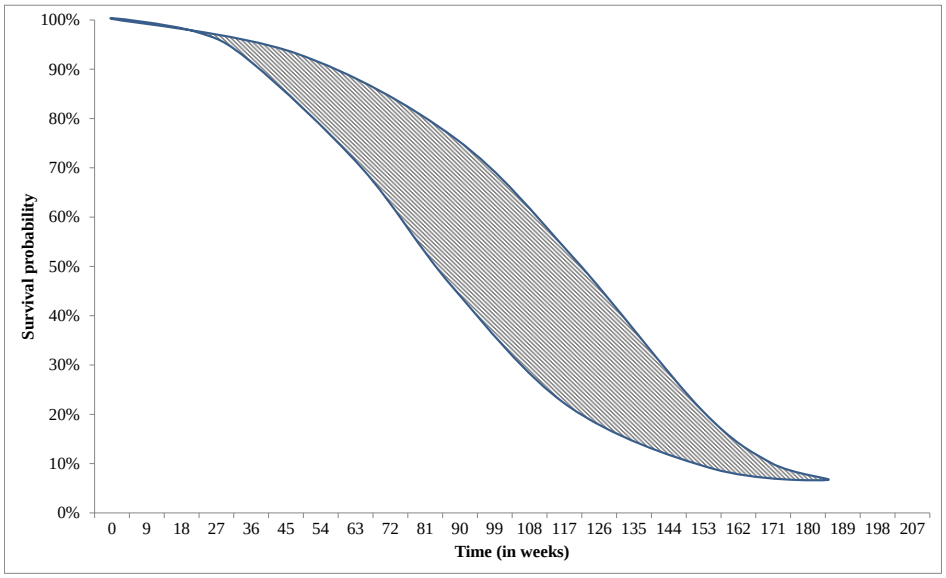
5.3.4 Time-to-death from discontinuation of BAT (derived parameter)

A key challenge in the economic model is to preserve the correlation that exists between the time-to-discontinuation of BAT and the time-to-death. Sampling distributions for OS and discontinuation separately would lead to inconsistencies (e.g. time to discontinuation being longer than time to death) as these parameters are correlated. Ideally, the time patients remain alive post-BAT discontinuation would be estimated directly from the trial. Although this is possible for the ITT OS (ie not corrected for

crossover), this is not straightforward when OS is corrected for crossover using the RPSFT method. The RPSFT method creates a counter-factual dataset and adjusts OS irrespective of the time to discontinuation or crossover, making it difficult to estimate the time-to-death post-discontinuation of BAT.

In traditional cohort models (notably partitioned-survival or area under the curve models), this is less of an issue as typically parametric curves would be fitted to the time-to-discontinuation (of BAT) and the OS data, with the time-to-death post-discontinuation (of BAT) being estimated indirectly from the difference in the area under the two curves, as illustrated in Figure 46 (shaded area).

Figure 46 Illustration of the difference in the area under two curves



Inspired by this approach, we first estimated the mean time alive after BAT discontinuation (post-BAT discontinuation survival) as the difference between the mean OS and the mean time on BAT (accounting for death while on BAT) assuming the following relationship.

$$OS = BAT * p + (BAT + postBAT) * (1 - p)$$

or

$$postBAT = \frac{os - BAT}{1 - p}$$

where :

OS = mean OS

BAT = mean time on BAT

postBAT = mean time alive post-BAT discontinuation

p = proportion of patients dying whilst on BAT

Knowing the mean time alive post-BAT discontinuation, we then made an assumption about the distribution and its shape. In the base case we assumed that the post-BAT discontinuation survival followed a Weibull distribution (with the given calculated mean). An arbitrary shape of 0.63 was chosen as this provided a reasonable visual fit to the OS data. This approach is similar to the approach traditionally used in cohort models where the time alive post-progression is estimated as the area under two curves. However, it was necessary to make an assumption regarding the distribution and shape of the curve. Although this is an unknown, the shape of the curve is likely to have a limited impact on the ICER given that the mean remains unchanged. However, there may be small variations due to discounting. Scenario analyses (Table 60) were conducted assuming different shapes (ranging from –1 to 1).

In order to explore fully the potential impact of this approach, three alternative approaches are presented in scenario analyses (Table 61):

1) OS and time to BAT discontinuation are sampled independently from each other. As previously mentioned this approach ignores the correlation between BAT discontinuation and OS and may create some inconsistencies such that the time to BAT discontinuation may be greater than OS on some occasions (which is not possible). In those circumstances, we adjusted the time to discontinuation down leaving OS unchanged.
2) the same approach as above (OS and time to BAT discontinuation are sampled independently) but in cases of inconsistency the time to death is adjusted upwards with the time to discontinuation unchanged.
3) the time alive post-BAT discontinuation is calibrated (assuming a Weibull distribution) using the Metropolis Hasting algorithm[167] so that the predicted OS matches the observed Kaplan–Meier OS. As this is a scenario analysis and for speed of calculation, the calibration was performed outside the economic model.

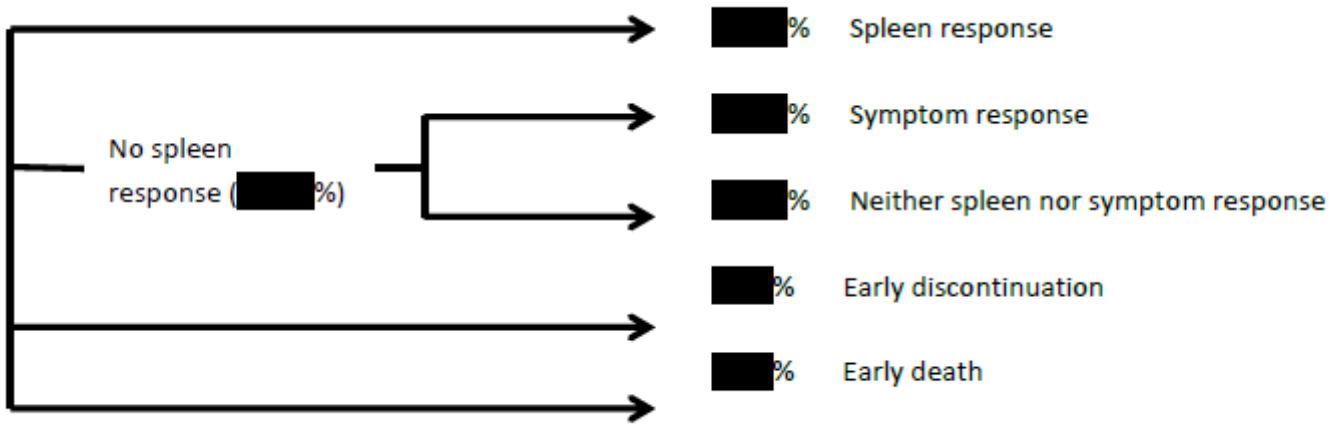
5.3.5 Proportion of patients on ruxolitinib in each of the five outcome categories

Patients initiating ruxolitinib are categorised into five groups according to outcomes at week 24 (Figure 47) as described in section 5.2.2. Data to determine the proportion of patients in each group are taken from COMFORT-II where these data are available (ie spleen response, no spleen response, early discontinuation and early death). Data on symptom response are required to distinguish between patients achieving a symptom response (but no spleen response, ie symptom responders, Group 2) and patients achieving neither a spleen response nor a symptom response (Group 3). In the base case, the definition of symptom response is based on the improvement in symptoms as assessed using the MF-SAF. This instrument was only used in COMFORT-I and hence data from COMFORT-I are used in the base case to determine the proportion of patients achieving a

symptom response (but no spleen response) and the proportion achieving neither a spleen nor symptom response.

The proportion of patients in each of the five outcome categories used in the economic model are summarised below in Figure 47.

Figure 47 Five outcome categories defined for patients receiving ruxolitinib



Data from the COMFORT-II trial were first analysed to calculate the proportion of patients in each of the following four outcome categories as summarised in Table 32:

- patients alive and on treatment at week 24 achieving a spleen response (with or without symptom response) ([redacted]%)
- patients alive and on treatment at week 24 not achieving a spleen response ([redacted]%) according to the base case definition of response. It should be noted that this category includes patients who achieved a symptom response but no spleen response and patients who achieved neither a spleen nor a symptom response.
- patients experiencing early discontinuation prior to week 24 ([redacted]%)
- patients experiencing early death prior to week 24 ([redacted]%)

As described in section 5.2.4, in the base case a spleen response (at week 24) is defined as:

- a reduction ≥ 50% in splenomegaly in patients with a baseline splenomegaly that is palpable at > 10 cm below the LCM

- non-palpable spleen in patients with a baseline splenomegaly that is palpable at 5–10 cm below the LCM

A scenario analysis (Table 62) was conducted for a spleen response defined as a

- reduction ≥ 25% in splenomegaly in patients with a baseline splenomegaly that is palpable at > 10 cm, below the LCM **or**
- non-palpable splenomegaly in patients with a baseline splenomegaly that is palpable at 5–10 cm, below the LCM

Table 32 Distribution of patients in four of the outcome categories in COMFORT-II

	Base case[a]		**Scenario analysis**[b]	
	Number of patients	**% of patients**	**Number of patients**	**% of patients**
Spleen response	[redacted]	[redacted]%	[redacted]	[redacted]%
No spleen response	[redacted]	[redacted]%	[redacted]	[redacted]%
Early discontinuation	[redacted]	[redacted]%	[redacted]	[redacted]%
Early death	[redacted]	[redacted]%	[redacted]	[redacted]%

[a]Spleen response defined as a reduction ≥ 50% in splenomegaly in patients with a baseline splenomegaly that is palpable at > 10 cm below the LCM or non-palpable splenomegaly in patients with a baseline splenomegaly that is palpable at 5–10 cm, below the LCM

[b]Spleen response defined as a reduction ≥ 25% in splenomegaly in patients with a baseline splenomegaly that is palpable at > 10 cm, below the LCM or non-palpable splenomegaly in patients with a baseline splenomegaly that is palpable at 5–10 cm, below the LCM

LCM, left costal margin.

Patients without a spleen response at week 24 may remain on ruxolitinib if they achieved a symptom response. Data from COMFORT-I were analysed in the base case to calculate the proportion of patients achieving a symptom response among those who did not achieved a spleen response at week 24 and the proportion of patients achieving neither a symptom response nor a spleen response at week 24 (Table 33).

As described in section 5.2.4, in the base case a symptom response (at week 24) is defined as:

- ≥ 50% reduction from baseline in MF-SAF TSS, based on data from COMFORT-I

Scenario analyses (Table 62) were conducted for a symptom response defined as a

- ≥ 25% reduction from baseline in MF-SAF TSS, based on data from COMFORT-I,

- Change from baseline in LymS of at least the upper bound of the previously reported MID (ie change ≥ 5.4), based on data from COMFORT-II,
- Change from baseline in LymS of at least the lower bound of the previously reported MID (ie change ≥ 2.9), based on data from COMFORT-II.

Table 33 Proportion of patients achieving a symptom response (according to four definitions of symptom response) amongst patients not achieving a spleen response (according to two different definitions) at week 24

	Neither spleen nor symptom response	**Symptom response but no spleen response**	**Data source**
Spleen response: reduction ≥ 50% in splenomegaly in patients with a baseline splenomegaly that is palpable at > 10 cm, below the LCM or non-palpable splenomegaly in patients with a baseline splenomegaly that is palpable at 5–10 cm, below the LCM			
50% reduction MF-SAF	[redacted]	[redacted]	COMFORT-I
25% reduction MF-SAF	[redacted]	[redacted]	COMFORT-I
Upper MID LymS	[redacted]	[redacted]	COMFORT-II
Lower MID LymS	[redacted]	[redacted]	COMFORT-II
Spleen response: Reduction ≥ 25% in splenomegaly in patients with a baseline splenomegaly that is palpable at > 10 cm, below the LCM or non-palpable splenomegaly in patients with a baseline splenomegaly that is palpable at 5–10 cm, below the LCM			
50% reduction MF-SAF	[redacted]	[redacted]	COMFORT-I
25% reduction MF-SAF	[redacted]	[redacted]	COMFORT-I
Upper MID LymS	[redacted]	[redacted]	COMFORT-II
Lower MID LymS	[redacted]	[redacted]	COMFORT-II

LCM, left costal margin; LymS, lymphoma subscale of the FACT-Lym ; MF-SAF, Myelofibrosis Symptom Assessment Form; MID, minimal important difference.

5.3.6 Duration of exposure to ruxolitinib

In spleen responders

In COMFORT-II, patients could discontinue due to death, AEs, disease progression, withdrawal of consent or loss of efficacy. Disease progression included protocol-defined progressive splenomegaly, defined as an increase in spleen volume of ≥ 25% from on-study nadir (the lowest out of either the baseline spleen volume or the smallest spleen volume measured on study). In the extension phase patients were able to remain on ruxolitinib until the clinician believed patients were no longer deriving a benefit, ie. there were no stipulated criteria for stopping therapy, and therefore the discontinuation rate is more likely to reflect what would happen in clinical practice. Consequently, in the economic analysis, the discontinuation rate from the COMFORT-II trial was used as a proxy for discontinuation of ruxolitinib. The overall discontinuation rate (irrespective of response) was similar in the COMFORT studies[7,26] and in the phase 1/2 study.[39]

Individual patient level data (from week 24 onwards) for time to ruxolitinib discontinuation were analysed for spleen responders (n = 57) from the COMFORT-II trial. A range of parametric survival models (Weibull, exponential, Gompertz, log-normal) was considered (Figure 48). Tested parametric curves showed broadly similar visual fit to the observed data and fit in terms of both the AIC and BIC (Table 34). The Gompertz and Weibull distributions provided similar long-term extrapolation. The exponential distribution had a slightly longer tail while the tail for the log-normal distribution was still longer. The exponential distribution is used in the base case as this provided a slightly better fit to the observed period and a reasonable and plausible long-term extrapolation. Scenario analyses were conducted using other distributions (Table 63).

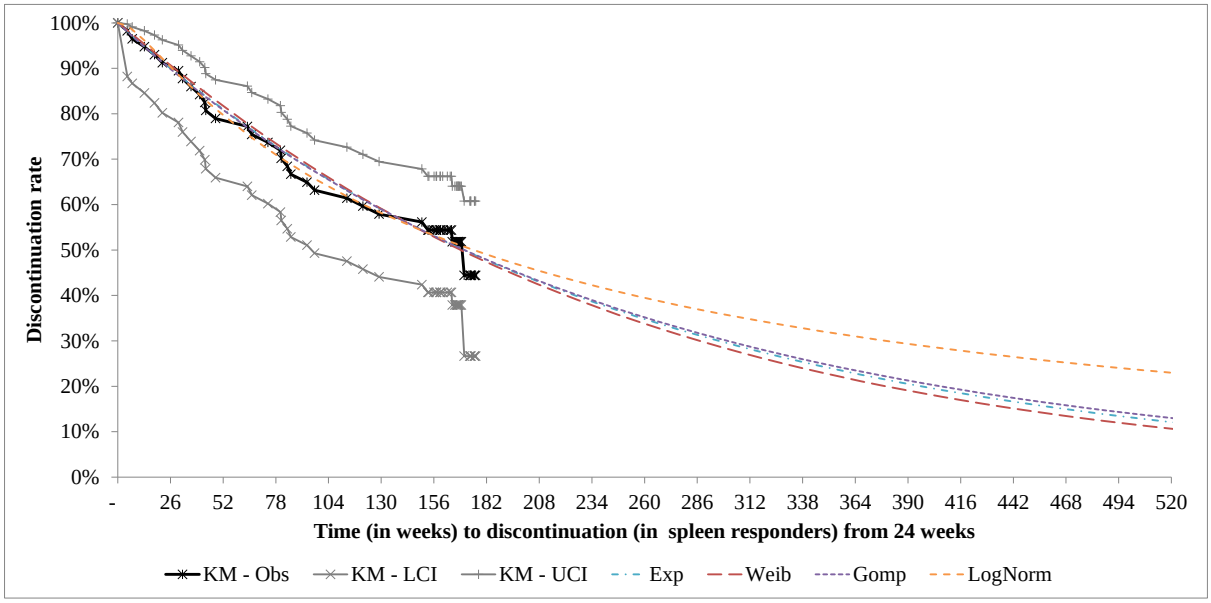
Patients are assumed to move to supportive care following withdrawal from ruxolitinib.

Table 34 Assessment of parametric survival models for time to discontinuation of ruxolitinib in spleen responders (taken from COMFORT-II)

Model	Obs	df	AIC	BIC	Predicted mean (in Weeks)
Exponential	57	1	142.88	144.92	246.30
Weibull	57	2	144.82	148.90	236.20
Gompertz	57	2	144.88	148.97	255.13
Log-normal	57	2	144.29	148.38	515.46

AIC, Akaike information criterion, BIC, Bayesian information criterion; df, degree of freedom; Obs, observations.

Figure 48 Kaplan–Meier curve for time to ruxolitinib discontinuation (in spleen responders at week 24) and fit of selected parametric distributions (taken from COMFORT-II)



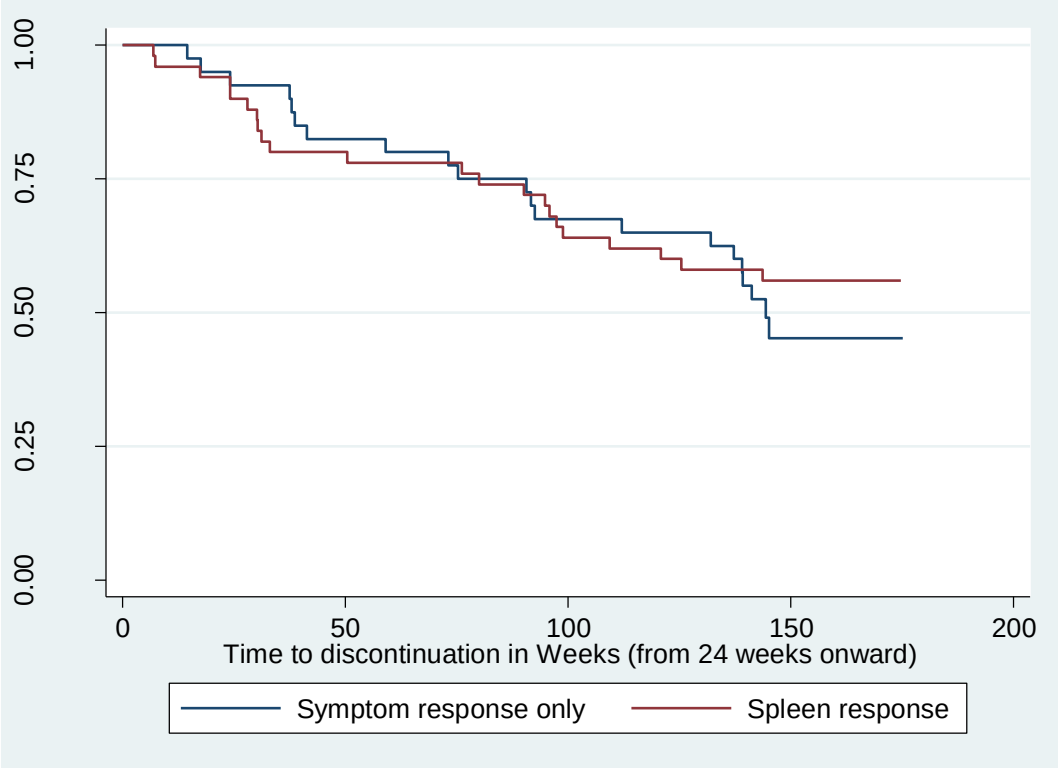
KM, Kaplan–Meier; LCI, lower confidence interval ; Obs, observations; UCI, upper confidence interval .

Data were only available up to about 3.5 years; therefore there are uncertainties with the long-term extrapolation. To explore this uncertainty, scenario analyses (Table 64) were conducted assuming all patients to discontinue treatment at the end of the evidence (3.5 years) and different time points (5, 7.5 and 10 years).

In symptom responders

The discontinuation rate for patients experiencing a symptom response (as measured using the MF-SAF) but not a spleen response is not available from COMFORT-II as the MF-SAF was not used in the trial. Evidence from COMFORT-I indicated that the discontinuation rate for this group of patients compared with patients experiencing a spleen response was relatively similar (HR: 1.17; 95% CI: 0.65 to 2.14; p = 0.60, Figure 49).

Figure 49 Discontinuation rate (from week 24 onwards) in patients achieving a symptom response (but no spleen response) compared with patients achieving a spleen response (with or without symptom response) (taken from COMFORT-I)



Hence, given the uncertainty in this parameter, we assumed that symptom responders have the same discontinuation rate as patients achieving a spleen response.

Patients are assumed to move to supportive care following withdrawal from ruxolitinib.

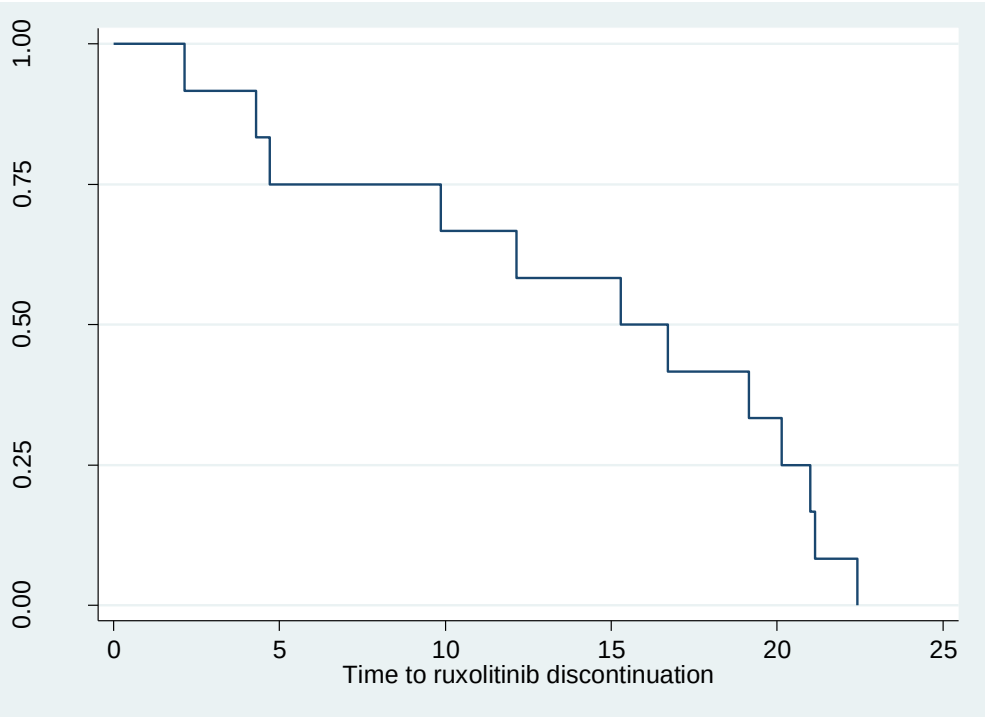
In non-responders

Patients who are alive and on treatment at week 24 and who achieved neither a spleen nor a symptom response (i.e primary non-responders) were assumed to withdraw from ruxolitinib treatment at week 24 as per SmPC and clinical guidelines.[8]

In patients experiencing early discontinuation (prior to week 24)

The Kaplan–Meier curve for the time to ruxolitinib discontinuation (Figure 50) was calculated for these patients from the COMFORT-II trial. As the Kaplan–Meier curve was complete and as this input is used for only a small number of patients, we sampled the time to ruxolitinib discontinuation in patients experiencing early discontinuation directly from the Kaplan–Meier curve. Based on these data, patients experiencing early discontinuation (8.22%) are assumed to be treated for 14.083 weeks (range: 2.143 to 22.43). This parameter is not varied in the PSA.

Figure 50 Kaplan–Meier plot for the time to ruxolitinib discontinuation in patients discontinuing early (before week 24) (taken from COMFORT-II)



In patients experiencing early death (prior to week 24)

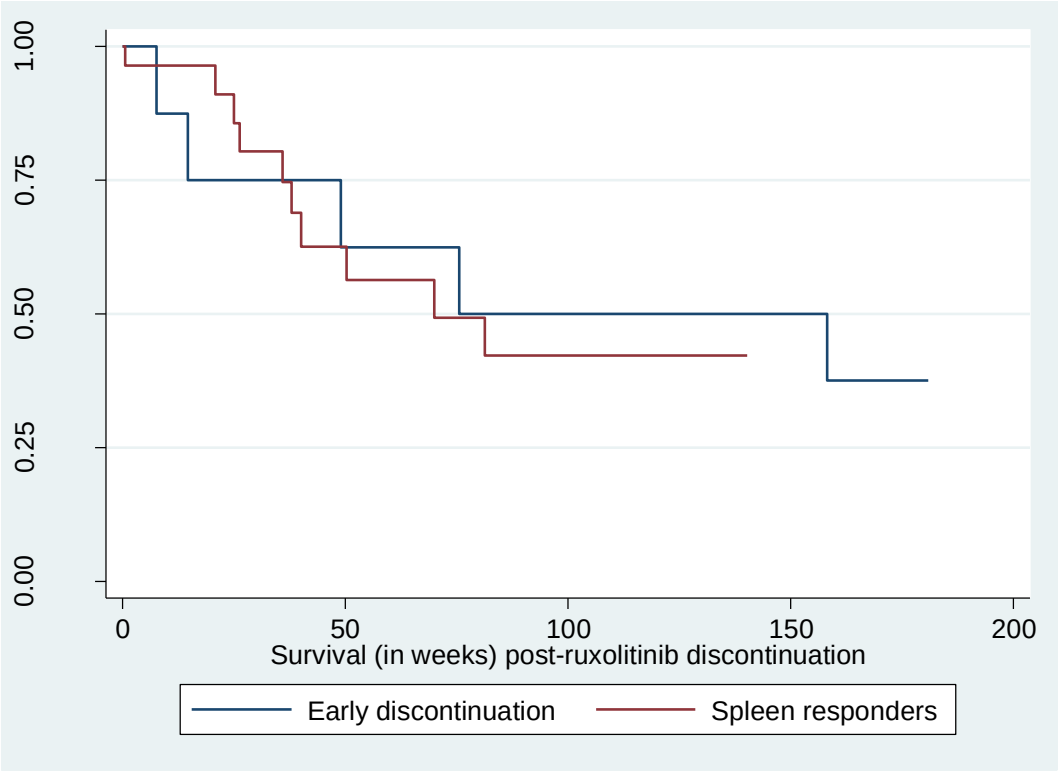
The duration on treatment is sampled from a triangular distribution from the mean, min and max Based on COMFORT-II data, patients experiencing early death (2.05%) are assumed to be treated for 7.857 weeks (range: 1.286 to 19.143).

5.3.7 Survival following discontinuation from ruxolitinib

In spleen responders (Group 1) & patients experiencing early discontinuation (Group 4)

Individual patient level data from the COMFORT-II trial were analysed to estimate the time to death following ruxolitinib discontinuation in spleen responders at week 24 (n=28) and patients experiencing early discontinuation (n=11). Given the small sample size and the absence of differences (HR: 1.08; CI: 0.60 to 1.94; p = 0.790) - between the survival following discontinuation from ruxolitinib for these two groups of patients (Figure 51), data were pooled to increase the statistical power and reduce the uncertainty. For completeness, scenario analyses are conducted using the survival following discontinuation from ruxolitinib from these two groups separately (Table 67).

Figure 51 Survival post-ruxolitinib discontinuation for early discontinuers (Group 4) and spleen responders (Group 1)



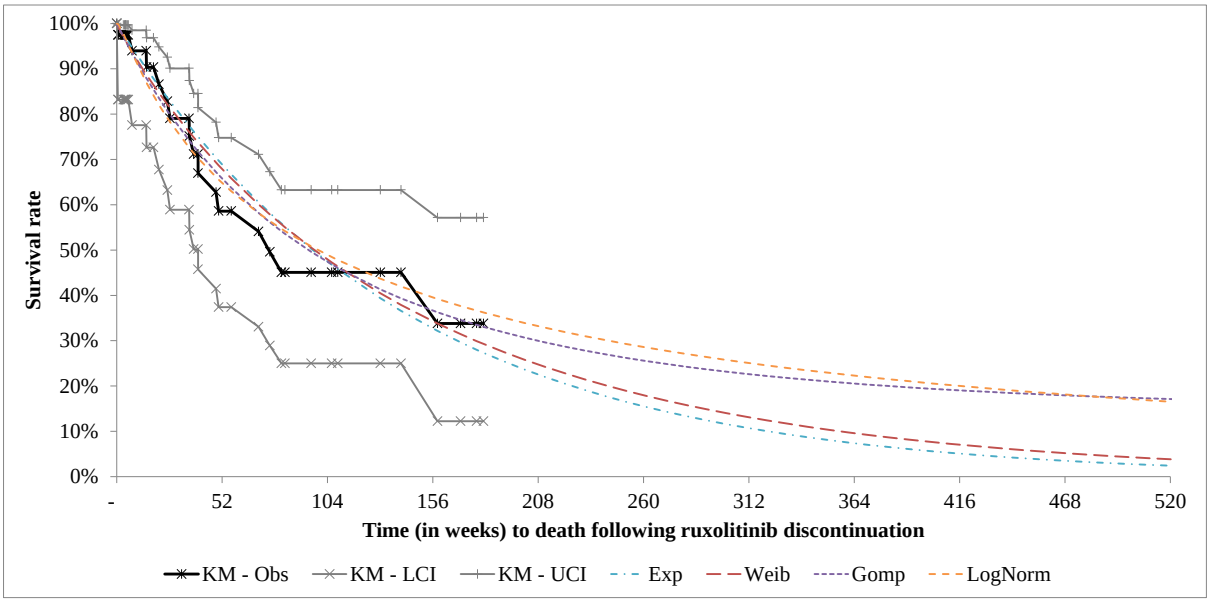
Among the 39 patients who discontinued, none of the patients did so due to death. Thus, in the base case we assumed that no patients would die while on ruxolitinib. Parametric curves (exponential, Weibull, Gompertz, log-normal distributions) were fitted to the observed KM curve (Figure 52)**.** Parametric curves showed broadly similar visual fit to the observed data and fit in terms of both the AIC and BIC (Table 35).

Table 35 Assessment of parametric survival models for post-ruxolitinib discontinuation in patients either achieving a spleen response (Group 1) or early discontinuation (Group 4) (taken from COMFORT-II)

Model	Obs	df	AIC	BIC	Predicted mean (in weeks)
Exponential	39	1	79.29	80.96	139.59
Weibull	39	2	81.15	84.47	150.35
Gompertz	39	2	80.71	84.04	1,555.31
Log-normal	39	2	82.25	85.58	423.45

AIC, Akaike information criterion, BIC, Bayesian information criterion; df, degree of freedom; Obs, observed.

Figure 52 Kaplan–Meier curve for the time to death following ruxolitinib discontinuation in patients either achieving a spleen response (Group 1) or early discontinuation (Group 4) and fit of selected parametric distributions (taken from COMFORT-II)



KM, Kaplan–Meier; LCI, lower confidence interval ; Obs, observations; UCI, upper confidence interval .

The exponential and Weibull distributions provided broadly similar long-term extrapolations. In contrast, the Gompertz and log-normal distributions had longer tails. The exponential distribution was used in the base case as this provided a slightly better fit to the observed period (compared with the Weibull distribution) and a reasonable long-term extrapolation. Scenario analyses were conducted using other distributions (Table 65).

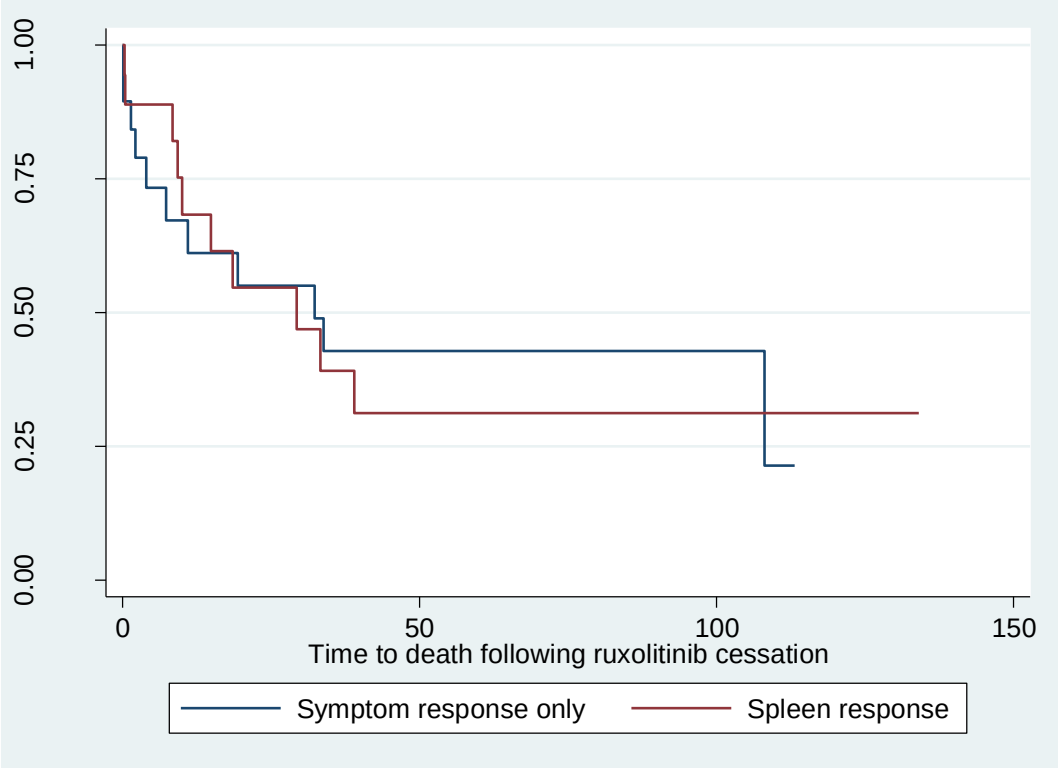
Patients are assumed to remain in supportive care for the rest of their time in the model after discontinuing ruxolitinib.

As for the discontinuation rate, data were only available up to about 3.5 years; therefore there are uncertainties with the long-term extrapolation. To explore this uncertainty, scenario analyses were conducted assuming all patients to die after 3.5, 5, 7.5 and 10 years (Table 66).

In symptom responders

Time to death following ruxolitinib discontinuation in patients experiencing a symptom response but no spleen response is not available from COMFORT-II as the MF-SAF was not used in the trial. Evidence from COMFORT-I indicated that the time to death following ruxolitinib discontinuation for this group of patients compared with patients experiencing a spleen response was relatively similar (HR: 0.99; 95% CI: 0.42 to 2.34; p = 0.98, Figure 53).

Figure 53 Time to death post ruxolitinib discontinuation in patients achieving a symptom response (but no spleen response) versus patients achieving a spleen response (with or without a symptom response) – Taken from COMFORT-I



Hence, given the uncertainty in this parameter, we assumed that symptom responders have the same same survival following ruxolitinib discontinuation as patients achieving a spleen response. Patients are assumed to remain in supportive care for the rest of their time in the model after discontinuing ruxolitinib.

In non-responders

Outcomes for this group of patients are uncertain given the design of the COMFORT-II trial where patients were treated for the whole duration irrespective of achievement of response at week 24. Clinical advisors felt that despite the absence of achievement of response at week 24, these patients may experience an improvement compared to if they were treated with BAT from initiation. Clinical advisors considered it was reasonable to assume a shift in survival of 24 weeks for these patients compared with patients initiating BAT. A scenario analysis was conducted relaxing this assumption (Table 68) assuming the time on ruxolitinib to be part of the time patients would have been treated with BAT.

In patients experiencing early death (prior to week 24)

The duration alive following stopping ruxolitinib is sampled from a triangular distribution from the mean, min and max. Based on COMFORT-II data, patients experiencing early death (2.05%) were assumed to be alive for 1.619 weeks (range: 0.143 to 3.429) following discontinuation from ruxolitinib. Patients were assumed to remain in supportive care for the rest of their time in the model after discontinuing ruxolitinib.

5.3.8 Transformation to acute myeloid leukaemia (AML)

Leukaemic transformation (LT) is an important aspect of the progression and natural history in MF and therefore the economic model attempts to capture its impact. The inclusion of LT is challenging as the effectiveness data used within the model already include patients with LT; therefore including LT as a separate health state could lead to double counting of the effect of LT. Consequently, the inclusion of LT was simplified and the economic model only considered the impact on cost and QALYs.

No evidence of an increased risk of LT with ruxolitinib therapy was observed in the 3-year follow-up of COMFORT-I or COMFORT-II (see section 4.12.5). In the 3-year follow-up of COMFORT-I[25] the rate of LT per person per year was estimated at 1.21%/person-year in patients originally randomised to ruxolitinib and 2.33%/person-year in patients originally randomised to placebo. In COMFORT-II,[23] eight cases of LT (defined as a peripheral blood blast count of 20% or greater, sustained for 8 weeks, or a bone marrow blast count of 20% or greater) were observed: 5 cases (3.4%) in the group of patients originally randomised to ruxolitinib (median duration of follow-up 151 weeks) and 3 cases (4.1%) in the group of patients originally randomised to BAT. An additional event of LT was reported in the safety database as a serious AE in the BAT arm. A re-analysis of the trial estimated the rate of LT per person per year to be 1.42% for patients randomised to ruxolitinib and 2.83% in patients originally randomised to BAT (Table 36).

Table 36 Incidence of LT in COMFORT-II

	Total number of patients	**Total follow-up (years)**	**Number of leukaemia events**	**Rate of LT per 100 years of follow-up**
Ruxolitinib	146	353.34	5	1.42%
BAT	73	141.36	4	2.83%

BAT, best available therapy; LT, leukaemic transformation.

Data from the COMFORT-II trial (Table 36) were used in the base case:

- the rate for patients randomized to BAT (2.83%) was used for patients entering the BAT arm,
- the rate for patients randomized to ruxolitinib (1.42%) was used for patients entering the ruxolitinib arm (until death) who achieve a spleen and/or symptom response (Group 1 & 2), experienced early death (Group 5) or early discontinuation (Group 4).
- we conservatively assumed that primary non-responders (Group 3) experience a reduced risk up to week 24 (1.42%) and then have the same risk as patients randomized to BAT (2.83%).

Of note, the rate from the COMFORT trials may be an under-estimate compared with clinical practice as patients were pre-selected and may therefore have a lower risk of LT.

In the economic model we calculated, for each patient, the probability of experiencing LT over their lifetime. A cost and QALYs decrement was applied to patients predicted to experience a LT event.

Scenario analyses are conducted assuming the same rate of LT (this is pessimistic) or excluding LT from the model (Table 69).

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

The NICE methods guide[150] stipulates that data obtained using the EQ-5D preference-based measure is the preferred choice for use in economic evaluations when available, although other preference-based instruments (such as the Short-Form Health Survey-6D - SF-6D, the Health Utilities Index – HUI or other condition specific measure) may be used in submissions if generic utility data are not available or appropriate. In addition, when utility data from generic validated instruments are not available, then methods can be used to estimate EQ-5D utility data by mapping (also known as 'cross-walking').

The COMFORT-I and II trials[7,26] did not include a generic measure of HRQoL. However, the EORTC QLQ-C30 and modified MF-SAF v2 were used in COMFORT-I,[26] and COMFORT-II[7] included the EORTC QLQ-C30 and FACT-Lym. Mapping algorithms between EORTC QLQ-C30 and EQ-5D are available.[168-171] For instance, Roskell et al (2012)[172] reported results from a mapping exercise of the EORTC QLQ-C30 to the EQ-5D from the COMFORT trials using the McKenzie algorithm.[169] It is also possible to derive a preference-based measure from the EORTC QLQ-C30 (the EORTC-8D).[173]

Although mapping algorithms are available between the EQ-5D and EORTC QLQ-C30, evidence from the psychometric analyses (described below) indicates that the performance of the EQ-5D and EORTC QLQ-C30 in MF is of concern.[49,50] As a result, a condition-specific preference-based measure

for MF, the MF-8D, was developed using appropriate existing measures, the MF-SAF and EORTC QLQ-C30 (described below).[51]

Lack of appropriateness of EQ-5D in MF

The lack of appropriateness of the EQ-5D in some cases is recognised within the NICE methods guide.[150] It is stated that: *"in some circumstances the EQ-5D may not be the most appropriate. To make a case that the EQ-5D is inappropriate, qualitative empirical evidence on the lack of content validity for the EQ-5D should be provided, demonstrating that key dimensions of health are missing. This should be supported by evidence that shows that EQ-5D performs poorly on tests of construct validity and responsiveness in a particular patient population. This evidence should be derived from a synthesis of peer-reviewed literature. In these circumstances alternative health-related quality of life measures may be used and must be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values."* In line with this guide, psychometric analyses of EQ-5D and EORTC QLQ-C30 were carried out.[49,50]

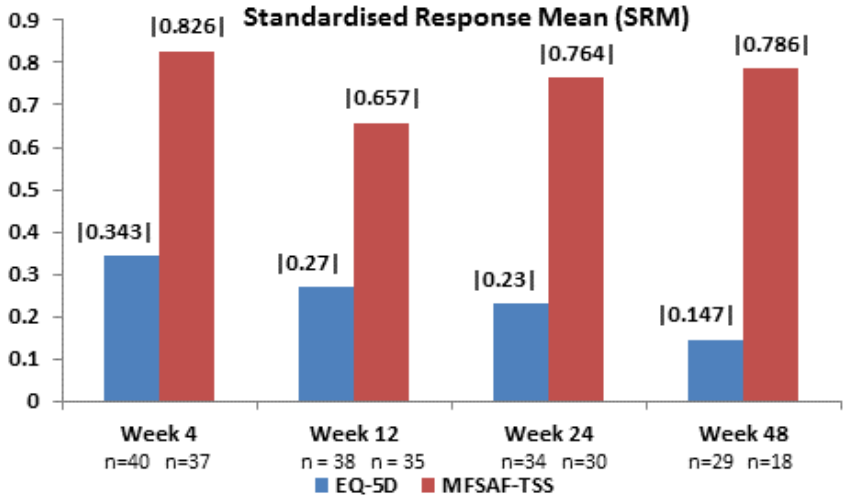
The modified MF-SAF v2 (hereafter referred to as MF-SAF) has been validated in MF and therefore can be used to assess the performance of the EQ-5D in this population. The MF-SAF includes the following symptoms: 'worst itchiness', 'worst night sweat', 'worst abdominal pain', 'worst bone and muscle pain', 'worst pain under the ribs' and 'worst satiety' (feeling of fullness). In order for the EQ-5D to be appropriate, the measure should be associated with key symptoms in MF captured by the MF-SAF, both at baseline and over time. Of note, generic measures such as the EQ-5D may not reflect symptom effects to the same degree as the condition-specific measure, but there should be evidence that they capture the impact of these symptoms.

The ROBUST study[53] collected data on both EQ-5D (5 levels) and MF-SAF in a small sample of patients (n = 48) with repeated measurement over 48 weeks (baseline, weeks 4, 12, 24 and 48) (see section 4.11.1). The appropriateness of the EQ-5D in the MF population was examined in terms of the psychometric criteria of convergent validity and responsiveness of the EQ-5D relative to the MF-SAF. The specific tests examined whether the EQ-5D was related to MF-specific symptoms (convergent validity) and reflected changes in symptoms over time (responsiveness).[49] Details and results of this study have recently been presented at the ISPOR 20th Annual International Meeting, May 2015.

A large proportion (15.56%) of patients reported no problems in all 5 EQ-5D dimensions at baseline. The MF-SAF total score did not show a comparable ceiling effect (4.76%). The exploratory analysis suggests that the EQ-5D preference based and health dimensions had poor association with key symptoms in MF, except for the 'pain/discomfort' and 'anxiety/depression' health dimensions in some respect. The correlation between the EQ-5D preference-based (and all EQ-5D health dimensions) and night sweat and itchiness was weak (<|0.3|). The correlation of the EQ-5D health dimensions with other symptoms from the MF-SAF were weak to moderate (<|0.5|) with the exception of the

correlation between the EQ-5D pain/discomfort health dimension and abdominal discomfort and EQ-5D usual activities health dimension with feeling of fullness. Although the EQ-5D captured some changes, these changes were much smaller than when assessed using the MF-SAF. The standardised response mean (SRM) for the EQ-5D preference based was small (<|0.5|). In comparison the SRM for the MF-SAF total score was large (>|0.8|) at 4 weeks indicating that participants had large improvement in MF key symptoms at week 4. The SRM remained small for the EQ-5D whilst the SRM for the MF-SAF was medium (close to large) at week 12, 24 and 48 (Figure 54)

Figure 54 Standardised response mean for the change in EQ-5D and MF-SAF from the ROBUST UK study



EQ-5D, 5-dimension European Quality of Life questionnaire; MF-SAF, Myelofibrosis Symptom Assessment Form

Overall, the psychometric analysis provides evidence that the EQ-5D performs poorly on tests of construct validity (the EQ-5D measures' ability to capture the effect of key symptoms in MF is limited to pain rather than the specific MF symptoms such as night sweat, itchiness), and responsiveness in MF (smaller changes assessed using the EQ-5D); however, this conclusion needs to be interpreted in the context of the small number of patients included in the analysis (n = 48).[49]

Analysis of the EORTC QLQ-C30 in MF

Results from the psychometric analysis of the EQ-5D are supported by an examination of the appropriateness of the EORTC QLQ-C30 for MF in a larger sample of MF patients in terms of the psychometric criteria of acceptability, convergent validity, known group validity and responsiveness of the EORTC QLQ-C30 relative to the MF-SAF and FACT-Lym using data from the COMFORT trials.[50] Specific tests examined whether the EORTC QLQ-C30: (a) is related to MF-specific symptoms (convergent validity) and is able to distinguish between severity groups (known group validity) and (b)

is able to reflect changes in symptoms over time (responsiveness). Details and results of this study have recently been presented at the ISPOR 20th Annual International Meeting, May 2015.

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The psychometric analysis provides evidence that some of the EORTC dimensions (ie physical, role, cognitive and social functioning, fatigue, pain, dyspnoea and appetite loss) reflect the effect of MF particularly when considering overall functioning. However, the EORTC dimensions were not associated with MF-specific items of itching and night sweats and did not reflect the changes in these and other MF-specific symptoms over time. The QLQ-C30 dimensions (physical, role, emotional and social functioning, pain and fatigue) were strongly correlated (ρ >|0.5|) with equivalent items/dimensions in the MF-SAF and FACT-Lym but all QLQ-C30 dimensions were weakly correlated (ρ <|0.3|) to MF symptoms such as weight loss, itching and night sweats. SRMs were < |0.2| for most QLQ-C30 dimensions including pain but > |0.2| for MF-SAF and FACT-Lym MF symptoms. The QLQ-C30 pain dimension showed less responsiveness than the MF-specific pain dimensions. A large proportion of patients (> 50%) reported no problems (i.e. ceiling effects) in several QLQ-C30 dimensions (nausea/vomiting, constipation/diarrhoea). There was some evidence of ceiling effects in MF symptoms in COMFORT-II due to missing data, which affected the analysis.[50]

Result from this analysis suggests that EORTC QLQ-C30 does not reflect all the relevant symptoms in patients with MF.

Development of the MF-8D, a condition-specific, preference-based measure for MF

A condition-specific preference-based measure for MF, the MF-8D, was developed to overcome the concerns related to using the EQ-5D and EORTC QLQ-C30.[49,50] This involved using appropriate existing measures, the MF-SAF and EORTC QLQ-C30. The development of the measure followed five stages.

1. psychometric and factor analyses determined the dimensions of the health state classification system.
2. psychometric and Rasch analyses selected an item to represent each dimension.
3. the item selection was validated using a different time point in the available dataset and using clinical input.
4. a selection of health states was valued by members of the general population using time trade-off (TTO) using face-to-face interviews.
5. health state values were modelled using regression analysis to produce utility values for every state.

The resulting MF-8D has eight dimensions:[51]

- physical functioning (from EORTC QLQ-C30),
- emotional functioning (from EORTC QLQ-C30)
- fatigue (from EORTC QLQ-C30),

- itchiness (from MF-SAF),
- pain under ribs on the left side (from MF-SAF),
- abdominal discomfort (from MF-SAF),
- bone or muscle pain (from MF-SAF), and
- night sweats (from MF-SAF).

The first three dimensions were derived from the EORTC QLQ-C30 and have four or five severity levels, and the remaining five dimensions were derived from the MF-SAF and have two severity levels: absent or worst imaginable.

Regression models were estimated using TTO data from 246 members of the general population valuing a total of 33 states. The best performing model was a random effects maximum likelihood model producing utility values ranging from 0.089 to 1. Two methods were used to enable utility weights to be generated for all possible responses to the MF-SAF dimensions on the 0 to 10 range: firstly assuming equal weighting for all responses and secondly using the results of the Rash analyses.

A manuscript describing the development of the MF-8D has been submitted for publication to Value in Health (available AiC).[51]

Using the MF-8D v1 (assuming equal weighting), the mean score at baseline was [redacted] (n = 233) for all patients randomised in COMFORT-I. The mean MF-8D v1 score at baseline was [redacted] in patients randomised to placebo (n = 112) and [redacted] in patients randomised to ruxolitinib (n = 121). At week 24, the mean MF-8D v1 score was [redacted] in patients randomised to placebo (n = 90) and [redacted] in patients randomised to ruxolitinib (n = 120).

5.4.2 Mapping

Roskell et al (2012)[172] reported results from a mapping exercise of the EORTC QLQ-C30 to the EQ-5D from the COMFORT trials using the McKenzie algorithm.[169] Although other mapping algorithms are available between the EORTC-QLC 30 and EQ-5D, results from the trials were not mapped to estimate the EQ-5D as it was shown that the EQ-5D lacked content validity in MF and performs poorly on tests of construct validity and responsiveness in MF (see section 5.4.1).

5.4.3 Health-related quality-of-life studies

A systematic review (SR) of the literature was performed to identify existing studies of HRQoL data in patients with MF. The first literature review was performed to support a previous NICE STA,[116] and searches were performed on 27 July 2011 and an update was performed on 19 March 2012. A

second SR performed to support this submission aimed to replicate these original search strings to identify the more recent evidence. A date limit from January 2012 to December 2014 was applied. Details of the electronic searches performed and the resulting hits for both SRs are provided in Section 8 Appendix 13.

The 2011/2012 SR identified two references reporting results for the impact of ruxolitinib on HRQoL in COMFORT-I and –II. These results are described in section 4.7.3. Five additional references were identified, describing four non-RCT studies which report HRQoL data in patients with MF. Two reported the effects of ruxolitinib on HRQoL based on COMFORT-II[174] or the phase 1/2 trial,[175] two report the impact of MF on HRQoL[11,15] and are described in section 3.2.1, and described HRQoL in patients with myeloid metaplasia who underwent splenectomy for transfusion-dependent anaemia, thrombocytopenia, abdominal swelling and pain.[176]

The 2012/2014 SR identified 17 references (see Section 8 Appendix 13, for a summary of all studies). Seven references reported on the humanistic burden of MF irrespective of treatment and the findings of these studies are described in section 3.2.1. Six references reported data from COMFORT-I or COMFORT-II and the results are described in section 4.7.3. Four further studies report the effects of treatment with pomalidomide,[177,178] the impact of cytoreductive therapies on pruritus,[179] and HRQoL following ASCT.[180] A further study was noted which reported the results of a phase 3 placebo-controlled trial of the investigational therapy, fedratinib, a JAK2-selective inhibitor, in patients with MF.[181]

Apart from the study of Roskell et al,[172] discussed in section 5.4.1, none of these studies provided utility data that could be used in the economic analysis.

5.4.4 Adverse reactions

Results of the phase 3 RCTs[23,25,130] and phase 1/2 study[39] demonstrated that ruxolitinib is generally well tolerated in patients with PMF, PPV-MF and PET-MF and that ruxolitinib has a safety profile comparable to that of BAT (see section 4.12). As changes in HRQoL were taken directly from the trial, the decrement in HRQoL associated with AEs and transfusion requirement is already implicitly included within the economic analysis.

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

Utilities used in the model

Table 37 summarises HRQoL values (baseline and changes) used within the economic model in patients treated with ruxolitinib, BAT and on supportive care.

Table 37 Summary of utility values used in the cost-effectiveness analysis

	Utility value: mean (standard error)	**Standard error**	**Source**	**Comment / justification**
Baseline HRQoL				
Unadjusted baseline	[redacted]	[redacted]	COMFORT-I	
Adjustment applied to baseline	0			The quality of life of patients in COMFORT-I is likely to be underestimated. No adjustment assumed in the base case
Change in HRQoL				
On BAT				
• in patients treated with BAT	0		assumption	Disease assumed to be temporarily controlled whilst on BAT
On ruxolitinib				
• change in HRQoL at week 4 in patients achieving a spleen (Group 1) and or symptom response (Group 2)	+[redacted]	[redacted]	COMFORT-I	The change in HRQoL at week 4 is maintained until ruxolitinib discontinuation. Long-term evidence suggests that the initial improvements in spleen length and MF-SAF-TSS happen as early as week 4 and are maintain over time.
• change in HRQoL at week 4 in patients achieving neither a spleen nor a symptom response (Group 3 - 5)	+[redacted]	[redacted]	COMFORT-I	
On supportive care				
• every 24 weeks	−[redacted]	[redacted]	COMFORT-I	
Events (decrement in QALYs)				
• AML	0.15		assumption	

BAT, best available therapy; HRQoL, health-related quality of life. MF-SAF, Myelofibrosis Symptom Assessment Form.

In the base case, HRQoL was measured using the MF-8D v1 (assuming equal weighting) as this relied on fewer assumption than the Rasch analysis.[51] A scenario analysis was conducted using the MF-8D v2 (Table 70). For completeness, a scenario analysis was also conducted using EQ-5D data from the ROBUST study[53] (Table 70).

Baseline HRQoL

The baseline utility value used in the economic model was assumed to be [redacted] based on the mean baseline MF-8D in COMFORT-I. Although patients enrolled in the two COMFORT trials are broadly similar, patients in COMFORT-I had to be resistant or refractory to, intolerant of, or, in the investigator's opinion, not candidates for available therapy, suggesting that the population may have had slightly more severe symptoms and a worse HRQoL compared with patients enrolled in COMFORT-II. In addition, patients in COMFORT-I had larger spleens (by length and volume) as well as worse ECOG performance at baseline. Hence, it may be possible that the baseline utility value in COMFORT-I is underestimated. A sensitivity analysis (Figure 72) is conducted assuming the utility values in COMFORT-I to be under-estimated by a factor of 5%.

Evidence from the general population using the EQ-5D indicates that HRQoL decreases with advanced age. It is unclear how the HRQoL in MF is affected by advanced age. Utility values from COMFORT-I at baseline were analysed by age group in order to determine whether the baseline utility value would be affected by age (Figure 55). There was no evidence that the baseline utility value would be affected with advanced age. Consequently, the baseline utility value was assumed to remain constant over time.

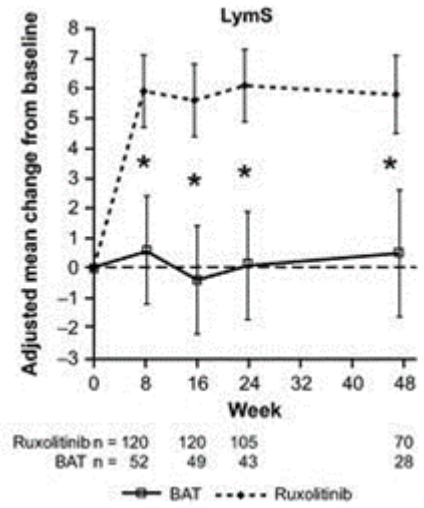
Figure 55 MF-8D by age group at baseline in COMFORT-I

On BAT

To date, there are no MF-SAF data for patients with MF treated with BAT. Although Mesa et al (2013)[34] reported similar outcomes for patients treated with BAT or placebo according to EORTC QLQ-C30 scores and spleen response (when comparing the two control groups of COMFORT-I and COMFORT-II), assuming the HRQoL on BAT to be the same as for placebo is likely to be pessimistic and therefore unfavourable to the BAT arm. The absence of a difference may be attributable to the lack of ability of the EORTC QLQ-C30 to capture changes in symptoms and HRQoL. A more realistic assumption is that some patients initiating BAT may experience some improvement in their HRQoL through symptom control while others may experience a deterioration in HRQoL. Therefore on average, the HRQoL is expected to remain unchanged as observed in COMFORT-II where no statistically significant changes in HRQoL were observed when assessed using the FACT-Lym (Figure 56).[35] Although this is a slightly different population to MF, the absence of improvement in disease status is also supported by recent evidence in PV in patients treated with BAT.[182]

In the base case analysis, HRQoL for patients on BAT was assumed to remain unchanged. This may be an optimistic assumption (ie conservative with respect to ruxolitinib). A range of sensitivity analyses (Figure 72) and scenario analyses (Table 71) were conducted assuming patients on BAT experience a deterioration or an improvement in HRQoL.

Figure 56 Adjusted mean change in LymS scores from baseline over time in COMFORT-II



BAT, best available therapy; LymS, lymphoma subscale of the FACT-Lym; QoL, quality of life.
Harrison et al 2013[35]

On ruxolitinib

After adjustment (for age, treatment & outcome group, risk category, gender, spleen and MF-SAF), the mean improvement in MF-8D v1 at week 24 was calculated to be;

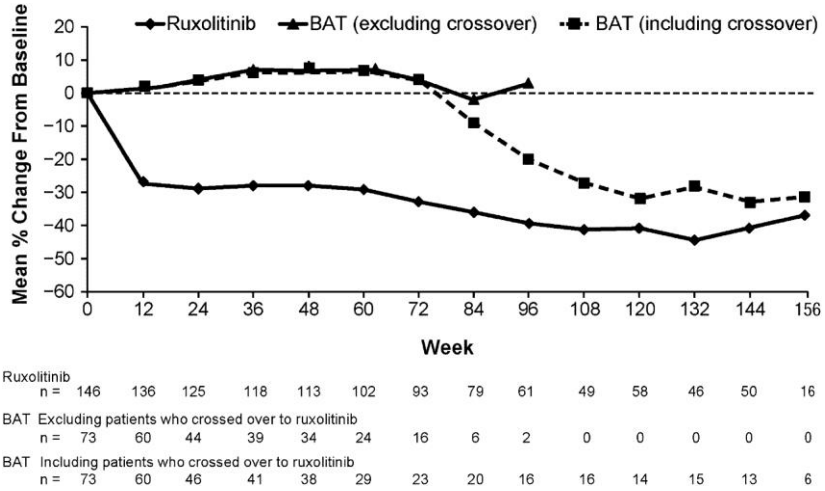
- +[redacted] in patients initiating ruxolitinib achieving neither a spleen response nor a symptom response (n = [redacted]),
- +[redacted] in patients (n = [redacted]) initiating ruxolitinib achieving a spleen or a symptom response.

Data on the change in HRQoL were only available at week 24. Evidence from the pivotal trials suggests that patients receiving ruxolitinib experience benefits as early as 4 weeks (Figure 57) and maintain a similar (or greater) level of improvement at week 24. Consequently, we assumed in the base case that the improvement in HRQoL is experienced as early as week 4. Scenario analyses were undertaken assuming the gain in HRQoL to occur at weeks 8, 12, 16, 20 or 24.

Responders continuing on ruxolitinib

Patients who achieve a response (spleen and/or symptoms) at week 24 remain on treatment. Evidence suggests that HRQoL benefits are sustained in patients who remain on ruxolitinib. Data from COMFORT-I demonstrated that patients originally randomised to ruxolitinib who continued on therapy experienced durable improvements in the Global Health Status /HRQoL and functional domains of the EORTC QLQ-C30.[26] Similarly, evidence from COMFORT-II demonstrated that on average patients on ruxolitinib experienced durable improvements in spleen volume after week 24 (Figure 57).[23]

Figure 57 Mean percentage change in spleen volume over time

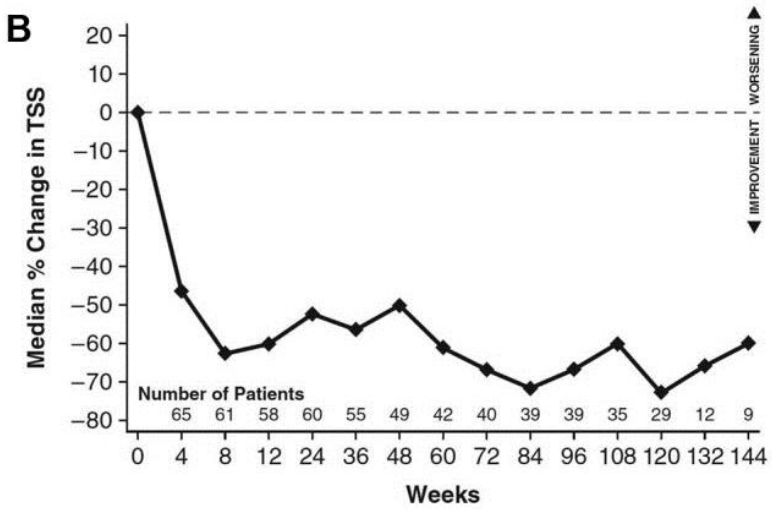


BAT, best available therapy

Cervantes et al., 2013[23]

Furthermore, evidence from the phase 1/2 study demonstrated that patients initiating ruxolitinib who continued on therapy maintained (on average) a similar (or greater) level of improvement in MF-SAF TSS after week 24 (Figure 58).[39] These long-term trends implicitly take into account loss of response as these are averages calculated for patients experiencing disease progression, stable disease or an improvement in disease status. Consequently, for the base case analysis, we assumed that patients on average maintain their initial gain in HRQoL until discontinuation from ruxolitinib therapy.

Figure 58 Effect of ruxolitinib on myelofibrosis symptoms for patients in the phase 1/2 study

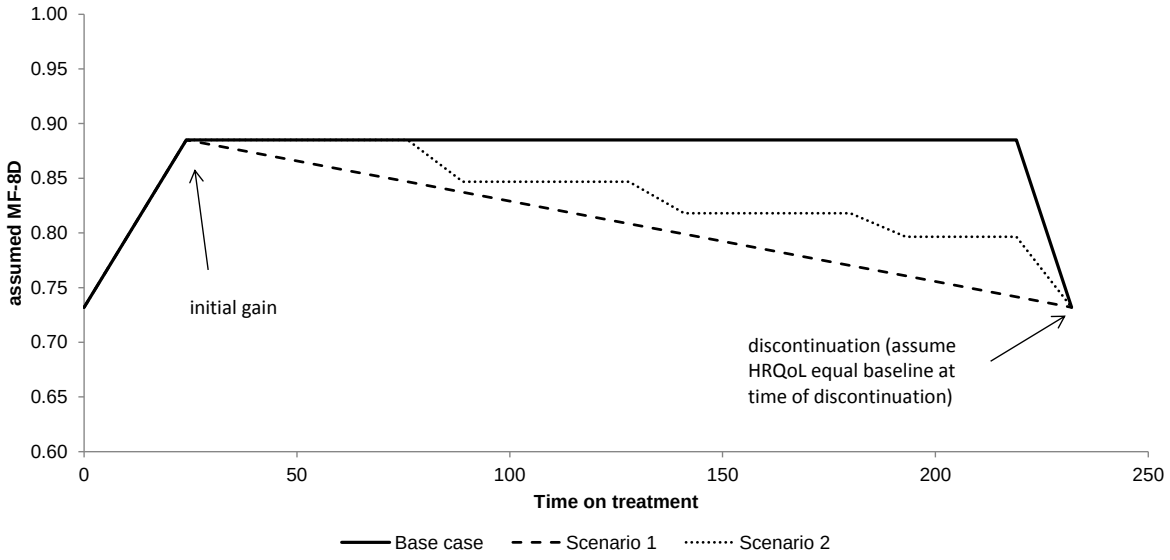


TSS, total symptom score,

Verstovsek et al. 2012[39]

An extreme scenario analysis (scenario 1 in Figure 59 below) is conducted assuming that patients lose the initial gain in HRQoL over time until the point of discontinuation (Table 75). In this scenario, we assumed that the initial gain in HRQoL is linearly lost until returning to baseline level at the time of discontinuation. This is a very pessimistic case and not supported by the data and is presented for completeness. A second scenario analysis (scenario 2 in Figure below) is conducted assuming patients to lose 25% of the gain every year (up to 6 years). Again, this scenario is pessimistic and is presented for completeness.

Figure 59 Example of scenario analyses assumptions

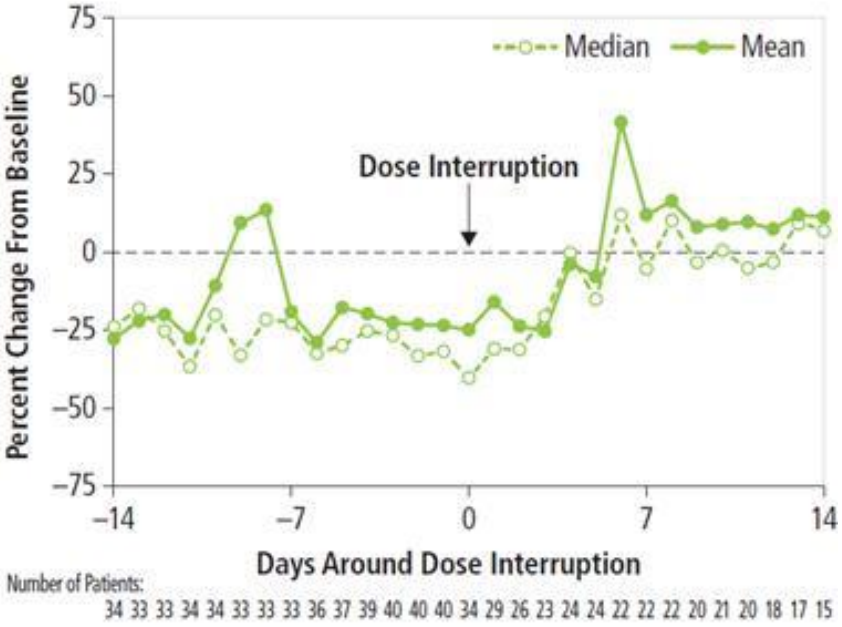


Change in HRQoL on discontinuing ruxolitinib

Non-responders at week 24 withdraw from therapy and an assumption is made regarding the level to which the symptoms and HRQoL return following stopping ruxolitinib. Similarly responders at week 24 could discontinue treatment at any time. Evidence suggests that after interruption of ruxolitinib treatment, symptoms (based on MF-SAF TSS) returned to baseline levels (on average) within approximately 7 days (Figure 60).[183]

Consequently, in the base case we assumed that the initial gain in HRQoL experienced on treatment initiation would be lost and that the HRQoL would return to baseline levels a week after discontinuing treatment. This may be a conservative assumption as, according to clinical experts, it may take longer for HRQoL to return to the baseline level. Assuming that HRQoL returns to the level it would have been if patients had been on supportive care throughout the treatment period (as typically examined within economic model for RA[159]) is likely to be very pessimistic and implausible and is not supported by the data. Hence such scenario was not considered relevant and was not explored.

Figure 60 Return of symptoms after ruxolitinib dose interruption



Verstovsek et al. 2012[183]

On supportive care

Once patients enter supportive care, they are assumed to experience progressive worsening of their disease status and HRQoL until death. Patients in COMFORT-I[26] had to be resistant or refractory to, intolerant of, or, in the investigator's opinion, not candidates for available therapy. This population thus corresponds to patients receiving supportive care. The change in HRQoL over the course of the study in the placebo group was therefore used as a proxy for the change in HRQoL whilst on supportive care.

After adjustment (for age, treatment & outcome group, risk category, gender, spleen and MF-SAF), the mean change in MF-8D at week 24 was calculated to be –[redacted] in patients receiving placebo. The adjusted change at week 24 was extrapolated over a lifetime horizon given patients on supportive care experience a progressive worsening of their disease status and HRQoL until death. Scenario analyses were conducted assuming the progression of HRQoL to be halved after 24, 48 or 72 weeks (Table 72).

Decrement in QALYs associated with transformation to AML

Evidence suggests that patients with AML have a significantly reduced survival and HRQoL. Mesa et al (2005)[16] reported that the median survival following transformation to leukaemia was 2.7 months (95% CI: 1.6 to 3.6). Evidence on the decrement in HRQoL associated with AML is scarce. In the economic analysis, we assumed that patients with AML have a decrement in HRQoL of [redacted] (based on

the difference between the baseline utility value used in the economic model and assuming the utility value with AML to be 0.257 as used in Tolley et al, 2010[184]) lasting 3.90 months on average (assuming the survival is exponentially distributed) leading to a decrement of 0.15 QALYs per AML event. Variation in this parameter was examined in sensitivity analysis (Figure 72).

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

The systematic literature review described in section 5.1 sought to identify references reporting resource use for the management of MF. No sources relevant to the UK were identified (see Section 8 Appendix 14).

5.5.2 Intervention and comparators' costs

The daily (weekly) treatment costs for patients treated with ruxolitinib, BAT and supportive care (excluding monitoring) were estimated to be £113.33 (£793.30), £4.34 (£30.37) and £0.17 (£1.18), respectively. Calculations are detailed below and include drug costs only. We assumed that no resource was required to administer the treatment (ie no administration costs are included). Monitoring costs (e.g. additional tests, consultations other than routine follow-up) are included separately.

Calculation of the weekly treatment costs for patients treated with ruxolitinib

Drug acquisition cost

The starting dose for ruxolitinib is 20 mg twice daily (bid) for patients with a platelet count of > 200,000/mm^3, 15 mg bid for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 5 mg bid for patients with a platelet count between 50,000/mm^3 and < 100,000/mm^3 according to the SmPC[21] and dosage used in the COMFORT studies.[7,26] Doses may be increased, reduced or interrupted if deemed appropriate.

Acquisition costs are provided below in Table 38.

Table 38 List price of ruxolitinib

Dose	Number of tablets per pack	Price per pack (NHS list price)
Ruxolitinib 5 mg	56	£1,680
Ruxolitinib 10 mg	56	£3,360
Ruxolitinib 15 mg	56	£3,360
Ruxolitinib 20 mg	56	£3,360

In the previous NICE appraisal, the Appraisal Committee recognized that a dose-intensity adjustment for ruxolitinib may be appropriate and that savings could be realised in clinical practice.[155] Consequently, the drug acquisition cost of ruxolitinib was calculated to account for this dose-intensity adjustment.

Although a typical approach in economic models is to calculate the drug costs based on the mean daily dosage (about 30 mg/day) and cost per mg, this approach is inappropriate in this case because (a) tablets cannot be split and (b) the differences in cost per mg according to the size of the tablet used (£6/mg using the 5 or 10 mg tablet, £4/mg using the 15 mg tablet, £3/mg using the 20 mg tablet, Table 39). Using such an approach, the daily cost could range from £90 to £180.

Consequently, a more robust approach was used to account for the cost structure of ruxolitinib.

- Step 1: Individual patient level data from the COMFORT-II trial were first obtained to calculate the number of days patients received the different dosages (range 0 to 25 mg bid/ qd) over the trial duration (see Table 40),
- Step 2: We assumed that the minimum number of tablets would be prescribed, e.g. two 15 mg tablets would be given instead of six tablets of 5 mg for patients requiring 15 mg bid,
- Step 3: We calculated the cost of ruxolitinib by multiplying the dosage received (Step 1) by the number of tablets received and respective costs (Step 2).

Such an approach accounts for both dose reductions and interruptions and reflects the dosage used in the COMFORT-II trial from which the efficacy data are taken.

Table 39 Cost per tablet

Dose	Cost per tablet
Ruxolitinib 5 mg	£30
Ruxolitinib 10 mg	£60
Ruxolitinib 15 mg	£60
Ruxolitinib 20 mg	£60

Table 40 Number of days treated with different dosage in COMFORT-II and assumption on costing used in the economic model

Dosage received in COMFORT-II	Number of days patients are treated with different dosage	Proportion of days treated with the different dosage	Assumption[a]	Cost per day according to dosage
Missing	41			
0 mg	1,757	1.38%	None	£0
10 mg bid	32,917	25.93%	2 x 10 mg	£120
10 mg qd	167	0.13%	1 x 10 mg	£60
15 mg bid	25,565	20.14%	2 x 15 mg	£120
15 mg qd	199	0.16%	1 x 15 mg	£60
20 mg bid	38,911	30.66%	2 x 20 mg	£120
20 mg qd	218	0.17%	1 x 20 mg	£60
25 mg bid	8,553	6.74%	2 x 20 mg + 2 x 5 mg	£180
25 mg qd*	65	0.05%	1 x 20 mg + 1 x 5 mg	£90
35 mg qd	78	0.06%	1 x 20 mg + 1 x 15 mg	£120
5 mg bid	18,409	14.50%	2 x 5 mg	£60
5 mg qd	85	0.07%	1 x 5 mg	£30

[a]It should be noted that in the COMFORT studies, only the 5 mg tablets were available. Ruxolitinib is currently available as 5, 10, 15 or 20 mg tablets.

bid, twice daily; qd, once daily.

We estimated the cost per day (week) to be £113.33 (£793.30), taking into account dose interruptions/reductions. While we expect treating physicians to minimise the cost (and number of tablets prescribed), it is possible to achieve a 25 mg dose by giving one 10 mg tablet and one 15 mg tablet, leading to a higher cost (compared to one 20 mg tablet and one 5 mg tablet). A sensitivity analysis (Figure 72) was conducted assuming that 50% of patients on the 25 mg dosage receive a tablet of 10 mg and a tablet of 15 mg.

Administration

Ruxolitinib is administered orally. Therefore, no additional resource is required to administer the treatment (no administration cost).

Monitoring

Patients with MF are regularly monitored by their consultants throughout the course of the disease. The SmPC[21] specifies that, for patients treated with ruxolitinib, a complete blood cell count, including a WBC count differential, must be performed before initiating therapy and patients should be monitored every 2–4 weeks until doses are stabilized, and then as clinically indicated. The Royal Surrey County Hospital NHS Foundation Trust[185] and London Cancer Alliance[186] recommend the following monitoring: full blood count to be monitored every 2–4 weeks until the dose is stabilized, then every 2–3 months; liver function, urea and electrolytes to be monitored monthly initially, then every 3–6 months. The monitoring assumed in the economic model is summarised in Table 41.

Table 41 Monitoring for patients treated with ruxolitinib: economic model assumptions

Test	Frequency
Outpatient visits and laboratory tests (FBCs, LFTs and U&Es)	• on initiation, then • every 3 weeks up to 12 weeks, then • at week 24, then • every 18 weeks thereafter

FBC, full blood count; LFT, liver function test; U & E, urea and electrolytes.

Calculation of the weekly treatment costs for patients treated with BAT

Drug acquisition cost

Data related to BAT are limited. As discussed in section 5.2.4, there is also no precise definition of what constitutes BAT, but clinical advisors felt that therapies used in the COMFORT-II trial were broadly representative of therapies used in the UK to treat patients with MF.

The proportion of patients receiving each different therapy (or no treatment) in the COMFORT-II trial was obtained for each 12-week interval (Table 42). The duration for which patients received treatment within these 12 weeks periods is unclear. Thus, we calculated the cost under two assumptions;

- a conservative assumption where we assumed the cost associated with only one pack (or injection) per 12 week period
- a more optimistic assumption where we calculated the cost associated with the necessary number of pack (or injections) for the full 12 weeks duration.

The dose intensity was taken from the BSCH guideline for the diagnosis and management of MF,[93] the London Cancer Myelofibrosis guideline[187] and British National Formulary (BNF)[188] when appropriate. Unit costs were taken from the BNF.[188]

Administration costs were not included. Thus medications administered either intravenously or subcutaneously were assumed to incur no additional costs. This is likely to be a conservative assumption. Unit costs and assumptions about the number of tablets (injections) are summarised in Table 43 and were applied to the proportion of patients receiving BAT therapies at each 12 week period (Table 42) to estimate the 12-week drug acquisition costs of BAT.

Table 42 Number of patients receiving each treatment included in BAT in the COMFORT-II trial by time period.

	Weeks 0–12	**Weeks 12–24**	**Weeks 24–36**	**Weeks 36–48**
Patients	n = 46/60	n = 42/45	n = 29/40	n = 24/34
Aspirin	2	2	1	
Anagrelide	4	4	2	2
Cholchicine	1			
Cytarabine		2		
Danazol	3	3	3	2
Epoetin	5	5	4	4
Deferasirox	1			
Folic acid	1	1		
Hydroxycarbamide	33	29	21	17
Lenalidomide		2	2	1
Lysine acetylsalicylate			1	1
Melphalan	2	1	1	1
Mercaptopurine	2	2	2	1
Methylprednisolone	2	2	1	1
Peginterferon alfa-2a)	1	1		1
Prednisolone		1	1	
Prednisone	6	5	4	4
Interferon alfa-2a	1	1		
Thalidomide	3	2		
Tioguanine	1	1	1	1
No treatment	14	3	11	10

BAT, best available therapy.

Assumptions used to cost BAT drug acquisition are summarised in Table 43.

Table 43 Assumptions on costing for medications included in the BAT bundle

Drugs	Dosage	Assumption about number of packs (injections)		Cost per pack/injection	Estimated cost per 12 week period	
		Optimistic	Conservative		Optimistic	Conservative
Aspirin	75 mg/day	3 packs of 28 tablets (75 mg)	1 pack of 28 tablets (75 mg)	£0.94	£2.82	£0.94
Anagrelide	0.5 mg/ BID	2 pack of 100 capsules (0.5 mg)	1 pack of 100 capsules (0.5 mg)	£404.57	£809.14	£404.57
Cholchicine	0.5 mg TID for 7 days	1 pack of 100 tablets (0.5 mg)	1 pack of 100 tablets (0.5 mg)	£33.48	£33.48	£33.48
Cytarabine	100 mg/QD for 3 days	3 injections (100 mg)	1 injections (100 mg)	£3.90	£11.70	£3.90
Danazol	100 mg/BID	6 packs of 28 tablets (100mg)	1 packs of 28 tablets (100mg)	£7.64	£45.84	£7.64
Epoetin	Eprex: 80000 units weekly	12 injections of 8000 units	1 injection of 8000 units	£44.25	£531.00	£44.25
Deferasirox *	500 mg / BID	6 packs of 28 tablets (500mg)	1 pack of 28 tablets (500mg)	£470.40	£2,822.40	£470.40
Folic acid	5 mg/QD	3 packs of 28 tablets (5mg)	1 pack of 28 tablets (5mg)	£1.09	£3.27	£1.09
Hydroxycarbamide	1000 mg/QD	2 packs of 100 tablets (500 mg)	1 packs of 100 tablets (500 mg)	£10.47	£20.94	£10.47
Lenalidomide**	10 mg for 3 weeks (and one week rest)	3 packs of 21 tablets (10mg)	1 pack of 21 tablets (10mg)	£3,780.00	£11,340.00	£3,780.00
Lysine acetylsalicylate	Assume same as aspirin	same as aspirin	same as aspirin	same as aspirin	£2.82	£0.94
Melphalan	2 mg every other day	2 packs of 25 tablets (2mg)	1 pack of 25 tablets (2mg)	£42.88	£85.76	£42.88

Mercaptopurin	50 mg twice weekly	1 pack	1 pack	£50.47	£50.47	£50.47
Methylprednisolone	8 mg (every other day)	3 packs of 30 tablets (4mg)	1 pack of 30 tablets (4mg)	£6.19	£18.57	£6.19
Peginterferon alfa-2a	135 ug/QIW	12 injections (135µg)	1 injection (135µg)	£107.76	£1,293.12	£107.76
Prednisolone	10 mg/day[47]	6 packs of 28 tablets (5mg)	1 packs of 28 tablets (5mg)	£1.29	£7.74	£1.29
Prednisone	10 mg/day (assumed)	2 packs of 100 tablets (5mg)	1 pack of 100 tablets (5mg)	£89.00	£178.00	£89.00
Interferon alfa-2a	3000000 IU / 3 times a week	36 injections (3 million unit)	1 injection (3 million unit)	£14.20	£511.20	£14.20
Thalidomide	50 mg/QD	3 packs of 28 tablets (50 mg)	1 pack of 28 tablets (50 mg)	£298.48	£895.44	£298.48
Tioguanine	40 mg/TID	11 packs of 25 tablets (40mg)	1 packs of 25 tablets (40mg)	£103.54	£1,138.94	£103.54

BAT, best available therapy; bid, twice daily; qd, once daily;qiw, four times a week; tid, three times a day.

We estimated the 12 week cost for BAT (excluding monitoring) to range between £171.84 (conservative approach) to £556.97 (optimistic approach) respectively. In the base case we used the average and assumed the cost of BAT (including no treatment) to be £364.40 per 12-week period (excluding monitoring), equating to a cost per day (week) of £4.34 (£30.37). It is unclear if this cost is an under- or over-estimation. Sensitivity analyses (Figure 72) were conducted assuming the cost to range from £171.84 (conservative approach) to £556.97 (optimistic approach) per 12-week period.

Monitoring

Monitoring is likely to represent an important component of the cost of BAT. Indeed, current therapies are associated with severe side effects, requiring close observation. For instance, patients initiating hydroxycarbamide (the most commonly prescribed therapy) require full blood count monitoring every 1 to 2 weeks until dose stabilisation and up to 3 months thereafter, and liver function and renal function are monitored every 3 months. Treatment with epoetin, anagrelide, lenalidomide and thalidomide must also be monitored on a regular basis.

The majority of outpatient attendances are likely to be related to the monitoring whilst on BAT. Hence, we assumed that patients on BAT have 0.24 outpatient visits per week based on the weighted number of outpatient visits (excluding visits associated for transfusion) per person per year reported in the HMRN audit in patients with intermediate-2 (10.48 ± 7.11; median, 8.01; range, 1.61 to 30.02) and high risk (12.45 ± 5.84; median, 11.80; range, 3.97 to 27.77) MF according to the IPSS classification.

For comparison, Gimenez et al (2014),[54] using a focus group of eight experts in Spain, reported the number of visits per year to range from 5 to 13 depending on the presence/absence of asymptomatic splenomegaly and constitutional symptoms.

We further assumed that patients on BAT have 0.32 full blood count tests per week based on the number of FBC tests per person per year reported in the HMRN audit in patients with high risk only (16.81 ± 14.16; median, 13.34; range, 3.73 to 70.69) according to the IPSS classification. Data on laboratory tests for high risk patients were used as one patient in the intermediate-2 risk group was an outlier and received 181.06 FBC tests. In the absence of data, liver function tests, urea and electrolytes were assumed to be monitored at the same time as performing full blood tests.

Calculation of the weekly treatment costs for patients on supportive care

Drug acquisition cost

Clinical advisors suggested that patients on supportive care typically receive pain relief medication. In the base case, we assumed that patients on supportive care receive the following analgesics per week:

- paracetamol 500 mg, net price 32-tab pack = 84p,[188]

- dihydrocodeine tartrate 30 mg, net price 28-tab pack = £1.15[188]

Monitoring

We assumed the number of outpatient visits and laboratory tests to be 50% lower compared with patients on BAT in the base case to reflect for the fact that patients on supportive care are less monitored due to AEs from BAT treatments. This is varied in sensitivity analysis (Figure 72).

5.5.3 Estimating other resources used in MF (GP, A&E, Urgent care and RBC transfusions) in patients treated with BAT

Estimates for the medical management of MF in the UK are scarce. Consequently, evidence from different sources was used, together with a number of assumptions, to approximate the potential healthcare burden of MF in the UK and healthcare costs from a NHS/PSS perspective.

Current treatment and management of MF is supportive rather than curative. The main components of the management of the disease include outpatient visits, RBC transfusions, A & E visits, urgent care (walk in visits), inpatient stays, primary care visits and treatment (including medication and/or procedures/interventions).[189-191]

As described above, outpatient attendances are already included in the monitoring (for BAT, ruxolitinib and supportive care). Hence, we sought to estimate other resources use (and impact of ruxolitinib) in terms of GP visits, A&E visits, urgent care visits and RBC transfusions.

Description of main sources used for resource use (excluding monitoring and drug acquisition costs) for patients on BAT

Two key UK data sources provide information on other resources use for the management of MF − the HMRN audit[52] and the UK ROBUST study.[53]

- The HMRN audit[52] provides information on the number of hospital nights, outpatient visits and laboratory tests amongst 98 patients diagnosed with primary or secondary MF (ICD-0-3 code: 9961/3) between 1 September 2004 and 31 August 2010 **prior to exposure to (and approval of) ruxolitinib**. The HMRN covers two adjacent former UK cancer networks with a total population of 3.6 million (previously Yorkshire Cancer Network and the Humber & Yorkshire Coast Cancer Network) and collects detailed information about all haematological malignancies diagnosed in the region. The mean age of included patients was 72.4 (standard deviation [SD]: 10.4) years. The median follow-up for survival was 2.62 (0.1 to 7.0) years. Of the 98 patients, 32 (32.7%) and 30 (30.6%) patients were classified as intermediate-2 and high risk according to the IPSS, respectively. The number of patients classified as

intermediate-2 and high risk according to the DIPSS by risk group was 40 (40.8%) and 4 (4.1%), respectively.

- The ROBUST study[53] is an open-label, 48-week, phase 2 study **in patients treated with ruxolitinib** (see also section 4.11.1). Patients eligible for inclusion in the ROBUST study were those with PMF, PPV-MF or PET-MF, with or without prior therapy, who had intermediate-1 risk, intermediate-2 risk or high-risk disease. The study collected data on resource use (hospitalisations, A&E visits, general practitioners, specialist visits and urgent care) from baseline to week 12 (ie 3 months), from week 20−24 ie 4 weeks), from week 32 −36 only ie 4 weeks) and from week 44−48 only (ie 4 weeks).

Estimate of resource use (excluding monitoring) used in the economic model for patients on BAT

Hospital nights

We assumed that patients on BAT spend on average 0.15 hospital nights per week based on the number of hospital nights (for any causes) per person per year reported in the HMRN audit in patients with high risk only (7.98 ± 11.18; median, 4.54; range, 0 to 54.92) according to the IPSS classification. Data on hospitalisation for high risk patients were used as one patient in the intermediate-2 risk group was an outlier and was hospitalised for 281 days.

GP visits

MF is primarily managed in the secondary care setting. We assumed in the base case that patients on BAT have 0.03 GP visits per week based on data from the ROBUST UK study. In the ROBUST study, patients (n = 45) had 0.36±0.83 GP visits at Q1 (total from baseline to week 12). Of note, using data at Q1 is possibly an under-estimation as data were collected for the first 12 weeks of the study during which patients were exposed to ruxolitinib.

Accident and emergency (A&E) visits

We assumed in the base case that patients on BAT have 0.013 A&E visits per week based on data from the ROBUST UK study. In the ROBUST study, patients (n = 48) had 0.15±0.412 A&E visits at Q1 (total from baseline to week 12).

Urgent care

We assumed in the base case that patients on BAT have 0.003 urgent care visit per week based on data from the ROBUST UK study. In the ROBUST study, patients (n = 48) had 0.04 urgent care visit at Q1 (total from baseline to week 12).

RBC transfusions

Platelet transfusions and RBC transfusions may be required to manage thrombocytopenia and anaemia respectively. These events may reflect complications of the underlying disease and its

progression, as well as AEs from treatments. Platelet transfusion was not considered given the lack of data and this is much less commonly used than RBC transfusion.

COMFORT-I reported the mean number of RBC units per person per month in patients randomised to placebo. This was not reported in COMFORT-II. It is expected that patients on BAT require fewer RBC units than patients on supportive care. In the absence of robust data we arbitrarily assumed that patients on BAT receive 20% fewer RBC units compared with patients on supportive care. This assumption is varied in sensitivity analysis (Figure 72).

5.5.4 Impact of ruxolitinib on other resources used in MF (GP, A&E, urgent care and RBC transfusions)

Description of sources used for the impact of ruxolitinib on resource use (excluding monitoring and drug acquisition costs)

Ideally, evidence of the treatment effect on resource use would be taken from reliable UK sources. However, resource utilisations are typically skewed, with a large proportion of patients with no resource use and outliers. Consequently a large sample size is usually required to allow an adequate estimate of the effect of a treatment on resource use. The time interval during which resource use is collected is also important. A further challenge is dealing with missing or incomplete follow-up data.

The ROBUST UK study included only 48 patients. At each 12-weekly visit participants were asked about resource utilisation in the previous 4 weeks. This short time interval (combined with the small sample size) limited the ability of the study to demonstrate a reduction in resource use. Thus data from the ROBUST UK study were not utilized as the study was considered inadequate to detect any changes in resource use (but was used to provide baseline resource use, as described above).

In contrast, interim analysis of a third study, JUMP, which included 511 patients where resource use in the previous 3 months were collected every 12 weeks up to week 60 was used to estimate the impact of ruxolitinib on resource use and is thus considered to provide a more adequate representation of the reduction in resource use associated with ruxolitinib.[145] The JUMP study is an open label, multicentre, expanded access study conducted in 25 countries with the majority of patients from Germany, Italy and Spain. The UK did not participate in the study, which included patients with intermediate-1, intermediate-2 and high risk disease plus splenomegaly (see section 4.11.2).

The impact of ruxolitinib on RBC transfusions was taken from COMFORT-II.

Impact of ruxolitinib on resource use assumed in the economic model

The following assumptions were made regarding the potential impact of ruxolitinib on healthcare resource use.

Hospital admissions Patients on ruxolitinib are expected to experience fewer complications compared with patients treated with BAT/supportive care and therefore are less likely to be hospitalised. Using data from the JUMP study, we assumed a reduction in hospitalisations of 66.3% after week 12, 80.6% after week 24, 85.8% after week 36 and 100% from 48 weeks onwards.

Primary care visits Using data from the JUMP study, we assumed a reduction in GP visits of 36.7% after week 12, 58.2% after week 24, 81.7% after week 36 and 97.7% from 48 weeks onwards.

A&E visits Using data from the JUMP study, we assumed a reduction in A&E visits of 51.7% after week 12, 73.3% after week 24, 72% after week 36 and 96.4% from 48 weeks onwards.

Urgent care visits Using data from the JUMP study, we assumed a reduction in urgent care visits of 51.5% after week 12, 100% after week 24, 80.3% after week 36 and 93.1% from 48 weeks onwards.

RBC transfusions Cervantes et al (2013)[23] reported that the transfusion rate was slightly higher in the ruxolitinib arm (compared with BAT) over the first week 24, but declined thereafter to a rate similar to that in the BAT arm. Hence, evidence from COMFORT-II was used to approximate the effect of ruxolitinib on transfusion. Data on the rate of patients transfused at the beginning of each 12 week period was available in COMFORT-II in patients randomised to ruxolitinib or BAT. It can be seen that the rate of patients transfused remained relatively constant in the BAT arm at around 30%[b]. In contrast, it can be seen that the rate of patients transfused is higher in the ruxolitinib in the first 24 weeks (around 43%), then reduces to a level close to BAT (around 30%) up to week 144, after which ruxolitinib is associated with a reduction in the rate of patients transfused (around 12.5%[c]).

Hence, in the economic model, we calculated the relative reduction of transfusion whilst on ruxolitinib (relative to BAT) before week 24, between weeks 24 – 108, week 108 – 144 and after week 144[d]. The rate of transfusion on BAT was calculated over the whole trial duration (up to Week 84[e]) and assumed to remain constant as evidenced by the COMFORT-II trial data.

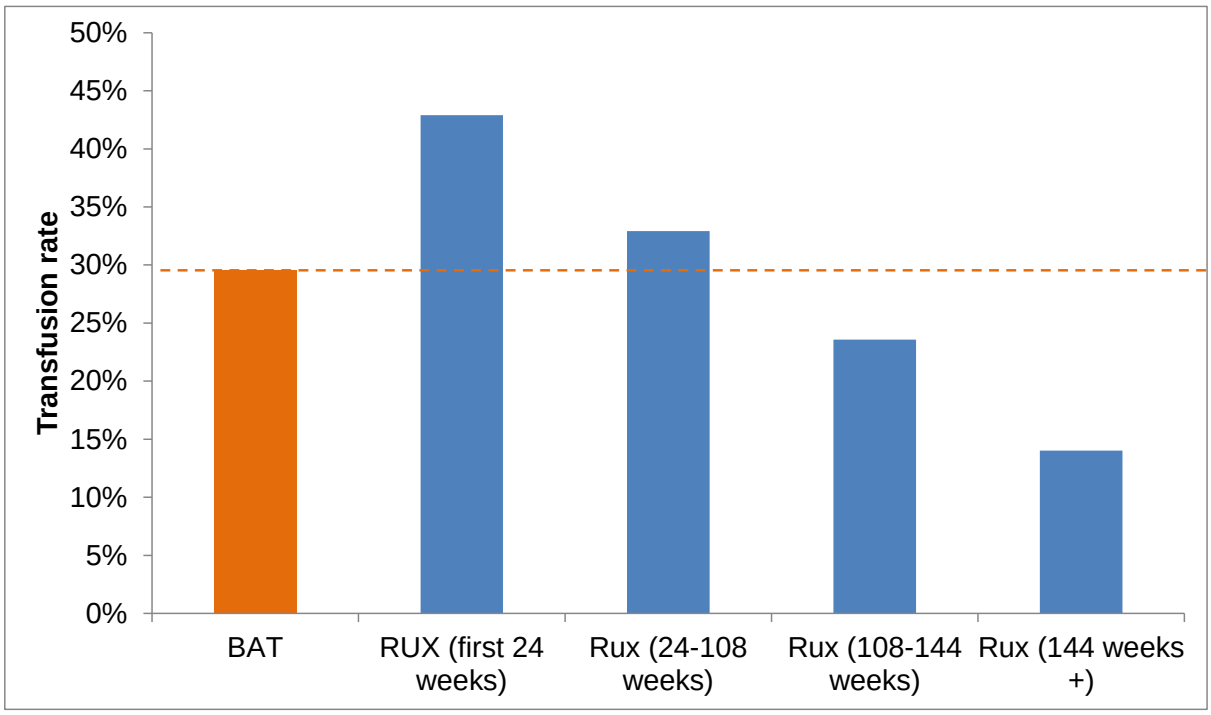
[b] Small sample size from week 96

[c] Small sample size from week 168

[d] Data at week 186 were excluded due to the very small sample size (n<5)

[e] Data at week 96 and 108 were excluded due to the very small sample size (n <5)

Figure 61 Rate of transfusion assumed per period in the economic model



BAT, best available therapy; RUX, ruxolitinib

It should be noted that this is an approximation as it is unclear from the COMFORT-II trial whether the mean number of RBC units was the same between patients transfused on ruxolitinib and BAT.

A scenario analysis is conducted assuming the same rate as for BAT (Table 76). In addition a second scenario analysis is conducted assuming ruxolitinib to be associated with a 5% increase in RBC units (compared with BAT) over the lifetime. This is a very pessimistic assumption and is presented for completeness.

5.5.5 Resource use whilst on supportive care

Hospitalisations, A&E, GP and urgent care visits

The same resource use in terms of hospitalisations, GP, A&E, urgent care visits were assumed for patients on BAT and on supportive care.

RBC units

We assumed a mean number of units per person per month of 0.775 (or 0.19 per week) based on the number of units in patients randomised to placebo in COMFORT-I. This equates to 9.3 units transfused per year (excluding transfusions at the end of life). The HMRN audit reported that, on average, patients with intermediate-2 and high risk (according to the IPSS definition) had 18.95 ± 34.12 (median, 6.78; range, 0 to 181.06) and 12.75 ± 12.08 (median, 8.45; range, 0 to 37.86) units of

blood transfused per person per year, respectively. However, there was an outlier skewing the average in the intermediate-2 risk group (one patient received 181 units of blood).
We assumed this value to be constant over time given data from COMFORT-I showing the rate per month in the placebo arm to remain constant with time. For completeness a scenario analysis is conducted assuming a 5% increase every 24 weeks (Scenario analyses were conducted assuming no impact of ruxolitinib on RBC (compared with BAT), an increase in RBC unit by 5% over the lifetime for patients on ruxolitinib, and an increase by 5% every 24 weeks in patients on supportive care (up to week 72). These assumptions had little impact on the ICER (Table 76).

5.5.6 Unit costs

Unit costs used in the economic model are summarised in Table 44.

Table 44 Unit costs

Resource use	Unit cost	Source
Follow-up appointment at the haematology clinic	£92.00	NHS Reference cost HRG (WF01A); Service Code (303): Non-Admitted Face to Face Attendance, Follow-up – Non-consultant led
Hospital night	£170.82	PSSRU (2010) uplifted to 2014
GP visit	£46.00	PSSRU (2014)
A & E visit	£162.17	PSSRU (2010) uplifted to 2014
Urgent care visit	£47.57	PSSRU (2010) uplifted to 2014
FBCs	£6.21	Private Patient Tariff 2008–2009[192] at the Sheffield Teaching Hospital NHS Foundation Trust uplifted to 2014 based on the PSSRU inflation indices[58]
Full profile (U&E, LFT, Ca)	£16.93	Private Patient Tariff 2008–2009[192] at the Sheffield Teaching Hospital NHS Foundation Trust uplifted to 2014 based on the PSSRU inflation indices[58]
RBC unit	£361.85	Varney (2003) uplifted to 2014

HRG, Healthcare Resource Group; NHS, National Health Service.
Ca, calcium; FBC, full blood count; LFT, liver function test; NHS, National Health Service; Personal Social Services Research Unit; U&E, urea and electrolytes.

The cost per hospital night was assumed to be £170.82 based on the cost per hospital day (£158) from the PSSRU report on "Unit Costs of Health and Social Care (2010)[193] uplifted to 2014 based on the PSSRU inflation indices .[58] The cost per hospital night was not available in the latest PSSRU

(2014). The cost associated with an outpatient attendance was taken from the NHS reference cost 2013–2014 and was assumed to be £92.00 (service code 303: Clinical Haematology) (see Table 44).[192] The cost of laboratory tests was taken from the Private Patient Tariff 2008–2009 at the Sheffield Teaching Hospital NHS Foundation Trust[192] and were uplifted to 2014 based on the PSSRU inflation indices[58]. The cost associated with a GP consultation (including qualifications) was assumed to be £46.00, taken from the PSSRU assuming a consultation lasting 11.7 minutes.[58] The cost associated with an A &E visit and urgent care visit were assumed to be £162.17 and £47.57 respectively based on the cost of A&E treatments leading to admission and the cost for Walk in services leading to admission , taken from the PSSRU (2010)[193] and uplifted to 2014 based on the PSSRU inflation indices.[58] The cost per A&E and urgent visit was not available in the latest PSSRU.

The total average cost associated with one unit of blood was assumed to be £361.85 based on the average NHS cost in 2000–2001[194] uplifted to 2014 prices.[58] This includes the costs incurred by the blood transfusion services in collecting, testing, processing and issuing blood products, hospital resources use associated with blood transfusions relating to hospital stay, managing blood transfusion-related complications and staff attendance at blood transfusion committee meetings.

Management cost associated with AML

The cost associated with the management of AML in the UK was taken from results of a probabilistic decision model. The authors estimated the 5-year medical costs to range between £8,170 and £81,636.[195] In the base case, we assumed a one-off cost of £44,903 (middle range of the cost reported). Sensitivity analysis (Figure 72) is conducted using the lower and upper range. Of note, a study conducted by Mahmoud et al (2012)[196] looking at the economic burden of AML in the UK and the US (an abstract presentation) estimated that in 2011, the total cost per patient was £29,858 for patients treated with standard induction chemotherapy.[196]

End of life (one-off cost)

Clinical advisors suggested that resource utilization typically increases in the period preceding death (3 to 6 months). Possible explanations include increased need for transfusions, management of thrombotic complications, pain control, antibiotics, cytotoxic drugs, surgical options, blood analyses and other types of testing. Patients also receive palliative care support, either in the community or in hospital.

This is not included as a separate health state to limit the number of assumption required. Based on clinical advice, we assumed that patients typically receive two units of transfused blood every week. Patients were also assumed to visit their haematologist every week leading to a one-off cost of £14,687 at the time of death (Table 45).

Table 45 Estimate of the cost for EOL

	Number per week	Cost per week	Cost per 18 weeks
Outpatient visits	1	£92	£1,661
RBC units	2	£724	£13,026
Total cost			£14,687

EOL, end of life

In addition to the cost associated with this increased requirement for transfusions (and specialist visit), we assumed an additional cost associated with palliative care/end of life based on the community and inpatient hospital care cost for patients with cancer in the last 8 weeks of life. Patients were assumed to incur an additional one-off cost of £6,016[197] (uplifted to 2013)[198] at the time of death. These assumptions are varied in sensitivity analysis (Figure 72).

5.5.7 Adverse reaction unit costs and resource use

Results of the phase 3 RCTs[23,25,130] and phase 1/2 study[39] demonstrate that ruxolitinib is generally well tolerated in patients with PMF, PPV-MF and PET-MF. The overall pattern of AEs observed was consistent across studies.

The most frequently occurring grade 3 or 4 AEs were anaemia and thrombocytopenia, but they rarely led to treatment discontinuation and were generally managed by dose modifications and/or transfusions. These AEs were expected given the mechanism of action of ruxolitinib, and generally declined over time with continued therapy. No additional costs were included for the management of thrombocytopenia and anaemia as a cost is already included in the model for monitoring and RBC transfusions (see section 5.5.5).

Grade 3 or 4 non-haematological AEs were infrequent overall. The adjusted rate of grade 3 or 4 non-haematological events per 100-patient year exposure was taken from the 3-year follow-up of COMFORT-II)[23] (see section 4.12.5). The authors reported data for four groups of patients: patients randomised to ruxolitinib (core study), patients randomised to ruxolitinib and who received ruxolitinib in the extension phase, patients randomised to BAT (core study) and patients randomised to BAT who crossed over to ruxolitinib (see Table 23). Data from patients randomised to ruxolitinib and who continued to receive ruxolitinib in the extension phase were used to characterise the safety profile of ruxolitinib as this provided a longer follow-up (304.87 weeks) compared with data for the core phase of the study alone (170.12 weeks).

Of note, whilst some of these events were counted as non-haematological AEs, some were likely to be associated with the disease rather than being related to treatment (e.g. fatigue and pain).

Therefore this may overestimate the incidence and hence the cost of non-haematological AEs associated with ruxolitinib. Some events, such as weight gain, may also be positive.

The costs for management of these AEs were taken from a range of sources and are summarised in Table 46. The annual costs associated with the management of grade 3 or 4 non-haematological AEs were estimated to be £61.11 for patients treated with ruxolitinib and £46.75 for patients treated with BAT. Patients were assumed to experience no AEs while receiving supportive care.

Table 46 Adjusted incidence (%) of grade 3 or 4 AEs in COMFORT-II and associated medical management/health care cost

Adjusted rate per 100-patient year exposure	**Ruxolitinib (core phase and extension) n = 146**	**BAT (core phase) n = 73**	**Management cost per adverse event**
Patient-year exposure	304.87	66.98	
	Grade 3/4	Grade 3/4	
Oedema peripheral	0	1.5	£914[199]
Diarrhoea	0.7	0	£47.03*
Asthenia	1.6	1.5	£12[199]
Dyspnoea	1.3	4.5	£0[199]
Pyrexia	1.3	0	£3076.99[200]
Fatigue	0.7	0	£12[199]
Bronchitis	1.3	1.5	£49.92**
Cough	0	1.5	£49.92**
Arthralgia	0.7	0	£101[199]
Weight increased	1.3	0	£92***
Nausea	0.3	0	£47.03*
Pain in extremity	0.3	0	£101[199]
Headache	0.7	0	£117[201]
Back pain	1.3	0	£460[199]
Abdominal pain	1.6	4.5	£697[199]
Epistaxis	0.7	0	£0[202]

AE, adverse event; BAT, best available therapy.

* assumed 1 GP consultation (£46)[58] and loperamide hydrochloride (£1.03)[188]

** assumed 1 GP consultation (£46)[58] and clarithromycin (£3.92)[188]

*** assumed 2 GP consultations (dietary advice)

Cervantes et al. 2013[23]

5.5.8 Miscellaneous unit costs and resource use

Economic impact on carers and patients

There is a growing body of evidence indicating that many MF patients have an impaired ability to carry out the normal activities of daily living, resulting in the need for both formal and informal care.[54,55,203]

Informal care

Studies indicate that various proportions of patients require the assistance of informal caregivers. A small study carried out in Spain (33 patients) found that 24.2% had informal carers.[54] In a study of 98 carers in Italy, Marini et al found that 57% of patients had non-paid carers.[55]

Estimates of time spent providing informal care vary widely. The Spanish study inferred that 3 hours of informal care were provided per day, while the Italian study found that non-paid carers gave 11 hours per day.

A study on "Valuing informal adult care in England" was carried out by the ONS[56] and provides useful input regarding the cost of informal care. They found that, in 2010, 7.6 billion hours of informal care was provided at a total value of £61.7 billion, ie £8.12 per hour. The informal care was valued using the wage rate for the equivalent service, assumed to be the hourly wage for a care assistant.

Based on 3–11 hours of informal care provided per day, the annual cost of informal care amounts to £8,900 to £32,000 for those patients requiring such care.

Formal care

It has been shown that 18–28% of people with MF have associated medical disability.[11,57] A survey conducted among a small sample of clinicians in the UK similarly found that up to 25% of people with MF could require formal care via Social Services as a result of their MF-related disability.[203]

The PSSRU "Unit Costs of Health and Social Care 2014" reports on various community care packages. The median cost of the community care package for older people, excluding accommodation and living expenses, is £370 per week.[58] This care package assumes that patients experience problems with four activities of daily living: using the stairs, getting around outside, dressing and bathing and could be regarded as representative of the care required for MF patients. The annual cost of such a package is £19,000.

Impact of ruxolitinib on carer costs

When patients respond to ruxolitinib, with a resultant improvement in symptom burden and quality of life, it is expected that carer requirements would reduce significantly. However, we currently do not have data to quantify such reductions and therefore carer costs have not been included in our consideration of cost and healthcare resource use in the economic model.

Impact on productivity

Studies have also shown that MF can have a considerable economic impact on patients and their carers. A third of patients (35%) included in the study in Italy were unable to continue in employment, resulting in a mean loss of income of €8,065 per year.[55] Only 19% of caregivers managed to maintain their normal level of work hours, resulting in an average loss of quantifiable income of €4,692 per year.[55] The small study in Spain estimated that costs associated with work loss were €15,077 per patient.[54] The MPN LANDMARK survey included 207 MF patients in the US and revealed considerable impact on patients' productivity.[57] A total of 59% of patients had ever reduced work hours while 31% had voluntarily terminated jobs. 28% were classified as having a medical disability and 30% took early retirement.

While comparable information is not available for UK patients and carers, a similar loss of productivity is possible.

5.6 Summary of base case de novo analysis inputs and assumptions

5.6.1 Summary of base case de novo analysis inputs

Inputs are summarised in Table 47.

Table 47 Summary of variables applied in the economic model

Parameters	Value	Distribution	Source
Time horizon	Lifetime		NICE reference cost
Time to BAT discontinuation (Gompertz distribution)			
Scale	[redacted]	Multivariate normal	COMFORT-II
Shape	[redacted]		
Proportion of patients experiencing dying while on BAT			
Proportion	[redacted]% (n = [redacted])	Beta	COMFORT-II
Time to death following BAT discontinuation (Gompertz distribution)			
Scale	[redacted]	Varied indirectly through other inputs	Derived
Shape	[redacted]		
Proportion of patients initiating ruxolitinib in the Four outcomes categories from COMFORT-II at Week 24			
Spleen response	[redacted] ([redacted]%)	Dirichlet	COMFORT-II

Parameters	Value	Distribution	Source
No spleen response	[redacted]		
Early discontinuation	[redacted]		
Early death	[redacted]		
Proportion of symptom responders amongst non-spleen responders			
Proportion of symptom responders	[redacted]	Beta	COMFORT-I
Time to ruxolitinib discontinuation in patients experiencing early death			
Mean time	[redacted] weeks (range: [redacted])	Triangular	COMFORT-II
Time to ruxolitinib discontinuation in patients experiencing early discontinuation (Kaplan–Meier curve)			
Kaplan–Meier	See Figure 50	Not varied	COMFORT-II
Time to ruxolitinib discontinuation in patients not achieving the required level of response			
Mean time	Week 24	Not varied	
Time to ruxolitinib discontinuation in patients achieving the required level of response (exponential distribution) – spleen and/or symptom response			
Scale	–[redacted]	Normal distribution	COMFORT-II
Time to death following ruxolitinib discontinuation in patients experiencing early death			
Mean time	[redacted]	Triangular	COMFORT-II
Time to death following ruxolitinib discontinuation in patients experiencing early discontinuation, spleen or symptom response (exponential distribution)			
Scale	–[redacted]	Normal distribution	COMFORT-II
Proportion of patients experiencing death whilst on treatment			
proportion	0	Not varied	COMFORT-II
Annual incidence of leukaemic transformation			
Ruxolitinib	1.42%	Beta	COMFORT-II
BAT/supportive care	2.83%	Beta	
HRQoL			
Unadjusted baseline HRQoL	[redacted]		COMFORT-I
Change in HRQoL whilst on BAT	0	NA	Assumption
Change in HRQoL whilst on ruxolitinib (responders)	+[redacted]	Beta distribution	COMFORT-I
Non-responders	+[redacted]	Beta distribution	COMFORT-I
Change in HRQoL whilst on supportive care (placebo) every Week 24	–[redacted]	normal distribution	COMFORT-I
Decrement in QALYs associated with AML	0.15		assumption
Ressource use whilst on BAT (per week)			
Hospital night	0.15 / week	Gamma	HMRN audit
Outpatient visits	0.22 / week	Gamma	HMRN audit
FBC & U&E	0.32 / week	Gamma	HMRN audit
Primary care visits – GP	0.030 / week	Gamma	ROBUST
A&E	0.013 / week	Gamma	ROBUST

Parameters	Value	Distribution	Source
Urgent care	0.003 / week	Gamma	ROBUST
RBC unit / week	0.16 / week		Assumption
Impact of ruxolitinib on resource use			
Reduction in hospital nights	After week 12: -66.3% After week 24: -80.6% After week 36: -85.8% After week 48: -100%	Beta	JUMP
Outpatient visits & laboratory tests (monitoring etc.)	Every 3 weeks up to 12 weeks Week 24 Every 18 weeks thereafter		assumptions
Reduction in primary care visits - GP	After week 12: -36.7% After week 24: -58.2% After week 36: -81.7% After week 48: -97.7%	Beta	JUMP
Reduction in A&E visits	After week 12: -51.7% After week 24: -73.3% After week 36: -72% After week 48: -96.4%	Beta	JUMP
Reduction in urgent care visits	After week 12: -51.5% After week 24: -100% After week 36: -80.3% After week 48: -93.1%	Beta	JUMP
Ressource use whilst on supportive care (per week)			
RBC units	0.19 / week	Gamma	COMFORT-I
Unit costs			
Ruxolitinib drug acquisition cost (per week) – including dose interruption/reduction	£793.30/ week	Dirichlet	Derived from COMFORT II and BNF
BAT drug acquisition cost (per week)	£30.37 / week	Dirichlet	Derived from COMFORT II and BNF
Cost medication during supportive care	£1.99 / week		BNF
Follow-up appointment at the haematology clinic	£92	Gamma	NHS Reference cost HRG (WF01A); Service Code (303): Non-Admitted Face to Face Attendance, Follow-up – consultant led
FBCs	£6.21	Gamma (SE assumed to be 10% around the mean)	Private Patient Tariff 2008-2009 at the Sheffield Teaching Hospital NHS Foundation Trust
Full profile (U&E, LFT, Ca)	£16.93	Gamma (SE assumed to be 10% around the mean)	Private Patient Tariff 2008-2009 at the Sheffield Teaching Hospital NHS Foundation Trust

Parameters	Value	Distribution	Source
Hospital night	£170.82	Gamma (SE assumed to be 10% around the mean)	PSSRU (2010) inflated to 2014
GP consultation	£46.00	Gamma (SE assumed to be 10% around the mean)	Taken from the PSSRU assuming a consultation lasting 11.7 minutes
Unit RBC transfusion (including cost associated with blood product, hospital staff, management of AEs)	£361.85	Gamma (SE assumed to be 10% around the mean)	Average NHS cost in 2000/2001 from Varney (2003) uplifted to 2014
A&E visits	£162.17	Gamma (SE assumed to be 10% around the mean)	PSSRU (2010) inflated to 2014
Urgent care	£47.57	Gamma (SE assumed to be 10% around the mean)	PSSRU (2010) inflated to 2014
Cost of end of life (palliative care)	£6,189	Gamma (SE assumed to be 10% around the mean)	Addicott (2008)[197] uplifted to 2014
Management of AML	£44,903	Triangular	Wang (2014) [195]
Unit cost management of AEs			
Oedema peripheral	£914		NICE TA316[199]
Diarrhoea	£47.03		assumption
Asthenia	£12		NICE TA316[199]
Dyspnoea	£0		NICE TA316[199]
Pyrexia	£3076.99		Woods et al 2012[200]
Fatigue	£12		NICE TA316[199]
Bronchitis	£49.92		assumption
Cough	£49.92		assumption
Arthralgia	£101		NICE TA316[199]
Weight increased	£92		assumption
Nausea	£47.03		assumption
Pain in extremity	£101		NICE TA316[199]
Headache	£117		McCrone et al 2011[201]
Back pain	£460		NICE TA316[199]
Abdominal pain	£697		NICE TA316[199]

A&E, accident and emergency; AE, adverse event; AML, acute myeloid leukaemia; BAT, best available therapy; BNF, British National Formulary; Ca, calcium; CSR, clinical study report; FBC, full blood count; GP, general practitioner; HMRN, Haematological Malignancy Research Network; HR, hazard ratio; HRG, Healthcare Resource Group; HRQoL, health-related quality of life; LFT, liver function test; MF, myelofibrosis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, Patient Access Scheme; PSSRU, Personal Social Services Research Unit; RBC, red blood cell; SE, standard error; U&E, urea and electrolytes.

5.6.2 Assumptions

Assumptions are summarised in Table 48.

Table 48 Assumptions and their justification

Theme and assumptions	Justifications
Response criteria whilst on ruxolitinib	
The economic model incorporates a stopping rule at Week 24 for patients initiating ruxolitinib.	A stopping rule was applied to reflect the SmPC, on clinical advice regarding expected clinical practice and the recommendations of the BCSH guidelines[8]
Response is based on the definition for clinical improvement proposed by the IWG-MRT/ELN for evaluating disease progression and treatment response in MF	Although clinical advisors felt that the IWG-MRT/ELN criteria may be too stringent for clinical practice, they acknowledged the absence of alternative clearly defined and accepted criteria for response for use in clinical practice. Use of the IWG-MRT/ELN criteria in the model is therefore a conservative approach. Scenario analyses are conducted using alternative definitions of response.
Response criteria whilst on BAT	
No stopping rule was assumed for patients initiating BAT.	Since the impact of BAT on symptoms and splenomegaly is transient, and BAT therapies are relatively inexpensive, the use of formal response criteria at Week 24 is not used in clinical practice. Clinical advisors felt this was appropriate.
Use of COMFORT-I	
Evidence from COMFORT-I was used where appropriate data from COMFORT-II were not collected	The economic analysis uses data from COMFORT-I when necessary, given that symptom data were not collected using the MF-SAF in the COMFORT-II trial. Clinical advisors felt this was reasonable..
Treatment phase	
The time to BAT discontinuation from the COMFORT-II trial was used as a proxy for the time patients treated under current practice experience a temporary control of the disease	Clinical advisors suggested that whilst on therapies, patients typically experience a temporary control of symptoms and haematological parameters but not splenomegaly.
The OS for patients on BAT was taken from an analysis of the COMFORT-II trial adjusted for crossover.	The ITT analysis (non-adjusted) is likely to be biased due to crossover. Selection bias and time bias are well-known caveats associated with the use of historical controls. Clinical advisors felt that the analysis adjusted for cross-over was the most reasonable representation of the OS in current practice, and may be less subject to bias than evidence based on the ITT population not adjusted for cross-over
The time to death following BAT discontinuation was calculated as the difference between OS and time to BAT discontinuation	This is a structural assumption. Scenario analyses were conducted assuming three alternative approaches.
The time to death following BAT discontinuation was assumed to follow a	This assumption was necessary in the absence of data. Although there are uncertainties, this assumption does not have a large impact on the

Weibull distribution with a shape of 0.63	ICER. Scenario analyses were conducted assuming different shapes.
With the exception of patients who discontinued ruxolitinib due to the absence of response at Week 24, patients are assumed to move directly to supportive care and experience an uncontrolled worsening of the disease following stopping ruxolitinib	Clinical advisors felt that after stopping ruxolitinib, a proportion of patients may receive BATalthough this proportion isunknown. The assumption is believed to be conservative.
HRQoL progression	
Changes in HRQoL were measured using the MF-8D (a condition-specific measure)	As suggested in the NICE reference case, change in HRQoL is taken from a condition-specific measure (the MF-8D) given the lack of sensitivity of the EORTC QLQ C-30 and EQ-5D in capturing changes in MF symptoms and their impact on HRQoL
The baseline HRQoL was assumed to remain constant over time	Although evidence using the EQ-5D indicates that the HRQoL decreases with advancing age, there was no evidence from the baseline MF-8D data in COMFORT-I that HRQoL was affected by age in MF.
We assumed that patients on BAT did not experience worsening or improvement in HRQoL	There is a lack of evidence on the impact of BAT on HRQoL. Data from COMFORT-II suggested no change in symptoms measured using the FACT-Lym. Clinical advisors felt that assuming no worsening of HRQoL during treatment with BAT was likely to be optimistic, it was more likely that patients would experience a gradual decline in HRQoL on BAT. Scenario analyses are conducted assuming patients on BAT to experience a worsening or improvement in HRQoL.
Changes in HRQoL for patients treated with ruxolitinib were taken from the COMFORT-I trial	This was necessary as it is not possible to calculate the MF-8D from data collected in COMFORT-II
We assumed that patients on ruxolitinib maintained their initial change in HRQoL until stopping treatment.	Clinical data showed that patients originally randomised to ruxolitinib who continued on therapy maintain their initial improvement in HRQoL as measured using the MF-SAF-TTS and spleen volume after 24 weeks. For completeness, scenario analyses are conducted assuming patients to lose some of the initial gain up to the point of discontinuation. These are pessimistic.
HRQoL was assumed to return to the baseline level after stopping ruxolitinib	Clinical data suggest that symptoms, as assessed using the MF-SAF, return to the baseline level approximately one week after stopping ruxolitinib
Changes in HRQoL for patients receiving supportive care were taken from the COMFORT-I trial	Patients in COMFORT-I had to be resistant or refractory to, intolerant of, or, in the investigator's opinion, not candidates for available therapy. Thus, clinical advisors felt that the change in HRQoL for patients randomised to the placebo group is a reasonable reflection of the HRQoL of patients receiving supportive care (following exhaustion of effective therapies)
We assumed that patients on supportive care have a progressive worsening of HRQoL until death	Clinical advisors highlighted that patients are typically in a progressive state whilst in supportive care and that the disease is usually characterised by a continued worsening in splenomegaly, symptoms, haematological parameters and HRQoL. Scenario analyses are conducted relaxing this assumption.

Haematological events	
Patients on BAT were assumed to have 20% fewer transfused RBC units compared with patients on supportive care	Evidence from COMFORT-II was not available on the number of units per patient per month. Patients on BAT are expected to have fewer RBC units compared with patients on supportive care. Hence assumption was made. This is tested in sensitivity analysis (Figure 72)
Treatment with ruxolitinib is associated with a short-term increase in RBC transfusion followed by a reduction after Week 144	This is based on clinical data. For completeness, scenario analyses are conducted assuming no differences between ruxolitinib and BAT, or an increase in RBC units in the ruxolitinib arm over the lifetime. These are pessimistic.
The mean number of RBC units is assumed to be constant in patients receiving supportive care	This is supported by evidence from COMFORT-I which showed that that the rate of transfusion per month was constant in the placebo arm. For completeness, scenario analyses are conducted.
Leukaemic transformation	
The inclusion of leukemic transformation in the data analysis model was simplified and limited to the cost and QALY impact	Including leukemic transformation as a separate health state would lead to double counting
Splenic irradiation/splenectomy	
Splenic irradiation and splenectomy were excluded from the model	Clinical opinion indicated that these are rare procedures in the UK
Drug acquisition costs	
Dose interruption/reductions for ruxolitinib were included in the base case	In the initial appraisal of ruxolitinib, the NICE Appraisal Committee commented that a dose-intensity adjustment may be appropriate and savings could be realised in clinical practice.
Resource use	
Patients on supportive care were assumed to have fewer (50% reduction) outpatient visits and laboratory tests compared with patients on BAT	It is expected that patients on supportive care are monitored less frequently as they would not experience AEs associated with BAT
Data from the JUMP study were used to represent the reduction in resource use associated with the use of ruxolitinib.	Resource utilisations are typically skewed, with a large proportion of patients having no resource use and outliers. A further challenge is dealing with missing or incomplete follow-up data. The time window during which resource are collected is also important. Consequently a large sample size is usually required to allow an adequate estimate of the effect of a treatment on resource use. Thus data showing the changes in resource utilisation were taken from the international JUMP study rather than from the small UK ROBUST study.

AE, adverse event; BAT, best available therapy; ELN, European LeukemiaNet; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-Core 30; EQ-5D, 5-dimension European Quality of Life questionnaire; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; IWG-MRT, International Working Group for MF Research and Treatment; MF, myelofibrosis; MF-SAF, Myelofibrosis Symptom Assessment Form; NICE, National Institute for Health and Care Excellence; OS, overall survival; QALY, quality-adjusted life years; QoL, quality of life; RBC, red blood cell; SmPC, summary of product characteristics; TSS, total symptom score

5.6.3 Summary of key points raised by the ERG and AC

Table 49 summarises the key points raised the ERG and AC during the previous submission to NICE and how the 'de novo' model addresses these key points.

Table 49 Summary of key points raised by the ERG and AC and how the 'de novo' economic model addresses these key points

NICE/ERG comments	How does the 'de novo' economic model addresses these key points
The analysis fails to consider structural uncertainty adequately	The revised model is constructed as an individual based model to allow exploration of structural uncertainty. A number of scenario analyses were conducted to examine structural uncertainties – see section 5.8.3
Use of a lifetime horizon of 35 years is inappropriate	In accordance with the NICE reference case, a patient lifetime horizon was used given the chronic nature of the disease, and in order to capture all the relevant costs and benefits associated with the introduction of ruxolitinib in England and Wales. Scenario analyses were conducted using 5, 10, 15 and 20-year time horizons – see section 5.8.3
The definition of response used in the model is a 35% reduction in spleen volume and is used as the stopping rule for ruxolitinib. This is a much narrower definition of response than that used in clinical practice, or defined within the IWG-MRT clinical improvement criteria	In the revised model, response to ruxolitinib and hence the stopping rule is based on a definition of response which includes a reduction in splenomegaly and/or symptoms – see section 5.2.4 Scenario analyses were conducted assuming alternative response definition
No definition of response is included for BAT and non-responders remain on BAT for the duration of the model	No formal response criteria are used in practice for standard therapies. Thus, no response criteria were considered in the revised model
Representation of disease progression is inadequate	In the revised model, patients initiating BAT are assumed to achieve some control of symptoms and haematological parameters but not splenomegaly. Patients may continue to receive BAT until death, or may stop receiving BAT (after exhaustion of possible options) and progress to receive supportive care (in the Supportive Care health state). Patients initiating therapy with ruxolitinib may respond by week 24 and then remain on ruxolitinib until discontinuation. They then move directly to supportive care and experience worsening in symptoms until death See section 5.2.2
Splenectomy and splenic irradiation should be included as separate health states in the model, rather than being included as complications, because the complications health state of the manufacturer's model is only applicable	In the revised model, splenectomy and splenic irradiation are not considered as these are rarely used in the UK due to the associated morbidity and mortality − see section 3.3

to the non-responder health state and response is determined by spleen size only.	
Transfusion dependence should be included in the base-case	RBC transfusions are considered in the base case – see section 5.5.3
The effects of treatment on haematological symptoms should be considered in the model, especially as ruxolitinib is associated with a short-term worsening of anaemia and thrombocytopenia	Ruxolitinib treats MF-related splenomegaly and symptoms but not the anaemia associated with MF. It can cause transient increase in anaemia. However, in the COMFORT trials, haematological events are managed effectively by dose modifications and temporary treatment interruptions, as well as with RBC transfusions in the case of anaemia. These aspects of therapy are included in the revised economic model – sections 5.5.2 and 5.5.3 Long-term evidence from the COMFORT-II trial are used to approximate the effect of ruxolitinib of RBC transfusion. Scenario analyses are conducted.
Exclusion of LT in the base case is inappropriate	LT is included in the base case – section 5.3.8
Complications of myelofibrosis should be included for both responders and non-responders as some of these complications may not be decreased by a reduction in spleen size	In the revised model, LT is the only complication considered given the absence of robust data for other complications. The probability of LT over the patient's life time is considered for each patient and cost was applied to patients predicted to have LT. See section 5.3.8 and 5.5.5
In the model an exponential distribution is used for survival	In the revised model, OS in patients initiating BAT is assumed to follow a Gompertz distribution in the base case. Different parametric distributions were explored in sensitivity analyses (Figure 72) – see section 5.3.1
The model uses splenomegaly as a proxy for survival	In the revised model, splenomegaly is not use as a surrogate for survival. OS for patients randomised to BAT is taken directly from the COMFORT-II corrected for crossover. For patients randomised to ruxolitinib, time to death following discontinuation of ruxolitinib is taken from COMFORT-II − see section 5.3.7
Uncertainty in the source used for survival benefit is not considered	In the revised model, the survival for patients on ruxolitinib is taken from COMFORT-II. Scenario analyses were conducted regarding OS for patients on BAT. In the base case OS was taken from COMFORT-II adjusted for crossover. Scenario analyses considered ITT OS from COMFORT-II – see section 5.3.1 Given the uncertainty of the long-term extrapolation and the amount of data available (about 3.5 years), scenario analyses are conducted assuming patients on ruxolitinib to be treated for a maximum duration of 3.5 years, 5 years, 7.5 years and 10 years. Similarly, scenario analyses are conducted assuming patients on ruxolitinib to remain alive for a maximum duration of 3.5 years, 5 years, 7.5 years and 10 years following ruxolitinib discontinuation.
In the model no adjustment for the cross-over of patients from BAT to ruxolitinib is considered	In the revised model, the OS for patients on BAT is taken from an analysis adjusted for cross-over using the RPFST − see section 5.3.7

Assuming patients achieving a response (reduction in splenomegaly) at 24 weeks remain on ruxolitinib for the duration of the model is inappropriate.	In the extension phase of COMFORT-II patients were able to remain on ruxolitinib until the clinician believed patients were no longer deriving a benefit. The discontinuation rate from COMFORT-II is therefore likely to reflect what would happen in clinical practice. Consequently, in the revised model, the discontinuation rate from the COMFORT-II trial was used as a proxy for discontinuation of ruxolitinib.– see section 5.3.6
There is a high level of uncertainty surrounding the appropriateness of the utility estimates assumed to represent myelofibrosis	In the revised model, changes in health utilities are taken directly from COMFORT-I. Given the lack of sensitivity of the EORTC QLQ C-30 and EQ-5D to capture change in MF symptoms and HRQoL, changes in HRQoL are based on a condition-specific measure, the MF-8D, which utilises data from the disease-specific instrument, the MF-SAF, used in COMFORT-I – see section 5.4.1
The model fails to capture all the symptomatic and HRQoL aspects of the disease such as those related to prominent symptoms such as itch and fatigue	In the revised model, changes in health utilities are based on a condition-specific measure, the MF-8D, which utilises data from the disease-specific instrument, the MF-SAF, used in COMFORT-I. The MF-SAF and hence the MF-8D, captures the impact of treatment on disease-specific symptoms. – see section 5.4.1
Utility values assumed to be constant over time, ie. the benefit from ruxolitinib assumed to be maintained The model does not explicitly model loss of response, ie people in the responder health state are assumed to maintain the same level of spleen reduction and the associated utility benefits over time	Additional evidence is available since the last appraisal of ruxolitinib. Although the evidence suggests that HRQoL using the EQ-5D decreases with advancing age, analysis of the COMFORT-I data indicated that the baseline MF-8D remained constant irrespective of age. Hence, in the revised model we assumed the baseline HRQoL to remain constant over time to reflect the trial data. Similarly, to reflect additional data available since the last appraisal, we assumed in the revised model that patients on ruxolitinib maintain their initial gain at 24 weeks. This reflects the long-term clinical evidence which showed that patients originally randomised to ruxolitinib who continued on therapy maintain their initial gain in the MF-SAF TTS and spleen volume over time after 24 weeks (see section 5.4.1). These long-term trends implicitly take into account the loss of response, and worsening of splenomegaly, symptoms and HRQoL as this is an average calculated for patients experiencing a worsening, no change in status or an improvement. Consequently, assuming patients maintain their initial gain in HRQoL until discontinuing therapy is not an assumption but reflects the new data available. However for completeness, extreme scenario analyses are presented assuming patients on ruxolitinib do not maintain their initial gain. These are pessimistic scenarios.
The model fails to capture the effect of the progressive nature of MF on HRQoL	In the revised model, HRQoL for patients on BAT was assumed to remain unchanged as BAT is believed to provide a temporary control of symptoms and HRQoL as demonstrated in COMFORT-II using FACT-Lym.

	In contrast, patients on supportive care are assumed to experience a progressive worsening of HRQoL until death (linear increase) Section 5.4.5
Dose adjustments were included in the model but would not necessarily result in cost savings given the pricing of the different doses. Treatment interruptions should however be considered as they are likely to generate cost savings.	In the revised model, cost savings resulting from dose reduction/interruption are included based on the number of days a patient receives each dose (range 0 to 25 mg BID) in the COMFORT-II trials. This takes into dose reduction and interruption and account for the different tablet strengths available and their difference prices. See section 5.5.2
Assuming that that BAT is given for the full 12 weeks of each treatment cycle may not be appropriate	In the revised model, the cost of BAT is calculated under two assumptions, a conservative assumption were the cost associated with one pack (injection) is assumed per 12 week period or a more optimistic approach where the necessary number of packs (injections) per 12 week period are assumed. The average of the estimated cost under these two approaches is used in the base case. Sensitivity analyses (Figure 72) are conducted assuming costs calculated under the conservative or optimistic assumption.
Specific modelling of resource use (e.g. consultations, test) associated with administration, monitoring and switching between treatment is not included in the analysis and is likely to be a conservative assumption in favour of ruxolitinib	In the revised model: No administration costs are included for BAT or ruxolitinib. This is likely to be conservative assumption in favour of BAT given that ruxolitinib is orally administered but some BAT therapies will incur administration costs. Resource use for monitoring and laboratory tests is included based on estimates of resource use for management of MF. See section 5.5.1 and 5.5.3

5.7 Base case results

5.7.1 Base case incremental cost effectiveness analysis results

Base case results are presented in Table 50. The model predicted that, over a lifetime, the total discounted QALYs for patients initiating BAT would be [redacted]. Patients initiating ruxolitinib accrued [redacted] QALYs over a lifetime (ie a gain of [redacted] discounted QALYs compared with BAT).
The model predicted the total discounted costs for patients initiating BAT to be £36,271. The total discounted costs predicted for patients initiating ruxolitinib was £[redacted] (ie an increment of £[redacted] compared with BAT).

Compared with BAT, the ICER for ruxolitinib therapy was £[redacted] per QALY gained. The model predicted an increase in the number of patients experiencing LT over time in the ruxolitinib arm due to the increase in life expectancy ([redacted]% versus [redacted]%); however, it is uncertain whether this would be true in practice.

Table 50 Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£36,271	2.15	1.476				£24,577	
Ruxolitinib	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

5.7.2 Clinical outcomes from the model

Overall survival

The predicted OS for all patients initiating BAT and all patients initiating ruxolitinib (accounting for the stopping rule at Week 24) is provided in Figure 62. As expected, patients initiating ruxolitinib have a predicted survival advantage compared with patients initiating BAT. The model predicted that no patients initiating BAT would be alive at 10 years compared with approximately [redacted]% in patients initiating therapy with ruxolitinib. Furthermore, in the COMFORT trials, patients were treated irrespective of response (ITT OS shown Figure 62– black line). As expected, the survival predicted by the model in patients initiating ruxolitinib (red dotted line) is lower than the survival observed in the trial (black line) as a proportion of patients (≈[redacted]%) at Week 24 are assumed to switch to BAT as they did not achieve a spleen or symptom response.

Figure 62 Predicted overall survival for patients initiating ruxolitinib (accounting for the stopping rule at Week 24)

BAT, best available therapy; ITT, intention-to-treat; OS, overall survival; Rux, ruxolitinib.

Predicted outcomes from the economic model were compared with clinical data from the COMFORT-II trial for patients initiating BAT. As expected, the model provided a reasonable prediction of the withdrawal rate from the COMFORT-II trial and OS rate corrected for crossover in patients initiating BAT (Figure 63). Overall, the model provided a reasonable fit to the observed data.

Figure 63 Predicted withdrawal and overall survival in patients initiating BAT compared with that observed in COMFORT-II

Similarly, predicted outcomes from the economic model were compared with clinical data from the COMFORT-II trial in patients initiating ruxolitinib when possible. Overall, the model provided good prediction of the proportion of patients in each of the 4 outcome categories (spleen response, no spleen response, early discontinuation and early death) in COMFORT-II (**Error! Reference source not found.**).

Figure 64 Proportion of patients in each of the outcome category compared with that observed in COMFORT-II

As expected, the model also provided a reasonable prediction for the proportion of patients who did not achieve a spleen response but who achieved a symptom response in COMFORT-I (Figure 65).

Figure 65 Predicted proportion of symptom responders amongst non-spleen responders compared with that observed in COMFORT-I

The model predictions in terms of OS and treatment discontinuation were reasonable in patients experiencing early death. The model predicted a mean survival of [redacted] weeks and mean time on treatment of [redacted] weeks in patients experiencing early death compared with [redacted] weeks and [redacted] weeks respectively.

Similarly, the model provided a reasonable prediction of the discontinuation rate (Figure 66) and OS (Figure 67) in patients initiating ruxolitinib experiencing early discontinuation

Figure 66 Predicted discontinuation rate in patients initiating ruxolitinib and experiencing early discontinuation

Predictions for patients initiating ruxolitinib who did not achieve a response (compared with patients initiating BAT) are shown in Figure 68. Unfortunately, it is not possible to validate the model prediction for this group of patients as these patients were treated for the full duration in the COMFORT-II trial. In the base case, we assumed that these patients would live an additional 24 weeks compared with patients initiating BAT. Clinical advisors felt this was appropriate and possibly conservative.

Figure 67 Predicted overall survival in patients initiating ruxolitinib and experiencing early discontinuation

Figure 68 Predicted overall survival in patients initiating ruxolitinib achieving neither a spleen nor a symptom response at week 24

Finally, the model provided a reasonable prediction of the discontinuation rate and OS in patients initiating ruxolitinib and experiencing a spleen response at Week 24 (Figure 69) from the COMFORT-II trial.

Figure 69 Predicted discontinuation and overall survival in patients initiating ruxolitinib experiencing a spleen response at week 24

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

As expected, most incremental QALYs gained and additional costs are incurred in the ruxolitinib health state whilst patients are treated with ruxolitinib.

Table 51 Summary of QALY gain by health state

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukaemic transformation (decrement)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BAT, best available therapy; QALY, quality-adjusted life year.

Table 52 Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Ruxolitinib	£[redacted]	£[redacted]	£[redacted]	£[redacted]	[redacted]%
BAT	£[redacted]	£[redacted]	-£[redacted]	£[redacted]	[redacted]%
Supportive care	£[redacted]	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Leukaemic transformation	£[redacted]	£[redacted]	£[redacted]	£[redacted]	[redacted]%
Total	£[redacted]	£[redacted]	£[redacted]	£[redacted]	[redacted]%

BAT, best available therapy.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to take into account the simultaneous effect of uncertainty relating to model parameter values. A total of 1,000 simulations were performed in order to provide sufficient information on uncertainty. Uncertainty surrounding all important model parameters was described by probability distributions (gamma for costs, beta for binomial and Dirichlet for multinomial proportion, multivariate normal for regression models) and propagated through the model using Monte Carlo sampling. The choice of distribution was based on consideration of the properties of the parameters and data informing the parameters. The results of the probabilistic sensitivity analysis are presented as cost-effectiveness planes and cost effectiveness acceptability curves. The choice of distribution is described in Table 47.

The results of the probabilistic sensitivity analyses using 1,000 iterations is shown below (Table 53). Over a lifetime, patients receiving ruxolitinib accrue more QALYs ([redacted] QALYs) compared with patients initiating BAT ([redacted]QALYs), but at a greater cost (£[redacted] versus £[redacted] respectively). The ICER is £[redacted]per QALY gained in the probabilistic sensitivity analysis.

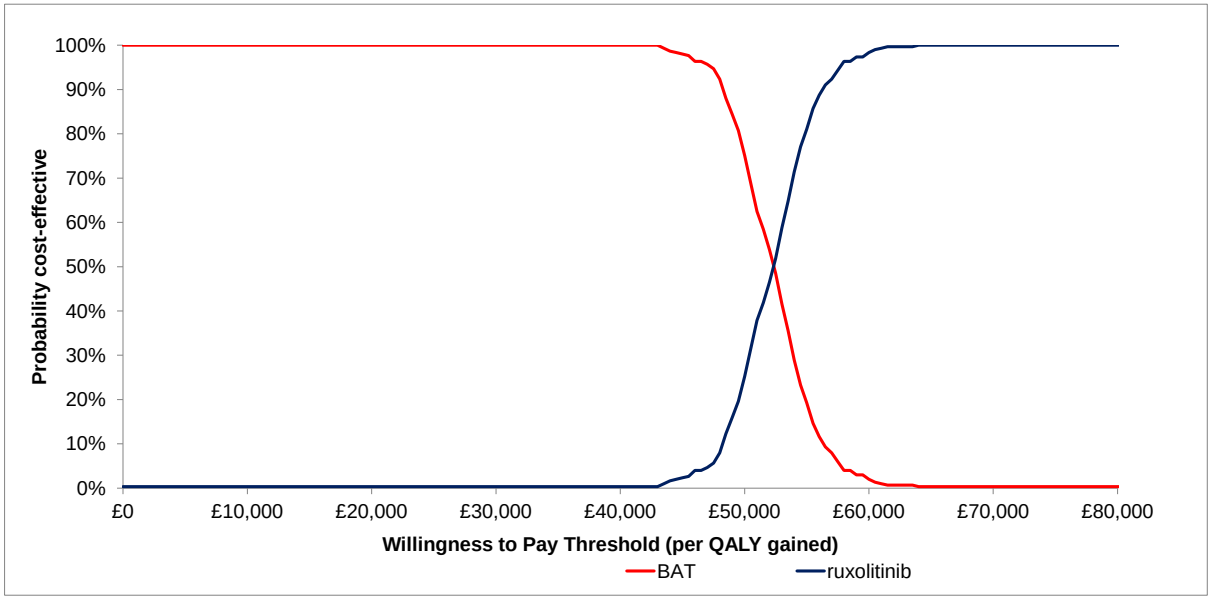
Table 53 Results of the probabilistic sensitivity analysis

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	[redacted]	[redacted]	£[redacted]	
BAT	[redacted]	[redacted]	£[redacted]	
Incremental	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

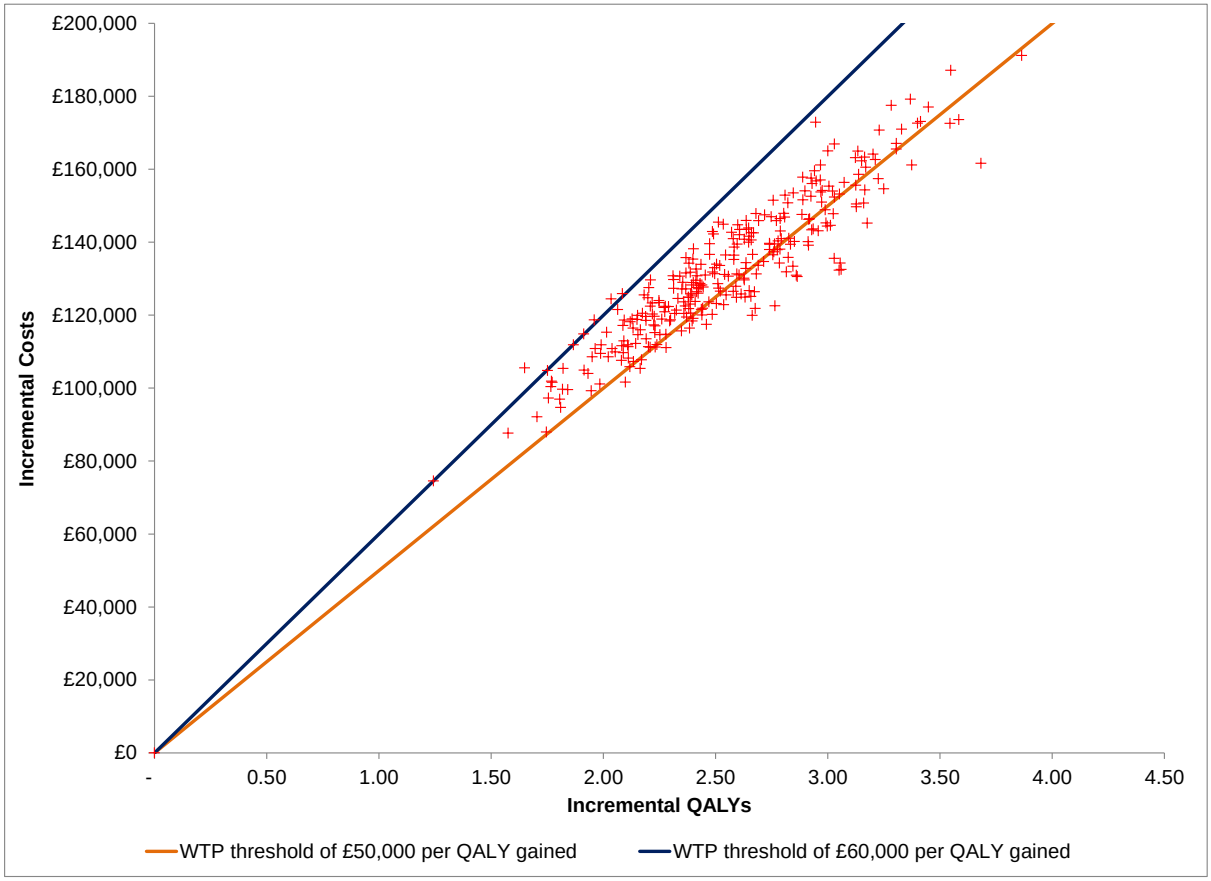
Figure 70 and Figure 71 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision maker may be willing to pay for an additional QALY. The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is [redacted]%, [redacted]%, [redacted]% and [redacted]% when using a threshold of £30,000, £40,000, £50,000 and £60,000 per QALY, respectively.

Figure 70 Cost effectiveness acceptability curves



BAT, best available therapy; QALY, quality-adjusted life year.

Figure 71 Cost effectiveness plane



QALY, quality-adjusted life year. WTP, willingness to pay threshold

5.8.2 Deterministic sensitivity analysis

All inputs to the model were included in a one-way sensitivity analysis. Parameters were varied within the reported range, CI or within reasonable range as shown in Table 54.

A Tornado diagram is presented in Figure 72 for the 20 parameters that had the largest impact on the ICER. The ICER was mostly sensitive to the parameters regarding the distribution for OS for BAT and the post-ruxolitinib discontinuation survival. Other input parameters had a limited impact in the ICER (less than £2,000)

Table 54 Summary of values used in the sensitivity analysis

Parameters	Value used in the base case	Lower Range	Upper Range	Distribution used
Outcome category in COMFORT-II	Parameters varied within 95% CI			Dirichelet (95%)
Proportion of symptom responders	[redacted]%	[redacted]%	[redacted]%	Beta (95% CI)
BAT discontinuation rate	Parameters varied within 95% CI			Multivariate (95%)
BAT overall survival	Parameters varied within 95% CI			Multivariate (95%)
Proportion dying upon BAT discontinuation	5.48%	1.53%	11.70%	Beta (95% CI)
Discontinuation - Group 5	Parameters varied within 95% CI			Multivariate (95%)
Post-discontinuation survival - Group 5	Parameters varied within 95% CI			Multivariate (95%)
Discontinuation - Group 4	Parameters varied within 95% CI			Multivariate (95%)
Discontinuation - Group 1	Parameters varied within 95% CI			Multivariate (95%)
Proportion dying upon rux discontinuation	-	-	-	Not varied
Post-discontinuation survival - Group 1 & 4	Parameters varied within 95% CI			Multivariate (95%)
Baseline HRQoL	[redacted]	[redacted]	[redacted]	Beta (95% CI)
Adjustment baseline HRQoL	[redacted]	[redacted]	[redacted]	Assumption
Change in HRQoL - BAT	[redacted]	[redacted]	[redacted]	Assumption
Change in HRQoL - supportive care	[redacted]	[redacted]	[redacted]	Beta (95% CI)
Change in HRQoL - non-responders (rux)	[redacted]	[redacted]	[redacted]	Beta (95% CI)
Change in HRQoL - responders (rux)	[redacted]	[redacted]	[redacted]	Beta (95% CI)
Leukemic transformation (duration of event)	2.70	1.60	3.60	Lognormal (95% CI)
Leukemic transformation (decrement in utility)	0.48	0.40	0.55	Assumption
Annual incidence LT on rux	1.42%	0.47%	2.86%	Beta (95% CI)
Annual incidence LT on BAT	2.83%	0.79%	6.04%	Beta (95% CI)
Drug cost - rux	£793.30		£807.50	Assumption
BAT cost	£364.40	£171.84	£556.97	Assumption
Supportive care drug cost	£1.99	£1.00	£3.98	Assumption
AEs costs − rux	£1.18	£0.59	£2.35	Assumption
AEs costs − BAT	£0.90	£0.45	£1.80	Assumption
AEs costs - supportive care	£0.00	£0.00	£0.00	Not varied
GP unit cost	£46.00	£37.43	£55.44	Gamma (95% CI) standard error assumed to be 10% around the mean
Outpatient visit unit cost	£92.27	£48.82	£119.34	
Urgent care unit cost	£44.00	£35.80	£53.03	
A&E unit cost	£150.00	£122.05	£180.79	
Cost per LT event	£44,903.00	£8,170.00	£81,636.00	Lower and

Parameters	**Value used in the base case**	**Lower Range**	**Upper Range**	**Distribution used**
				upper range
Cost per RBC unit	£235.00	£191.21	£283.24	Gamma (95% CI) standard error assumed to be 10% around the mean
Number of RBC unit per week at EOL	2.00	1.00	3.00	Assumption
Number of outpatient visits per week at EOL	1.00	0.50	2.00	Assumption
Cost palliative care	5,324.00	4,460.43	6,262.85	Gamma (95% CI)
Unit cost - hospital night	£158.00	£128.56	£190.44	Gamma (95% CI) standard error assumed to be 10% around the mean
Unit cost - FBC	£5.50	£4.48	£6.63	
Unit cost - U&E	£14.98	£12.19	£18.06	
Hospital nights per week (BAT)	7.98	4.44	12.53	Gamma (95% CI)
Outpatient visits per week (BAT) – intermediate-2 risk	10.48	8.16	13.08	Gamma (95% CI)
Outpatient visits per week (BAT) - high risk	12.45	8.59	17.01	Gamma (95% CI)
Number of GP visits per week	0.36	0.16	0.64	Gamma (95% CI)
Number of A&E visit per week (BAT)	0.15	0.06	0.29	Gamma (95% CI)
Number of urgent care visits per week (BAT)	0.04	0.00	0.11	Gamma (95% CI)
Number of FBC tests per week (BAT)	16.81	12.13	22.24	Gamma (95% CI)
RBC assumption on BAT (compared with supportive care)	80.00%	70.00%	100.00%	Assumption
RBC units per week whilst on supportive care	0.78	0.56	1.02	Gamma (95% CI)
Impact of ruxolitinib on resource use	Parameters varied within 95% CI			
Monitoring ruxolitinib (interval in weeks)	18	12	24	Assumption
Monitoring whilst on supportive care (compared with BAT)	50.00%	20.00%	100.00%	Assumption
Resource use supportive care (compared with BAT)	100.00%	75.00%	125.00%	Assumption

BAT, best available therapy; EOL, end of life; FBC, full blood count ; HRQoL, health-related quality of life; LT, leukaemic transformation; RBC, red blood cell; Rux, ruxolitinib; U & E, urea and electrolytes

Figure 72 Univariate sensitivity analysis

5.8.3 Scenario analysis

Important variables in the model were altered in scenario analyses. Results of scenario analyses are presented below.

Time horizon

In the base case analysis, the costs and benefits of treatment were examined over the lifetime of patients as per NICE reference case. Scenario analyses were conducted assuming everyone would die (and therefore discontinue) after 5 years, 10 years, 15 and 20 years.
As expected, the pessimistic assumption of all patients dying at 5 years led to increase in the ICER. However, reducing the time horizon to 10, 15 or 20 years had little impact on the ICER.

Table 55 Scenario analysis 1: reducing the time horizon

	Ruxolitinib			**BAT**			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Time horizon = 5 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Time horizon = 10 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Time horizon = 15 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Time horizon = 20 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

BAT discontinuation

In the base case, BAT discontinuation is assumed to follow a Gompertz distribution. Scenario analyses were conducted assuming the BAT discontinuation rate to follow an exponential, Weibull or log-normal distribution. The impact was minimal.

Table 56 Scenario analysis 2: BAT discontinuation – parametric curves

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation = exponential	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation = Weibull	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation = Log-normal	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In the base case analysis, the BAT discontinuation rate is taken from the COMFORT-II trial. Clinical advisors felt that the BAT discontinuation rate from the trial may be higher than in practice due to the trial design. Scenario analyses were conducted assuming the BAT discontinuation rate to be underestimated by 10−40%. There are uncertainties regarding the duration patients remain on BAT. Increasing the duration patients remain on BAT (with symptom control) had a limited impact on the ICER.

Table 57 Scenario analysis 3: Duration on BAT

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation reduced by 10%	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation reduced by 20%	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation reduced by 30%	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT discontinuation reduced by 40%	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

OS in patients treated under current practice (ie in the absence of ruxolitinib)

In the base case, the OS was taken from the COMFORT-II trial corrected for crossover assuming a Gompertz distribution as this provided a reasonable fit to both the observed and unobserved period. As expected, the ICER increases if the survival follows the exponential and log-normal distribution. However, these distributions had very long tails and do not provide a clinically plausible extrapolation of the survival as shown in Figure 44. In contrast the impact on the ICER was minimal using the Weibull distribution which provided a reasonable and plausible fit to the data.

Table 58 Scenario analysis 4: overall survival for BAT corrected for crossover: parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT OS (cross-over adjusted) = exponential	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT OS (cross-over adjusted)= Weibull	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT OS (cross-over adjusted)= Log-normal	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Similarly, although this was not considered to be realistic, scenario analyses were conducted using the ITT OS from the COMFORT-II trial for completeness. Results are only presented using the Weibull and the Gompertz as the log-normal and exponential were not plausible (Figure 73). As expected the ICER increased (Table 59).

Table 59 Scenario analysis 5: overall survival for BAT, COMFORT-II, intention-to-treat: parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT OS (ITT)= Weibull	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
BAT OS (ITT)= Gompertz	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; QALY, quality-adjusted life year.

Figure 73 Kaplan–Meier curve for overall survival in patients initiating BAT and fit of selected parametric distributions: COMFORT-II, intention-to-treat

Post-BAT discontinuation survival

In the base case, we assumed the post-BAT discontinuation survival (survival after BAT discontinuation) to follow a Weibull distribution with an arbitrary shape of 0.63 as this provided a reasonable fit the observed OS. To examine the impact of this structural uncertainty, we varied the shape from –1 to 1. As expected, the impact on the ICER is minimal (Table 60) given that the mean survival post-BAT discontinuation remains relatively unchanged (with the exception of small variations due to sampling errors). However, the shape of the curve may have an impact because of discounting.

Table 60 Scenario analysis 6: Shape of the post-BAT survival curve

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = -1)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = -0.8)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = -0.6)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = -0.4)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = -0.2)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = 0)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = 0.2)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = 0.4)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = 0.6)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
BAT post-discontinuation survival (shape of Weibull = 0.8)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
BAT post-discontinuation survival (shape of Weibull = 1)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In the base case analysis, we calculated the area under the curve and assumed that the mean post-BAT discontinuation survival follows a Weibull distribution with an arbitrary shape of 0.63. Whilst necessary, this approach is unconventional. Consequently to examine this structural uncertainty, three alternative approaches are examined, where

Approach 1: the OS and time to BAT discontinuation are sampled independently of each other. As previously mentioned this approach ignores the correlation between BAT discontinuation and OS and may create some inconsistencies such that the time to BAT cessation may on some occasions be greater than OS (which is not possible). In those circumstances, we adjusted the time to discontinuation down leaving OS unchanged.

Approach 2: the same approach as above (OS and time to BAT discontinuation are sampled independently) but the time to death is adjusted up with the time to discontinuation unchanged.

Approach 3: the time alive post-BAT discontinuation is calibrated (assuming a Weibull distribution) using the Metropolis-Hasting algorithm so that the predicted OS matches the observed OS Kaplan–Meier. For speed of calculation, the calibration is done outside the economic model.

The impact on the ICER was minimal (Table 61).

Table 61 Scenario analysis 7: Examining structural assumption regarding the estimate for post-BAT survival

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Approach 1: BAT OS and discontinuation sampled (discontinuation adjusted)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Approach 2: BAT OS and discontinuation sampled (OS adjusted)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Approach 3: BAT post-discontinuation survival calibrated	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Response criteria

The impact of different response criteria has been examined (see Table 29). The impact on the ICER is minimal (Table 62).

Table 62 Scenario analysis 8: response criteria

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥50% spleen reduction & ≥25% MF-SAF reduction)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥25% spleen reduction & ≥50% MF-SAF reduction)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥25% spleen reduction & ≥25% MF-SAF reduction)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥50% spleen reduction & ≥ upper MID FACT-Lym)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥50% spleen reduction & ≥ lower MID FACT-Lym)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥25% spleen reduction & ≥ upper MID FACT-Lym)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Response definition (≥25% spleen reduction & ≥ lower MID FACT-Lym)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Ruxolitinib discontinuation

In the base case analysis, the discontinuation rate for patients on ruxolitinib achieving a spleen response was assumed to follow an exponential distribution. A scenario analysis was conducted assuming other distributions (Weibull, Gompertz, log-normal). The impact on the ICER was minimal.

Table 63 Scenario analysis 9: ruxolitinib discontinuation rates in patients a spleen response; parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Discontinuation responder (Group1) = Weibull	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Discontinuation responder (Group1) = Gompertz	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Discontinuation responder (Group1) = Log-normal	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In addition, given the uncertainty regarding the long-term extrapolation, scenario analyses were conducted assuming all patients to remain on treatment for a maximum duration of 3.5 years, 5 years, 7.5 and 10 years. Assuming patients to remain on ruxolitinib for a maximum of 3.5 years had a limited impact on the ICER.

Table 64 Scenario analysis 10: Maximum duration on ruxolitinib

	Ruxolitinib			BAT			ICER
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Basecase	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Ruxolitinib is stopped at 3.5 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Ruxolitinib is stopped at 5 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Ruxolitinib is stopped at 7 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Ruxolitinib is stopped at 10 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Survival post-ruxolitinib discontinuation

In the base case analysis, the (pooled) survival following ruxolitinib discontinuation in patients experiencing early discontinuation (Group 4) and spleen responders (Group 1) was assumed to follow an exponential distribution. Scenario analyses were conducted assuming the discontinuation to follow a Weibull or a log-normal distribution. The impact on the ICER was minimal. The Gompertz was not examined as the extrapolation was not realistic.

Table 65 Scenario analysis 11: survival following ruxolitinib discontinuation (pooled); **parametric survival distributions**

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Post-discontination survival (rux) - Weibull	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Post-discontination survival (rux) - log-normal	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; PPS, QALY, quality-adjusted life year.

In addition, given the uncertainty regarding the long-term extrapolation, scenario analyses were conducted assuming all patients to be alive for a maximum duration of 3.5 years, 5 years, 7.5 and 10 years following ruxolitinib discontinuation. Assuming patients to remain alive for a maximum of 3.5 years following ruxolitinib cessation had a limited impact on the ICER.

Table 66 Scenario analysis 12: Maximum duration alive post-ruxolitinib discontinuation

	Ruxolitinib			BAT			ICER
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Basecase	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
post-discontinuation maximum = 3.5 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
post-discontinuation maximum = 5 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
post-discontinuation maximum = 7.5 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
post-discontinuation maximum = 10 years	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

Furthermore, in the base case analysis, the survival following ruxolitinib discontinuation in patients achieving a spleen response (Group 1) and early discontinuation (Group 4) was pooled. Scenario analysis are conducted using the post-discontinuation survival specific to each group. The impact on the ICER was minimal (Table 67). The Gompertz was not examined as the extrapolation was not realistic.

Table 67 Scenario analysis 13: survival following ruxolitinib discontinuation in patients achieving a spleen response; parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Separate post-discontinuation survival (Group 1 & 4) - exponential	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Separate post-discontinuation survival (Group 1 & 4) - Weibull	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Separate post-discontinuation survival (Group 1 & 4) - log-normal	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Finally, in the base case analysis, we assumed that patients on ruxolitinib not achieving a primary response at Week 24 lived an additional 24 weeks compared with patients initiating BAT. A scenario analysis was conducted relaxing this assumption, assuming that the time spent on ruxolitinib is part of the period of time on treatment on BAT. Consequently, these patients will be treated for a shorter duration on BAT, thereby reducing the survival of these patients. The impact on the ICER was minimal (Table 68).

Table 68 Scenario analysis 14: survival following ruxolitinib discontinuation in patients not achieving response

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Reduced survival for patients on ruxolitinib (Group 3)	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Leukaemic transformation

In the base case LT was included. A scenario analysis was conducted excluding LT, given the uncertainty and possible double counting. For completeness, a scenario analysis was also conducted assuming the same rate of LT between treatment arms. However, this is unrealistic and lead to more LT in the ruxolitinib arm due to the increased survival (Table 69).

Table 69 Scenario analysis 15: leukaemic transformation

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Incidence of LT assumed to be the same	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Removal of LT	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Assumptions regarding HRQoL

In the base case analysis, HRQoL was measured using the MF-8D v1. Scenario analyses were conducted measuring HRQoL using the MF-8D v2 or the baseline EQ-5D data from the ROBUST UK study (Table 70).

Table 70 Scenario analysis 16: HRQoL measure

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
HrQoL measured using the MF-8Dv2	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
HrQoL measured using the EQ-5D	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In the base case analysis, in the absence of data, we assumed no worsening in HRQoL in patients treated with BAT. Clinical advisors felt this was optimistic and that patients may experience some gradual worsening in symptoms and HRQoL. Scenario analyses were conducted assuming patients on BAT experience a worsening in QoL. For completeness, scenario analyses were also conducted assuming patients on BAT can experience an improvement in HRQoL (Table 71).

Table 71 Scenario analysis 17: HRQoL assumptions while on BAT

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Change in HRQoL for BAT = half change in supportive care	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Change in HRQoL for BAT = 1/3 change in supportive care	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Change in HRQoL for BAT = 1/4 change in supportive care	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Change in HRQoL for BAT = half change on ruxolitinib	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Change in HRQoL for BAT = 1/3 change on ruxolitinib	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Change in HRQoL for BAT = 1/4 change on ruxolitinib	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life.

In the base case, patients on supportive care were assumed to have a progressive worsening in HRQoL based on Week 24 data from COMFORT-I. Scenario analyses were conducted assuming the rate to be halved after 24, 48 and 72 weeks. The impact was minimal (Table 72).

Table 72 Scenario analysis 18: HRQoL assumptions while on placebo

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Progression of HRQoL on supportive care halved after 24 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Progression of HRQoL on supportive care halved after 48 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Progression of HRQoL on supportive care halved after 72 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In the base case analysis, we assumed that patients on ruxolitinib experience the change in HRQoL as early as 4 weeks. Scenario analyses were conducted assuming the improvement in HRQoL occurs at 8, 12, 16 or 20 weeks respectively. The impact was minimal (Table 73).

Table 73 Scenario analysis 19: short-term HRQoL assumptions while on ruxolitinib

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Patients on ruxolitinib experience an improvement in HrQoL at 8 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Patients on ruxolitinib experience an improvement in HrQoL at 12 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Patients on ruxolitinib experience an improvement in HrQoL at 16 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Patients on ruxolitinib experience an improvement in HrQoL at 20 weeks	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In the base case analysis, we assumed that patients on ruxolitinib maintain their initial improvement in HRQoL while on treatment as supported by clinical evidence. Two pessimistic scenario analyses were conducted assuming that patients do not maintain their initial gain. These are very pessimistic and unlikely to be true but lead to only a moderate increase in the ICER (Table 74).

Table 74 Scenario analysis 20: long-term HRQoL progression assumption while on ruxolitinib

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Patients on ruxolitinib do not maintain their initial gain in HrQoL	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
25% reduction in gain in HRQoL every 52 weeks for patients on ruxolitinib	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Finally, a scenario analysis was conducted assuming constant HRQoL within the health states (Table 75). The impact on the ICER was minimal.

Table 75 Scenario analysis 21: structural assumptions regarding HRQoL

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]
Constant HrQoL	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Assumptions regarding red blood cell transfusion units

Scenario analyses were conducted assuming no impact of ruxolitinib on RBC requirements (compared with BAT), an increase in RBC units by 5% over the lifetime for patients on ruxolitinib, and an increase by 5% every 24 weeks in patients on supportive care. These assumptions had little impact on the ICER

Table 76 Scenario analysis 22: assumptions regarding RBC transfusions

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Basecase	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
No impact of ruxolitinib on RBC units	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Ruxolitinib is associated with a 5% increase in RBC units over the lifetime	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Increase in RBC units by 5% every 24 weeks for patients on supportive care	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; RBC, red blood cell; QALY, quality-adjusted life year.

Discount rates

Finally, scenario analyses were conducted varying the discount rates. As expected discount rates had a moderate impact on the ICER.

Table 77 Scenario analysis 23: discount rate

Description	**Ruxolitinib**			**BAT**			**ICER**
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Discount rate (1.5% cost)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Discount rate (1.5% QALYs)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]
Discount rate (both 1.5%)	[redacted]	[redacted]	**£**[redacted]	[redacted]	[redacted]	**£**[redacted]	**£**[redacted]

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.8.4 Summary of sensitivity and scenario analyses results

A range of sensitivity (Figure 72) and scenario analyses was conducted to test the robustness of the model input and structural assumptions. Overall, results were robust to most parameters and structural assumptions.

Reducing the time horizon to 10 years or over had little impact on the ICER. As expected, results were sensitive to the assumption used for the survival of patients initiating BAT. Of note, clinical advisors felt that the survival based on the ITT analysis (not corrected for cross-over) was an overestimate and a less robust representation of the survival of patients initiating BAT compared with the survival adjusted for crossover in the COMFORT trials.

Structural assumptions were also examined. Assuming a longer duration on BAT had a limited impact on the ICER. Assuming that patients who do not achieve the required level of response at Week 24 remain on BAT for a shorter duration compared with patients initiating BAT had limited impact on the ICER. The exclusion of leukaemic transformation had a limited impact on the ICER. Similarly, assuming all patients on ruxolitinib to remain on treatment for a maximum duration of 3.5 years or alive for a maximum duration of 3.5 years following ruxolitinib discontinuation had a minimal impact on the ICER.

Different assumptions were explored for the progression of HRQoL. Most assumptions had limited impact on the ICER. A scenario was examined assuming that patients on ruxolitinib do not maintain their initial gain in HRQoL. This is very pessimistic, given that, on average, the evidence suggests that patients on treatment maintain their initial gain. As expected, the ICER increased, although even in this pessimistic scenario the increase was only moderate. We also examined changes in HRQoL measured using the MF-8D v2 and the EQ-5D. The increase in the ICER was minimal.

A range of sensitivity analyses were conducted on costs and resource use. Varying these parameters had limited impact on the ICER.

5.9 Subgroup analysis

As outlined in section 5.2.1 analysis for specific subgroups was not explored.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

The conceptual model was developed with the aid of an Advisory Group, composed of three haematologists through a series of interactive meetings, teleconferences and email exchanges, supplemented by a review of the evidence available to ensure that the proposed model structure closely reflect the natural history and real-world clinical practice and that all model assumptions are clinically valid.

Excel formulas, model logic and input data were verified for accuracy as part of quality-control procedures by the experienced modeller involved in the model development. Notably, excel formulas

were checked to ensure their reflect the logic of the model. In addition, the model was varied within extreme value beyond what would be considered “reasonable” to ascertain whether the change in the simulated costs and utilities was consistent with a priori expectation.

To ensure external validity, model predictions were also compared to observed data when possible (see section 5.7.2).

5.11 Interpretation and conclusions of economic evidence

The study has a number of strengths. The model was developed with the aid of an Advisory Group supplemented by a review of the published literature. The economic analysis is based on three and a half years efficacy data from the COMFORT-II trial, supplemented with evidence from three open label studies. These studies included patients who were representative of those who would receive ruxolitinib in clinical practice, and included patients with all MF subtypes. Data on current management of MF is taken, where possible, from the UK data sources, including the HMRN MF audit and evidence from an open label study (ROBUST UK study).

The model considered the important aspects of the course and nature of the disease, including splenomegaly and symptoms and included important complications such as LT. Haematological aspects of the disease are captured through the requirement for RBC transfusions. The model included a stopping rule at 24 weeks to reflect the ruxolitinib licence and expected clinical practice. The economic analysis is also consistent with recommendations from the NICE reference case and uses a NHS/PSS perspective and benefits are expressed in terms of QALYs. Health-related quality of life (HrQoL) was measured using both the EQ-5D (taken from ROBUST UK study) and a condition specific measure (the MF-8D measured in COMFORT-I).

As with any evaluation, the study has several limitations. These include the lack of a clear definition of response to treatment in clinical practice. Clinical opinion indicated that there are no well-defined, validated or accepted definitions of response, and that in clinical practice the decision to discontinue treatment is usually taken on a case-by-case basis. The economic analysis uses the recent IWG-MRT / ELN consensus-based definition of response criteria for use in clinical trials. However different definitions were explored in scenario analyses and showed little impact on the ICER.

One key area of uncertainty is the OS for patients initiating BAT. In the pivotal trials, patients on BAT were allowed to cross-over to ruxolitinib; therefore over-estimating the OS for patients initiating BAT. Clinical advisors felt that the OS corrected for cross-over was the most appropriate source to use within the economic model. For transparency, the OS from ITT analysis was used in scenario analysis. As expected the ICER deteriorated when assuming a greater survival for patients initiating

BAT, but the increase was moderate when considering only the parametric distribution that provided a plausible extrapolation.

Long term discontinuation was taken from the COMFORT-II study. Clinical opinion indicated that the discontinuation rate from this study was reflective of clinical practice. The survival benefit following ruxolitinib discontinuation was taken from the COMFORT-II study. The parametric distribution was fitted to the current data (3.5 years) and therefore the extrapolation may be uncertain although scenario analyses were conducted assuming different distributions.

There were also some structural uncertainties in the method used to depict the treatment pathway and the natural course in MF such as estimating the survival post-BAT cessation or the survival following ruxolitinib discontinuation in patients not achieving a primary response at Week 24. Scenario analyses were conducted to examine the impact of these structural assumptions and showed that the impact on the ICER was limited.

The long term impact of ruxolitinib on resource use is also unclear; however, this again had limited impact on results.

Simplification was made in terms of the modelling LT in order to avoid double counting its impact. However, again the impact on results was limited.

Finally, the assumption about progression of HrQoL had limited impact on the ICER.

The economic analysis does not include the impact on carers and social services or productivity. This is likely to underestimate the benefit of ruxolitinib in England and Wales.

6 Assessment of factors relevant to the NHS and other parties

6.1 People eligible for treatment in England

The prevalence of MF is estimated to be 2.2/100.000.[59] Based on a population of 53,865,800 in England in mid-2013[204] and at a growth rate of 0.7%, this would suggest that there were 1,202 patients with MF in England in 2015. Based on an incidence of 0.4 per 100,000,[205] it is estimated that there would be approximately 219 newly-diagnosed MF patients each year (Table 78).

Table 78 Number of patients with MF in England and Wales

	2015	2016	2017	2018	2019
Population of England and Wales	54,622,561	55,004,919	55,389,953	55,777,683	56,168,126
Prevalence: 2.2/100,000	1,202	1,210	1,219	1,227	1,236
Incidence: 0.4/100,000	219	220	222	223	225

Ruxolitinib is for indicated for the treatment of disease-related splenomegaly or symptoms in adults with MF. Given that the majority of patients are symptomatic and have splenomegaly, most could potentially benefit from ruxolitinib treatment.[10] However, market research among clinical experts indicates that, in clinical practice, treatment will depend on the risk classification of patients as well as the extent of splenomegaly.[60] The estimated number of patients likely to be eligible for treatment is therefore calculated according to the following classifications: low/intermediate-1 risk and spleen <5 cm; low/intermediate-1 risk and spleen >5cm; intermediate-2/high risk and spleen <5cm; intermediate-2/high risk and spleen >5 cm and is given in Table 79. According to this estimate, about half of all MF patients would be considered to be eligible for treatment with ruxolitinib.

Table 79 Estimated number of patients eligible for ruxolitinib treatment according to risk group

	Low/Int-1, < 5 cm	Low/Int-1, > 5 cm	Int-2/HR, < 5 cm	Int-2/HR, > 5 cm	Total
Proportion of total patients	31%	25%	22%	22%	
No. of patients by classification	373	301	264	264	1,202
Proportion of patients eligible for therapy	26%	48%	60%	77%	
No. of patients eligible for therapy	97	144	158	204	603

Int-1, intermediate-1 risk; int-2, intermediate-2 risk; HR, high-risk

6.2 Assumptions regarding current treatment options

The current standard treatment for MF, where busulphan is the only licensed therapy, is BAT. BAT covers a range of treatment options, including no treatment. It is assumed that the current market share is 50% and that the market share of these treatment options will decline as more effective, licensed drugs become available for the treatment of MF.

6.3 Assumptions regarding ruxolitinib market share and eligible patients in England

Conventional best available therapy is of limited benefit in the treatment of MF. It is therefore assumed that the uptake of ruxolitinib in eligible patients will be 70% in 2015, rising to a steady share of 80% by 2017. The share of our defined market for eligible patients is relatively high in year 1 (2015) due to the fact that ruxolitinib has been available through the Cancer Drugs Fund since 2012.

The estimated ruxolitinib market share is given in Table 80.

Table 80 Estimated ruxolitinib market share

	2015	2016	2017	2018	2019
Market share – eligible patients	70%	75%	80%	80%	80%

Each year, a new cohort of patients will start ruxolitinib treatment. After the initial 24 weeks, only responders will continue with ruxolitinib treatment. Based on the economic model, the discontinuation rate at the end of year 1 will be 44% (to account for non-responders stopping treatment at 24 weeks);

the discontinuation rate for subsequent years is estimated to be 21%. The number of patients receiving treatment each year, taking into account discontinuations, is shown in Table 81.

Table 81 Estimated number of patients treated with ruxolitinib by year

	2015	2016	2017	2018	2019
Number of initial cohort (ie prevalent cohort) treated over time	422	186	147	116	91
Incident cohorts entering in subsequent years		82	123	155	181
Total number of patients on treatment	422	268	270	271	272
Cumulative number of patients treated	422	504	592	680	769

6.4 Technology and other costs associated with treatment with ruxolitinib

The cost of ruxolitinib in the first year (to account for non-responders) is estimated to be £[redacted] from the cost effectiveness model. The cost of subsequent weeks of treatment is £[redacted] per week. The estimated cost of ruxolitinib treatment is summarised in Table 82.

Table 82 Estimated costs of ruxolitinib treatment

	2015	2016	2017	2018	2019
Initial cohort (ie prevalent cohort) treated over time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident cohorts entering in subsequent years		[redacted]	[redacted]	[redacted]	[redacted]
Total ruxolitinib costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 Unit cost assumptions

Unit costs are based on the unit costs used in the cost effectiveness model.

6.6 Estimates of resource savings

The resource savings generated by response to ruxolitinib treatment relate to reduced use of other medical therapies and savings associated with a reduction in number of GP visits, hospitalisations, consultant visits, A&E admissions and urgent visits. Short-term additional costs associated with blood transfusions are taken into account for patients treated with ruxolitinib. The annual cost of BAT is estimated to be £[redacted]. Table 83 shows the estimated net overall savings.

Table 83 Savings associated with ruxolitinib use

	2015	**2016**	**2017**	**2018**	**2019**
BAT costs	666,808	422,414	426,975	428,203	429,811
Savings: reductions in resource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BAT, best available therapy

6.7 Estimated annual budget impact of ruxolitinib on the NHS in England

The estimated budget impact of ruxolitinib is summarised in Table 84.

Table 84 Estimated budget impact of ruxolitinib

	2015	**2016**	**2017**	**2018**	**2019**
Total ruxolitinib costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET BUDGET IMPACT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact is therefore estimated to be £[redacted] million in year 1, which takes into account the prevalent population of MF patients who would be eligible for ruxolitinib treatment, before stabilizing at approximately £[redacted] million per year.

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Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) [ID831]

Dear Company

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 16 June by Novartis Pharmaceuticals Ltd. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Tuesday 28 July**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals.

If you have any further queries on the technical issues raised in this letter then please contact Helen Tucker, Technical Lead (helen.tucker@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A1. The inclusion/exclusion criteria were changed for the updated 2013/2014 review; please explain why health related quality of life was removed from the list of eligibility criteria? Please also explain why studies only reporting adverse event risk/incidence were excluded from the review and whether any studies were excluded based on this exclusion criterion.

A2. **Priority question:** Please provide study details and reference numbers for the 61 included references (as per Figure 8 on page 58) and explain any that are not included in the review.

A3. **Priority question:** The JUMP and EXPAND studies have only been reported as conference abstracts/posters – is there a draft manuscript or other report available?

A4. An ongoing phase 1b dose-finding study referred to at the end of the third paragraph on page 113. Is this the EXPAND study? If not, please give a reference and further details of this study.

A5. A large proportion of patients in the COMFORT trials had doses reduced (Section 4.12.3), please present the reasons for dose titration, e.g. anaemia, thrombocytopenia, other reasons.

A6. **Priority question:** Please present the analysis of overall survival for COMFORT II with an adjustment for cross-over, as presented for COMFORT I and the pooled analysis on pages 102 and 103.

A7. **Priority question:** Adverse event data have not been consistently presented for the COMFORT I and COMFORT II trials (Tables 21 to 24). Please present the incidence (%) of new-onset adverse events (any grade) using the long term follow-up data for COMFORT I and COMFORT II, for the different durations of ruxolitinib treatment (6 month intervals), also stating the number of patients for each time point (which is missing from Table 21). Please provide this information for both haematological and non-haematological adverse events, not just adverse events of special interest.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The clinical advisor to the ERG has advised that in addition to the comparators in the final NICE scope, allogenic-Stem cell transplant (SCT) is used and is effective in Int2 and high risk patients. This is supported by a recent publication (Kroger et al. Blood 2015; 125: 3347-50). Therefore, allogenic-SCT and ruxolitinib as a bridge to allogeneic-SCT could be considered as comparators. Please provide further justification for the absence of allogeneic-STC as a comparator in the cost-effectiveness analysis.

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B2. **Priority question:** The mortality while on ruxolitinib post 24 weeks is unclear. – On page 176 it suggests that there is zero mortality because no discontinuations due to death were observed in the Comfort II study. This seems implausible; please consider adding a strictly positive mortality rate (using an appropriate source) for the ruxolitinib responder's group post 24 weeks to the cost-effectiveness model.

B3. **Priority question:** Please confirm if the mortality rate of 5.48% of BAT patients described on page 166 is of all patients receiving BAT and not just those who discontinued BAT. Please provide details of the causes of death for these 4 patients, at least stating whether the deaths were myelofibrosis related.

B4. **Priority question:** It is assumed in the cost-effectiveness model that non-responders to ruxolitinib survive an additional 24 weeks compared with those on BAT. Please provide further justification for this assumption. Can a drop down menu be added on the options sheet to relax this assumption as per scenario analysis number 14 (page 249).

B5. **Priority question:** Please conduct an alternative analysis assuming that the stopping rule for treatment with ruxolitinib is applied at 12 weeks instead of 24 weeks. If possible, please incorporate an option in the model to allow the user to select when the stopping rule is applied?

B6. **Priority question:** The NICE scope defined the comparator of interest to be established clinical practice without ruxolitinib. Lenolidamide has been used as a comparator in the submission, but as hydroxycarbamide is commonly used to treat adults with myelofibrosis, please conduct an alternative analysis assuming that patients currently receiving lenalidomide receive hydroxycarbamide instead.

B7. The DIPPS database provides information on patients receiving BAT therapy. Please comment on the comparability of predicted overall survival in BAT patients from the COMFORT II study adjusting for crossover and that observed in comparable patients in the DIPPS database.

B8. Sleep and symptom responders are likely to experience different HRQoL gains, but the utility gains from being in the responder group in the model do not account for different proportions of spleen and symptom responders. Please comment on how changes in the composition of this group will influence the mean utility gain from being a responder.

B9. Within the executable model the utility values for each health state change according to the response definitions. Please confirm that this reflects differences in the mean health related quality of life gain observed in the COMFORT I study for these groups?

B10. On page 160 of the submission the importance of the common treatment effect assumption is noted when using rank-preserving structural failure time models (RPSFT) models. Please discuss the plausibility of this assumption in the present context.

Section C: Textual clarifications, searches and additional points

Textual clarifications

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C1. **Priority question:** Figure 32, please present the number of patients for the 150 week time point.

C2. On page 72, it appears that the proportion discontinuing due to adverse events should read 5%, not 10.6% - please clarify.

C3. In Figure 10 on page 73, 3 patients are unaccounted for; please supply a corrected version of Figure 10.

C4. The final sentence on page 72 states that disease progression was the primary reason for discontinuation of treatment (23.1% of patients in the ruxolitinib group, 32.5% in the placebo group and 27.8% in the crossover group). Please explain where the figures 23.1% and 32.5% are from, as they do not appear to correspond with Figure 10 on page 73.

C5. Please provide a key for 'a' in Table 21.

C6. Please provide a key for * and ** in Table 43.

C7. In table 29, there is a key for 'a', and the text in the table was not marked using the key, please clarify.

Searching - Clinical effectiveness

C8. Please clarify why the search of the BIOSIS database for the 2011/2012 review not updated for the 2013/2014 review? (Appendix 2, Section 8.2.1, page 5)

C9. Please clarify why the search of clinical trials.gov for the 2011/2012 review not updated for the 2013/2014 review? (Appendix 2, Section 8.2.3, page 32)

C10. Which platforms were used to search EMBASE and the Cochrane Library? (Appendix 2, Section 8.2.1, page 5)

C11. The cost effectiveness analysis registry is listed as being searched as part of the Cochrane Library. Is this correct? (Appendix 2, Section 8.2.1, page 5)

C12. Were any particular study design search filters used in the search strings listed for each database? (Appendix 2, Section 8.2.2 pages 6-31)

C13. For the 2013/2014 review the conference proceedings are reported as being searched from January 2012 onwards. Why were they not searched from July 2011 onwards (the date of the last update) (Appendix 2, Section 8.2.3, page 32)?

C14. How were the conference proceedings searched? (Appendix 2, Section 8.2.3, page 127)

C15. How were the studies on adverse reactions identified? (Section 4.12, page 117)

Searching – Cost-effectiveness

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C16. The searches from the first literature review to support a previous NICE STA are not reported in the Appendix 11, Section 8.11, page 39. Please provide them.

C17. Which platforms were used to search EMBASE and the Cochrane Library? (Appendix 11, Section 8.11.3, page 39)

C18. The cost effectiveness analysis (CEA) registry is listed as being searched as part of the Cochrane Library. Is this correct? (Appendix 11, Section 8.11.3, page 39)

C19. How was the conference proceedings searched? Were the online or paper copies used? Were they searched or browsed? Were any keyword searches carried out? (Appendix 11, Section 8.11.3, page 40)

Searching – Health-related quality-of-life studies

C20. It appears that the same search was used to identify cost-effectiveness and health-related-quality-of-life studies. Please could this be confirmed? If they were the same, then the further questions C20-C23 do not apply.

C21. The searches from the first literature review to support a previous NICE STA are not reported in the Appendix 13, Section 8.13.2, page 71. Please could they be provided?

C22. Which platforms were used to search EMBASE and the Cochrane Library? (Appendix 13, Section 8.13.3, page 71)

C23. How were the conference proceedings searched? Were the online or paper copies used? Were they searched or browsed? Were any keyword searches carried out? (Appendix 13, Section 8.13.3, page 71)

C24. The search strings for EMBASE, 1st update only are provided in Appendix 13, Section 8.13.4, page 72-75. There are further strategies on page 98-112 which look like they are the rest of the health-related-quality-of-life studies searches. Please could this be confirmed?

Confidentiality marking in the submission

C25 Please reconsider the confidentiality marking in your documentation to be in line with NICE processes: most importantly please remove the confidentiality status of the following:

- base case results of the economic analysis (QALYs, incremental QALYs, costs, incremental costs, life years gained, incremental life years gained and ICERs)
- mean and median overall survival estimates from the COMFORT II trial
- the estimated number of patients eligible for treatment with ruxolitinib

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Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) [ID831]

Dear Company

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 16 June by Novartis Pharmaceuticals Ltd. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Tuesday 28 July**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under '[redacted]' in turquoise, and all information submitted under '[redacted]' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals.

If you have any further queries on the technical issues raised in this letter then please contact Helen Tucker, Technical Lead (helen.tucker@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A1. The inclusion/exclusion criteria were changed for the updated 2013/2014 review; please explain why health related quality of life was removed from the list of eligibility criteria? Please also explain why studies only reporting adverse event risk/incidence were excluded from the review and whether any studies were excluded based on this exclusion criterion.

A2. **Priority question:** Please provide study details and reference numbers for the 61 included references (as per Figure 8 on page 58) and explain any that are not included in the review.

A3. **Priority question:** The JUMP and EXPAND studies have only been reported as conference abstracts/posters – is there a draft manuscript or other report available?

A4. An ongoing phase 1b dose-finding study referred to at the end of the third paragraph on page 113. Is this the EXPAND study? If not, please give a reference and further details of this study.

A5. A large proportion of patients in the COMFORT trials had doses reduced (Section 4.12.3), please present the reasons for dose titration, e.g. anaemia, thrombocytopenia, other reasons.

A6. **Priority question:** Please present the analysis of overall survival for COMFORT II with an adjustment for cross-over, as presented for COMFORT I and the pooled analysis on pages 102 and 103.

A7. **Priority question:** Adverse event data have not been consistently presented for the COMFORT I and COMFORT II trials (Tables 21 to 24). Please present the incidence (%) of new-onset adverse events (any grade) using the long term follow-up data for COMFORT I and COMFORT II, for the different durations of ruxolitinib treatment (6 month intervals), also stating the number of patients for each time point (which is missing from Table 21). Please provide this information for both haematological and non-haematological adverse events, not just adverse events of special interest.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The clinical advisor to the ERG has advised that in addition to the comparators in the final NICE scope, allogenic-Stem cell transplant (SCT) is used and is effective in Int2 and high risk patients. This is supported by a recent publication (Kroger et al. Blood 2015; 125: 3347-50). Therefore, allogenic-SCT and ruxolitinib as a bridge to allogeneic-SCT could be considered as comparators. Please provide further justification for the absence of allogeneic-STC as a comparator in the cost-effectiveness analysis.

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B2. **Priority question:** The mortality while on ruxolitinib post 24 weeks is unclear. – On page 176 it suggests that there is zero mortality because no discontinuations due to death were observed in the Comfort II study. This seems implausible; please consider adding a strictly positive mortality rate (using an appropriate source) for the ruxolitinib responder's group post 24 weeks to the cost-effectiveness model.

B3. **Priority question:** Please confirm if the mortality rate of [redacted] of BAT patients described on page 166 is of all patients receiving BAT and not just those who discontinued BAT. Please provide details of the causes of death for these 4 patients, at least stating whether the deaths were myelofibrosis related.

B4. **Priority question:** It is assumed in the cost-effectiveness model that non-responders to ruxolitinib survive an additional 24 weeks compared with those on BAT. Please provide further justification for this assumption. Can a drop down menu be added on the options sheet to relax this assumption as per scenario analysis number 14 (page 249).

B5. **Priority question:** Please conduct an alternative analysis assuming that the stopping rule for treatment with ruxolitinib is applied at 12 weeks instead of 24 weeks. If possible, please incorporate an option in the model to allow the user to select when the stopping rule is applied?

B6. **Priority question:** The NICE scope defined the comparator of interest to be established clinical practice without ruxolitinib. Lenolidamide has been used as a comparator in the submission, but as hydroxycarbamide is commonly used to treat adults with myelofibrosis, please conduct an alternative analysis assuming that patients currently receiving lenalidomide receive hydroxycarbamide instead.

B7. The DIPPS database provides information on patients receiving BAT therapy. Please comment on the comparability of predicted overall survival in BAT patients from the COMFORT II study adjusting for crossover and that observed in comparable patients in the DIPPS database.

B8. Sleep and symptom responders are likely to experience different HRQoL gains, but the utility gains from being in the responder group in the model do not account for different proportions of spleen and symptom responders. Please comment on how changes in the composition of this group will influence the mean utility gain from being a responder.

B9. Within the executable model the utility values for each health state change according to the response definitions. Please confirm that this reflects differences in the mean health related quality of life gain observed in the COMFORT I study for these groups?

B10. On page 160 of the submission the importance of the common treatment effect assumption is noted when using rank-preserving structural failure time models (RPSFT) models. Please discuss the plausibility of this assumption in the present context.

Section C: Textual clarifications, searches and additional points

Textual clarifications

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C1. **Priority question:** Figure 32, please present the number of patients for the 150 week time point.

C2. On page 72, it appears that the proportion discontinuing due to adverse events should read 5%, not 10.6% - please clarify.

C3. In Figure 10 on page 73, 3 patients are unaccounted for; please supply a corrected version of Figure 10.

C4. The final sentence on page 72 states that disease progression was the primary reason for discontinuation of treatment (23.1% of patients in the ruxolitinib group, 32.5% in the placebo group and 27.8% in the crossover group). Please explain where the figures 23.1% and 32.5% are from, as they do not appear to correspond with Figure 10 on page 73.

C5. Please provide a key for 'a' in Table 21.

C6. Please provide a key for * and ** in Table 43.

C7. In table 29, there is a key for 'a', and the text in the table was not marked using the key, please clarify.

Searching - Clinical effectiveness

C8. Please clarify why the search of the BIOSIS database for the 2011/2012 review not updated for the 2013/2014 review? (Appendix 2, Section 8.2.1, page 5)

C9. Please clarify why the search of clinical trials.gov for the 2011/2012 review not updated for the 2013/2014 review? (Appendix 2, Section 8.2.3, page 32)

C10. Which platforms were used to search EMBASE and the Cochrane Library? (Appendix 2, Section 8.2.1, page 5)

C11. The cost effectiveness analysis registry is listed as being searched as part of the Cochrane Library. Is this correct? (Appendix 2, Section 8.2.1, page 5)

C12. Were any particular study design search filters used in the search strings listed for each database? (Appendix 2, Section 8.2.2 pages 6-31)

C13. For the 2013/2014 review the conference proceedings are reported as being searched from January 2012 onwards. Why were they not searched from July 2011 onwards (the date of the last update) (Appendix 2, Section 8.2.3, page 32)?

C14. How were the conference proceedings searched? (Appendix 2, Section 8.2.3, page 127)

C15. How were the studies on adverse reactions identified? (Section 4.12, page 117)

Searching – Cost-effectiveness

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C16. The searches from the first literature review to support a previous NICE STA are not reported in the Appendix 11, Section 8.11, page 39. Please provide them.

C17. Which platforms were used to search EMBASE and the Cochrane Library? (Appendix 11, Section 8.11.3, page 39)

C18. The cost effectiveness analysis (CEA) registry is listed as being searched as part of the Cochrane Library. Is this correct? (Appendix 11, Section 8.11.3, page 39)

C19. How was the conference proceedings searched? Were the online or paper copies used? Were they searched or browsed? Were any keyword searches carried out? (Appendix 11, Section 8.11.3, page 40)

Searching – Health-related quality-of-life studies

C20. It appears that the same search was used to identify cost-effectiveness and health-related-quality-of-life studies. Please could this be confirmed? If they were the same, then the further questions C20-C23 do not apply.

C21. The searches from the first literature review to support a previous NICE STA are not reported in the Appendix 13, Section 8.13.2, page 71. Please could they be provided?

C22. Which platforms were used to search EMBASE and the Cochrane Library? (Appendix 13, Section 8.13.3, page 71)

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- mean and median overall survival estimates from the COMFORT II trial
- the estimated number of patients eligible for treatment with ruxolitinib

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national charity; founded in 1967 and first registered with the Charity Commission in 1969; which exists to provide vital support services to patients, their families and carers during the difficult journey through the diagnosis and treatment of all forms of blood cancer (leukaemia, lymphoma; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; myelodysplastic syndrome; myeloproliferative disorders & aplastic anaemia).

Our current membership database stands at approximately 13,500 (this includes patients, carers and members of the patients immediate family members.)

Leukaemia CARE offers this support through its head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line and live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- Nurse conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets (Information Standard Approved.)

Since its inception over 25 years ago our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes information on the emotional impact of a blood cancer and help for those caring for a patient. Our focus is purely on supporting anybody affected by a diagnosis of blood cancer, simply supporting a quality of life for all (see - http://www.leukaemiacare.org.uk)

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a cancer of the blood to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 90% of our total funding come from our own fund raising activities, either via our members and fund raisers, legacies, grants, on-line shop, Christmas card sales, recycling exercises etc.

Leukaemia CARE receives funds from a wide range of Pharmaceutical companies, but in total those funds on average do not exceed more than 10% of our total income. The funds received from the Pharmaceutical Industry are received and dispersed strictly within the Guidelines as laid down by the ABPI Code of Practice 2015, Clause 27 - Relationships with Patient Organisations.[1]

We also operate strictly within the Guidelines defined by the "Leukaemia CARE Code of Practice."[2] This Code of Practice governing corporate funding is a commitment undertaken by Leukaemia CARE regarding our financial relationships with all commercial entities and the pharmaceutical industry in particular. Both of these documents can be examined via the hyperlinks listed below, or they are available in hard copy upon request.

We pride ourselves on our independence from any external influence/undue pressure arising from any of the other stakeholder bodies operating within the same sphere of activity as ourselves – the Industry, the NHS, the DoH, NICE, the Medical Profession etc., all bodies that we work closely with but are independent from. We will maintain our independence to the best of our ability and eschew any support that could adversely impact our reputation. This fact is made clear to any drug company (or other body) seeking our advice/assistance at the time of first contact. Our Code of Practice is also shared with them at that time.

1 - http://www.pmcpa.org.uk/thecode/InteractiveCode2015/Pages/clause27.aspx
2 - http://www.leukaemiacare.org.uk/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Patients with myelofibrosis (MF) usually experience a gradual onset of symptoms. Many patients experience few or no symptoms in the early stages of MF and may often be diagnosed after having tests for an unrelated condition. When symptoms do appear in patients, usually in the later stages of MF, they often vary greatly. Common symptoms include severe fatigue; night sweats; itching; bone pain; fevers; loss of appetite and undesired weight loss. We would like to stress that for patients with myelofibrosis fatigue is not just general tiredness; it may be totally debilitating and can hugely impact on quality of life.

In patients with MF abnormal stem cells take over the bone marrow, leading to fibrosis (scarring) and chronic inflammation, which prevents the bone marrow from producing enough normal blood cells. The spleen and liver then try to compensate by producing blood cells, which often leads to the spleen becoming enlarged (splenomegaly if the spleen becomes enlarged – or hepatomegaly if the liver becomes enlarged). If the spleen does become enlarged patients often report feelings of pain or discomfort in the abdominal area and a feeling of fullness or a loss of appetite. Patients can also suffer from the physical pressure of an enlarged liver/spleen on the lungs/thoracic cavity leading to rapid and prolonged exhaustion on even the slightest exertion. The impact of all this on a patient's (and consequently the patients carer, family and friends) quality of life can be very significant. About 10-20% of MF cases develop into acute myeloid leukaemia (AML).

Whilst symptoms do vary greatly from patient to patient, they often affect every aspect of normal life including a patient's ability to work, socialise and play a part in family life.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The goal of current treatments is to prolong life where possible, reduce any symptoms and improve patients' quality of life.

The main aspects which patients require help with are:

1. Prolonging life
2. The symptoms of myelofibrosis
3. The intolerable side effects of current treatments

All of these treatment outcomes are extremely important to patients. However, of primary importance would be improving quality of life and prolonging life.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

With the exception of stem cell transplants, which are not suitable for most patients and in themselves carry a high risk of morbidity and mortality, treatments do not offer a curative option. Current treatments (with the exception of SC treatments) also usually have a limited impact on prolonging life.

Current treatments are often either unsuitable for a number of patients or they come with a number of side effects which patients have difficulty tolerating. Some of the chemotherapy treatments can also increase the chances of MF developing into AML.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

1. Prolonging life

Recent data appears to show that ruxolitinib can offer an improvement in life expectancy to patients, which current treatments (other than stem cell transplants) do not offer.

2. The management of symptoms such as pain and extreme tiredness.

Ruxolitinib appears to address many of the symptoms of MF, but the main benefit of this treatment is the reduction on the size of the spleen and the symptoms that go with this element of the condition. Without this particular treatment it is possible that the removal of the spleen is a treatment option which results in life long treatment needs. Ruxolitinib addresses all core symptoms of MF and general quality of life is improved. Ruxolitinib acts very quickly on symptoms and as a result quality of life can improve very quickly for patients.

3. The intolerable side effects of current treatments

A further benefit of ruxolitinib is that by providing an alternative treatment option with limited, manageable side effects the intolerable side effects of the current treatment options are avoided, which results in an improvement in patients' quality of life.

4. Helping relieve psychological distress

For MF patients (friends, family and carers, employers and employees), knowing that there is realistic treatment available should their disease progress to a stage where quality of life becomes severely impaired and symptomatic control become a necessary option, will have a huge positive impact on their psychological well-being, even though only a few may ever need to access the treatment.

The psychological impact this would have on the few patients that will need to be prescribed ruxolitinib, where their QoL could be greatly improved, would be very reassuring.
The psychological outlook of the patients, carers and the patients' extended family/friends and indeed all the Healthcare Professionals involved in the treatment of those patients would be enhanced by the availability of this treatment option.

5. Convenience of how and where the treatment is received

Ruxolitinib is an oral preparation, and can be safely taken at home.

6. The ability to self-care or maintain independence and dignity.

If ruxolitinib is successful in controlling the debilitating symptoms than can occur with MF, then those patients who do respond, will be fully able to return to self-care and full independence.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Existing Treatment	Advantages of new medicine
Stem Cell/ bone marrow transplant	1. Not all patients are suitable for SC/BMT – they are often only considered for fit patients with advanced disease who have a matched donor. 2. The transplant process itself comes with an increased risk of multiple morbidities & mortality that would not be present with the use of ruxolitinib. 3. Ruxolitinib would also take away the need for such invasive treatment – which would reduce the trauma suffered by patients.
Chemotherapy (most commonly hydroxycarbamide)	1. Ruxolitinib offers increased life expectancy over chemotherapy. 2. Ruxolitinib addresses symptoms more quickly. 3. Ruxolitinib reduces the risk of patients developing AML. 4. Patients on chemotherapy may develop anaemia and possible increased risk of infections such as shingles.
Splenectomy	1. No surgical procedure required – reduced trauma for patients. 2. Risks of surgery reduced – involves its own morbidities and mortalities. 3. Splenectomy is considered a last resort – ruxolitinib would offer an earlier treatment option.
Thalidomide	1. Reduces fatigue. 2. Thalidomide is not suitable for patients who are pregnant.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Existing Treatment	Disadvantages of New medicine
Stem Cell/ bone marrow transplant	Whilst ruxolitinib does offer a prolonged life expectancy for patients, it is not a curative option

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the

treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership;

being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The treatment options for patients with MF historically have been very poor. Cytotoxic chemotherapy with a drug (hydroxyurea/hydroxycarbamide) considered to be more palliative than effective, or more recently thalidomide, a drug that comes with predetermined baggage of its own, offer patients a poor choice.

The novel use of a new class of drugs called Janus Kinase inhibitors (JAK1/JAK2) has finally offered patients with MF a real chance of improved outcomes for the first time in many years.

Are there any other issues that you would like the Appraisal Committee to consider?

Ruxolitinib has been approved by the Scottish Medicines Consortium (SMC) for use within NHS Scotland for the treatment of disease-related splenomegaly or symptoms in adult patients with myelofibrosis. Ruxolitinib is also currently available to patients in England via the Cancer Drugs Fund (CDF), providing they meet specific criteria.

However, patients in Wales are currently unable to access ruxolitinib. As such we feel that a failure to recommend the use of ruxolitinib would lead to an inequitable situation where the treatment available to patients would be vastly different in different across the devolved nations of the UK.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Myelofibrosis can be an extremely debilitating disease, with a wide range of symptoms that may impact hugely on the quality of life of patients.
- There are currently very limited treatment options for patients. In particular there is a clear unmet need for a treatment that can prolong patients' lives and improve the management of symptoms (consequently improving their quality of life).
- Ruxolitinib appears to address many of the symptoms of myelofibrosis, in particular a reduction in spleen size (and the associated symptoms), whilst also offering improved survival times.
- Ruxolitinib offers patients the ability to maintain their independence and dignity (by allowing them to self-care) as well as helping relieve psychological distress for all myelofibrosis patients (and their carers, family and friends) who would be comforted knowing that should their disease progress there is an available , effective treatment.

- Ruxolitinib has been approved for NHS use in Scotland and is available in England via the CDF. There would be clear inequality – with patients in Wales unable to access ruxolitinib - if it were not to be recommended.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] submitting comments on behalf of:

Name of your organisation: NCRI/RCP/ACP

Comments coordinated by [redacted]
Are you (tick all that apply):

a specialist in the treatment of people with the condition for which NICE is considering this technology?

a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

other? (please specify) a patient advocate

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

What is the expected place of the technology in current practice?

This condition is currently treated in secondary and tertiary care; there is no geographical variation in clinical practice. An area where professionals may differ is with regard to the benefit of using stem cell transplantation since this is often complex and more risks occur when this is used to treat myelofibrosis.

Current alternatives to Ruxolitinib include – watch and wait, hydroxyurea, interferon, IMIds such as thalidomide, steroids, danazol, and anaemia treatments such as ESA. Supportive care such as transfusions are common and other supportive care for symptoms such as itch include antihistamines. A very small number of patients undergo splenectomy, or splenic irradiation and also stem cell transplantation.

It is our understanding that ruxolitinib has been used to treat over 500 patients in the UK with myelofibrosis. There are some subgroups of patients where ruxolitinib may not be the ideal therapy these include patients with active infections, severe anaemia and severe thrombocytopenia. It is our belief that ruxolitinib should be used to treat symptoms and symptomatic splenomegaly; patients who lack these features should not be treated with this drug until there is further established evidence of its benefit.

The BCSH (British Committee for Standards in Haematology) has produced two guidelines for the management of myelofibrosis, the most recent ones were updated in 2014.

The advantages and disadvantages of the technology

Ruxolitinib is already in wide use in England for treating myelofibrosis thus we would consider that there are unlikely to be practical implications once it becomes available.

With regard to starting or stopping rules and subgroups for special consideration; the BCSH guidelines reflect the need to consider target response, duration of treatments and occurrence of toxicitiy such as myelosupression and infection in whether to continue with ruxolitinib. Since the issues addressed by the drug are not readily quantifiable and since the clinical trials have shown that even a 10% reduction in spleen volume which is hard to equate to a specific reduction in clinical practice (ie palpable spleen length) we think the determination of success and therefore therapy continuation is likely to need to be an individual determination. However, we do think this should be formally determined and there are tools to do this.

The clinical trial populations are broadly reflective of UK practice though often we would in standard practice treat sicker patients than those involved in clinical trials. In addition there is very little clinical trial data available for patients with just symptoms not splenomegaly, nor is there significant available data for patients with platelet counts below 100 x 10^9/L.

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Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Major side effects are myelosupression and risks of infection (the latter have emerged since the clinical trials). In addition caution is needed when stopping this drug as rebound in splenomegaly and symptoms can indeed be very severe.

Any additional sources of evidence

Our experts are not aware of any unpublished sources of clinical evidence for the benefits of Ruxolitinib that would not be accessible through standard searches. However patient testimonials are not widely available although these may be biased towards those patients with a positive experience.

Implementation issues

This drug has been widely used via clinical trials and the cancer drug fund, we do not think there are major needs for additional education or implementation issues should it be approved.

Equality

We do not think there are any equality issues with this appraisal

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Pathologists
Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

X other? (please specify) a patient advocate

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

What is the expected place of the technology in current practice?

MF is currently treated in a predominantly secondary and tertiary care setting with support from the community teams; a range of treatments are used. Dependent upon the disease stage and symptom burden, treatment approaches can range from observation alone; erythropoietin or transfusion support for disease associated anaemia, cytoreductive therapy with hydroxycarbamide or interferon, danazol or immunomodulatory drugs, and in some cases intensive therapy and allogeneic stem cell transplantation. More recently, first within the trial setting, and now through the CDF we have had access to Ruxolitinib. The fast track approval, and the subsequent European licencing of Ruxolitinib for MF patients with symptoms or splenomegaly, was based upon the lack of a prior standard and efficacious therapy and on robust data gained from two large phase III randomised trials called the COMFORT (COntrolled MyeloFibrosis study with Oral JAK inhibitoR Treatment) trials. More recent updates from these trials also suggest survival advantages amongst those on the agent for adequate duration. Current practice in the UK is to institute JAKi therapy for those with problematic splenomegaly or a significant disease-related sympom burden. We have to be aware of the cautions of use in those with severe thromobocytopaenia or who have concomitant active infection. The role of the drug in low risk disease is not fully established as yet.

Current alternatives to Ruxolitinib include – watch and wait, hydroxyurea, interferon, IMIds such as thalidomide, steroids, danazol, and anaemia treatments such as ESA. Supportive care such as transfusions are common and other supportive care for symptoms such as itch include antihistamines. A very small number of patients undergo splenectomy, or splenic irradiation and also stem cell transplantation.

It is my understanding that ruxolitinib has been used to treat over 500 patients in the UK with myelofibrosis. There are some subgroups of patients where ruxolitinib may not be the ideal therapy these include patients with active infections, severe anaemia and severe thrombocytopenia. It is my belief that ruxolitinib should be used to treat symptoms and symptomatic splenomegaly; patients who lack these features should not be treated with this drug until there is further established evidence of its benefit.

The BCSH (British Committee for Standards in Haematology) has produced 2 guidelines for the management of myelofibrosis, the most recent ones were updated in 2014.

The advantages and disadvantages of the technology

Ruxolitinib is already in wide use in England for treating myelofibrosis thus I would consider that there are unlikely to be practical implications once it becomes available.

Current data suggests that ruxolitinib is very well tolerated with predictable and manageable side effects. It can often control or attenuate disease-related symptoms and splenomegaly. Given the pivotal role of JAK2-STAT signalling in normal

haematopoiesis, a degree of reversible myelosuppresion is an expected consequence of therapeutic JAK inhibition. Thrombocytopenia – which is often mild and very manageable- is a common adverse event as we have seen from the phase I/II studies with ruxolitinib and also the COMFORT trials. Importantly, the COMFORT trials excluded patients with a platelet count of less than 100 x 10^9/L. More recent data suggests, however, that dose attenuated ruxolitinib can be given to those patients with more marked thrombocytopaenia safely with close montoring. The recently published BCSH guidelines suggest when the drug should be used in the clinical setting.. Two- and 3-year follow-up data further suggest that the benefits of ruxolitinib are durable and associated with a survival advantage compared with conventional therapies. However, careful management of treatment-related thrombocytopenia and anemia with dose modifications and supportive care is critical to allow chronic therapy. Treatment with ruxolitinib has also been shown to improve measures of metabolic and nutritional status of patients with intermediate-2 or high-risk MF

Low rates of non-haematological toxicity with diarrhoea, fatigue and headaches being the most common events were demonstrated in the clinical trials and are what we see in day-to-day clinical practice. The most common infectious complication was either respiratory or urinary tract infections in the clinical trial setting. Reactivation of herpes zoster has also been reported as well as case reports of more unusual infections. In context however, the incidence of these infectious complications remains low.

With regard to starting or stopping rules and subgroups for special consideration; the BCSH guidelines reflect the need to consider target response, duration of treatments and occurrence of toxicitiy such as myelosupression and infection in whether to continue with ruxolitinib. Since the issues addressed by the drug are not readily quantifiable and since the clinical trials have shown that even a 10% reduction in spleen volume which is hard to equate to a specific reduction in clinical practice (ie palpable spleen length) I think the determination of success and therefore therapy continuation is likely to need to be an individual determination. However I do think this should be formally determined and there are tools to do this.

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Major side effects are myelosupression and risks of infection (the latter have emerged since the clinical trials). In addition caution is needed when stopping this drug as rebound in splenomegaly and symptoms can indeed be very severe.

Any additional sources of evidence

I am not aware of any other available evidence outwith what is published or been presented at conferences and hence available for consideration. Collation of patient

subjective responses to the drug is probably under represented in the currently available data. There has been a recent update at ASH 2014 with 'real life non-trial' data from multiple centres concerning the efficacy of this agent. Reassuringly, this data demonstrated the benefits and efficacy of the agent that was observed within the phase III clinical trials.

Implementation issues

Initially through the trials and more recently with usage via the cancer drug fund, most clinicians with an interest in MPN who prescribe the drug are familiar with the dosing profile and side effect profile of the agent so I do not foresee many complications with planned implementation.

Equality

I do not think there are any equality issues with this appraisal

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Tim Somervaille PhD FRCP FRCPath
Honorary Consultant in Haematology
The Christie NHS Foundation Trust, Manchester, M20 4BX.

1. Introduction

Myelofibrosis is a type of blood cancer which in its more severe forms is associated with dramatically reduced quality and length of life. A typical untreated patient exhibits profoundly disabling symptoms which may include fatigue, progressive weight loss, drenching night sweats, intractable itch (sometimes precluding bathing), bone pain, spleen pain and the inability to complete a meal due to pressure on the stomach from the enlarged spleen. Blood abnormalities such as severe anaemia and thrombocytopaenia necessitating transfusion often accompany the disease. Less frequent consequences can include life threatening thrombosis, portal hypertension with consequent oesophageal varices, splenic infarction, cardiac failure, infections, pulmonary hypertension and evolution to acute myeloid leukaemia. This constellation of symptoms and the associated treatment requirements have the potential to make life miserable.

The diagnosis is based on features such as presence of bone marrow fibrosis, the presence of an associated mutation (i.e. in *JAK2*, *CALR* or *MPL*), splenomegaly, leucoerythroblastosis, tear drop poikilocytes, evidence of extramedullary haematopoiesis and presence of constitutional symptoms. Myelofibrosis may occur as a primary disease or evolve from polycythaemia vera or essential thrombocythaemia. It is predominantly a disease of the elderly. The incidence rate approximates to 0.5-1 per 100,000 per year.

Risk scores (e.g. Dynamic International Prognostic Scoring System, DIPSS) enable physicians to group patients into low, intermediate and high risk groups based on five key features: age >65, blood white cell count >25x10^9/L , severe anaemia (Hb <100g/L), proportion of immature blast cells in the blood >1% and the presence of constitutional symptoms.

The median survival for patients with high risk disease from diagnosis in the pre-JAK2 inhibitor era was 27 months and for those with intermediate-high risk disease, 48 months (Passamonti et al., 2010; Blood 115:1703).

The only curative treatment for myelofibrosis is allogeneic bone marrow transplantation although this is associated with significant procedure-related morbidity and mortality, impacting over 50% of recipients in multiple series. Five year survival rates following transplantation of 30-40% are typical. This is currently only considered for younger patients (<60-65 yr) with intermediate-high and high risk disease.

Prior to the advent of JAK2 inhibitors, patients with myelofibrosis had a profound unmet need for better therapies to improve both quality and length of life. Ruxolitinib has changed the therapeutic landscape for this troublesome disease by delivering significantly improved symptom relief, enhanced quality of life and prolonged survival.

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2. Development of ruxolitinib and clinical trials

The discovery of the gain-of-function *JAK2* V617F mutation (James et al., 2005; Nature 434:1144) highlighted constitutive JAK2 signalling as a critical oncogenic driver in human myeloproliferative neoplasms. This observation led to pre-clinical studies of pharmacological inhibitors of JAK2 which in turn supported the decision to proceed to early phase trials of this first-in-class molecularly targeted therapy.

A phase 1-2 trial of ruxolitinib (Verstovsek et al., 2010; NEJM 363:1117) demonstrated its efficacy, with ~50% of patients demonstrating a 50% reduction in splenomegaly. Importantly, there was rapid and sustained improvement in debilitating symptoms such as weight loss, fatigue, night sweats and pruritus. There was also a significant reduction in levels of circulating inflammatory cytokines that are commonly elevated in myelofibrosis and which may be major drivers of patient fatigue and malaise.

This study was followed by the flagship phase 3 trials COMFORT-1 and COMFORT-2 (Verstovsek et al., 2012; NEJM 366:799) (Harrison et al., 2012; NEJM 366:787). COMFORT-1 was a double blind placebo-controlled trial for patients with intermediate-high or high risk myelofibrosis, and 42% on ruxolitinib demonstrated a ≥35% reduction in spleen volume versus 1% of control patients. The spleen volume reduction was sustained in 67% of patients for the 48 week duration of the study. There was an improvement of 50% or more in the total symptom score at 24 weeks in 46% of ruxolitinib-treated patients versus 5% on placebo. Thirteen deaths occurred in the ruxolitinib group versus 24 in the placebo group (hazard ratio, 0.50; 95% confidence interval, 0.25 to 0.98; p=0.04). Discontinuation rates were 11% in both the ruxolitinib and placebo groups. The most common adverse events with ruxolitinib were anaemia and thrombocytopaenia.

COMFORT-2 was a randomized trial for patients with intermediate-high or high risk myelofibrosis of ruxolitinib versus best available therapy. Best available therapies used were hydroxycarbamide (46%), glucocorticoids (16%), erythropoietic agents (7%), anagrelide (5%), thalidomide (4%), danazol (4%), interferon (4%), mercaptopurine (4%), lenalidomide (3%), melphalan (3%), cytarabine (3%) or thioguanine (1%). Of the patients in the BAT group 33% were followed by watchful waiting. A total of 28% of patients on ruxolitinib demonstrated a ≥35% reduction in spleen volume versus 0% of BAT patients. The spleen volume reduction was sustained in 80% of patients at one year. Patients in the ruxolitinib group, but not the BAT group, had an improvement in overall quality-of-life measures and a reduction in symptoms associated with myelofibrosis. The most common adverse events with ruxolitinib were anaemia and thrombocytopaenia.

The data from these trials supported the FDA approval of ruxolitinib in 2011 for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythaemia vera myelofibrosis and post-essential thrombocythaemia myelofibrosis. In 2014 the FDA approved ruxolitinib for an additional indication, the treatment of polycythaemia vera resistant to or intolerant of hydroxycarbamide.

In a pooled analysis of the two COMFORT studies (both of which had a crossover design ensuring that all patients had access to ruxolitinib treatment, either at start of trial or 26 weeks later), intent-to-treat analysis showed that ruxolitinib-treated patients had prolonged survival at three years versus patients treated with placebo or BAT. The Kaplan-Meier estimate of overall survival at week 144 was 78% in the ruxolitinib arm, 61% in the intent-to-treat control arm, and 31% in the crossover-adjusted control arm (Vannucchi et al., 2015; Haematologica Epub).

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Together these studies demonstrated that ruxolitinib induces durable symptom improvement and spleen shrinkage, and provides a survival benefit for symptomatic patients with myelofibrosis.

3. Myelofibrosis treatment guidelines & the role of ruxolitinib in clinical practice

The British Committee for Standards in Haematology (BCSH) guideline for myelofibrosis was published in 2012 (Reilly et al., 2012; BJ Haem 158:453) and updated in 2014 in view of emerging data on the use of ruxolitinib (Reilly et al., 2014; BJ Haem 167:418). ***The updated guideline explicitly recommended ruxolitinib as first line therapy for myelofibrosis patients with symptomatic splenomegaly and/or constitutional symptoms, regardless of JAK2 mutation status.***

Treatment for myelofibrosis patients is tailored to the needs of the individual and depends on the predominant symptoms.

Clinical scenarios

A) The asymptomatic patient with low or intermediate risk myelofibrosis

- watchful waiting

B) The patient with symptoms of anaemia only, but no other constitutional symptoms

- erythropoietic agents (expect responses in 30-40%)
- blood transfusion
- danazol (expect responses in 30-40%)
- thalidomide (+/- prednisolone) (expect response in 20-30%)

C) The patient with symptomatic splenomegaly and/or constitutional symptoms

- ruxolitinib, or other JAK2 inhibitor available through a clinical trial
- hydroxycarbamide

In the pre-ruxolitinib era patients with splenomegaly and constitutional symptoms were typically treated with hydroxycarbamide which is effective in transiently reducing spleen size in up to 50% of patients, but at the cost of exacerbation of cytopaenias. It is typically ineffective for disabling constitutional symptoms such as sweats, weight loss and itch. Any benefit from hydroxycarbamide is usually short term and side effects can be difficult to manage. There remains a role for this drug in current clinical practice for patients where abdominal discomfort due to an enlarged spleen is the predominant symptom, but where accompanying constitutional symptoms are lacking. Data from COMFORT-2 demonstrate the clear and durable superiority of ruxolitinib over hydroxycarbamide (among other best available therapies) for symptom control in myelofibrosis patients needing treatment.

Other agents such as melphalan, busulphan, thalidomide, lenalidomide, interferon and cladribine have all been trialled but are less effective still. Splenectomy is a high risk procedure which can deliver symptomatic improvement and improvement in cytopaenias, but at the cost of a 10-20% peri-operative

mortality. Splenic irradiation has been used in the past but typically delivers a transient response at the expense of exacerbation of cytopaenias.

The primary benefit of ruxolitinib is its ability to treat effectively the disabling constitutional symptoms of myelofibrosis, which to date no other class of medication has achieved.

Other JAK2 inhibitors are under investigation in phase 3 trials. Pacritinib from Cell Therapeutics Inc may have a role in the treatment of myelofibrosis patients with concomitant thrombocytopaenia. Momelotinib from Gilead may have a role in the treatment of myelofibrosis patients with concomitant anaemia, or who become transfusion dependent on ruxolitinib.

The role of ruxolitinib in patients awaiting allogeneic transplantation is currently under investigation.

4. The future place of the ruxolitinib in clinical practice & its advantages and disadvantages

The BCSH recommendation is that myelofibrosis patients with symptomatic disease be treated with ruxolitinib. Treatment should be supervised by a haemato-oncologist experienced in the treatment of patients with myelofibrosis. BCSH guidelines recommend screening tests for hepatitis B virus and tuberculosis prior to commencement of therapy because treatment with ruxolitinib is infrequently associated with reactivation of latent viral and other infections.

Recommendations for starting or stopping ruxolitinib are in the BCSH guideline (Reilly et al., 2014; BJ Haem 167:418) and outlined above. Indications for stopping treatment are absence of efficacy, or disease transformation (with a requirement for an alternative therapeutic approach). While longer therapeutic trials of drug might be considered, whether the patient will respond or not is usually apparent within the first four weeks of treatment, often sooner. Discontinuation is typically associated with rapid (~7 days) relapse of constitutional symptoms and spleen enlargement in those who have derived symptomatic benefit from therapy.

The patient cohorts in the COMFORT studies are mostly reflective of patients seen in every day practice, although there are some patients with lower platelet counts than permitted by the trial who benefit from therapy. If anything, in my experience, the results from the COMFORT studies underestimate the proportion of patients who experience clinical benefit from ruxolitinib. For example, clinically significant improvements in quality of life do not necessarily require dramatic spleen shrinkage.

Ruxolitinib is generally very well tolerated. Associated side effects are predominantly those of anaemia and thrombocytopaenia which may be managed by transfusion, addition of erythropoietic agents or dose reduction if required.

Ruxolitinib is currently available through the English Cancer Drugs Fund. Patients in Wales and Northern Ireland do not have routine access and have to enter clinical trials to get treatment, although very occasional Individual Funding Requests have been granted. Novartis has provided two of my trial-ineligible patients from Wales who urgently needed treatment access to ruxolitinib as part of their compassionate use programme. NICE approval will remove the current inequity whereby patients with Welsh and Northern Irish postcodes are denied an effective treatment for their disease which is available to patients in England. Regulatory authorities in Scotland have recently approved ruxolitinib.

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16. Equality and Diversity; implementation issues.

No equality and diversity or implementation issues are identified.

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Single Technology Appraisal (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **The Royal College of Pathologists** and consequently I will not be submitting a personal statement.

Name: .....Claire Harrison.....

Signed: ....

Date: .....22nd July 2015.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) [ID831]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Caroline Thomas
Name of your nominating organisation: MPN Voice
Do you know if your nominating organisation has submitted a statement?

X☐ Yes – we submitted to the scope, and this is my submission for the appraisal

☐ No

Do you wish to agree with your nominating organisation's statement?
See above – it's one and the same

x☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes X☐ No

In the previous STA, two patients attended. Sadly, one has passed away, and the other is reluctant to travel. As you will see below, the cumulative symptom burden placed on MF patients is huge, and it has meant that no patients were able to make the journey to Manchester for this assessment. I have a related disease, described below, so can also be considered a patient.

- a carer of a patient with the condition?

☐ Yes X☐ No

- a patient organisation employee or volunteer?

X☐ Yes ☐ No

I am a patient with Essential Thrombocythaemia (ET). ET is like MF in that it's a blood cancer which is part of the group of disorders known as Myeloproliferative Neoplasms (MPNs). ET does, in some cases, progress to Myelofibrosis. Both conditions share the same set of symptoms and, for the most part, treatment options. As such I feel I am able to relate quite closely to MF patients. I meet MF patients regularly through my volunteer status with the patient organisation MPN Voice so I have a good understanding of how the disease impacts their lives.

Do you have experience of the treatment being appraised?

☐ Yes X☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

As mentioned above, I am neither an MF patient nor carer. However, as a volunteer representative of MF patients, having interacted with MF patients on multiple occasions at forums, and as an MPN patient who experiences the below symptoms, I am able to describe the experience as such:

MF is associated with a large range of symptoms which severely reduce patients' quality of life. The cumulative burden of these symptoms impacts on all aspects of our lives – social, work, family, etc; it is a burden shared by all the people who make up these worlds.

<u>Fatigue</u>

Many patients experience debilitating fatigue. It's important to emphasise here that fatigue doesn't mean feeling tired every now and again, or being a bit run down, but instead means a patient's entire life is disrupted, and eventually governed, by a tiredness that will not allow them to do anything from their former life. This debilitating exhaustion can go on for years without respite.

One patient has commented “I was avoiding exercise of any sort, even walking across the car park by parking as close to the door as possible’. He even took to lying down, rather than sitting, to watch TV, in order to conserve the little energy he had.

I personally have experienced fatigue so severe that I have been unable to climb the stairs in my home, let alone maintain an exercise regime that will keep me as fit and as healthy as possible.

This fatigue not only impacts on patients’ ability to go about their social, family or home activities, but also on their work, which impacts directly on their economic status, and that of their family and their community. Early MF-induced retirement is common amongst patients. In addition to economic impact, this affects their sense of self-worth since while early retirement may seem attractive, for these patients their choice to work has been removed and replaced with extremely poor quality of life.

Another effect of fatigue is to create a vicious circle connected with aspects of patients’ health. The inability to do exercise, coupled with an increased tendency to consume high-sugar/high-fat foods in an attempt to boost energy levels, can lead to an increased risk of developing, or worsening, high cholesterol or diabetes. MF patients who have these conditions are in a higher risk bracket than those without. Additionally, the inability to do exercise, and a poor diet, leads to worse fatigue, and greater risk of developing other conditions.

<u>Enlarged spleen</u>

This leads to pain, discomfort and early satiety, with its accompanying unwanted weight loss, but also less obvious effects. I recently met a female patient in her 50s who talked about her disfiguring appearance – her spleen protrudes through her clothes and she has lost all pride in her appearance as a result. The psychological effect of this is shattering. Other patients talk about how they can no longer lie comfortably on their front, thus affecting their sleep patterns, with further secondary effects on their lives.

Patients who are used to leading an active life are often forced to give up these activities for fear of rupturing their spleen. This then impacts on their social and family life.

Itching

A very common symptom of MF is severe itching, often associated with bathing or showering. The word ‘itching’ does not really convey the extreme nature of the sensation - one patient hasn’t showered or bathed for five years because the puritis it causes is so unbearable. Another patient likened the feeling to being repeatedly rolled naked in nettles. I’ve also heard patients talk of razor blades covering their bodies, being covered in tropical mosquito bites and being poked with needles every second all over the body. This extreme and constant level of irritation understandably impacts terribly on patients’ ability to maintain relationships with loved ones, to work and to get on with normal life activities. One patient, a GP, says “I would frequently sit at work squirming in my chair as I tried to cope with the itching and consult with patients at the same time.”

Depression

Patients have to find ways of coping with these severe symptoms while at the same time coming to terms with the fact that there are no available treatments to alleviate them, and they will live this altered life, with pain and discomfort, until they die. This, understandably, has a severe effect on their mental well-being. Words used frequently by patients include ‘helplessness’ and ‘despair’. It’s hard to remain positive when there is no end in sight.

Other symptoms

Night sweats and hot flushes – some patients have to change their bed linen during the night, on a regular basis. Other patients report frequently having to leave social engagements because the hot flushes make them feel so uncomfortable and irritable.

Unwanted weight loss – many patients' relationship with food changes completely, also impacting on their sense of self. They are unable to eat a full meal, and will often associate food with discomfort and pain. One patient says 'being able to eat gives a sense of well-being', but in his MF reality he is faced with poor nutrition due to feeling full very quickly while eating.

Libido – patients often speak about the impact of the fatigue and low mood on their sex lives. Their relationships suffer and patients often associate a loss of libido with a sense of helplessness.

Bone pain – I've heard patients compare this to a constant toothache, deep inside the bone. It's a constant pain that inhibits patients' ability to carry on with their normal lives. One patient has mentioned that she can no longer drive for more than 15 minutes because of the pain in her leg bones.

Impact on patient

Any one of these symptoms can be highly disruptive to a person's life. When experienced together, they are devastatingly transformative. The cumulative strain placed on patients by these collective burdens makes life miserable. They are no longer able to interact in their social worlds, and are reduced to accepting that their remaining time will be uncomfortable, restricted and lonely. The worst thing for many patients is that there's no way out of this – none of the existing NHS therapies make a sufficient difference, and they are forced to be passive sufferers with very few options.

Impact on others

It's important to highlight how each of these symptoms have a devastating effect not just on the patient but also on others in their life. Carers, family, friends, colleagues, peers, clients, teammates etc. all have to make adjustments to cope, not just with the diagnosis, but with the debilitating symptoms. Often, more than one member of the household has to give up their livelihood, and other members of the household have to compensate for this. This has further knock-on effects, economically, socially and

psychologically. Additionally, families have to find a way to cope, emotionally and relationally, with one member who is in constant discomfort.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

There are two fundamental needs that MF patients have that are unmet by the available treatments. Firstly, the need for a therapy that reduces the severe and debilitating symptoms of MF that are described above. None of the treatments prescribed today are sufficiently effective in this regard.

Secondly, the need for a treatment that has the potential to improve patients' chances of survival. The only option that is available that can cure MF is a stem-cell transplant, which is only possible in a small proportion of patients, namely those aged under 60 who are clinically fit, and importantly, have a matched donor available. In any case, this option has a relatively high risk of failure, in over 50% of cases fatal.

A new therapy that offers the potential to improve survival and improve patients' quality of life is therefore hugely beneficial, both directly and indirectly in the sense that it offers hope, it gives patients back a sense of control and agency over their own lives, and, despite the continuing onset of their disease, they are able to enjoy the time they have remaining, with relatively good quality of life and managed symptoms.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

There is a range of NHS treatments available, none of which has a reliable impact, even on symptom reduction. They are acknowledged to have no survival benefit or curative effect.

The most common treatment in the UK is Hydroxycarbamide. In the two cases presented in the previous STA for this drug, one patient had tried

Hydroxycarbamide and developed pneumonitis as a result and had to stop treatment. The other patient experienced no impact on his symptoms. Other patients I've met have reported the same lack of impact. Hydroxycarbamide is also accompanied by severe side effects which compete with the severe symptoms we would like to be rid of. These include mouth and leg ulcers, stomach problems, and it affects fertility, ruling out its use for pregnant patients or those planning to have children.

Another treatment is Interferon, which is taken as an injection. A high percentage of people who use Interferon complain of flu-like symptoms which are often as debilitating as the symptoms we're trying to address. Interferon use is also linked to the development of clinical depression.

None of the current therapies act directly on the fundamental disease mechanism itself.

In some cases, patients have some or all of their spleens' removed, a procedure that is very invasive and can be dangerous in cases of severe enlargement.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

In the experience of MF patients, Ruxolitinib has had dramatic effects on the disease's symptoms.

The drug reduces the size of patients' spleens, reducing the associated pain, discomfort and disfigurement. Women suffer particularly from the effects of enlarged spleens as it can radically affect their body image and self-confidence.

The drug can have radical benefits in terms of reducing patients' fatigue. For example, a patient who previously did not have the energy to sit and watch TV, was able to resume his lifelong passion for hill-walking after starting on Ruxolitinib.

It also significantly reduces itching, enabling patients to shower and bathe normally. This one effect alone can be transformative in patients' lives.

Other benefits of the drug include, with the reduced spleen size, improved eating as patients no longer feel full as quickly, which leads to better nutrition. Patients report better sleeping and increased libido, with the consequent beneficial effects on self-esteem and mental health.

The most recent research has also shown that Ruxolitinib can significantly extend patients' lives – the simple fact that, other than bone marrow transplantation, this is the only MF therapy that has this potential is extremely important. Research in MPN treatments is a very active field at the moment and a year or two of additional life for a patient opens up the possibility of even more effective therapies becoming available during that time.

The psychological effect of receiving effective treatment is also very important, as patients feel they are taking control to some extent and are no longer passive observers of their own decline. They are able to enjoy their lives again, and be part of their social worlds.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

As mentioned above, none of the treatments currently used are very effective in reducing MF's symptoms and they have no curative effect at all. I have described the specific benefits of Ruxolitinib above and its availability would therefore represent a massive improvement in the options available.

One patient who has been taking Ruxolitinib for 18 months, after failed attempts to manage the symptoms with Hydroxycarbamide, described the drug as a wonder drug. I've heard this accolade time and again from patients – they really can't believe the massive change in quality of life that they experience. This particular lady talked about being able to 'manage to live again' and how it 'eliminated all the symptoms' – the best available therapies available now on the NHS don't come anywhere close to giving patients back their lives. This lady described being 'given an extension before the end'.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I feel that I have represented the opinions of MF patients from having met many MF patients over the past two years. Ihave also received written input from several other patients.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)

- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

The side-effects of current MF treatments are well documented and are directly experienced by all of the patients I have encountered. More importantly, none of these treatments offer any benefits in terms of the likelihood of survival.

Please list any concerns you have about the treatment being appraised.

The studies have revealed some side effects but in the case of the patients I have interacted with who have received Ruxolitinib, the side effects have been minimal and much more tolerable than MF's symptoms. In most cases, the side effects subside with dosage adjustments.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None that I am aware of.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

The condition of patients with MF varies a lot. I have been describing the experiences of patients who fail to respond to currently available treatments and for whom their quality of life and their prognosis is dire. These are the patients for whom Ruxolitinib would have the most benefit.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

See above

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Not applicable – it is not part of routine care

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

(a) Yes (b) I am not qualified to comment

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not applicable – it is not part of routine care

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

We are anxious that the fact that this disease often affects older patients does not disadvantage patients in the economic analysis. We are also concerned that the small patient population will disadvantage us. Linked to this, I am concerned that I will be discriminated against since I am not an MF patient, and therefore my statement may be disregarded. The small patient population means that it is difficult to find actual patients to appear in front of the committee, forcing representation by a third party.

9. Other issues

Do you consider the treatment to be innovative?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The fact that Ruxolitinib directly targets the mechanism of the disease is what makes it completely different to the existing treatments. It also has much better effect on the symptoms and has now been shown to extend patients' lives.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Ruxolitinib is the only treatment that reliably gives patients the two things they need: more life, better life. It's known as the wonder drug in our community – the holy grail. It transforms patients' lives, minimising the heavy burden of illness and allowing them to function again, with dignity.
- Ruxolitinib doesn't only allow patients to function again, but also allows their families to function again. It allows family members and patients to go back to work, to enjoy social activities, to play an active role in their communities. It has a wide impact on patients' social and economic worlds.
- Ruxolitinib fills an unmet need for MF patients. The best available therapies are incomparable and not acceptable. They offer limited effective symptom control, and contribute new side effects to an already debilitating list of symptoms. Patients who are on it say simply that it is 'unfair' that other patients are suffering on alternative therapies when their own lives have been given back to them.
- Ruxolitinib provides a lifeline for patients. Living with a severely life-altering incurable condition has a devastating psychological effect, and knowing that there's nothing they can do about it makes patients feel completely helpless. Then, a wonder drug comes along and the effect of knowing they're taking something that actually works is enough to change patients entire outlook – it makes them active in their treatment and gives them hope for the future.

- Ruxolitinib contributes to the evolution of MPN therapy. Patients need access to innovative therapies in order for the medical community to learn and research to progress. MPN is a very active research area and new disease mechanisms and therapeutic interventions are emerging frequently. I believe that a targeted therapy like Ruxolitinib will pave the way for new curative therapies, or more effective maintenance therapies, but more patients will need access to the treatments for this to happen. For us, knowing that money is being invested in the advancement of treatments for our diseases gives us hope. For patients with access to Ruxolitinib, a year or two of survival could offer a lifeline to patients. It's not inconceivable that something will come along in the next few years that could actually save these peoples' lives, not just extend them...

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission

Ruxolitinib in myelofibrosis

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Technology: ruxolitinib (Jakavi®)

Disease area: myelofibrosis

3.2 Please outline the rationale for developing the patient access scheme.

The simple discount scheme was developed to improve the cost-effectiveness of ruxolitinib and enable patients to receive access this innovative medicine

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Simple discount scheme

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme will apply to the full licensed population, which is also the population covered by the STA submission: 'the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis'

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme applies to all eligible patients from the time of treatment initiation

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients eligible for treatment with ruxolitinib as per the licensed indication will meet the scheme criteria

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The confidential PAS price will be applied directly on the original invoice produced by Novartis to the purchasing organization at the point of positive NICE guidance. The scheme does not increase administrative burden to the NHS and there will be no need for rebates for be calculated and paid.

The scheme will operate as a fixed price scheme (which will not vary with any change to the UK list price), therefore the % discount could vary. However, at the current list price, the discount will be [redacted]%.

	Cost per 56-tablet blister pack (excluding VAT)	
	List price	With PAS
5 mg	£1,680	[redacted]
10 mg	£3,360	[redacted]
15 mg	£3,360	[redacted]
20 mg	£3,360	[redacted]

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As a simple discount provided at the point of invoice, there are no administration requirements. No additional information will be collected.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The PAS price will be applied directly to the original invoice and the scheme will therefore operate no differently from any other order placed by an NHS hospital.

3.10 Please provide details of the duration of the scheme.

The scheme will be in place from the date of guidance publication and until NICE next reviews the guidance on the product and a final decision has been published on the NICE website

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equalities issues relating to the scheme

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

There are no forms associated with the provision of this simple discount.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The scheme applies to the same population as that presented in the main submission of evidence for the STA

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The daily cost of ruxolitinib has been reduced by [redacted]%

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable – not an outcomes-based scheme

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

No additional costs are associated with the implementation and operation of the patient access scheme.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

No additional treatment-related costs are incurred by implementing the patient access scheme.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Base case results without the PAS are presented in Table 1. Compared with BAT, the ICER for ruxolitinib therapy was £[redacted] per QALY gained without the PAS.

Table 1 Base-case cost-effectiveness results (without the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£[redacted]	[redacted]	[redacted]				£[redacted]	
Ruxolitinib	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]	£[redacted]

With the PAS, the ICER for ruxolitinib therapy was £44,905 per QALY gained.

Table 2 Base-case cost-effectiveness results (with the PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BAT	£36,271	2.15	1.476				£24,577	
Ruxolitinib	£149,114	5.96	3.989	£112,843	3.81	2.51	£37,384	£44,905

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

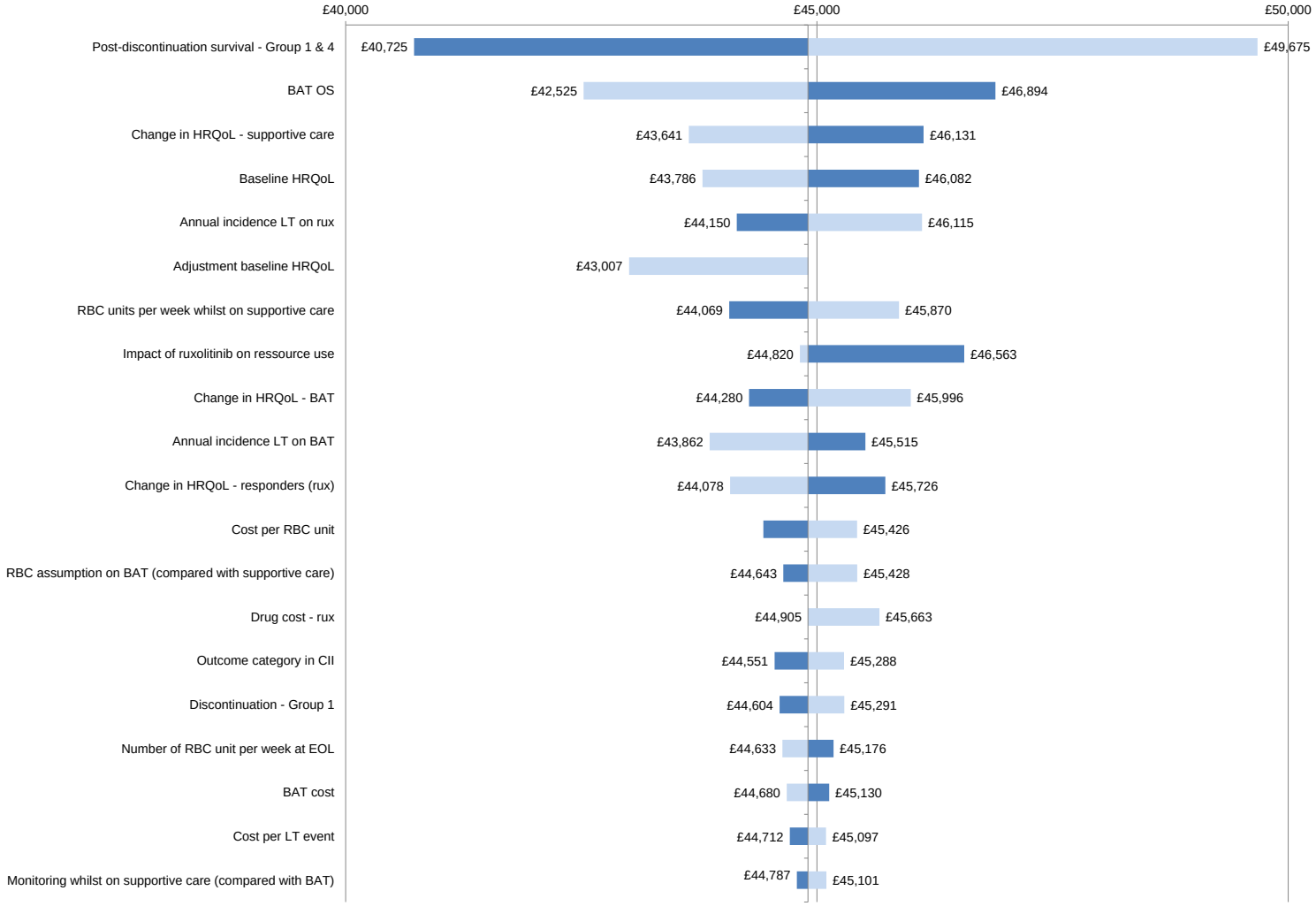
[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Not applicable – only one comparator and one intervention

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1 Univariate sensitivity analysis



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The ICER is £44,625 per QALY gained in the probabilistic sensitivity analysis (with the PAS).

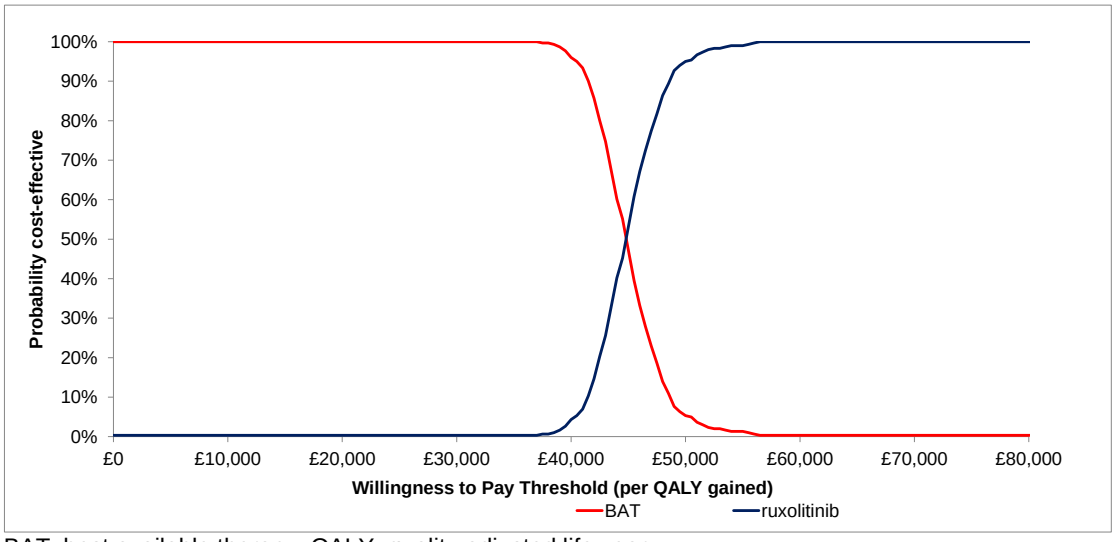
Table 3 Results of the probabilistic sensitivity analysis

	Life years (undiscounted)	QALYs (discounted)	Cost (discounted)	ICER
Ruxolitinib	6.12	4.04	£150,794	
BAT	2.16	1.48	£36,349	
Incremental	3.96	2.56	£114,445	£44,625

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

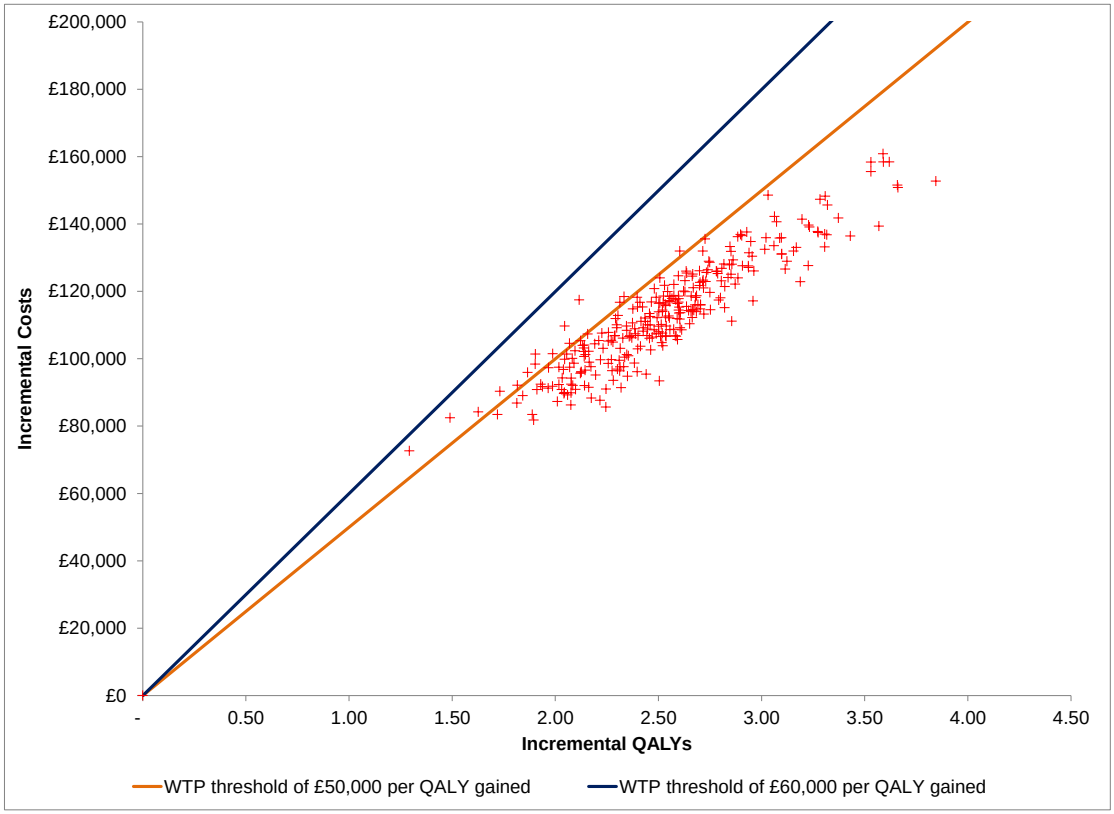
Figure 2 and Figure 3 show the cost effectiveness plane and cost effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost effective for different levels that the decision maker may be willing to pay for an additional QALY. The cost effectiveness acceptability curves show that the probability of ruxolitinib being is a cost-effective strategy is 0.33%, 4.32%, 95.02% and 100% when using a threshold of £30,000, £40,000, £50,000 and £60,000 per QALY, respectively.

Figure 2 Cost effectiveness acceptability curves



BAT, best available therapy; QALY, quality-adjusted life year.

Figure 3 Cost effectiveness plane



QALY, quality-adjusted life year. WTP, willingness to pay threshold

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Results are presented with the PAS

Time horizon

Table 4 Scenario analysis 1: reducing the time horizon

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Time horizon = 5 years	3.642	2.761	£112,469	2.153	1.475	£36,264	£59,266
Time horizon = 10 years	5.077	3.615	£138,399	2.154	1.476	£36,271	£47,730
Time horizon = 15 years	5.659	3.885	£146,171	2.154	1.476	£36,271	£45,625
Time horizon = 20 years	5.860	3.960	£148,284	2.154	1.476	£36,271	£45,096

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

BAT discontinuation

Table 5 Scenario analysis 2: BAT discontinuation – parametric curves

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT discontinuation = exponential	5.959	3.986	£149,099	2.151	1.466	£36,205	£44,799
BAT discontinuation = Weibull	5.960	3.988	£149,136	2.153	1.472	£36,239	£44,874
BAT discontinuation = Log-normal	5.962	3.988	£149,139	2.151	1.466	£36,369	£44,706

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 6 Scenario analysis 3: Duration on BAT

Description	Ruxolitinib			BAT			**ICER**
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT discontinuation reduced by 10%	5.960	3.990	£149,123	2.154	1.479	£36,356	£44,920
BAT discontinuation reduced by 20%	5.960	3.991	£149,158	2.154	1.483	£36,444	£44,947
BAT discontinuation reduced by 30%	5.960	3.991	£149,212	2.154	1.487	£36,520	£44,994
BAT discontinuation reduced by 40%	5.959	3.992	£149,237	2.154	1.491	£36,676	£44,996

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

OS in patients treated under current practice (ie in the absence of ruxolitinib)

Table 7 Scenario analysis 4: overall survival for BAT corrected for crossover: parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT OS (cross-over adjusted) = exponential	6.732	4.356	£153,424	5.055	2.864	£52,560	£67,633
BAT OS (cross-over adjusted)= Weibull	6.034	4.032	£149,612	2.432	1.639	£37,941	£46,676
BAT OS (cross-over adjusted)= Log-normal	6.807	4.383	£153,792	5.335	2.965	£54,046	£70,371

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Table 8 Scenario analysis 5: overall survival for BAT, COMFORT-II, intention-to-treat: parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT OS (ITT)= Weibull	6.584	4.298	£152,657	4.498	2.648	£49,685	£62,391
BAT OS (ITT)= Gompertz	6.431	4.233	£151,810	3.924	2.402	£46,492	£57,507

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; QALY, quality-adjusted life year.

Post-BAT discontinuation survival

Table 9 Scenario analysis 6: Shape of the post-BAT survival curve

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
BAT post-discontinuation survival (shape of Weibull = -1)	5.917	3.907	£148,627	2.075	1.191	£34,841	£41,885
BAT post-discontinuation survival (shape of Weibull = -0.8)	5.934	3.928	£148,820	2.124	1.269	£35,366	£42,659
BAT post-discontinuation survival (shape of Weibull = -0.6)	5.941	3.946	£148,922	2.143	1.332	£35,775	£43,294

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
BAT post-discontinuation survival (shape of Weibull = -0.4)	5.947	3.959	£149,005	2.150	1.381	£35,963	£43,844
BAT post-discontinuation survival (shape of Weibull = -0.2)	5.951	3.969	£149,060	2.151	1.415	£36,107	£44,229
BAT post-discontinuation survival (shape of Weibull = 0)	5.954	3.977	£149,069	2.152	1.439	£36,219	£44,473
BAT post-discontinuation survival (shape of Weibull = 0.2)	5.956	3.982	£149,093	2.152	1.456	£36,184	£44,697
BAT post-discontinuation survival (shape of Weibull = 0.4)	5.958	3.986	£149,115	2.153	1.467	£36,226	£44,823
BAT post-discontinuation survival (shape of Weibull = 0.6)	5.959	3.988	£149,113	2.154	1.475	£36,258	£44,899
BAT post-discontinuation survival (shape of Weibull = 0.8)	5.961	3.990	£149,122	2.154	1.480	£36,300	£44,947
BAT post-discontinuation survival (shape of Weibull = 1)	5.962	3.992	£149,156	2.155	1.485	£36,303	£45,006

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 10 Scenario analysis 7: Examining structural assumption regarding the estimate for post-BAT survival

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Approach 1: BAT OS and discontinuation sampled (discontinuation adjusted)	5.965	3.991	£149,105	2.162	1.477	£36,252	£44,899
Approach 2: BAT OS and discontinuation sampled (OS adjusted)	5.981	4.002	£149,226	2.215	1.515	£36,681	£45,255
Approach 3: BAT post-discontinuation survival calibrated	5.959	3.990	£149,131	2.146	1.478	£36,257	£44,925

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Response criteria

Table 11 Scenario analysis 8: response criteria

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Response definition (≥50% spleen reduction & ≥25% MF-SAF reduction)	6.351	4.220	£160,215	2.154	1.476	£36,271	£45,169
Response definition (≥25% spleen reduction & ≥50% MF-SAF reduction)	6.358	4.141	£156,204	2.154	1.475	£36,271	£44,992
Response definition (≥25% spleen reduction & ≥25% MF-SAF reduction)	6.613	4.292	£162,896	2.154	1.476	£36,271	£44,966
Response definition (≥50% spleen reduction & ≥ upper MID FACT-Lym)	5.923	3.965	£148,159	2.154	1.476	£36,271	£44,952
Response definition (≥50% spleen reduction & ≥ lower MID FACT-Lym)	6.421	4.267	£162,161	2.154	1.476	£36,271	£45,112
Response definition (≥25% spleen reduction & ≥ upper MID FACT-Lym)	6.412	4.173	£157,552	2.154	1.475	£36,271	£44,952
Response definition (≥25% spleen reduction & ≥ lower MID FACT-Lym)	6.752	4.382	£166,957	2.154	1.476	£36,271	£44,981

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Ruxolitinib discontinuation

Table 12 Scenario analysis 9: ruxolitinib discontinuation rates in patients a spleen response; parametric survival distributions

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Discontinuation responder (Group1) = Weibull	5.836	3.922	£146,245	2.154	1.476	£36,271	£44,955

Discontinuation responder (Group1) = Gompertz	6.058	4.039	£151,293	2.154	1.476	£36,271	£44,875
Discontinuation responder (Group1) = Log-normal	7.590	4.766	£183,231	2.154	1.476	£36,271	£44,665

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 13 Scenario analysis 10: Maximum duration on ruxolitinib

	Ruxolitinib			**BAT**			**ICER**
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Ruxolitinib is stopped at 3.5 years	4.350	2.947	£103,869	2.154	1.476	£36,271	£45,954
Ruxolitinib is stopped at 5 years	4.787	3.266	£117,804	2.154	1.476	£36,271	£45,532
Ruxolitinib is stopped at 7 years	5.277	3.602	£132,337	2.154	1.476	£36,271	£45,188
Ruxolitinib is stopped at 10 years	5.569	3.785	£140,334	2.154	1.476	£36,271	£45,058

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Survival post-ruxolitinib discontinuation

Table 14 Scenario analysis 11: survival following ruxolitinib discontinuation (pooled); **parametric survival distributions**

Description	**Ruxolitinib**			**BAT**			**ICER**
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Post-discontination survival (rux) - Weibull	6.108	4.021	£149,689	2.154	1.476	£36,271	£44,555
Post-discontination survival (rux) - log-normal	7.902	4.239	£155,102	2.154	1.476	£36,271	£42,998

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; PPS, QALY, quality-adjusted life year.

Table 15 Scenario analysis 12: Maximum duration alive post-ruxolitinib discontinuation

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
post-discontinuation maximum = 3.5 years	5.441	3.828	£146,992	2.154	1.476	£36,271	£47,081
post-discontinuation maximum = 5 years	5.663	3.915	£147,964	2.154	1.476	£36,271	£45,789
post-discontinuation maximum = 7.5 years	5.845	3.971	£148,712	2.154	1.476	£36,271	£45,066
post-discontinuation maximum = 10 years	5.916	3.985	£148,987	2.154	1.476	£36,271	£44,923

Table 16 Scenario analysis 13: survival following ruxolitinib discontinuation in patients achieving a spleen response; parametric survival distributions

Description	**Ruxolitinib**			**BAT**			**ICER**
	Life years	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Separate post-discontinuation survival (Group 1 & 4) - exponential	6.010	4.008	£149,355	2.154	1.476	£36,271	£44,667
Separate post-discontinuation survival (Group 1 & 4) - Weibull	6.185	4.042	£150,020	2.154	1.476	£36,271	£44,320
Separate post-discontinuation survival (Group 1 & 4) - log-normal	7.895	4.241	£155,095	2.154	1.476	£36,271	£42,968

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 17 Scenario analysis 14: survival following ruxolitinib discontinuation in patients not achieving response

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Reduced survival for patients on ruxolitinib (Group 3)	5.892	3.943	£148,582	2.154	1.476	£36,271	£45,526

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Leukaemic transformation

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Table 18 Scenario analysis 15: leukaemic transformation

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Incidence of LT assumed to be the same	5.960	3.980	£151,682	2.154	1.476	£36,271	£46,089
Removal of LT	5.960	3.999	£145,979	2.154	1.485	£33,727	£44,634

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Assumptions regarding HRQoL

Table 19 Scenario analysis 16: HRQoL measure

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
HrQoL measured using the MF-8Dv2	5.960	3.725	£149,114	2.154	1.349	£36,271	£47,499
HrQoL measured using the EQ-5D	5.960	3.853	£149,114	2.154	1.468	£36,271	£47,313

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 20 Scenario analysis 17: HRQoL assumptions while on BAT

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Change in HRQoL for BAT = half change in supportive care	5.960	3.982	£149,114	2.154	1.452	£36,271	£44,590
Change in HRQoL for BAT = 1/3 change in supportive care	5.960	3.985	£149,114	2.154	1.460	£36,271	£44,694
Change in HRQoL for BAT = 1/4 change in supportive care	5.960	3.986	£149,114	2.154	1.464	£36,271	£44,747
Change in HRQoL for BAT = half change on ruxolitinib	5.960	4.031	£149,114	2.154	1.636	£36,271	£47,120
Change in HRQoL for BAT = 1/3 change on ruxolitinib	5.960	4.017	£149,114	2.154	1.583	£36,271	£46,358
Change in HRQoL for BAT = 1/4 change on ruxolitinib	5.960	4.010	£149,114	2.154	1.556	£36,271	£45,986

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life.

Table 21 Scenario analysis 18: HRQoL assumptions while on placebo

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Progression of HRQoL on supportive care halved after 24 weeks	5.960	4.070	£149,114	2.154	1.489	£36,271	£43,726
Progression of HRQoL on supportive care halved after 48 weeks	5.960	4.055	£149,114	2.154	1.482	£36,271	£43,870
Progression of HRQoL on supportive care halved after 72 weeks	5.960	4.042	£149,114	2.154	1.479	£36,271	£44,015

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 22 Scenario analysis 19: short-term HRQoL assumptions while on ruxolitinib

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Patients on ruxolitinib experience an improvement in HrQoL at 8 weeks	5.960	3.980	£149,114	2.154	1.476	£36,271	£45,055
Patients on ruxolitinib experience an improvement in HrQoL at 12 weeks	5.960	3.972	£149,114	2.154	1.476	£36,271	£45,206
Patients on ruxolitinib experience an improvement in HrQoL at 16 weeks	5.960	3.964	£149,114	2.154	1.476	£36,271	£45,356
Patients on ruxolitinib experience an improvement in HrQoL at 20 weeks	5.960	3.955	£149,114	2.154	1.476	£36,271	£45,507

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 23 Scenario analysis 20: long-term HRQoL progression assumption while on ruxolitinib

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Patients on ruxolitinib do not maintain their initial gain in HrQoL	5.960	3.799	£149,114	2.154	1.476	£36,271	£48,569
25% reduction in gain in HRQoL every 52 weeks for patients on ruxolitinib	5.960	3.805	£149,114	2.154	1.476	£36,271	£48,441

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 24 Scenario analysis 21: structural assumptions regarding HRQoL

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Constant HrQoL	5.960	4.154	£149,114	2.154	1.498	£36,271	£42,486

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Assumptions regarding red blood cell transfusion units

Table 25 Scenario analysis 22: assumptions regarding RBC transfusions

	Ruxolitinib			BAT			
Description	**Life years**	**QALYs**	**costs**	**Life years**	**QALYs**	**costs**	**ICER**
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
No impact of ruxolitinib on RBC units	5.960	3.989	£150,735	2.154	1.476	£36,271	£45,550
Ruxolitinib is associated with a 5% increase in RBC units over the lifetime	5.960	3.989	£151,178	2.154	1.476	£36,271	£45,726
Increase in RBC units by 5% every 24 weeks for patients on supportive care	5.960	3.989	£150,082	2.154	1.476	£36,794	£45,082

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; RBC, red blood cell; QALY, quality-adjusted life year.

Discount rates

Table 26 Scenario analysis 23: discount rate

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base case	**5.960**	**3.989**	**£149,114**	**2.154**	**1.476**	**£36,271**	**£44,905**
Discount rate (1.5% cost)	5.960	3.989	£160,949	2.154	1.476	£37,224	£49,235
Discount rate (1.5% QALYs)	5.960	4.305	£149,114	2.154	1.498	£36,271	£40,201
Discount rate (both 1.5%)	5.960	4.305	£160,949	2.154	1.498	£37,224	£44,077

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Results with the PAS (base case and scenario analysis) are presented above. Results without the PAS are available in the original NICE submission.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

No forms of additional documents are required for the operation of this Patient Access Scheme

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group Report

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289)

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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None.

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Rider on responsibility for report

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Contributions of authors

Robert Hodgson and Mousumi Biswas wrote the cost effectiveness sections of the report and conducted the economic analyses. Ros Wade wrote the clinical effectiveness sections of the report. Melissa Harden wrote the sections on the search strategies. Nerys Woolacott commented on drafts of the report and took overall responsibility for the clinical effectiveness sections of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

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List of abbreviations

AE	Adverse event
Allo-HSCT	Allogeneic haematopoietic stem cell transplantation
AML	Acute myeloid leukaemia
BAT	Best available therapy
BCSH	British Committee for Standards in Haematology
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CML	Chronic myeloid leukaemia
COMFORT	COntrolled MyeloFibrosis study with Oral JAK inhibitoR Treatment
CS	Company's submission
CSR	Clinical study report
CT	Computed tomography
DES	Discrete event simulation
DIPSS	Dynamic international prognostic scoring system
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	5-dimension European Quality of Life questionnaire
ERG	Evidence Review Group
ET	Essential thrombocythaemia
FACIT	Functional assessment of chronic illness therapy
FACT-Lym	Functional assessment of cancer therapy - lymphoma
FDA	Food and Drug Administration
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IPSS	International Prognostic Scoring System
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK2	Janus kinase 2
JAK/STAT	Janus kinase-signal transducers and activators of transcription

LT	Leukaemic transformation
MDACC	MD Anderson Cancer Center
MF	Myelofibrosis
MF-SAF	Myelofibrosis symptom assessment form
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PET-MF	Post-essential thrombocythaemia myelofibrosis
PGIC	Patient's global impression of change
PMF	Primary myelofibrosis
PROMIS	Patient-reported outcomes measurement information system
PS	Patient access scheme submission
PSS	Personal social services
PV	Polycythaemia vera
PPV-MF	Post-polycythaemia vera myelofibrosis
QALY	Quality-adjusted life year
RPSFT	Rank-preserving structural failure time
RBC	Red blood cell
RCT	Randomised controlled trial
SAE	Serious adverse event
SPC	Summary of product characteristics
STA	Single technology appraisal
TSS	Total symptom score
WHO	World Health Organisation

1 Summary

1.1 Critique of the decision problem in the company's submission

The population in the company submission (CS) matched that specified in the NICE scope: adults with disease-related splenomegaly or symptoms of primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF) and post essential thrombocythaemia myelofibrosis (PET-MF). This is within the licenced indication of ruxolitinib. However, the clinical effectiveness evidence is primarily from two randomised controlled trials (RCTs) of ruxolitinib, the COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment (COMFORT) trials, which included patients with intermediate-2 or high risk myelofibrosis (MF) and a platelet count of at least $100x10^9$/L, which is only a subset of the licensed population. This is the evidence used to construct and populate the economic model. While the CS also presented supporting evidence from four non-RCT studies of ruxolitinib in patients with intermediate-1 risk MF or a low platelet count, overall the submission's decision problem addresses mainly the inter-mediate-2/high risk subgroup.

The intervention in the CS matched that specified in the NICE scope: ruxolitinib with established clinical practice. The starting doses used in the COMFORT trials and the non-RCT studies were in accordance with the licence. The comparator in the CS matched that specified in the NICE scope: established clinical practice without ruxolitinib, which was appropriate. However, the company excluded allogeneic haematopoietic stem cell transplantation (allo-HSCT) from the economic analysis because of the small number of patients that are eligible for allo-HSCT and lack of relevant data. As allo-HSCT is a potentially curative treatment for MF the ERG suggests that allo-HSCT, and possibly also ruxolitinib as a bridge to allo-HSCT, should have been included as a comparator. The comparators used in the COMFORT trials were generally appropriate.

The outcomes presented in the CS matched those specified in the NICE scope, with the exception of progression free survival (PFS), which the company states was not included as an outcome because it is not a measure that is generally applied in MF. The company's justification for not assessing PFS seems reasonable.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence presented in the CS was primarily based on two good quality RCTs; one comparing ruxolitinib with BAT (COMFORT-II) and one comparing ruxolitinib with placebo (COMFORT-I). These trials demonstrated that ruxolitinib confers significant benefits in terms of spleen size reduction and improvement in symptom burden. Spleen volume reduced from baseline by approximately 29-32% in ruxolitinib-treated patients at week 24, whereas spleen volume increased in BAT-treated

patients and placebo patients at week 24. The primary endpoint was the same in both COMFORT trials; proportion of patients achieving a 35% or greater reduction of spleen volume. This endpoint was met in significantly more patients in the ruxolitinib group than the control group in both trials (28% of ruxolitinib patients versus 0% of BAT patients at 48 weeks in the COMFORT-II trial), with most patients achieving this level of response by week 12 and maintaining their response for a year or more. However, most patients (63%) had discontinued treatment at 3.5 year follow-up in the COMFORT-II trial and half of the patients in the COMFORT-I trial had discontinued treatment at 3 year follow-up, primarily because of disease progression or adverse events.

Ruxolitinib was associated with clinically meaningful improvements in MF-associated symptoms at week 24, whereas placebo-treated patients had worsening of symptoms. Both COMFORT trials also assessed HRQoL as an exploratory endpoint, ruxolitinib patients in both trials had an improvement from baseline in Global Health Status/QoL assessed using the EORTC QLQ-C30 scale.

Long term data from the COMFORT-II trial (3.5 years) demonstrated a statistically significant difference in overall survival favouring ruxolitinib over BAT, using both ITT and RPSFT analyses. However, the overall survival benefit at 3 years in the COMFORT-I trial did not reach statistically significance, even after adjustment for crossover. Because median overall survival was not reached in the ruxolitinib arm of the COMFORT-II trial it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT directly from the data. An indirect comparison using a subset of the ruxolitinib arm of COMFORT-II and the DIPSS cohort (Primary MF patients only) generated a median survival of 5 years on ruxolitinib compared with 3.5 for the DIPSS cohort

The incidence of serious adverse events was similar between treatment groups in both COMFORT trials. However, the incidence of grade 3 or 4 adverse events was higher in the ruxolitinib group than the BAT group in the COMFORT-II trial (42% versus 25%). In the COMFORT-II trial the incidence of adverse events of special interest generally decreased over time, although the incidence of infections remained quite high at between 25 to 43% over the 3 year follow-up (dropping from 50% during the first 24 weeks). The incidence of bronchitis increased over time. It should be noted that the data presented were for those patients who remained on treatment, excluding those who dropped out because of adverse events. Haematological adverse events were very common with ruxolitinib.

The CS presented supporting evidence from four non-RCT studies of ruxolitinib that included patients with intermediate-1 risk MF or a low platelet count (the ROBUST study, the JUMP study, Study 258 and the EXPAND study). The results of the studies were generally consistent with the COMFORT trials, suggesting that ruxolitinib may also be effective at reducing spleen size and symptoms in intermediate-1 risk patients and patients with low platelet counts, although patient numbers were low, reducing the reliability of the results. However, thrombocytopenia was much more frequently reported in patients with low platelet counts, as might be expected. The evidence for the use of ruxolitinib in patients with lower risk disease and low platelet counts is not as robust as that in intermediate-2 and high-risk patients with platelet counts over $100x10^9$/L.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS included a reasonably good quality systematic review. The search strategy was adequate and inclusion criteria were appropriate (after exclusion of non-ruxolitinib studies); no relevant RCTs of ruxolitinib appear to have been missed. The flow chart of the study selection process presented in the CS was incorrect. Adequate data were presented for the included RCTs, but insufficient data were presented for the non-RCT studies. Quality assessment of the RCTs was appropriate and the trials were good quality. However, no quality assessment was undertaken for the non-RCT studies.

The two RCTs comparing ruxolitinib with BAT and placebo were appropriate for the decision problem and both were good quality. The results of the COMFORT trials relating to reduction of splenomegaly are likely to be reliable, although a large proportion of patients had discontinued treatment at longer term follow-up (3/3.5 years), reducing the reliability of the longer-term results. The results relating to MF-associated symptoms are likely to be reliable. Data relating to HRQoL were missing for a large proportion of patients, therefore, the reliability and generalisability of these results is unclear.

The overall survival (OS) data were subject to some limitations. Firstly, neither of the COMFORT trials was designed to be sufficiently powered to detect a significant difference in survival outcomes. Secondly, both trials permitted patients to cross over from the control group to ruxolitinib, potentially diluting differences in treatment effect. The company used a rank-preserving structural failure time (RPSFT) model to estimate the true effect of ruxolitinib on overall survival, adjusting for crossover. All methods of adjusting survival estimates in the presence of treatment switching have limitations; the RPSFT method relies critically on the 'common treatment effect' assumption. However, despite the limitations, this method appears to have been appropriate. Thirdly, median survival was not reached so the data are not mature and the duration of any survival benefit due to ruxolitinib cannot be calculated from the trial data.

The evidence for the use of ruxolitinib in patients with lower risk disease and low platelet counts is much less robust than that in intermediate-2 and high-risk patients with platelet counts over $100x10^9$/L.

1.4 Summary of cost effectiveness submitted evidence by the company

The company presented a systematic review of the cost-effectiveness studies of ruxolitinib for the treatment of MF. The review identified two studies, one study compared ruxolitinib to BAT from a Canadian societal perspective the other was the model presented in the previous STA of ruxolitinib. Neither study was considered relevant; a *de novo* model was therefore developed.

The *de novo* model present by the company was a discrete event simulation model (DES), which represents the base-case scenario primarily using data from the COMFORT-I/II trials. The model compares the cost-effectiveness of ruxolitinib to BAT which is assumed to consist of the basket of therapies used in the comparator arm of the COMFORT-II trial. The population modelled was as in the COMFORT-II and consisted of intermediate-2 and high risk MF patients.

The model structure was based on the therapy being received and consisted of three phases of treatment:

- Ruxolitinib: in which patients have some moderate improvement in symptoms and splenomegaly and HRQoL;
- BAT: which provides only limited symptom control and has minimal impact on HRQoL;
- Supportive care: which can consist of patients where other treatment options have failed and is associated with progressive worsening of symptoms until death.

Patients initiating on ruxolitinib are subject to a stopping rule at 24 weeks where treatment is only continued if patients are considered to be responding to treatment. This stopping rule is based on definitions of response set out in the recent IWG-MRT/ELN[1]guidelines and includes both symptom response and splenomegaly response. Time in each "health state" is dependent upon initial treatment decision and treatment response; and is modelled based on data on OS and time on treatment observed in the COMFORT-I/II studies.

The model takes a National Health Service (NHS) and Personal Social Services (PSS) perspective and costs are separated into drug acquisition costs, costs associated with the management of MF, adverse event costs, cost associated with Leukaemic transformation (LT) and end of life costs. The economic model tracks changes in HRQoL according to the different phases of treatment with utility values based on time-trade-off (TTO) analysis of a condition-specific preference-based measure of disease

severity in MF patients. A 35 year time-horizon is used in the model. Both costs and benefits are discounted at 3.5%.

The CS presents both deterministic and probabilistic sensitivity analyses to demonstrate the robustness of the estimated ICER along with extensive scenario analysis examining the impact of a number structural assumptions made in the base-case model. The base-case incremental cost-effectiveness ratio (ICER) presented in the CS (including PAS) is estimated to be £44, 905 per QALY in the deterministic analysis, and £44,625 per QALY in the probabilistic sensitivity analysis. The cost the probability of ruxolitinib being is a cost-effective strategy at thresholds of £30,000, £40,000, £50,000 and £60,000 per QALY was 0.33%, 4.32%, 95.02% and 100%, respectively. The sensitivity and scenario analyses presented by the company showed that the ICER rarely exceeded £50,000. Exceptions to this included:

- Reducing the time horizon to 5 years;
- Using an alternative parametric function to estimate OS in BAT patients;
- Using ITT (rather than cross-over adjusted) analysis to estimate OS on BAT.

None of these scenarios can be considered particularly plausible.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model described in the CS is considered by the ERG to address the decision problem specified by NICE and meets the NICE reference case. The following issue were however identified in by the ERG:

- For patients who are considered non-responders to ruxolitinib after an initial 24 week treatment period it is assumed that overall survival will be increased by 24 weeks over patients initiating on BAT. No clinical evidence was provided to support this assumption, and while the ERG accepts that some OS benefit may be experienced by these patients, the evidence does not support the OS benefit assumed in the model.
- The comparator used in the model was BAT which comprised of a basket of treatments used in the COMFORT-II trial. There were concerns regarding the composition of this basket of therapies and how well it represented UK practice. In particular the inclusion of lenalidomide was considered inappropriate as this drug is not used in the UK. Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments [2].

- The model presented in the CS does not allow for any drug wastage. This was considered inappropriate due to the relatively short shelf life of ruxolitinib of 30 days once opened, and the fact that adverse events are often treated with either dose reductions or interruptions.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The evidence presented for the effectiveness of ruxolitinib was identified through a systematic review and primarily based on two good quality RCTs. The effectiveness of ruxolitinib was compared with generally relevant comparators and the outcomes assessed were appropriate.

The company presented a well conducted review of cost-effectiveness studies. The *de novo* model was well presented and an appropriate model structure used, which shows good validation with the trial data from the COMFORT-II study. The CS presents extensive scenario and sensitivity analysis and the cost-effectiveness results appear to be robust: the majority of the sensitivity analyses did not alter the ICER substantially.

1.6.2 Weaknesses and areas of uncertainty

The RCTs of ruxolitinib included patients with intermediate-2 or high risk MF and a platelet count of at least $100x10^9$/L, which is only a subset of the licensed population. The evidence for the use of ruxolitinib in patients with lower risk disease or low platelet counts was less robust, being based on four studies that did not include a non-ruxolitinib control group and three of the studies were very small.

The DES structure used in the model makes significant demands on the clinical data, which forces the adoption of a number of assumptions with regards to how patients move through the model. These assumptions are generally well justified by empirical evidence presented in the CS and the uncertainty explored in the scenario analysis included in the CS. However, this analysis only allows the uncertainty resulting from the assumptions to be explored on a univariate basis and the joint uncertainty resulting from these assumptions remains unexplored.

The presented *de novo* model very closely models the presented clinical evidence and in particular the COMFORT-II trial. Using alternative clinical evidence may therefore have a significant impact on the estimated ICER. The *de novo* model can therefore is only as generalizable to the UK setting in so a far as the COMFORT-II trial can be considered to be representative of UK clinical practice. Particular areas of concern regards the generalizability of the COMFORT-II trial include the treatments included

within BAT, and the patient population which as noted above excludes low and intermediate-I risk patients. The model also excludes patients suitable for allo-HSCT and therefore the presented model does not allow comparison of ruxolitinib with allo-HSCT.

The resource use data used in the model is based on very limited evidence and the impact of ruxolitinib on the costs of managing MF patients is drawn from non-UK studies. Uncertainty regarding the impact of treating patients with ruxolitinib therefore remains.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of additional analyses considering a number of alternative assumptions and exploring their impact on the estimated ICER. This analysis addressed the following issues:

- Assumption of no drug wastage for ruxolitinib patients;
- Inclusion of lenalidomide in BAT basket of therapies;
- Mortality of responders while receiving ruxolitinib.

In addition to the above exploratory analysis the ERG also presented an alternative base-case based on a combination of a number of scenario analyses present by the company and assuming a 5% rate of drug wastage and excluding lenalidomide from the basket of therapies that constitute BAT. This analysis was conducted assuming two alternative mortality rates for ruxolitinib responders while on therapy, one based on the CS and another rate derived by the ERG. The deterministic results of these analyses are summarised in Table 1 below, the ERG were not able to carry out probabilistic analysis for all scenarios due to the long running time of the DES model. All results include the PAS discount.

Table 1 Summary of additional analysis carried out by ERG

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	5.96	3.989	£148,920	2.15	1.476	£36,238	£44,831
5% ruxolitinib wastage in every cycle	5.96	3.989	£154,243	2.15	1.476	£36,238	£46,949
Exclusion of lenalidomide	5.96	3.989	£148,698	2.15	1.476	£35,397	£45,077
ERG mortality rate	5.84	3.931	£148,396	2.15	1.476	£35,397	£45,683
Alternative ERG base-case with CS mortality rate	5.90	3.948	£153,621	2.15	1.483	£35,435	£47,950
Alternative ERG base-case with ERG mortality rate	5.78	3.890	£153,097	2.15	1.483	£35,435	£48,894

Drug wastage had the greatest individual impact on the estimated ICER, but all the alternative assumptions explored by the ERG all only had relatively modest impacts on the estimated ICER. The ERG's additional analysis is consistent with sensitivity and scenario analysis presented in the CS that the estimated ICER is robust to a wide range of alternative input values and assumptions.

With these modifications to the model the probability of ruxolitinib representing a cost-effective treatment strategy is 0.0%, 0.3%, 66.2% and 100% at a respective threshold of £30,000, £40,000, £50,000 and £60,000 (including the PAS discount).

1.8 Conclusions

Evidence from two good quality RCTs demonstrates that ruxolitinib is effective at reducing splenomegaly and its associated symptoms and can increase overall survival in intermediate-2 and high risk MF patients who can tolerate ruxolitinib and remain on therapy. However withdrawal rates are high and more than half of patients will have discontinued therapy after three years. Evidence relating to patients with lower risk disease or low platelet counts (50 to 100 x 10^9/L) is less robust.

The *de novo* model was well presented and had an appropriate model structure, which shows good validation with the trial data from the COMFORT-II study. The extensive sensitivity and scenario analysis presented in the company show the estimated ICER to be largely robust to a range of input values and assumptions made in the model. The alternative scenarios presented by the ERG show a modest increase in the estimated ICER primarily as a result of including an element of drug wastage within the model.

2 Background

2.1 Critique of company's description of underlying health problem

The description of the underlying health problem in the company's submission (CS) is appropriate and relevant to the decision problem under consideration.

Myelofibrosis (MF) is a myeloproliferative neoplasm which can develop *de novo* as primary MF (PMF) or secondary to polycythaemia vera or essential thrombocythaemia, known as post-polycythaemia vera MF (PPV-MF) and post-essential thrombocythaemia MF (PET-MF). MF is a rare and debilitating disease associated with substantial morbidity and early mortality. The clinical features of MF are described in the British Committee for Standards in Haematology (BCSH) guideline as "variable and include progressive anaemia, leucopenia or leucocytosis, most commonly causing hepatomegaly and symptomatic splenomegaly. Patients with advanced disease experience severe constitutional symptoms, the consequences of massive splenomegaly (pain, early satiety, splenic infarction, portal hypertension and dyspnoea), progressive marrow failure, pulmonary hypertension, transformation to leukaemia and early death."[3]

The over-activation of the JAK/STAT signalling pathway, resulting in over-proliferation of blood cell precursors, is described in the CS. The clinical course of the disease and symptoms are appropriately described. Survival varies considerably and the life expectancy figures reported in the CS seem reasonable, according to the evidence review group's (ERG) clinical advisor. The CS states that median survival following diagnosis for patients with PMF is 4.0 to 5.7 years overall, according to historical data,[4, 5] while for patients with secondary MF, median survival following diagnosis is 5.7 to 7.5 years.[6, 7] However, these figures are low compared to other estimates and furthermore, within each of these groups survival varies considerably. More recently prognostic systems have been devised with the aim of assisting therapeutic decision making.[4, 8, 9]

The CS did not describe the relevant prognostic systems, summarised here by the ERG as follows. A highly discriminative prognostic system was developed by the International Working Group for Myelofibrosis research and Treatment (IWG-MRT) – the International Prognostic Scoring System (IPSS).[4] A study was conducted using a database of 1054 MF patients. Five prognostic factors present at diagnosis were identified: age greater than 65 years, presence of constitutional symptoms, haemoglobin level less than 10 g/dL, leukocyte count greater than 25 _ 109/L, and circulating blast cells 1% or greater. Four risk categories were defined based on the presence of these prognostic

factors: 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2) and 3 or more (high risk). To allow risk categorisation to be applied as MF progressed over time, a later study by the IWG-MRT developed a second risk score: the Dynamic International Prognostic Scoring System (DIPSS).[9] This study based on data from 525 patients found that the 5 previously identified variables were still prognostic but different weights were to be applied. In particular a higher weight is given to anaemia (though not treatment induced anaemia): the presence of anaemia counts as two. An age adjusted version of DIPSS was also developed so that risk stratification could be applied to patients aged less than 65 years.

The CS reported that median survival using the various prognostic scoring systems varies from 1.3 to 15.4 years, depending on the system and the risk classification. Data from a recent Haematological Malignancy Research Network (HMRN) audit of 98 patients indicated that the median survival for the total cohort, regardless of risk classification, was 3.36 years (range 2.8 to 4.4).[10] The ERG reports the figures from the IPSS and DIPSS development studies.[4, 9] Using IPSS median overall survival is: low >10 years; intermediate-2 approximately 8 years; intermediate-2 approximately 4 years; and high risk approximately 2 years (27 months (95% CI: 23-31). Using DIPSS median survival was not reached in low-risk patients; it was 14.2 years in intermediate-1, 4 years in intermediate-2, and 1.5 years in high risk patients.

The CS reported that the prevalence of MF is estimated to be 2.2 per 100,000 population based on audit data for a region of England, thus 1185 patients in England and 70 patients in Wales are estimated to be living with the disease. These figures appear reasonable. Ruxolitinib is also licenced for the treatment of patients with polycythaemia vera who are resistant or intolerant to hydroxycarbamide (HC), however, this appraisal only relates to ruxolitinib for the treatment of disease-related splenomegaly or symptoms in adults with MF.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is generally appropriate and relevant to the decision problem under consideration. It correctly states that there is no clear standard therapy; treatments such as hydroxycarbamide, steroids and thalidomide are commonly used in the UK and are recommended for use by the BCSH guidelines. A survey of UK physicians treating patients with MF reported that erythropoiesis stimulating agent (ESA) and thalidomide were principally used to treat anaemia, hydroxycarbamide for leucocytosis, thrombocytopenia, splenomegaly, night sweats and

fever, and steroids for weight loss.[11] Lenalidomide is not included in the CS description of commonly used treatments; the ERG's clinical advisor agrees that lenalidomide is not used in UK practice.

Ruxolitinib is licenced for the treatment of disease-related splenomegaly or symptoms in adults with PMF, PPV-MF or PET-MF. The BCSH guideline for the diagnosis and management of MF was revised in 2014 to include the recommendation of ruxolitinib as first line therapy for symptomatic splenomegaly and/or myelofibrosis-related constitutional symptoms regardless of JAK2 V617F mutation status. Ruxolitinib is not currently recommended for asymptomatic patients and/or those who lack bothersome splenomegaly.[12]

Figure 6 of the CS 'Algorithm for management of symptomatic MF based on BCSH guidelines' is generally appropriate, although the guideline states that ruxolitinib 'can be considered' for hepatomegaly and portal hypertension due to MF, rather than recommending it as first line therapy. In addition, Figure 6 states that allogeneic haematopoietic stem cell transplantation (allo-HSCT) is only recommended in rare circumstances in young patients (aged <60 years), but in the text on page 51 of the CS it states that allo-HSCT is generally reserved for patients under 45 years of age. However, the BCSH guidelines have slightly broader recommendations in that they include a recommendation for reduced intensity allo-HSCT in patients aged over 45 years or who have a HSCT co-morbidity index of 3 or more, but only in those who are transplant eligible and at high or intermediate-2 risk. Across both age groups the BCSH guideline recommends allo-HSCT (or reduced intensity allo-HSCT) if the patient is transfusion dependent and/or has adverse cytogenetic abnormalities.[3] Thus, it might be reasonable to consider allo-HSCT as a comparator to ruxolitinib, or even a more appropriate treatment option, given that it is potentially curative. However, allo-HSCT is only used in a small proportion of patients in the UK: where ruxolininib is not available allo-HSCT is more widely used, due to the lack of alternatives. There is also the potential for ruxolitinib to be used as a 'bridge' to allo-HSCT, i.e. improving the patient's condition to a level where their risk of adverse outcome form allo-HSCT is minimised, allowing them to receive the potentially curative treatment.

3 Critique of company's definition of decision problem

3.1 Population

The population in the CS matched that specified in the NICE scope: adults with disease-related splenomegaly or symptoms of primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis and post essential thrombocythaemia myelofibrosis. This is within the licenced indication of ruxolitinib for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF, PPV-MF or PET-MF.[13] However, the clinical effectiveness evidence is primarily from two randomised controlled trials (RCTs) of ruxolitinib, the COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment (COMFORT) trials, in which the populations comprise only a subset of the licensed population. COMFORT-I and COMFORT-II included patients with intermediate-2 or high risk MF and a palpable spleen measuring 5cm or more below the costal margin, and restricted inclusion criteria to patients with a life expectancy of at least 6 months and platelet count of at least $100x10^9$/L and peripheral blood blast count of less than 10%.[14, 15] Also, the COMFORT-I trial included only patients whose disease was resistant or refractory to available treatment, or who were intolerant of, or not candidates for such therapy.[15] Importantly, the COMFORT trials included only patients who were not considered to be suitable candidates for allo-HSCT at the time of enrolment.

The company stated that patients in the COMFORT-II trial could be healthier than the general MF population because of clinical trial exclusion criteria, such as uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. The ERG understands this to mean healthier than the general intermediate-2 or high risk MF population as lower risk MF patients were not included in the trial.

The CS also included four non-RCT studies of ruxolitinib in patients with MF as supporting evidence.[16-19] These additional non-RCTs included 3 studies that included patients with a low platelet count ($50\text{-}100x10^9$/L) (study 258, a subset of patients in the JUMP study and the EXPAND trial)[17-19] and two studies that included patients with earlier stage disease (intermediate-1 as well as intermediate-2 and high risk) (the ROBUST study and the JUMP study).[16, 19] In addition, the CS referred to a dose finding study[20] and seven 'real world' studies and reports of routine clinical use, which included specific subgroups of patients such as low-risk and intermediate-1 risk patients.[20-27] Therefore, the evidence for the use of ruxolitinib in patients with lower risk disease and low platelet counts is not as robust as that in intermediate-2 and high-risk patients with platelet counts over $100x10^9$/L.

3.2 Intervention

The intervention in the CS matched that specified in the NICE scope: ruxolitinib with established clinical practice. The licensed dose of ruxolitinib is 5-25 mg twice daily. The maximum recommended starting dose is 5 mg twice daily for patients with platelet counts of 50,000 to 100,000/mm^3, 15 mg twice daily for patients with platelet counts of 100,000 to 200,000/mm^3 and 20 mg twice daily for patients with platelet counts over 200,000/mm^3.[28] The starting doses used in the COMFORT trials and the non-RCT studies were in accordance with the licence.

3.3 Comparators

The comparator in the CS matched that specified in the NICE scope: established clinical practice without ruxolitinib, which was appropriate. The company excluded allo-HSCT from the economic analysis because of the small number of patients that are eligible for allo-HSCT and also because of a lack of relevant data. Patients included in the COMFORT trials were not considered to be suitable candidates for allo-HSCT, therefore, it is not possible to use these data to compare ruxolitinib with allo-HSCT. However, as allo-HSCT is a potentially curative treatment for MF and there is evidence of a positive benefit-risk balance in intermediate-2 and high-risk MF patients[2] the ERG suggests that allo-HSCT should have been included as a comparator or as part of the basket of therapies that made up BAT. Ruxolitinib followed by allo-HSCT could also have been included as a comparator. The issue of these potential comparators is discussed further in Section 5.

The CS states that patients with MF with an enlarged spleen may also undergo splenic irradiation and splenectomy in practice. However, splenectomy and splenic irradiation are rarely used in the UK due to the associated morbidity and mortality and these were also excluded from the economic analysis.

The comparator used in the COMFORT-II trial was best available therapy (BAT), whilst in the COMFORT-I trial (which included patients who were refractory or not suitable candidates for available therapies) the comparator was placebo. Therefore, the comparators used in the COMFORT trials were generally appropriate, although some of the BAT therapies in the COMFORT-II trial are used more or less frequently in UK practice than in this trial conducted in Europe and the UK. This is discussed further in Section 4.2.1. None of the other studies included a non-ruxolitinib control group.

3.4 Outcomes

The outcomes presented in the CS matched those specified in the NICE scope, with the exception of progression free survival (PFS), which the company states was not included as an outcome because it is not a measure that is generally applied in MF. The company states that there is no accepted definition of progression, and therefore there is no accepted definition of PFS. The ERG's clinical

advisor commented that the company's justification for not assessing PFS seems reasonable, agreeing that there is no good definition of progression in MF. PFS was assessed in the COMFORT-II trial, but it was (not very usefully) defined as the interval between randomisation and the occurrence of any one of these events: a spleen volume increase (25% or greater increase in spleen volume from the on-study nadir (including baseline)); leukaemic transformation; splenic irradiation; splenectomy; or death.

The outcome measures included in the CS were appropriate and assessed in one or both of the COMFORT trials; symptom relief, overall survival, changes in spleen size, adverse effects and health-related quality of life (HRQoL).

3.5 Other relevant factors

The CS states that MF is a highly rare orphan disease and is generally diagnosed in individuals over 60 years of age. Therefore, patients with MF may be less likely to receive extensive cancer treatment because of their age, and may also be at risk of receiving poorer treatment because of the rarity of their disease.

The manufacturer submitted a price discount patient access scheme (PAS). The scheme will operate as a fixed price scheme offering a reduction of [redacted] off the current list price. Table 2 presents the price per 56 tablet blister pack with and without the PAS. This PAS has been approved by the Department of Health.

Table 2 Price of Ruxolitinib with and without PAS

	Cost per 56-tablet blister pack (excluding VAT)	
	List price	With PAS
5 mg	£1,680	[redacted]
10 mg	£3,360	[redacted]
15 mg	£3,360	[redacted]
20 mg	£3,360	[redacted]

4 Clinical Effectiveness

This section contains a critique of the methods of the systematic review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies. The ERG's conclusions on the clinical effectiveness of ruxolitinib for disease-related splenomegaly or symptoms in adults with MF are presented at the end of this section.

4.1 Critique of the methods of review(s)

The CS described an update of a systematic review evaluating the clinical effectiveness and tolerability of ruxolitinib for patients with MF. The original review, referred to as the 2011/2012 review in the CS, was critically appraised in a previous NICE STA of ruxolitinib for the treatment of myelofibrosis (TA289).[29] The previous appraisal concluded that evidence from two good quality RCTs (the COMFORT-I and COMFORT-II trials) demonstrated that ruxolitinib was effective at reducing splenomegaly and its associated symptoms. However, haematological symptoms of MF (in particular anaemia and thrombocytopenia) were worsened by ruxolitinib in some patients, at least in the short term. There was no evidence of any improvement in progression-free survival with ruxolitinib, although there was some evidence that overall survival may be increased with ruxolitinib, although data were uncertain (follow-up data were available up to 112 weeks).

The update was referred to as the 2013/2014 review in the CS.

4.1.1 Search strategy

The CS described the search strategies used to identify relevant clinical effectiveness studies for ruxolitinib and other agents for the treatment of disease-related splenomegaly or symptoms in adult patients with primary MF, PPV-MF or PET-MF. The searches were designed to capture any new studies since the last searches for the 2011/2012 review. Brief details of the searches were provided in the main submission with full details, including the information sources searched, reported in Appendix 2, Section 8.2. Search strategies for both the previous 2011/2012 review and the 2013/2014 update review were reported in Appendix 2, Section 8.2.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, the Cochrane Library (including Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), NHS Economic Evaluations database (NHS EED)) and the Cost

Effectiveness analysis (CEA) registry were searched in December 2013 and again in December 2014 to identify clinical studies of myelofibrosis. In addition, the company searched the abstracts of conference proceedings (online versions) from the following 6 conferences: European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA) American Society of Hematology (ASH), British Society of Haematology (BSH) and European LeukemiaNet.

The searches for the 2013/2014 review covered the period January 2012 – December 2014. The searches were limited to human only studies and excluded letters, editorials, commentaries, case reports, case studies, case series and phase 1 clinical trials.

The methods used to identify both published and unpublished studies for the systematic review were appropriate and for the most part well reported. There were some minor details missing from the reporting of the searches in Appendix 2, Section 8.2, however the company supplied further details in their response to the ERG's Points for Clarification.

Update searches of the main medical databases and of resources for unpublished and ongoing studies were carried out. However the company did not update the search of the BIOSIS database. In the CS it appeared that the search of clinicaltrials.gov for ongoing studies was not updated. The company clarified that this was a reporting error and the search of clinicaltrials.gov was updated for the 2013/2014 review and that the relevant trials are listed in Table 25, Section 4.14 of the CS.

The search strategies for the 2013/2014 update searches contained in Appendix 2, Section 8.2, were appropriate and would result in a sensitive search. Terms for myelofibrosis, including relevant subject headings, text word searches, and synonyms were included in the strategies. The set of terms for myelofibrosis were combined correctly with a second set of terms for study designs. Field searching and truncation have been used appropriately.

Extra study design terms have been added to the strategy since the 2011/2012 review. These extra terms are a useful addition to help identify further studies on adverse effects of treatments for myelofibrosis. These terms include case-control studies, observational studies, non-randomised trials, longitudinal studies and before and after studies, in addition to the terms for randomised controlled trials and cohort studies.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the 2011/2012 review were very broad. For the 2013/2014 update the inclusion and exclusion criteria were modified; the criteria relating to intervention were

made more specific to ruxolitinib or alternative treatments currently available in the UK. The ERG considers this appropriate. One reviewer screened studies for inclusion, with a second reviewer performing a random quality-control check of 30% of all studies selected. The ERG considers this method more open to error and bias than having two reviewers independently assessing all studies.

The inclusion criteria for populations, interventions, outcomes and study designs of interest appear to have been generally appropriate. However, one of the exclusion criteria relating to population is studies with fewer than 40 participants, but the EXPAND study[18] and one of the 'real world' studies referred to in the CS had fewer than 40 participants so should have been excluded from the review. In addition, the exclusion criteria for study design includes phase 1 studies; the EXPAND study was a phase 1b dose finding study so also met this exclusion criterion.

Only English language articles were selected for the review, creating the potential for language bias. However, it is unlikely that any relevant RCTs of ruxolitinib were excluded from the review on the basis of language of publication.

The flow chart of the study selection process states that 61 references were included in the systematic review, 50 relating to ruxolitinib and 11 relating to other therapies, as per the intervention inclusion criteria. The ERG requested clarification regarding the 61 included references. The company responded that 30 of the 61 references were actually included in the NICE submission document and provided reasons for exclusion of the additional 31 references: 25 studies were not clinically relevant and 6 publications were superseded by more recent publications or duplicates.

The company reported that eight of the 30 included references described further analysis of the COMFORT-I data, seven contained COMFORT-II data and two publications examined both COMFORT RCTs; making a total of 17 references relating to the COMFORT trials. In addition, the company stated that twelve publications describing 11 relevant non-RCTs were included in the NICE submission document. A table of these additional relevant non-RCTs was presented, which included the ROBUST study,[16] the JUMP study,[19] Study 258,[17], the dose finding study[20] and six of the seven 'real world' studies and reports of routine clinical use.[21-26] The table did not include the EXPAND trial[18] or the report of 25 patients with low risk and intermediate-1 risk disease[27] which were included in the CS. Therefore, the flow chart of the study selection process presented in the CS and the additional information provided by the company in response to the ERG's points for clarification were both inaccurate in reporting the studies which were actually referred to in the CS.

4.1.3 Data extraction

Data extraction was undertaken by one reviewer and verified by a second reviewer, reducing the potential for error and bias.

Adequate data from the two COMFORT trials were presented in the CS. The ROBUST study, JUMP study, Study 258 and the EXPAND study were described only briefly in the CS. The dose finding study[20] was described in an appendix to the CS (Appendix 8.18). Some of the additional 'real world' studies and reports of routine clinical use were also described in Appendix 8.18, although insufficient data were reported.

4.1.4 Quality assessment

A table of the quality assessment results for the COMFORT trials was presented as an appendix to the CS (Appendix 3), which included all the quality criteria specified by NICE. Quality assessment results were checked by the ERG.

Quality assessment does not appear to have been performed for the ROBUST study, JUMP study, Study 258, the EXPAND study or the other non-RCTs used as additional supporting data.

4.1.5 Evidence synthesis

The company described the results of the individual studies separately, which was appropriate in view of the differences in study design and participant and intervention characteristics. The company stated that although some of the efficacy outcomes are the same for COMFORT-I and II, there are considerable differences between studies with regard to the patient population, treatments, and study duration, therefore, a meta-analysis was not undertaken. However, 3-year follow-up overall survival data from the COMFORT trials were pooled (page 103 of the CS). Therefore, the results of the pooled analysis should be interpreted with caution, in view of these differences between the studies.

4.1.6 Conclusions from the critique of systematic review methods

The search strategy was adequate and inclusion criteria were appropriate (after exclusion of non-ruxolitinib studies); no relevant RCTs of ruxolitinib appear to have been missed. However, the inclusion screening process and exclusion of non-English language studies means that additional non-RCT supporting data may have been missed. The flow chart of the study selection process presented in the CS was inaccurate, as it stated that 61 references were included, whereas only 30 references were included in the submission. Adequate data were presented for the included RCTs, but insufficient data were presented for the non-RCT studies. Quality assessment of the RCTs was appropriate and the trials were good quality. However, no quality assessment was undertaken for the non-RCT studies or the other studies used as additional supporting data. The pooling of 3-year

follow-up overall survival data from the COMFORT trials was not appropriate, in view of the differences between the two trials.

4.1.7 Ongoing studies

The CS states that further long-term follow-up data are being collected for the COMFORT trials and the JUMP study. Other ongoing trials which may report data within the next 12 months are:

- Study NCT01317875 is a phase 1 study of ruxolitinib
- Study NCT00509899 is a phase 1/2 study of ruxolitinib
- Study NCT01392443 is a phase 2 study of ruxolitinib
- Study NCT01969838 is a phase 3 study of momelotinib versus ruxolitinib

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Two RCTs were included in the review; COMFORT-I[15] which compared ruxolitinib with placebo in patients who were refractory or not suitable candidates for available therapies, and COMFORT-II[14] which compared ruxolitinib with best available therapy.

Additional non-RCT evidence was presented: the ROBUST study[16] and the JUMP study[19] included patients with earlier stage disease (intermediate-1 as well as intermediate-2 and high risk), Study 258[17] and the EXPAND study[18] (as well as a subgroup of the JUMP study) assessed patients with a low platelet count (50-100x10^9/L). Whilst these studies did not include a non-ruxolitinib control group, their results provide supporting evidence for the use of ruxolitinib in subgroups of patients that were not included in the COMFORT trials.

In addition, the CS referred to a dose finding study[20] and seven 'real world' studies and reports of routine clinical use, some of which included specific subgroups of patients such as low-risk and intermediate-1 risk patients.[21-27] Limited details of these studies were reported in the appendices of the CS (Appendix 8.18).

4.2.1 RCT evidence

Two multi-centre parallel-group RCTs of ruxolitinib were included in the 2011/2012 review and the 2013/2014 update review undertaken for this appraisal; COMFORT-I and COMFORT-II.[14, 15]

The COMFORT trials assessed ruxolitinib at starting doses of 15 mg or 20 mg twice daily (the starting dose was dependent on baseline platelet count) in patients with splenomegaly and intermediate-2 or high-risk PMF, PPV-MF and PET-MF. In the COMFORT-I trial only patients refractory to all other therapies were included and the comparator was placebo.[15] In the COMFORT-

II trial included patients were or were not refractory to other therapies and the comparator was best available therapy (BAT) which could be no therapy, where appropriate.[14]

The study design and baseline patient characteristics of the COMFORT trials are summarised in Table 3.

Table 3 Study design and patient characteristics of the included RCTs

Study details	**COMFORT-I**	**COMFORT-II**
Location	112 sites in the United States, Canada, Australia	61 sites in Europe (included United Kingdom)
Design	Randomised, double-blind, placebo-controlled	Randomised, open-label
Duration of core study	24 weeks	48 weeks
Method of randomisation	Interactive Voice Response System; 1:1 ratio	Interactive Voice Response System; 2:1 ratio
Method of blinding (care provider, patient and outcome assessor)	Patients received matching placebo tablets, unblinding could occur after week 24; investigators were blind to treatment assignment as database was frozen until primary analysis was complete; MRI and CT scans were assessed by a central review process that was blinded to treatment	None
Intervention(s)	Oral ruxolitinib tablet 15 mg or 20 mg twice daily (n = 155)	Oral ruxolitinib tablet 15 mg or 20 mg twice daily (n = 146)
Comparator(s)	Matched placebo (n = 154)	BAT (n = 73)
Primary outcome	Proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume, assessed by MRI or CT scan	
Timing of primary outcome	Week 24	Week 24 (secondary) and 48 (primary)
Secondary outcomes	Duration of maintenance of reduction in spleen volume in patients initially randomised to receive ruxolitinib, assessed by MRI or CT scan Proportion of patients who had a ≥ 50% reduction from baseline in week 24 Total Symptom Score, measured by the modified MF-SAF v2.0 diary Change from baseline in week 24 Total Symptom Score, measured by the modified MF-SAF v2.0 diary Overall survival HRQoL assessments using EORTC QLQ-C30 and PROMIS Fatigue scale (exploratory endpoints)	Duration of maintenance of spleen volume reduction ≥ 35% reduction from baseline and 25% above the on-study nadir Time to achieve a first ≥ 35% reduction in spleen volume from baseline Progression-free survival Leukaemia-free survival Overall survival Transfusion dependency/independency Change in bone marrow histomorphology HRQoL assessments using EORTC QLQ-C30 and FACT-Lym (exploratory endpoints)
Duration of follow-up for reported analysis	Median, 32 weeks (51 weeks for additional analysis of overall survival) Median 3 years follow-up	Median, 12 months (for overall survival) and 61 weeks (for a pre-planned safety update) Median 3.5 years follow-up
Patient inclusion criteria	Age ≥ 18 years	
	Life expectancy of ≥ 6 months	
	Diagnosis of PMF, PPV-MF or PET-MF according to WHO criteria (2008)	

Study details	**COMFORT-I**		**COMFORT-II**	
	An IPSS score of 2 (intermediate-2 risk level) or ≥ 3 (high-risk)			
	Palpable spleen measuring ≥ 5 cm below the left costal margin			
	ECOG performance status of ≤ 3 (scale of 0 to 5)			
	Peripheral blood blast count of < 10%			
	Absolute peripheral blood CD34+ cell count > 20 x 10^6/L		Platelet count ≥ 100 x 10^9/L without assistance of growth or thrombopoietic factors, or platelet transfusions. Absolute neutrophil count ≥ 1 x 10^9/L	
	Disease that was resistant or refractory to available treatment or intolerant of or not candidates for such therapy			
	Disease that required treatment defined by any of the following: IPSS prognostic score ≥ 3, palpable spleen length > 10 cm, score of > 3 on at least 2 items or score of 5 on 1 item on the MF-SAF v2.0			
Patient exclusion criteria	Absolute neutrophil count ≤ 1 x 10^9/L or platelet count < 100 x 10^9/L)		History of absolute neutrophil count ≤ 0.5 x 10^9/L or platelet count < 50 x 10^9/L except during treatment for myeloproliferative neoplasm or cytotoxic therapy	
	Direct bilirubin ≥ 2 x ULN; alanine aminotransferase ≥ 2.5 x ULN; creatinine > 2.0 mg/L)			
	History of malignancy in past 5 years			
	Splenic irradiation within 12 months prior to randomisation/screening			
	Previous treatment with JAK inhibitor			
	Concurrent treatment with other prohibited medications		Pregnant or breastfeeding	
Characteristic	**COMFORT-I (n = 309)**		**COMFORT-II (n = 219)**	
	Ruxolitinib (n = 155)	**Placebo (n = 154)**	**Ruxolitinib (n = 146)**	**BAT (n = 73)**
Median age (range), years	66 (43–91)	70 (40–86)	67 (35–83)	66 (35–85)
Male, %	51.0	57.1	57	58
Disease type, % PMF PPV-MF PET-MF	 45.2 32.3 22.6	 54.5 30.5 14.3	 53 33 14	 53 27 19
IPSS risk status, % High Intermediate-2	 58.1 41.3	 64.3 35.1	 60 40	 59 40
Prior hydroxy-carbamide use, %	67.1	56.5	75	68
Palpable spleen length, median (range), cm	16 (0–33)[a]	16 (5–34)	14 (5–30)	15 (5–37)
Spleen volume, median (range), cm^3	2598 (478–7462)	2566 (521–8881)	2408 (451–7766)	2318 (728–7701)

Platelet count, median (range), x 10^9/L	262 (81–984)	238 (100–887)	244 (–)	228 (–)
Haemoglobin Median (range), g/dL < 10 g/dL, %	 10.5 (6.6−17.0) –	 10.5 (3.5−17.3) –	 – 45	 – 52
JAK2V617F mutation positive,%	72.9	79.9	75	67

[a] One patient had a baseline spleen length recorded as non-palpable in error but had a prior measurement of 16 cm and a baseline spleen volume of 2450 cm^3; BAT, best available therapy; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HRQoL, health-related quality of life; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis; PROMIS, Patient-Reported Outcomes Measurement Information System; RCT, randomised controlled trial; ULN, upper limit of normal, WHO, World Health Organisation.

As shown in Table 3, the COMFORT trials were conducted only in patients with splenomegaly and intermediate-2 or high-risk MF, who had a platelet count ≥ 100 x 10^9/L and an absolute neutrophil count >1 x 10^9/L,[14, 15] therefore the results may not be generalisable to patients without splenomegaly or with lower risk disease or lower platelet or absolute neutrophil count. In addition, patients suitable for allo-HSCT at the time of study enrolment were excluded from the trials. Within this narrower population, the trial inclusion criteria appear to have been appropriate, and were similar between the two trials, with the exception that patients in the COMFORT-I trial had disease that was refractory to available therapies, had side effects requiring their discontinuation, or were not candidates for available therapies, therefore, in this trial ruxolitinib was used in the second-line setting.[15]

The company stated that patients in the COMFORT-II trial may be healthier than the general MF population because of clinical trial exclusion criteria, such as uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. The ERG understands this to mean healthier than the general intermediate-2 or high risk MF population as lower risk MF patients were not included in the trial.

The COMFORT-II trial compared ruxolitinib with best available therapy (BAT), including observation alone (33% patients), hydroxycarbamide (47% patients), glucocorticoids (16% patients), epoetin-alpha (7% patients), immunomodulators (thalidomide and lenalidomide, 7% patients), purine analogs (6% patients), androgens (4% patients), interferons (4% patients), nitrogen mustard analogues (3% patients) and pyrimidine analogues (3% patients). These comparators were generally appropriate, although the ERG's clinical advisor stated that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is not used in UK practice. The COMFORT-I trial compared ruxolitinib with placebo. However, as patients in this trial were refractory to, or were not candidates for available therapies or had side effects requiring their discontinuation, and were not candidates for allo-HSCT, there were no alternative therapies for these patients; therefore the comparator in this trial could be interpreted as a form of BAT for this population.

The primary endpoint was the same in both trials; proportion of patients achieving a 35% or greater reduction of spleen volume (at 48 weeks in COMFORT-II and 24 weeks in COMFORT-I). The company states that this degree of response (i.e. 35% or greater reduction in spleen volume by magnetic resonance imaging (MRI)) corresponds to a 50% reduction in palpable spleen length. This seems reasonable and, whilst this method of measuring spleen size is not generally used in practice, provides a more objective measurement than palpation. The 35% reduction cut-off was applied across all baseline spleen volumes. A 35% reduction in spleen volume for those patients with a smaller spleen at baseline may have little impact on patients' symptoms or HRQoL (although patients may still see improved symptoms or HRQoL). The COMFORT trials also assessed duration of maintenance of spleen response and time to first spleen response, as well as mean or median percentage change from baseline in spleen volume and length over time.

The COMFORT-I trial assessed symptom reduction using a modified version of the Myelofibrosis Symptom Assessment Form (MF-SAF), which was an appropriate tool to use. This tool is disease-specific and assesses seven symptoms of MF; abdominal discomfort, pain under the ribs on the left side, early satiety, night sweats, itchiness, bone/muscle pain and inactivity. The COMFORT-I trial assessed the proportion of patients achieving a ≥50% reduction in total symptom score (TSS) using the MF-SAF and the mean change from baseline in TSS. The COMFORT-I trial also assessed symptoms using the PGIC instrument, where patients rated the improvement or worsening of their condition, which also appears to be an appropriate tool to use. The COMFORT-II trial did not assess symptom reduction, other than in terms of HRQoL.

Both COMFORT trials assessed HRQoL as an exploratory endpoint using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). In addition, the COMFORT-I trial used the PROMIS Fatigue scale and the COMFORT-II trial used the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) scale. These tools appear to have been appropriate.

Neither of the COMFORT trials were designed to be sufficiently powered to detect a significant difference in survival outcomes. The COMFORT-II trial assessed overall survival, progression-free survival and leukaemia-free survival. The COMFORT-I trial assessed overall survival. Both COMFORT trials permitted patients to cross over from the control group to ruxolitinib; therefore, the possible survival benefits of ruxolitinib are likely to be underestimated, as in both studies all patients in the control groups discontinued therapy or crossed over to receive ruxolitinib over the 3-year follow-up period. Therefore, the company used a rank-preserving structural failure time (RPSFT) model to estimate the true effect of ruxolitinib on overall survival, adjusting for crossover. All methods of adjusting survival estimates in the presence of treatment switching have limitations; the RPSFT method relies critically on the 'common treatment effect' assumption - that is, the treatment effect experienced by patients who crossover must be the same (relative to the time the treatment is taken for) as the treatment effect experienced by patients initially randomised to the experimental treatment.[30] At the point for clarification the ERG asked the company to provide a consideration of the plausibility of the common treatment effect assumption in the present context. The company considered the common treatment effect was likely to hold for two reasons:

- BAT treatment is not known to alter the underlying disease course and as such patient symptoms are likely to be unchanged from baseline;
- Clinical experience of ruxolitinib indicates that patients experience significant benefit regardless of the stage disease.

The ERG considers these arguments sensible and that the common treatment assumption is likely to hold in the current context. This method therefore appears to have been appropriate. The ERG however, notes that the common treatment assumption cannot be formally tested and any resulting analysis is particularly sensitive to violations of this assumption. Some uncertainty as to the validity of the adjusted analysis therefore remains.

4.2.1.1 Summary of the quality of the included RCTs

Results of the quality assessment for the COMFORT trials were presented in Table 15 of the CS. In general, both trials were well conducted but there were some areas of concern related to the blinding

in the trials. The COMFORT-I trial was a double-blind trial, but patients were eligible for early unblinding if they had a 25% or greater increase in spleen volume from baseline (with worsening early satiety accompanied by weight loss or worsening splenic pain accompanied by increased narcotic requirements). Also, the trial was unblinded when all patients had completed the week 24 evaluation or discontinued treatment and 50% patients had completed the week 36 visit. The COMFORT-II trial was not double-blind, although for the primary outcome of ≥35% reduction in spleen volume assessed by MRI or CT, the outcome assessors were blinded: images were read centrally by a reader unaware of the treatment group. Overall, both trials can be considered to be at low risk of bias for the primary outcome.

Both trials had clear eligibility criteria, had adequate sample sizes, an appropriate method of randomisation and adequately reported the participants' baseline characteristics. The proportion of patients with baseline palpable spleen length less than 10 cm in the ruxolitinib group was greater than that in the comparator group in both trials (32.2% versus 23.3% in the COMFORT-II trial and 20.6% versus 17.5% in the COMFORT-I trial, as reported in the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) assessment report[13]), therefore, a smaller absolute reduction in spleen volume would be required to achieve a ≥35% reduction from baseline in the patients in the intervention group with smaller spleens than those in the comparator group. The proportion of patients with baseline palpable spleen length less than 10 cm was not reported in the CS.

In both COMFORT trials analyses were on an intention-to-treat basis for the primary endpoint: patients who discontinued therapy, crossed-over before 24 weeks (in the COMFORT-I trial) or did not have a 48-week assessment of spleen volume (in the COMFORT-II trial due to discontinuation or entering the open-label extension phase of the trial) were counted as non-responders for change in spleen volume and symptom score, which is a conservative approach. Pre-planned and *post hoc* subgroup analyses were performed for the primary outcome in both COMFORT trials, according to patient characteristics (for example gender, MF subtype, IPSS risk category and JAK2 mutation status), although the trials were not designed to be sufficiently powered to detect a statistically significant difference in spleen volume reduction for subgroups.

4.2.1.2 Summary of the results of the included RCTs

Table 4 presents the efficacy results for the COMFORT trials, as presented in the previous ERG report (which includes the number of patients included in the analyses),[29] updated using the longer term trial data.

Table 4 Summary of efficacy results of the included RCTs

Outcome	COMFORT-II	COMFORT-I
Spleen volume		
Patients achieving ≥ 35% spleen volume reduction		
at week 12	29.5% vs 1.4% (n=144/146 ruxolitinib, n=72/73 BAT)	39.4% vs 0% (n=155/155 ruxolitinib, n=153/154 placebo)
at week 24	32% vs 0%, p < 0.001 (n=144/146 ruxolitinib, n=72/73 BAT)	41.9% vs 0.7%, p < 0.001[a] OR: 134.4, 95% CI 18.0 to 1004.9 (n=155/155 ruxolitinib, n=153/154 placebo)
at week 48	28% vs 0%, p < 0.001[a] (n=144/146 ruxolitinib, n=72/73 BAT)	–
Mean change in spleen volume		
at week 24	−29.2% vs +2.7%, p < 0.001 (n=125/146 ruxolitinib, n=45/73 BAT)	−31.6% vs +8.1% (n=139/155 ruxolitinib, n=106/154 placebo)
at week 48	−30.1% vs +7.3%, p < 0.001 (n= 98/146 ruxolitinib, n=34/73 BAT)	–
at week 156	Approximately –35% in ruxolitinib responders (n=16)	–
Symptoms		
Patients achieving ≥ 50% reduction in TSS at week 24	–	45.9% vs 5.3%, p < 0.001 OR: 15.3, 95% CI 6.9 to 33.7 (n=149/155 ruxolitinib, n=152/154 placebo)
Mean change from baseline in TSS at week 24	–	46.1% vs −41.8%, p < 0.001 (n=129/155 ruxolitinib, n=103/154 placebo) Mean absolute change in symptom score: -8.6 vs 3.2
PGIC: patients rating condition much/very much improved at week 24, %	–	66.9% vs 11.2% (n=139/155 ruxolitinib, n=107/154 placebo)
HRQoL		
Mean change from baseline in Global Health Status/QoL (EORTC QLQ-C30)	At week 48: +9.1 vs +3.4 (n= 66/146 ruxolitinib, n=27/73 BAT)	At week 24: +12.3 vs −3.4, p < 0.001 (n=136/155 ruxolitinib, n=104/154 placebo)
Mean change from baseline in FACT-Lym total score at week 48	At week 48: + 11.3 vs −0.9 (n= 70/146 ruxolitinib, n=29/73 BAT)	–
Survival		
Overall survival	At median follow-up of 61 weeks: 92.0% vs 95.0%, (HR, 1.01; 95% CI 0.32 to 3.24) At median follow-up of 112 weeks: 86% vs 78%, (HR, 0.52; 95% CI 0.27 to 1.00)	At median follow-up of 51 weeks: 91.6% vs 84.4%, (HR, 0.50; 95% CI 0.25 to 0.98; p = 0.04) At median follow-up of 102 weeks: 27 ruxolitinib patients died vs 41 placebo patients, (HR, 0.58;

	At median follow-up of 3 years: 29 ruxolitinib patients died vs 22 BAT patients (HR 0.48; 95% CI 0.28 to 0.85) At median follow-up of 3.5 years: 40 ruxolitinib patients died vs 30 BAT patients (HR 0.58; 95% CI 0.36 to 0.93)	95% CI 0.36 to 0.95; p=0.028) At median follow-up of 3 years: 42 ruxolitinib patients died vs 54 placebo patients (HR 0.69, 95% CI 0.46 to 1.03)
Progression-free survival	At week 48: 69.9% vs 74.0%, (HR, 0.81; 95% CI 0.47 to 1.39)	–

[a]Primary endpoint; CI, confidence interval; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HR, hazard ratio; HRQoL, health-related quality of life; PGIC, Patient's Global Impression of Change; TSS, Total Symptom Score.

Spleen response

As shown in Table 3, both RCTs met their primary efficacy endpoint with significantly more patients in the ruxolitinib group achieving a 35% or greater reduction in spleen volume compared with placebo (at 24 weeks) or BAT (at 48 weeks). The results for this specific outcome were in favour of ruxolitinib at all three time points evaluated (12, 24 and 48 weeks).

The CS also presented data to demonstrate the speed of response to ruxolitinib. In COMFORT-II the median time to first observation of a ≥35% reduction in spleen volume (assessed by MRI or CT) was 12.3 weeks and in COMFORT I most of the patients who achieved a ≥35% spleen volume reduction had achieved this by week 12 (the median time to first observation was not reported for the COMFORT-I trial).

Since a reduction in spleen volume of less than 35% can also be clinically important and associated with considerable symptom relief, results for mean reduction in spleen volume are also of interest. In the COMFORT-II trial, spleen volume had decreased by approximately 29% in ruxolitinib-treated patients (n=125) at week 24, whereas spleen volume had increased in BAT patients (n=45) and this difference was statistically significant. Similar results were seen at week 48, although at that time point the mean increase in spleen volume in the BAT group was numerically higher than at week 24.

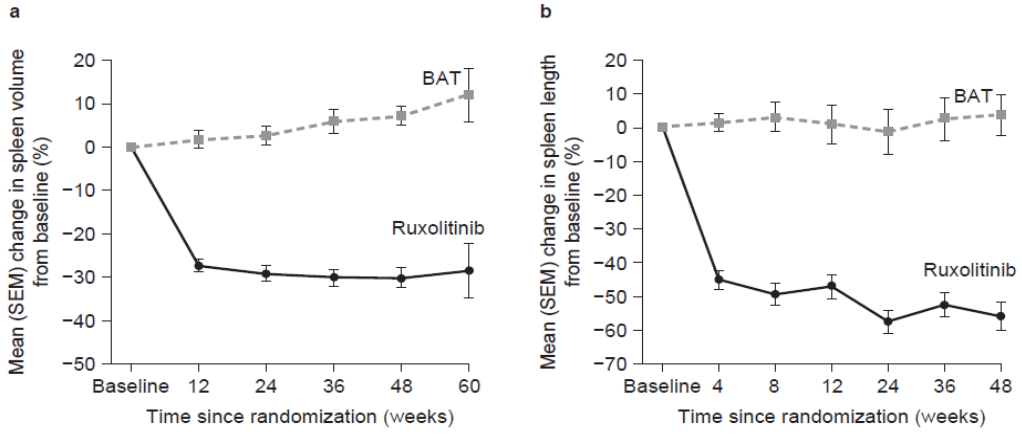
In the COMFORT-I trial, spleen volume had decreased by approximately 32% in ruxolitinib-treated patients (n=139) by week 24, compared with an 8% increase in the placebo group (n=106). It should be noted that not all patients provided data for this analysis - only those with both baseline and week 24 measurements.

The CS reported that a number of subgroup analyses of COMFORT-I and COMFORT-II data have been undertaken and generally show that the benefits of ruxolitinib over placebo or BAT are consistent in all subgroups considered (Figure 33 of the CS).

Maintenance of response to ruxolitinib

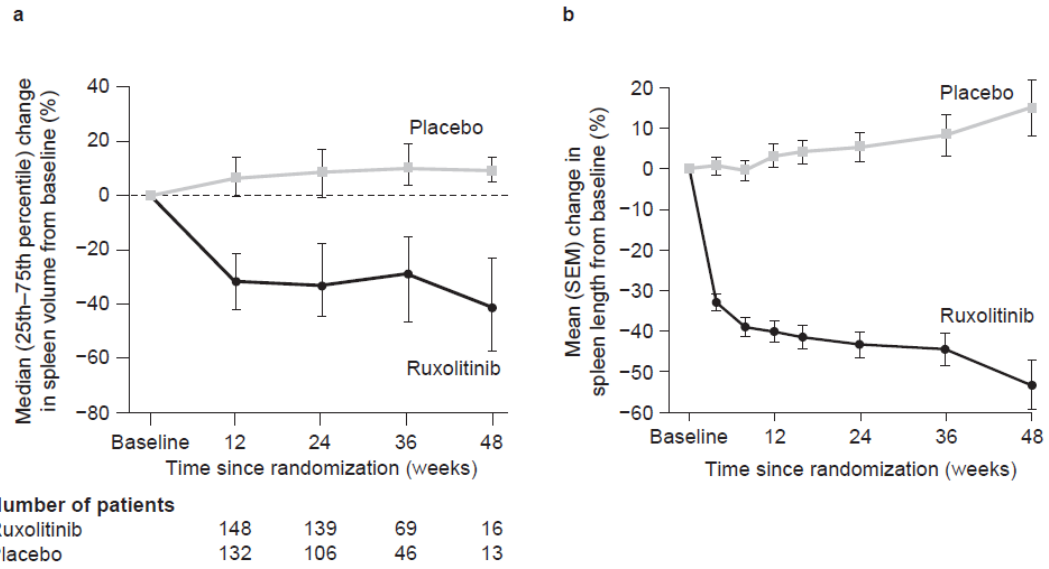
Data were presented in the CS to demonstrate that the effect of ruxolitinib was maintained over time. Amongst patients who achieved a ≥35% spleen volume reduction, this was maintained for a year or more in the majority of patients who continued therapy; 80% of patients maintained this response at a median follow-up of 12 months in the COMFORT-II trial and 67% of patients maintained this response for 48 weeks or more in the COMFORT-I trial, although the number of patients continuing therapy at 48 weeks was low. Figure 1 (Figure 13 in the CS) presents the mean percentage change in (a) spleen volume and (b) palpable spleen length from baseline over time in the COMFORT-II trial and Figure 2 (Figure 14 in the CS) presents the median percentage change in (a) spleen volume and (b) palpable spleen length from baseline over time in the COMFORT-I trial. The number of patients included in the analyses is not reported for the COMFORT-II trial. The number of patients included at the later time points is low for the COMFORT-I trial, which limits the reliability of the results.

Figure 1 Mean percentage change in (a) spleen volume and (b) palpable spleen length from baseline over time in the COMFORT-II trial: core study



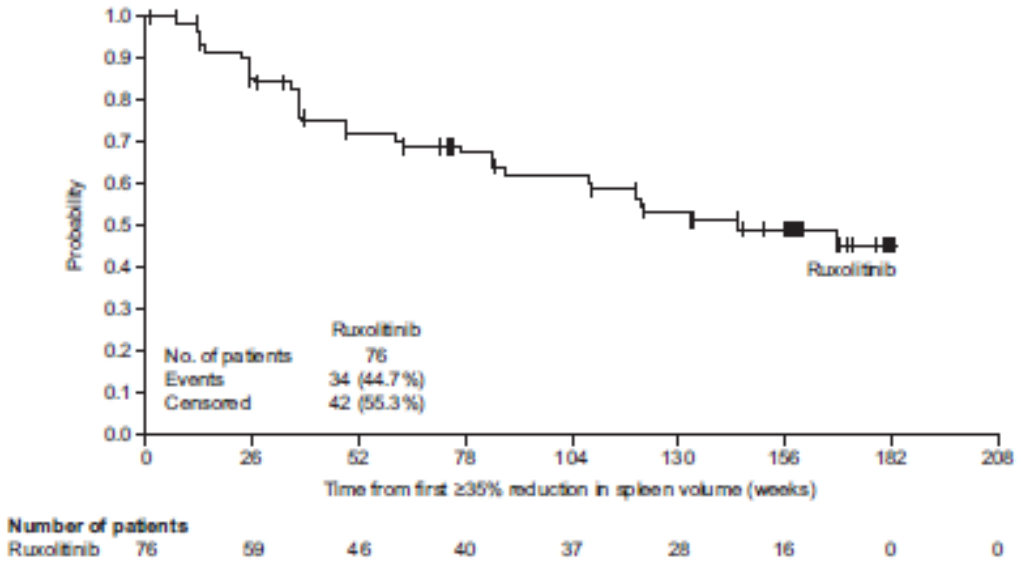
BAT, best available therapy; SEM, standard error of the mean

Figure 2 Median percentage change in (a) spleen volume and (b) palpable spleen length from baseline over time in the COMFORT-I trial: core study



Over the 3.5 year follow-up of the COMFORT-II trial 52.1% (76 patients) receiving ruxolitinib achieved a ≥35% spleen volume reduction at least once during treatment, with loss of response noted in 45% (34 patients) by 3.5 years. The median duration of maintenance of spleen response was 2.76 years in the ruxolitinib group, as shown in Figure 3 (Figure 15 in the CS).

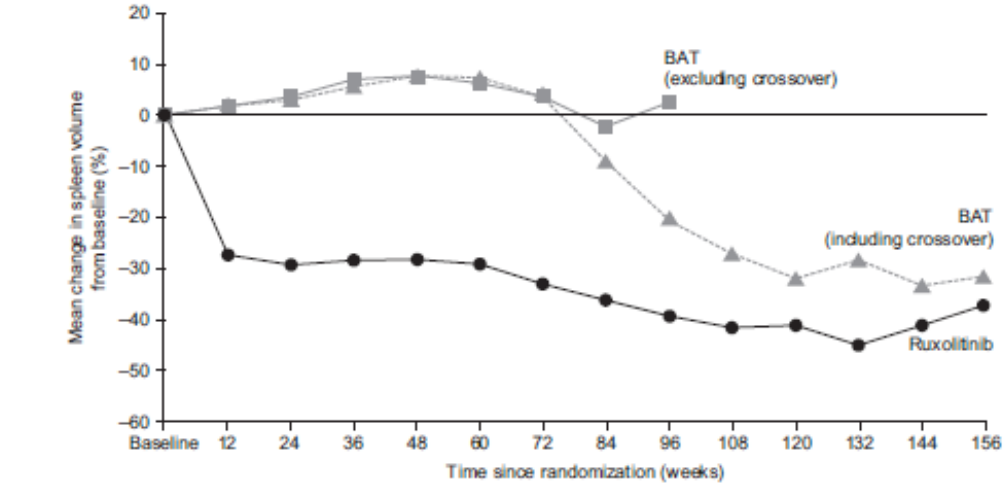
Figure 3 Duration of spleen response in COMFORT-II: extension



Over the 3 year follow-up of the COMFORT-I trial 59% (91 patients) receiving ruxolitinib achieved a ≥35% spleen volume reduction at least once during treatment. Mean reductions in spleen volume were similar at 6 months (31.6%), 2 years (34.9%) and at a median follow-up of 144 weeks (34.1%).

In both COMFORT trials, improvements in splenomegaly were observed in the control group when patients crossed over to receive ruxolitinib. In the COMFORT-II trial, the mean reduction in spleen volume from baseline in the BAT group reached approximately 30% at 144 weeks; however, spleen volume reduction appears to have been less rapid after cross-over from BAT than for patients initially randomised to ruxolitinib, as shown in Figure 4 (Figure 16 in the CS). In the COMFORT-I trial, patients who crossed over from placebo experienced a mean 30% reduction in spleen volume from the time of crossover, equating to a mean reduction of 18% from baseline.

Figure 4 Mean change in spleen volume from baseline over time for COMFORT-II: extension



Number of patients

Ruxolitinib	146	136	125	118	113	102	93	79	61	49	58	46	50	16
BAT (excluding patients who crossed over to ruxolitinib)	73	60	44	39	34	24	16	6	2	0	0	0	0	0
BAT (including patients who crossed over to ruxolitinib)	73	60	46	41	38	29	23	20	16	16	14	15	13	6

BAT, best available therapy

Summary of ERG's opinion of effect of ruxolitinib on spleen symptoms in the short and long term

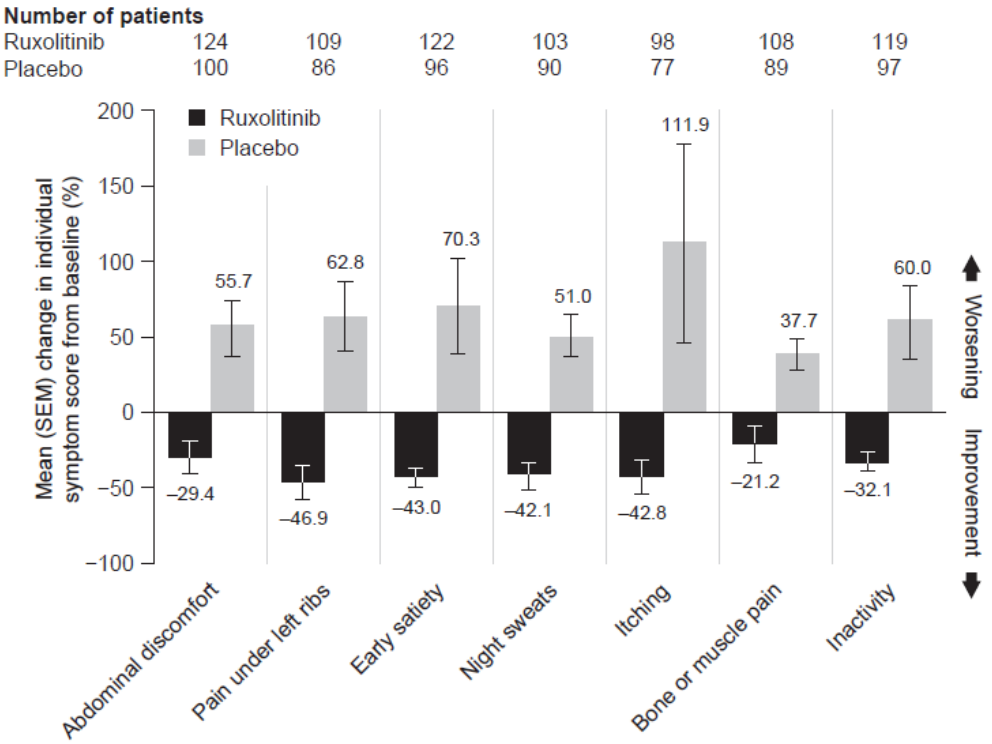
Data presented in the CS demonstrate that significantly more patients receiving ruxolitinib achieve a 35% or greater reduction in spleen volume compared with placebo (at 24 weeks) or BAT (at 48 weeks), with most patients achieving this level of response by week 12. Spleen volume reduced from baseline by approximately 29-32% in ruxolitinib-treated patients at week 24, whereas spleen volume increased in BAT-treated patients and placebo patients at week 24. Reductions in spleen volume and palpable spleen length appear to be maintained amongst responders who remain on treatment. In COMFORT-II the median duration of maintenance of spleen response on ruxolitinib was 2.76 years in the ruxolitinib group.

MF-associated symptoms

Only the COMFORT-I trial assessed symptom reduction. Significantly more patients in the ruxolitinib group achieved a ≥50% reduction in total symptom score (TSS), assessed using the MF-SAF version 2, at week 24 than in the placebo group (45.9% vs 5.3%); the tool used to measure this outcome was appropriate and the analysis included over 95% of randomised patients, therefore this

result is likely to be reliable. At 24 weeks, ruxolitinib-treated patients had a 46.1% mean improvement in TSS, whereas placebo-treated patients had a 41.8% mean worsening in TSS. The majority of responses occurred within 4 weeks after treatment initiation. Ruxolitinib-treated patients also had significant improvements in all MF-SAF individual symptom scores at 24 weeks, while all scores in placebo-treated patients worsened, as shown in Figure 5 (Figure 23 of CS).

Figure 5 Mean percentage change in Myelofibrosis Symptom Assessment Form individual symptom scores at 24 weeks



The proportion of patients rating their condition as "much improved" or "very much improved" (assessed using the PGIC instrument) at week 24 was considerably higher in the ruxolitinib group than the placebo group (66.9% versus 11.2%). However, data were missing for many of the placebo group patients in these analyses, at baseline and week 24 which undermines the reliability of the results.

Ruxolitinib-treated patients also experienced an increase in body weight over time, while patients receiving placebo lost weight (Figure 24 of CS). However, the number of patients included in this analysis is not reported, therefore, it is unclear how complete the data are.

Whilst symptom reduction was not specifically assessed in the COMFORT-II trial, a *post hoc* exploratory analysis of HRQoL and symptom analyses were performed on the primary analysis data set (48 weeks). Of the nine symptom scores assessed by the EORTC QLQ-C30 quality of life questionnaire, six were improved in the ruxolitinib group compared with the BAT group (appetite loss, dyspnoea, fatigue, insomnia, pain and diarrhoea); Figure 26 of the CS shows the change from baseline in symptom scores for the symptoms fatigue, pain, dyspnoea, insomnia and appetite loss: all mean changes were improvements with ruxolitinib compared with a worsening with BAT. Again, the number of patients included in this analysis is not reported; therefore, it is unclear how complete the data are. In addition, data are not shown for diarrhoea or the three symptoms which were not improved in the ruxolitinib group compared with the BAT group.

Summary of ERG's opinion of effect of ruxolitinib on symptom reduction

The data indicate that ruxolitinib was associated with clinically meaningful improvements in MF-associated symptoms at week 24, whereas placebo-treated patients had worsening of symptoms. However, missing data and poor reporting of the number of patients in some analyses mean the results are not as robust as they should be.

HRQoL

In the COMFORT-II trial greater improvements in Global Health Status/QoL were observed in the ruxolitinib group than the BAT group at 48 weeks (+9.1 vs +3.4 BAT) , although there were missing data for many patients in the analysis, with only 66/146 ruxolitinib patients and 27/73 BAT patients included (see Table 3) reducing the reliability of the results. It is unclear whether the difference in the level of improvement is clinically significant.

In the COMFORT-I trial Global Health Status/QoL was statistically significantly better with ruxolitinib than placebo at week 24, with ruxolitinib patients' Global Health Status/QoL improving from baseline and placebo patients' worsening: +12.3 vs −3.4, $p < 0.001$ (n=136/155 ruxolitinib, n=104/154 placebo). Again there was missing data particularly in the placebo group, therefore, results for the placebo group may not be reliable. Global Health Status/QoL remained improved from baseline for ruxolitinib-treated patients at 144 weeks (Figure 27 of the CS), although the number of patients included in this analysis is not reported, therefore, it is unclear how complete the data are.

Individual FACT-Lym scores were also improved in the ruxolitinib group in the COMFORT-II trial, whilst BAT patients had worsening scores at 48 weeks: Mean change from baseline in FACT-Lym total score + 11.3 vs −0.9; although again there were missing data for many patients in the analysis,

with only 70/146 ruxolitinib patients and 29/73 BAT patients included, again reducing the reliability of the results. The differences in scores at week 48 were clinically significant.

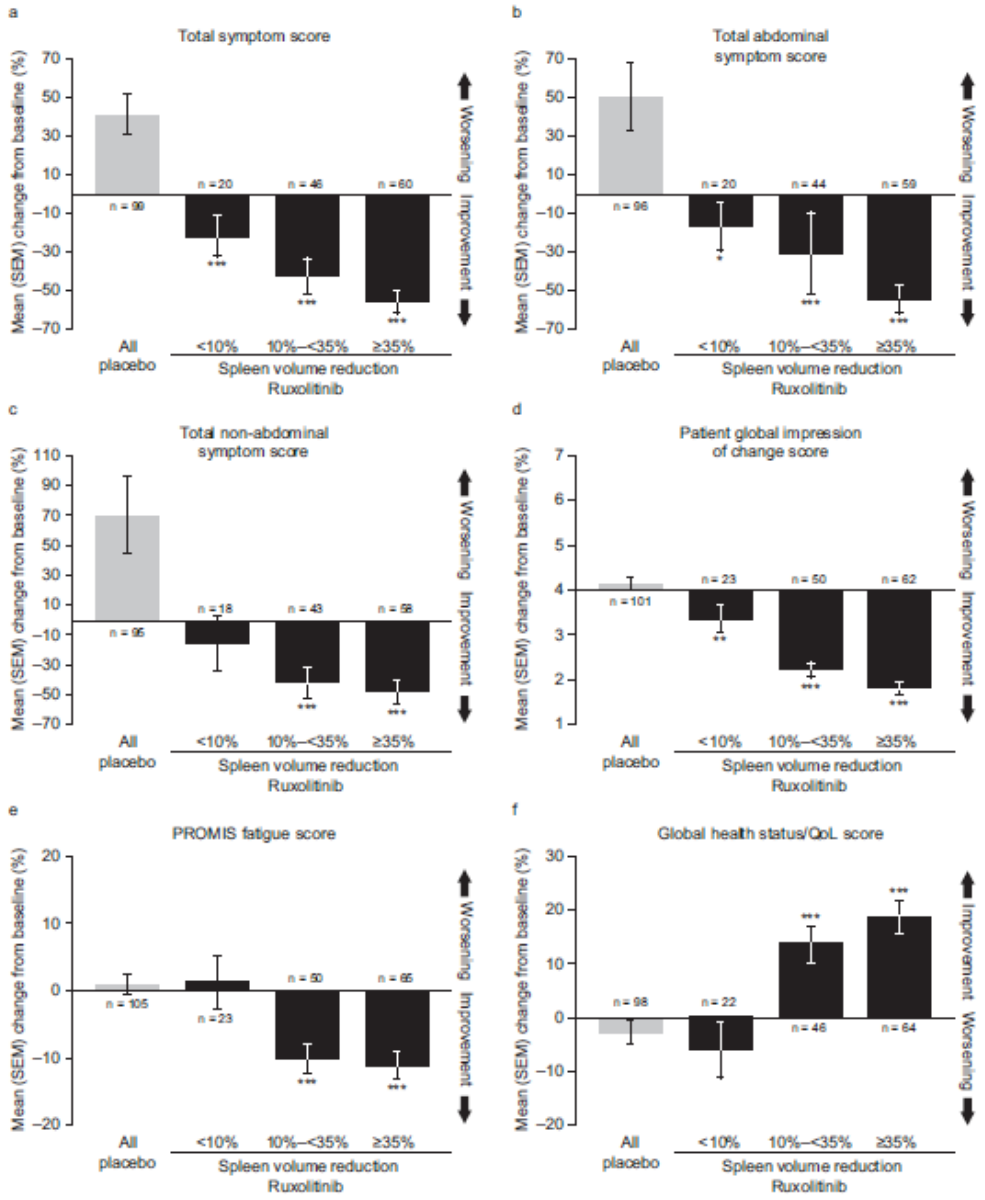
The CS states that in the COMFORT-I trial patients receiving ruxolitinib reported a significantly greater mean percentage improvement from baseline in fatigue at 24 weeks according to the PROMIS Fatigue scale, compared with the placebo group (15.6% improvement versus 9.1% worsening). However, data were missing for many of the placebo group patients, which undermines the reliability of the results.

Figure 6 (Figure 28 in the CS) indicates that there is a relationship between spleen volume reduction with ruxolitinib and symptoms and HRQoL, using data from the COMFORT-I trial: patients who achieved a larger spleen volume response also achieved a better response in terms of symptoms and HRQoL. The analysis indicates that patients who achieve a ≥10% spleen volume reduction show an improvement in TSS, total abdominal symptom score, total non-abdominal symptom score, Patient Global Impression of Change score, PROMIS fatigue score, and Global health status/QoL score. The CS concludes that even small reductions in spleen volume with ruxolitinib are meaningful.

Summary of ERG's opinion of effect of ruxolitinib on HRQoL

The data indicate that ruxolitinib was associated with some improvements in HRQoL in terms of Global health Status/QoL score, FACT-Lym and fatigue at at variously 24 or 48 weeks. However, there was a large amount of missing data, undermining the reliability of the findings. Furthermore it is unclear whether the improvements in Global health Status/QoL score with ruxolitinib were clinically significantly better than those on BAT.

Figure 6 Relationship between spleen volume reduction with ruxolitinib and symptoms and HRQoL in COMFORT-I



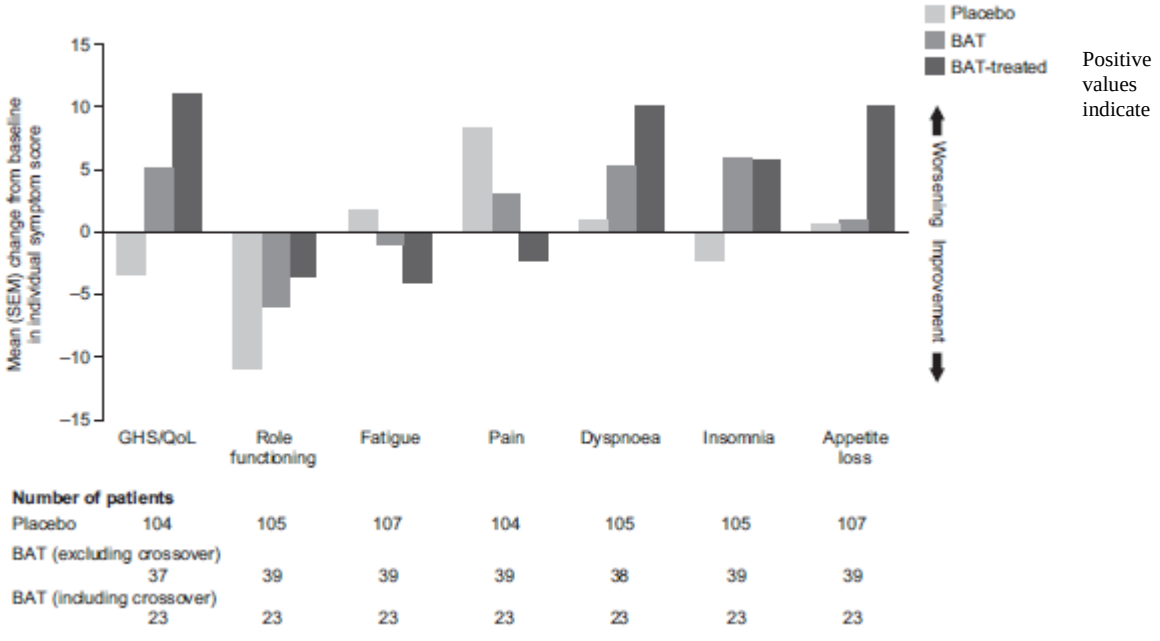
*p ≤ 0.05; ** p ≤ 0.001; *** p < 0.0001

Relationship between symptoms as assessed by the modified Myelofibrosis Symptom Assessment Form v2.0, with quality of life (QoL) as assessed by EORTC QLQ-C30 at baseline. Patients receiving ruxolitinib who were categorised as ≥ 50% Total Symptom Score (TSS) responders achieved significantly greater improvements in the EORTC QLQ-C30 subscales versus patients in the placebo group.

BAT versus placebo

In order to compare BAT with placebo the CS presented the results of a *post hoc* analysis comparing the placebo arm of the COMFORT-I trial and the BAT arm of the COMFORT-II trial for the outcomes mean change in EORTC QLQ-C30 Global Health Status and subscales at week 24, shown in Figure 7 (Figure 29 of the CS). The company states that this *post hoc* analysis suggests that current therapies for MF provide little improvement in spleen size, symptoms or HRQoL and have similar efficacy to placebo for the treatment of MF. However, this is not fully supported by the data presented, which shows that for the subgroup of BAT patients who received treatment (rather than observation), a clinically meaningful improvement (over 10 points from baseline) was achieved for Global Health Status/QoL, dyspnoea and appetite loss. That clinically meaningful improvement can be achieved with current therapies. Furthermore the equivalent data were not presented for ruxolitinib. It is difficult to draw conclusions from this implicit comparison. A more useful analysis would have been a formal statistical indirect comparison. However, the ERG agrees that it was not appropriate to conduct such an analysis due to the difference in the BAT and placebo populations.

Figure 7 Mean change in EORTC QLQ-C30 GHS and subscales at week 24 in the placebo arm of COMFORT-I and BAT arm of COMFORT-II



Improvement in GHS/QoL; negative scores indicate improvement in fatigue, pain, dyspnoea, insomnia and appetite loss. BAT, best available therapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS, global health status; QoL, quality of life; SD, standard deviation.

Overall survival

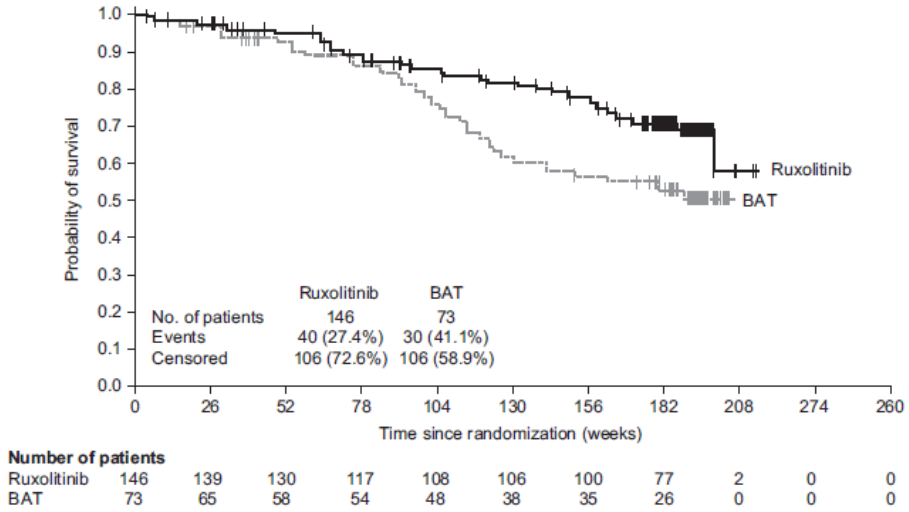
Overall survival was a secondary endpoint in both COMFORT trials and neither trial was designed to be sufficiently powered to detect a statistically significant difference in overall survival between treatment groups.

Ruxolitinib versus BAT – COMFORT-II

Results of the COMFORT-II trial are the most relevant because this trial included a more representative intermediate-2 or high-risk population (and hence a more generally relevant comparator group). Overall survival was not statistically significantly different between ruxolitinib and BAT at a median follow-up of 61 weeks, although it reached borderline statistical significance at a median of 112 weeks of follow-up; 86% versus 78% (HR 0.52, 95% CI 0.27 to 1.00).[29] At median follow-up of 3 years of the COMFORT-II trial, 20% (29 patients) in the ruxolitinib group and 30% (22 patients) in the BAT group had died and ruxolitinib was associated with a 52% reduction in the risk of death compared with BAT (HR 0.48, 95% CI 0.28 to 0.85). The probability of survival at 144 weeks was 81% in the ruxolitinib group and 61% in the BAT group.

The CS reports the results of a further analysis performed at median follow-up of 3.5 years, which included additional survival information for 15 of 41 patients who were previously deemed lost to follow-up. At 3.5 years of follow-up 27% (40 patients) in the ruxolitinib group and 40% (30 patients) in the BAT group had died. Ruxolitinib was associated with a 42% reduction in the risk of death compared with BAT (HR 0.58, 95% CI 0.36 to 0.93); median overall survival has not yet been reached. The probability of survival at 3.5 years was 71% in the ruxolitinib group and 54% in the BAT group (p=0.02). Figure 8 shows the Kaplan-Meier analysis of overall survival by treatment group at a median follow-up of 3.5 years (Figure 30 of the CS). An earlier separation of the OS curves is seen at approximately week 72 (versus week 96) as a result of inclusion of the additional survival information.

Figure 8 Overall survival in COMFORT-II: median follow-up of 3.5 years



BAT, best available therapy

It must be remembered that the majority of patients randomised to BAT crossed over to receive ruxolitinib (at a median of 66 weeks); therefore, the analyses presented above are likely to underestimate the survival benefit of ruxolitinib. The CS presented an overall survival analysis with adjustment for crossover using the rank-preserving structural failure time (RPSFT) model for the COMFORT-I trial, but not for the COMFORT-II trial. The ERG requested an adjusted overall survival analysis for COMFORT-II, which was provided by the company and is presented as Figure 9.

Figure 9

[redacted] **(confidential)**

BAT = Best Available Therapy, RPSFTM = Rank Preserving Structure Failure Time Model

[redacted]

Because median overall survival was not reached in the ruxolitinib arm it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT. The CS included a summary of an indirect comparison made between the ruxolitinib arm of COMFORT-II and the DIPSS cohort.[31] This comparison included only a subset of the COMFORT-II ruxolitinib patients – those who were Primary MF only, but included all who had taken ruxolitinib whether initially randomised to it or not. The DIPSS database includes 519 PMF patients not receiving any experimental drug and are censored at time of HSCT, so are generally equivalent of BAT. Matched patients from the DIPSS cohort were used to construct the comparator group. The analysis included 100 patients from the COMFORT-II cohort and 350 from DIPSS. The data of diagnosis was considered as the starting point of the time scale for the analysis; by back dating the COMFORT-II data from enrolment to diagnosis left-truncated data were generated, excluding potentially eligible patients who died before they had a chance to enter the trial. To avoid this introducing bias appropriate statistical methods for left-truncated (and right censored) survival data were applied. The number of observed deaths in the two cohorts were 30 (30%) on ruxolitinib and 256 (86%) on conventional care, generating estimates of median survival of 5 years (95% CI: 2.9-7.8) on ruxolitinib compared with 3.5 years (95% CI: 3.0- 3.9) for the DIPSS cohort. The ERG considers the methods adopted to generate this comparison acceptable. The estimate for the DIPSS cohort in this analysis is comparable with that previously reported for intermediate-2/high risk patients from the IPPS and DIPSS cohorts: 4 years/2 years and 4 years/1.5 years respectively. [4, 9]

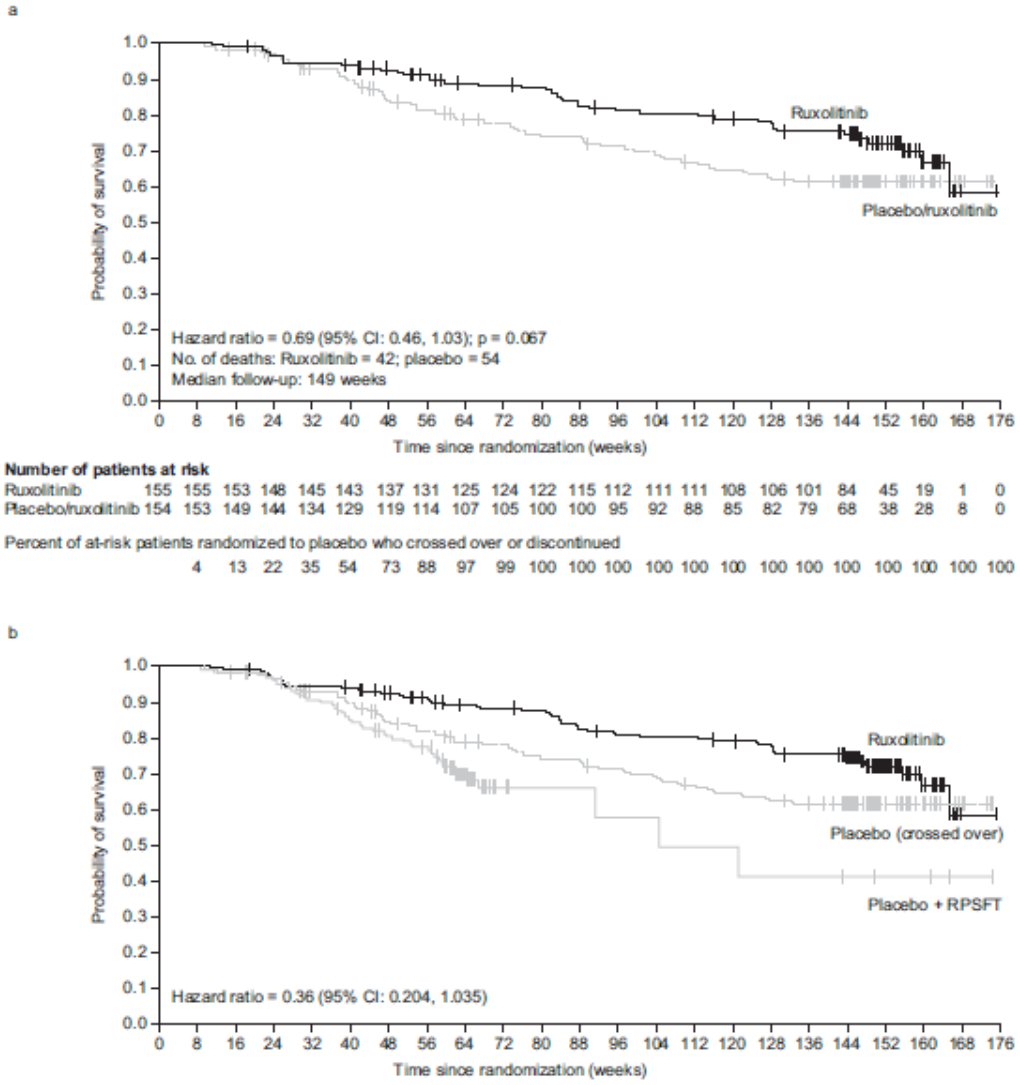
Ruxolitinib versus placebo – COMFORT-I

The overall survival results from COMFORT-1 are less generalisable than those from COMFORT-II as they are from a population of patients who are not eligible for any other active treatment (hence the placebo control group). In COMFORT-1 overall survival was statistically significantly improved with ruxolitinib over placebo at a median follow-up of 51 weeks; 91.6% versus 84.4% (HR 0.50, 95% CI 0.25 to 0.98) and 102 weeks (HR 0.58, 95% CI 0.36 to 0.95).[15] At a median follow-up of 3 years 42

patients in the ruxolitinib group and 54 patients in the placebo group had died and the difference in overall survival was no longer statistically significant (HR 0.69, 95% CI 0.46 to 1.03). However, by week 80 all patients originally randomised to placebo had either discontinued from the study or crossed over to ruxolitinib, therefore, this analysis is comparing patients who had received ruxolitinib since randomisation with patients who had received ruxolitinib for a median of 105 weeks.

In order to estimate the true effect of ruxolitinib on overall survival, the CS presented an overall survival analysis with adjustment for crossover using the RPSFT model. The result of the analysis favoured ruxolitinib more than the ITT analysis (HR 0.36, 95% CI 0.20 to 1.04); the difference was not statistically significant though this could be due to the lack of power in the study. Figure 10 presents the overall survival results for COMFORT-I according to the (a) ITT analysis and (b) RPSFT analysis.

Figure 10 Overall survival in COMFORT-I: (a) ITT analysis, (b) RPSFT analysis



CI, confidence interval; ITT, intent-to-treat; RPSFT, rank-preserving structural failure time

The CS presented a pooled analysis of 3-year follow-up overall survival data from the COMFORT trials (page 103 of the CS), combining the BAT and placebo control groups. The company had previously stated that there are considerable differences between these studies with regard to the patient population, treatments, and study duration; therefore, a meta-analysis was not undertaken. In view of these differences between the COMFORT trials, the results of the pooled analysis should be interpreted with caution. However, the ERG points out that it could be argued that the placebo control in COMFORT -1 represents BAT for the patients enrolled and hence a meta-analysis across COMFORT –I and –II would provide a result generalisable to a broader population of MF patients. From the limited methods described in the submission and the published paper of this analysis[32, 33] it

is not clear that methods of meta-analysis were used, but rather that the data from the two trials were analysed as a single data set. If this is the case then randomisation will have been broken and the resulting study must be considered to be a comparative observational study. This pooled analysis, which did include a correction for crossover from control to ruxolitinib, generated a statistically significant survival benefit in favour of ruxolitinib (HR 0.29 (95% CI: 0.13 to 0.63). A multivariate Cox regression model was used to assess treatment effect, with adjustment for selected patient baseline characteristics. This analysis found that increased baseline spleen size and greater spleen reduction in response to treatment were both associated with greater overall survival: the HR for OS for patients who achieved at least a 50% reduction in spleen length compared with those that achieved less than 10% reduction from baseline (or had no assessment) was 0.18 (95% CI: 1.03-1.15). Given the uncertainty regarding the statistical methods employed, particularly regarding whether heterogeneity and clustering of effect at sites was accounted for in analysis, he ERG consider that these analyses should be interpreted with a degree of caution.

ERG's conclusions on the effect of ruxolitinib on OS

Longer term data from the COMFORT-II trial demonstrated a statistically significant difference in overall survival favouring ruxolitinib over BAT, which was more pronounced when the analysis was adjusted to account for patients crossing over from BAT to ruxolitinib. Longer term data from the COMFORT-I trial also demonstrated an overall survival benefit with ruxolitinib compared with placebo). However using the 3 year data the difference did not reach statistically significance difference even after adjustment for crossover, possibly due to a lack of power in this trial.

Progression-free survival

Progression-free survival was an outcome in COMFORT-II only. The issues regarding this as a relevant outcome in MF have been discussed earlier in Section 3.4. PFS was defined as the interval between randomization and the earliest of either increase in spleen volume ≥ 25% from on-study nadir, splenic irradiation, splenectomy, leukemia or death. The CS reports that at 3.5 years follow-up patients who received ruxolitinib had a reduced risk of disease progression (HR, 0.80; 95% CI 0.54 to 1.19) compared with that of patients who received BAT. The Kaplan–Meier estimate PFS at 3.5 years was 0.27 for the ruxolitinib arm (95% CI 0.18 to 0.35) and 0.23 for the BAT arm (95% CI 0.1 to 0.37). The ERG could not find the source of the table presented. However the results are similar to that reported in the

CSR [redacted]. Whilst there was no statistically significant improvement in progression-free survival with ruxolitinib it is difficult to

interpret the results: the analysis did not censor patients who crossed over from BAT, nor was it adjusted to account for crossover; and also because the vast majority of events were 'increase in spleen volume of ≥ 25% from on-study nadir', which was more common on ruxolitinib than BAT, and reflects a lessening (but not necessarily complete failure) of a good response to ruxolitinib.

Leukemia free survival was defined as the interval between randomization and the earliest date of either (1) the bone marrow blast count of 20% or greater; (2) the date of the first peripheral blast count of 20% or greater that was subsequently confirmed to have been sustained for at least 8 weeks; (3) the date of death from any cause. The CS reported that the risk of leukemia or death was reduced by ruxolitinib by 39% (HR=0.61, 95% CI 0.30- 0.88). However, the CSR makes it clear that, whilst leukemia free survival showed a significant difference between the ruxolitinib and BAT arms, the difference should be attributed only to the reduction of risk of death since it was a more frequent event than Leukaemic transformation and there was a difference in the overall frequency of deaths in favour of ruxolitinib and no difference observed in a small number of Leukaemic transformations.

Overall it is not clear to the ERG how the overall survival benefit of ruxolitinib is produced i.e. what events that result in death are being prevented by ruxolitinib?

Discontinuation rates

At the time of the primary analysis data cut-off of the COMFORT-II trial (when the last patient had completed the 48-week visit) 38% ruxolitinib patients had discontinued treatment. By median 3.5 years of follow-up 63% ruxolitinib patients had discontinued treatment, primarily because of adverse events (20%) and disease progression (18%); other reasons included withdrawal of consent (6%), non-compliance with study medication (3%), protocol deviation (1%) and 'other' (15%). Of those patients who had crossed-over to ruxolitinib from the BAT arm, 60% had discontinued treatment by 3.5 years of follow-up, primarily because of adverse events (18%); other reasons included disease progression (11%), protocol deviation (11%), unsatisfactory therapeutic effect (9%), non-compliance with study medication (2%) and 'other' (9%).[34] In the COMFORT-I trial, at 3 years of follow-up 50% of patients had discontinued treatment, primarily because of disease progression (23%).

Adverse events

The CS stated that ruxolitinib was generally well tolerated, with the most frequently occurring grade 3 or 4 adverse events (anaemia and thrombocytopenia) being generally managed by dose modifications and/or blood transfusions, improving over time and rarely leading to treatment discontinuation (1% and 3.6% of patients, respectively).

Table 4 presents a summary of the adverse event results for the COMFORT trials (Table 20 of the CS). As shown in Table 5, the incidence of serious adverse events was similar between treatment groups in both COMFORT trials. However, the incidence of grade 3 or 4 adverse events was higher in the ruxolitinib group than the BAT group in the COMFORT-II trial (42% versus 25%).

Haematological adverse events were very common with ruxolitinib, particularly anaemia and thrombocytopenia. Haemoglobin levels decrease rapidly following initiation of ruxolitinib treatment, but then they increase over time almost returning to the baseline level. Platelet levels decrease rapidly following initiation of ruxolitinib treatment, then remain reasonably constant, as shown in Figure 11 (Figure 38 of CS), however this figure does not include patients who may have dropped out of the trials because of haematological adverse events. The mean number of blood transfusions per month was similar between ruxolitinib and placebo groups in the COMFORT-I trial (1.7 and 2.2, respectively) and between ruxolitinib and BAT groups in the COMFORT-II trial (0.86 and 0.91, respectively).

Other adverse events affecting more than 20% of ruxolitinib patients were diarrhoea, peripheral oedema and fatigue, although these were also reported in over 20% of patients in the placebo group of the COMFORT-I trial, suggesting that they are likely to be manifestations of MF, and not necessarily related to ruxolitinib treatment. However, diarrhoea was much more frequently reported in ruxolitinib patients than BAT patients in the COMFORT-II trial (23% versus 12%).

In the COMFORT-I trial the incidence of new-onset non-haematological adverse events decreased over time, with incidence rates much higher in the first six months of ruxolitinib treatment than during six month intervals thereafter, with over three years of follow-up. In the COMFORT-II trial the incidence of adverse events of special interest generally decreased over time, as shown in Table 5 (Table 24 of the CS). The incidence of anaemia and thrombocytopenia reduced greatly after the first 24 weeks of treatment. However, the incidence of infections dropped from 50% in the first 24 weeks, but remained at between 25 to 43% over the 3 year follow-up. The incidence of bronchitis increased over time, as shown in Table 5. It should be noted that this table does not include the patients who dropped out of the trial because of adverse events.

Table 5 Adverse events across randomised groups in COMFORT-I and COMFORT-II: primary analysis

System organ/ class/ adverse events	COMFORT-I (24 weeks)			System organ/ class/ adverse events	COMFORT-II (48 weeks)		
	Ruxolitinib % of patients (n = 155)	Placebo % of patients (n = 151)	Relative risk (95% CI)		Ruxolitinib % of patients (n = 146)	BAT % of patients (n = 73)	Relative risk (95% CI)
Death[a], n (%)	9 (5.8)	11 (7.3)		Death[b], n (%)	6 (4.1)	4 (5.5)	
SAEs, n (%)	43 (27.7)	53 (35.1)		SAEs, n (%)	44 (30.1)	21 (28.8)	
Grade 3 or 4 AEs, n (%)	73 (47.1)	67 (44.4)		Grade 3 or 4 AEs, n (%)	61 (41.8)	18 (24.7)	
Withdrawal due to AEs, n (%)	17 (11.0)	16 (10.6)		Withdrawal due to AEs, n (%)	12 (8.2)	4 (5.5)	
Any AEs, n (%)	151 (97.4)	148 (98.0)		Any AEs, n (%)	145 (99.3)	66 (90.4)	
Non-haematological adverse events (≥ 10% of ruxolitinib-treated patients), % any grade/grade 3 or 4							
Fatigue	25/5	34/7		Diarrhoea	23/1	12/0	
Diarrhoea	23/2	21/0		Peripheral oedema	22/0	26/0	
Peripheral oedema	19/0	23/1		Asthenia	18/1	10/1	
Ecchymosis	19/0	9/0		Dyspnoea	16/1	18/4	
Dyspnoea	17/1	17/4		Nasopharyngitis	16/0	14/0	
Dizziness	15/1	7/0		Pyrexia	14/2	10/0	
Nausea	15/0	19/1		Cough	14/0	15/1	
Headache	15/0	5/0		Nausea	13/1	7/0	
Constipation	13/0	12/0		Arthralgia	12/1	7/0	
Vomiting	12/1	10/1		Fatigue	12/1	8/0	
Pain in extremity	12/1	10/0		Pain in extremity	12/1	4/0	
Insomnia	12/0	10/0		Abdominal pain	11/3	14/3	
Arthralgia	11/2	9/1		Back pain	10/2	11/0	

System organ/ class/ adverse events	**COMFORT-I (24 weeks)**			**System organ/ class/ adverse events**	**COMFORT-II (48 weeks)**		
	Ruxolitinib % of patients (n = 155)	**Placebo % of patients (n = 151)**	**Relative risk (95% CI)**		**Ruxolitinib % of patients (n = 146)**	**BAT % of patients (n = 73)**	**Relative risk (95% CI)**
Pyrexia	11/1	7/1		Headache	10/1	4/0	
Abdominal pain	10/3	41/11		Pruritus	5/0	12/0	
Haematology laboratory values[c]							
Anaemia (grade 3 or 4)	45.2	19.2		Haemoglobin (grade 3 or 4)	42	31	
Thrombocytopenia (grade 3 or 4)	12.9	1.3		Platelets (grade 3 or 4)	8	7	
Neutropenia	7.1	2.0					

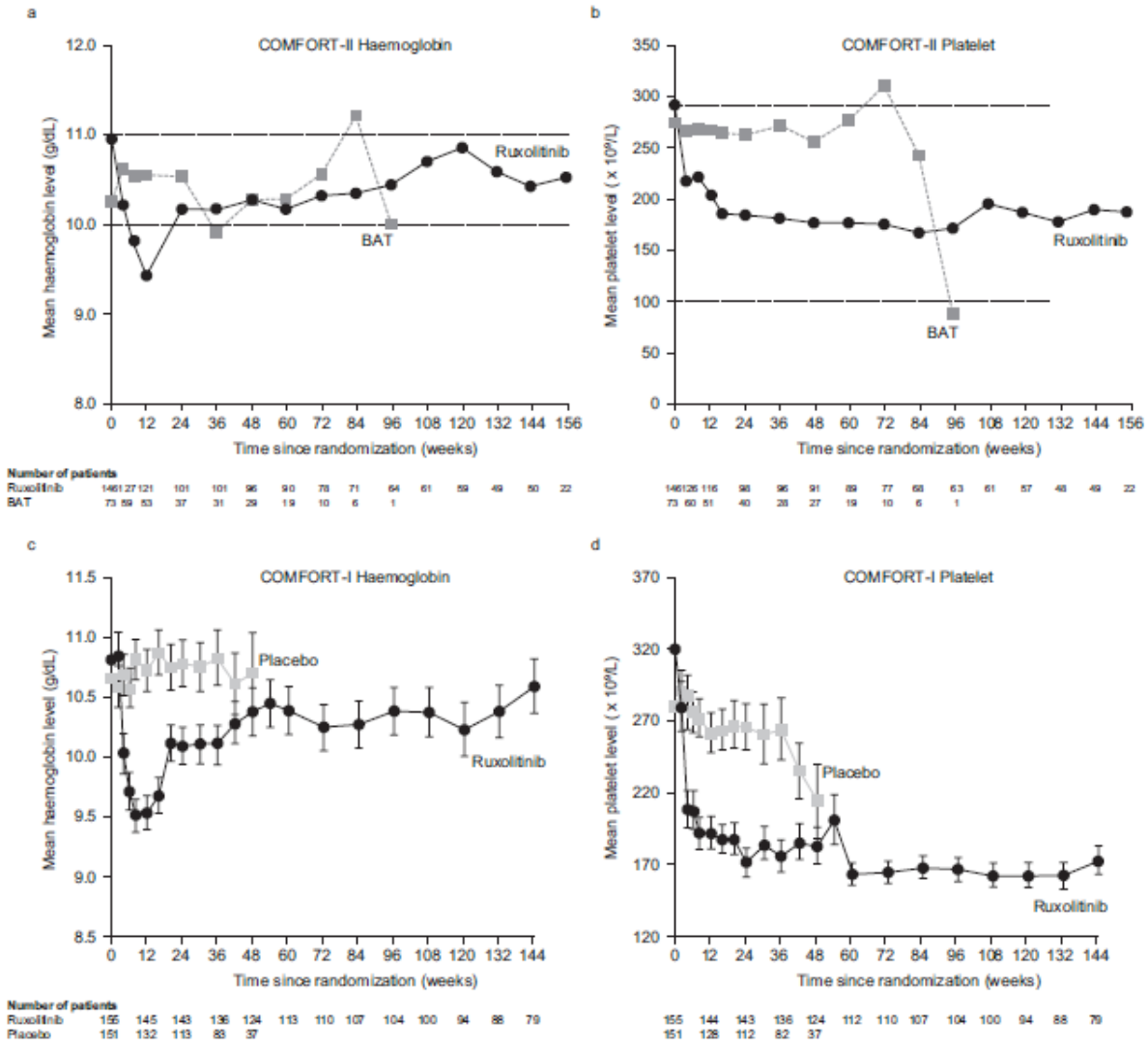
[a]Deaths during study or within 28 days of last dose. Principal causes of death in the ruxolitinib group were muscle weakness and general deterioration, subdural haematoma, renal failure, non-small cell lung cancer, acute myeloid leukaemia (AML), pneumonia (in 2 patients), and sepsis (in 2 patients). Principal causes of death in the placebo group were staphylococcal infection, gastrointestinal haemorrhage, intestinal perforation, multi-organ failure, pneumonia, sepsis (in 2 patients), and disease progression (in 4 patients).One patient in the placebo group died after crossover to ruxolitinib therapy.

[b]The causes of death in the ruxolitinib group were hepatic failure, cerebral haemorrhage, and portal-vein thrombosis after surgery for metastatic squamous-cell carcinoma of the head and neck (in 1 patient); pulmonary oedema and cardiac arrhythmia (1); retroperitoneal haemorrhage after an orthopaedic procedure (1); intestinal perforation associated with terminal ileitis (1); respiratory infection (1); cardiac arrest and myelofibrosis (1); cardiac failure (1); pulmonary extramedullary haematopoiesis and pulmonary failure (1); post-transplantation lymphoproliferative disorder and multiorgan failure (1); and myelofibrosis (2). The causes of death in the BAT group were pneumonia, septic shock, multisystem organ failure, and acute myeloid leukaemia (in 1 patient); post-splenectomy *Klebsiella pneumoniae* sepsis (1); splenectomy, peritoneal haemorrhage, and respiratory failure (1); and renal failure and acute myeloid leukaemia (1).

[c]Worst laboratory value occurring on the randomised treatment phase only

AE, adverse event; BAT, best available therapy; CI, confidence interval; SAE, serious adverse event.

Figure 11 (a) Haemoglobin and (b) platelet levels in COMFORT-II over time: 3 year follow-up and (c) haemoglobin and (d) platelet levels in COMFORT-I over time: 3 year follow-up



BAT, best available therapy

Table 6 Incidence (%) of AEs (any grade) of special interest during treatment with ruxolitinib: COMFORT-II 3-year follow-up

Adverse event	Duration of ruxolitinib treatment						
	0 to 24 weeks (n = 146)	24 to 48 weeks (n = 134)	(n = 116)	72 to 96 weeks (n = 101)	96 to 120 weeks (n = 93)	120 to 144 weeks (n = 81)	144 to 168 weeks (n = 72)
Anaemia	34.9	12.7	8.6	13.9	8.6	7.4	8.3
Thrombocytopenia	43.2	22.4	15.5	12.9	10.8	12.3	2.8
Bleeding	17.1	14.2	9.5	11.9	7.5	9.9	6.9
Epistaxis	6.8	1.5	0.9	4.0	0	1.2	1.4
Haematoma	5.5	4.5	3.4	1.0	0	2.5	1.4
Infections	50.0	35.1	37.9	25.7	43.0	33.3	25.0
Bronchitis	3.4	6.7	8.6	3.0	10.8	4.9	4.2
Gastroenteritis	5.5	3.0	0.9	1.0	2.2	1.2	0
Nasopharyngitis	13.7	5.2	7.8	4.0	10.8	3.7	4.2
Urinary tract infection	4.8	2.2	5.2	4.0	5.4	3.7	2.8
Weight gain	8.2	8.2	5.2	5.0	2.2	0	0

Dose modifications

Dose modifications were common in both COMFORT trials. In the COMFORT-II trial, in patients who started ruxolitinib at a dose of 20 mg twice daily, the median daily dose remained stable during the double-blind phase of the study, then decreased to 34.3 mg/day at week 144. In patients who started ruxolitinib at a dose of 15 mg twice daily, the median daily dose decreased over the first 24 weeks of treatment then stabilised at approximately 20 mg/day (20.8 mg/day at week 144). In the COMFORT-I trial, approximately 70% of patients had dose adjustments during the first 12 weeks of treatment, and by week 24, patients who started ruxolitinib at a dose of 15 mg twice daily were titrated to a mean dose of approximately 20 mg/day, while those who started ruxolitinib at a dose of 20 mg twice daily were titrated to doses of between 30 and 40 mg/day.

In the COMFORT-I trial 40% of patients in the ruxolitinib group and 9% of patients in the placebo group had treatment-emergent adverse events leading to dose reductions. In the COMFORT-II trial 72% of patients in the ruxolitinib group and 18% of patients in the BAT group had adverse events requiring dose reduction or interruption; thrombocytopenia was the most common reason for dose modifications in both groups (41% in the ruxolitinib group and 1% in the BAT group).

4.2.2 Non-RCT evidence

The CS described four additional non-RCT studies; the ROBUST study, the JUMP study, Study 258 and the EXPAND study.[16-19] Whilst these studies did not include a non-ruxolitinib control group, they provide supporting evidence for the use of ruxolitinib in subgroups of patients that were not included in the COMFORT trials.

The ROBUST study was a small phase 2 study of patients from the UK who had intermediate-1, intermediate-2 or high risk disease. The JUMP study was a large phase 3b extended access study in 25 countries for patients who had intermediate-1, intermediate-2 or high risk disease. Study 258 was a small phase 2 dose-finding study of patients with low platelet counts (50 to 100 x 10^9/L). The EXPAND study was a small phase 1b dose-finding study of patients with low platelet counts (50 to 99 x 10^9/L). Brief study details are presented in Table 7.

Table 7 Brief study details of included non-RCTs

Trial	Population	Intervention (starting dose)	Primary outcome
ROBUST[16]	Intermediate-1, intermediate-2 or high risk PMF, PPV-MF or PET-MF patients from the UK (n=48)	Oral ruxolitinib tablet 15 mg or 20 mg twice daily	Proportion of patients achieving a ≥ 50% reduction from baseline in spleen length (assessed by palpation) and/or a ≥ 50% decrease in the modified MF-SAF TSS at week 48
JUMP[19]	Intermediate-1, intermediate-2 or high risk PMF, PPV-MF or PET-MF patients in 25 countries (n=1144 in reported analysis)	Oral ruxolitinib tablet 5 mg (for patients with platelet count 50-99 x 10^9/L), 15 mg or 20 mg twice daily	Assessment of safety and tolerability of ruxolitinib by the frequency, duration and severity of adverse events
Study 258[17]	Intermediate-1, intermediate-2 or high risk PMF, PPV-MF or PET-MF patients with platelet count 50-100 x 10^9/L (n=50 in reported analysis)	Oral ruxolitinib tablet 5 mg twice daily	Percentage change from baseline in spleen volume (measured by MRI or CT) and percentage change from baseline in MF-SAF TSS at week 24
EXPAND[18]	PMF, PPV-MF or PET-MF patients with platelet count 50-99 x 10^9/L (n=34)	Oral ruxolitinib tablet 5 mg twice daily. The study includes a dose escalation phase	Evaluate safety and establish the maximum safe starting dose

MF-SAF TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis

4.2.2.1 Summary of the quality of the included non-RCT studies

Quality assessment does not appear to have been performed for the ROBUST study, JUMP study, Study 258 or the EXPAND study. All four non-RCT studies did not have a non-ruxolitinib control group. Three of the studies were very small, with 50 patients or less in the reported analyses; therefore, the results of these studies are less reliable than those of the large COMFORT RCTs.

4.2.2.2 Summary of the results of the included non-RCT studies

Table 8 presents a summary of the efficacy and safety results for the four non-RCT studies. The results of the ROBUST study and the JUMP study, which included patients with intermediate-1 risk MF, as well as intermediate-2 and high risk disease, were generally consistent with the results of the COMFORT trials. Where subgroup data were reported, results for spleen length reduction and total symptom score were similar between patients with intermediate-1 risk disease and high risk disease, although patient numbers were extremely low for the different risk subgroups.[16]

The CS states that the results of Study 258 and the low platelet count subgroup of the JUMP study indicate that ruxolitinib, initiated at a dose of 5 to 10 mg twice daily, can benefit patients with low platelet counts (of at least 50 x 10^9/L). It also states that the results of the EXPAND study suggest that starting doses of 10 mg twice daily and 15 mg twice daily may be appropriate in patients with platelet counts of 50 to 74 x 10^9/L and 75 to 99 x 10^9/L, respectively, but that further data are required to confirm the optimum starting dose of ruxolitinib in patients with low platelet counts. The results of the studies in patients with low platelet counts were also generally consistent with the results of the COMFORT trials, except that adverse events were more frequently reported; particularly thrombocytopenia, as might be expected in patients with low platelet counts (50 to 100 x 10^9/L).

Table 8 Summary of efficacy results of the included non-RCT studies

Outcome	**ROBUST (n=48)**	**JUMP study (n=1144)**	**Study 258 (n=50)**	**EXPAND (n=34)***
Reduction in splenomegaly				
Patients achieving ≥ 35% spleen volume reduction at week 24	–	–	20%	–
Median reduction in spleen volume at week 24	–	–	24.2% (n=30)	–
Patients achieving ≥ 50% spleen length reduction at week 24	–	55% (n=782)[b] Low platelet count subgroup: 38.2% (n=34)	–	–
Patients achieving ≥ 50% spleen length reduction at week 48	Overall: 39.6% Intermediate-1 risk: 50.0% Intermediate-2 risk: 15.4% High risk: 47.6%	61% (n=497)[b]	–	–
Mean reduction in spleen length at week 48	Overall: 46.7% Intermediate-1 risk: 51.6% Intermediate-2 risk: 37.0% High risk: 48.6%	–	–	–
Symptoms				
Patients achieving ≥ 50% reduction in TSS at week 24	–	–	34.1% (n=41)	–
Patients achieving ≥ 50% reduction in TSS at week 48	Intermediate-1 risk: 21.4% Intermediate-2 risk: 23.1% High risk: 19.0%	–	–	–
Median reduction from baseline in TSS at week 24	–	–	43.8% (n=32)	–
Mean reduction from baseline in TSS at week 48	Overall: 50.6%	–	–	–
HRQoL				
Mean change from baseline in Global Health Status/QoL	–	–	13 (n=32)	–

(EORTC QLQ-C30) at week 24				
Mean change from baseline in FACT-Lym total score at week 12	–	10.6 (n=854) Low platelet count subgroup: 9.6	–	–
Mean change from baseline in FACT-Lym total score at week 24	–	9.9 (n=716)[b]	–	–
Mean change from baseline in FACT-Lym total score at week 48	–	9.4 (n=438)[b]	–	–
Mean change from baseline in FACIT-Fatigue score at week 24	–	3.1 (n=745)[b]	–	–
Mean change from baseline in FACIT-Fatigue score at week 48	–	3.0 (n=448)[b]	–	–
Mean EQ-5D score	Baseline: 0.72 (n=43) Week 4: 0.78 (n=40)	–	–	–
Survival				
Overall survival (48 week estimate)	–	0.92 (95% CI 0.90 to 0.94)	–	–
Progression-free survival (48 week estimate)	–	0.89 (95% CI 0.86 to 0.90)	–	–
Leukaemia-free survival (48 week estimate)	–	0.91 (95% CI 0.89 to 0.93)	–	–
Adverse events				
Anaemia Grade 3/4 anaemia Thrombocytopenia Grade 3/4 thrombocytopenia	45.8% 20.8%[a] 37.5% 12.5%[a]	56.3%[b] 33.0% (28% in low platelet count subgroup) 42.2%[b] 12.5% (30% in low platelet count subgroup)	64.4%[c] 42% 64.0%[c] 56%	57% (75-99x10^9/L) and 31% (50-74x10^9/L)[d] 43% (75-99x10^9/L) and 23% (50-74x10^9/L) 81% (75-99x10^9/L) and 85% (50-74x10^9/L)[d] 67% (75-99x10^9/L) and 85% (50-74x10^9/L)
Non-haematological adverse events affecting >20% of patients:				

Diarrhoea				
Peripheral oedema	25.0%	14.5%[b]	28%	33% (75-99x10^9/L) and 23% (50-74x10^9/L)[d]
Fatigue	–	9.2%[b]	26%	14% (75-99x10^9/L) and 15% (50-74x10^9/L)[d]
Abdominal pain	22.9%	12.9%[b]	22%	14% (75-99x10^9/L) and 8% (50-74x10^9/L)[d]
Bruising	27.1%	8.0%[b]	24%	10% (75-99x10^9/L) and 8% (50-74x10^9/L)[d]
Epistaxis	22.9%	–	12%[c]	5% (75-99x10^9/L) and 23% (50-74x10^9/L)[d]
Headache	27.1%	5.2%[b]	–	24% (75-99x10^9/L) and 0% (50-74x10^9/L)[d]
Lethargy	22.9%	9.2%[b]	–	19% (75-99x10^9/L) and 23% (50-74x10^9/L)[d]
Nausea	20.8%	–	–	–
	–	7.2%[b]	24%	19% (75-99x10^9/L) and 8% (50-74x10^9/L)[d]

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACIT, Functional Assesment of Chronic Illness Therapy; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HR, hazard ratio; HRQoL, health-related quality of life; PGIC, Patient's Global Impression of Change; TSS, Total Symptom Score
*Spleen response results were presented in a different format for this study and could not be incorporated into the table
[a] Mead et al., 2015[16]
[b] Martino et al., 2014[19]
[c] Talpaz et al., 2013[17]
[d] te Boekhorst et al., 2014[35]

4.2.3 Supporting data from other non-RCTs

In addition, the CS referred to a dose finding study (n=153)[20] and seven 'real world' studies and reports of routine clinical use, some of which included specific subgroups of patients such as low-risk and intermediate-1 risk patients.[21-27] Two studies carried out in the USA (n=108 and n=25) were briefly mentioned on page 116 of the CS as supporting evidence for the efficacy and safety of ruxolitinib in early disease (low risk).[23, 27] The dose finding study was described in the appendices (Appendix 8.18),[20] along with very limited details of a study of 120 Asian patients,[25] a study of 241 French patients,[21] a study of 88 patients from Mexico,[26] a study of 93 patients from Israel[24] and a 48-country patient supply programme involving 1240 patients.[22] Brief study details are presented in Table 9. These additional studies provide additional supporting data, reflecting the RCT and non-RCT evidence presented in the CS. In view of this, and the extremely limited reporting of these uncontrolled studies, they have not been assessed further for this report.

Table 9 Brief study details of supporting data studies

Study	Population	Intervention (starting dose)	Outcomes assessed
Phase 1/2 dose finding study[20]	Intermediate-2 or high risk PMF, PPV-MF or PET-MF patients from the US (n=153)	Oral ruxolitinib tablet 10 mg, 15 mg, 25 mg or 50 mg twice daily, or 25 mg, 50 mg, 100 mg or 200 mg once daily	Response (using response criteria of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)), safety and tolerability
Retrospective observational review of medical records[23]	Low risk and intermediate-1 risk MF patients from the US (n=108)	Ruxolitinib	Changes in spleen size and constitutional symptoms
Case series of 25 patients[27]	Low risk and intermediate-1 risk MF patients from the US (n=25)	Oral ruxolitinib tablet 5mg or 10 mg twice daily	Clinical response
Open label phase 2 study in Asian patients[25]	Intermediate-2 or high risk PMF, PPV-MF or PET-MF patients from China, Japan, Korea and Taiwan (n=120)	Oral ruxolitinib tablet 15 mg or 20 mg twice daily	Proportion of patients achieving a ≥ 35% reduction from baseline in spleen volume (assessed by MRI/CT) at week 24. Symptomatic response was assessed using the MF-SAF and EORTC QLQ-C30
Analysis of patients treated in Compassionate Use (French 'ATU') Program[21]	PMF, PPV-MF or PET-MF patients from France (n=241)	Oral ruxolitinib tablet 15 mg or 20 mg twice daily	Spleen size, constitutional symptoms and adverse events
Individual patient supply program outside the US[22]	Intermediate-1, intermediate-2 or high risk PMF, PPV-MF or PET-MF patients requiring treatment from outside the US (n=1240 patients from 48 countries)	Oral ruxolitinib tablet 15 mg or 20 mg twice daily	Spleen response data available for 247 patients, constitutional symptoms data available for 203 patients, dose modification data available for 259 patients, safety data available for 266 patients
Real world study in patients from	PMF, PPV-MF or PET-MF patients from Israel (n=102)	Ruxolitinib median initial dose 30 mg per day (range	Spleen length, constitutional symptoms and adverse events

Israel[24]		10-40 mg)	
Analysis of patients treated in Compassionate Use Program in Mexico[26]	Low, intermediate-1, intermediate-2 or high risk PMF, PPV-MF or PET-MF patients from Mexico (n=88)	Oral ruxolitinib tablet	Splenomegaly, haemoglobin level, platelet count

4.3 Conclusions of the clinical effectiveness section

The CS evaluation of ruxolitinib was primarily based on two good quality RCTs; one comparing ruxolitinib with BAT (COMFORT-II) and one comparing ruxolitinib with placebo (COMFORT-I). However, the COMFORT trials were conducted only in patients with splenomegaly and intermediate-2 or high-risk MF, who had a platelet count $\geq 100 \times 10^9$/L and an absolute neutrophil count $>1 \times 10^9$/L, which is a narrower population than that defined in the NICE scope. Four non-RCT studies that included patients not eligible for the COMFORT trials were also included in the CS. The search strategy was adequate and, despite limitations in the inclusion screening process, it is unlikely that any relevant RCTs of ruxolitinib were missed.

The primary endpoint was the same in both COMFORT trials; proportion of patients achieving a 35% or greater reduction of spleen volume. This endpoint was met in significantly more patients in the ruxolitinib group than the control group in both trials (28% of ruxolitinib patients versus 0% of BAT patients at 48 weeks in the COMFORT-II trial), with most patients achieving this level of response by week 12 and maintaining their response for a year or more. However, 63% of patients had discontinued treatment at 3.5 year follow-up in the COMFORT-II trial and half of the patients in the COMFORT-I trial had discontinued treatment at 3 year follow-up, primarily because of disease progression or adverse events. Dose modifications were common in both COMFORT trials.

The COMFORT-I trial also assessed symptom reduction using a modified version of the Myelofibrosis Symptom Assessment Form (MF-SAF), which demonstrated clinically meaningful improvements in MF-associated symptoms at week 24 for ruxolitinib patients, compared with a worsening of symptoms for placebo patients; the tool used to measure this outcome was appropriate and the analysis included over 95% of randomised patients, therefore this result is likely to be reliable.

Both COMFORT trials also assessed HRQoL as an exploratory endpoint, although the health related quality of life results were limited by missing data for many patients, which undermines the reliability of the results. However, data for ruxolitinib patients in the COMFORT-I trial were reported for the majority of patients (136/155) and showed an improvement from baseline in Global Health Status/QoL assessed using the EORTC QLQ-C30 scale.

Neither of the COMFORT trials were designed to be sufficiently powered to detect a significant difference in survival outcomes. Both COMFORT trials permitted patients to cross over from the control group to ruxolitinib; therefore, the company used a rank-preserving structural failure time (RPSFT) model to estimate the true effect of ruxolitinib on overall survival, adjusting for crossover. All methods of adjusting survival estimates in the presence of treatment switching have limitations; however, the method used appears to have been appropriate. Longer term data from the COMFORT-II trial (3.5 years) demonstrated a statistically significant difference in overall survival favouring ruxolitinib over BAT, using both ITT and RPSFT analyses. However, the overall survival benefit at 3 years in the COMFORT-I trial did not reach statistically significance, even after adjustment for crossover.

The incidence of grade 3 or 4 adverse events was higher in the ruxolitinib group than the BAT group in the COMFORT-II trial (42% versus 25%). The most frequently occurring grade 3 or 4 adverse events (anaemia and thrombocytopenia) were generally managed by dose modifications and/or blood transfusions and improved over time.

In the COMFORT-II trial the incidence of adverse events of special interest generally decreased over time, although the incidence of infections remained quite high at between 25 to 43% over the 3 year follow-up (dropping from 50% during the first 24 weeks). The incidence of bronchitis increased over time. It should be noted that the data presented were for those patients who remained on treatment, excluding those who dropped out because of adverse events. Haematological adverse events were very common with ruxolitinib.

The four additional non-RCT studies (the ROBUST study, the JUMP study, Study 258 and the EXPAND study) did not include a non-ruxolitinib control group and three of the studies were very small. Two of the studies included patients with intermediate-1 risk MF, as well as intermediate-2 risk and high risk disease, whilst three of the studies included patients with low platelet counts (50 to 100 x 10^9/L). The results of the studies were generally consistent with the COMFORT trials, suggesting that ruxolitinib may also be effective at reducing spleen size and symptoms in intermediate-1 risk patients and patients with low platelet counts, although patient numbers were low, reducing the reliability of the results. However, thrombocytopenia was much more frequently reported in patients with low platelet counts, as might be expected.

In conclusion, for intermediate-2 or high risk patients who can tolerate and remain on ruxolitinib, the evidence suggests that splenomegaly and MF-associated symptoms can be reduced and overall survival increased. However discontinuation rates are high, with fewer than 50% of patients

remaining on therapy after 3 years. Evidence relating to patients with lower risk disease or low platelet counts (50 to 100 x 10^9/L) is less robust.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided to the ERG following points for clarification. The submission was subject to a critical review on the basis of the company's report and direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to address some remaining uncertainties.

The company's initial economic submission included:

- A description of the search strategy and databases used in the literature review of cost-effectiveness studies, resource use studies and quality-of-life studies (CS, pg. 143 to 146).
- A report on the *de novo* economic evaluation conducted by the manufacturer. The report outlined the intervention; comparators and patient population; the modelling methodology; the resource components and unit costs; data input sources and assumptions; the base-case results; and sensitivity analysis (CS, pg. 146 to 259).
- The company's electronic Excel-based *de novo* model.

Following the points of clarification raised by the ERG, a number of addenda were submitted by the company. These included:

1. A descriptive reply to the ERG's points for clarifications. This is referred to in the following sections as the company's response.
2. An updated Excel-based model adding additional options to the model.

During the ERG evaluation of the submission a Patient Access Scheme (PAS) submission describing a price reduction agreed by the Department of Health was also made available to the ERG. This included a revised cost-effectiveness analysis reporting an ICER using the PAS price in the company's base-case analysis and some sensitivity and scenario analyses.

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer conducted a systematic literature review to identify relevant economic evidence associated with MF (including PMF, PPV-MF, and PET-MF). The ERG's critique of the systematic review presented by company is given below.

5.1.1 Searches

The company conducted a systematic literature review to identify relevant economic evidence associated with MF (including PMF, PPV-MF, and PET-MF). The searches were designed to update the previous 2011/2012 review.

The CS described the search strategies used to identify relevant economic evaluations, resource use studies and quality of life studies on the treatment of MF (including PMF, PPV-MF, and PET-MF). Brief details of the searches were provided in the main submission with full details, including the information sources searched, reported in Appendix 11, Section 8.11.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, the Cochrane Library (including Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), NHS Economic Evaluations database (NHS EED)) and the Cost Effectiveness Analysis (CEA) registry were searched on 2nd January 2014 (1st update) and again on 10th December 2014 (2nd update) to identify relevant economic evidence associated with MF. In addition, the company searched the abstracts of conference proceedings (online versions) from the following 6 conferences: European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA) American Society of Hematology (ASH), British Society of Haematology (BSH) and European LeukemiaNet.

Taken together, the 1st and 2nd update searches covered the period January 2012 – December 2014. The searches were limited to human only studies and excluded letters, editorials, commentaries, case reports, case studies, case series and phase 1 clinical trials.

The methods used to identify both published and unpublished studies for the systematic review were appropriate and for the most part well reported. There were some minor details missing from the reporting of the searches in Appendix 11, Section 8.11, however the company supplied further details in their response to the ERG's Points for Clarification.

The main medical databases were searched together with sources for unpublished and ongoing studies. However the company did not update the search of BIOSIS or EconLit which were both searched for the 2011/2012 review.

The search strategies for the 2013/2014 update searches contained in Appendix 11, Section 8.11, were appropriate and would result in a sensitive search. Terms for myelofibrosis, including relevant subject headings, text word searches, and synonyms were included in the strategies. Field searching and

truncation have been used correctly throughout. For MEDLINE and EMBASE the set of terms for myelofibrosis are combined correctly with a set of terms for economic evaluations, resource use terms and quality of life terms.

For the search of the Cochrane Library databases, the set of terms for economic evaluations, resource use terms and quality of life terms should not have been included in the search strategy, as these databases are already limited by study design. The inclusion of these terms may have excluded potentially relevant records.

5.1.2 Inclusion/exclusion criteria used for study selection

Economic evaluations of patients undergoing any treatment for MF (including PMF, PET-MF and PPV-MF MPNs if data specific to MF are also reported) were eligible for inclusion. Relevant outcomes included ICERs; QALYs; direct costs (e.g. resource use or cost estimates for hospitalisation, consultation, medication, nursing costs associated with management of patients with MF); indirect costs associated with sick leave, disability, etc; resource use or cost estimates for adverse events.

5.1.3 Studies included and excluded in the cost effectiveness review

It would appear from the PRISMA diagram presented (CS, pg.39, Appendix 11, Section 8.11) that the screening of cost-effectiveness and resource use studies were done concurrently. It is therefore not possible to clearly define how many cost-effectiveness studies were identified, but later excluded.

The CS's search identified two relevant studies - El Ouagari et al 2012[36] and Wade et al 2013[37] (summary report of NICE STA 289 2013)[38].

The first study (published abstract) reported the results of a cost–utility study that compared ruxolitinib with BAT for treatment of MF from a Canadian societal perspective. The investigators developed a four-health-state Markov model, using 12-week cycles to simulate a hypothetical cohort of patients with MF. Clinical data inputs were taken from the COMFORT-II randomised controlled trial, which enrolled patients with intermediate-2- or high-risk PMF, PPV-MF or PET-MF. The outcomes of the Markov model included costs over the time horizon, life-years, quality-adjusted life-years (QALYs) and time spent as a responder to treatment. The results of the analysis showed an incremental cost-effectiveness ratio (ICER) of CAD61, 444 per QALY (deterministic average) and CAD59,216 per QALY (mean ICER from simulations) for ruxolitinib compared with BAT. Though, this study is not relevant to the UK as it compared ruxolitinib with BAT from a Canadian societal perspective. (See table 9 for more details)

The second study (published full paper) provided a summary of the ruxolitinib NICE single technology appraisal (STA) submitted in 2013. Table 10 provides an overview of the submission including the cost-effectiveness modelling presented by Novartis, and the revised analysis developed by the Evidence Review Group (ERG). This submission describes a revised economic assessment which makes use of additional data which have become available since the previous submission and aims to address the issues raised by the ERG (see CS, pg. 219 for further details).

5.1.1 Conclusions of the cost effectiveness review

ERG concludes the Canadian study is not relevant to the UK and the UK study was the part of the previous NICE STA submission for ruxolitinib and therefore based on more limited data.

Table 10 Summary of cost-effectiveness evaluations identified [CS, Table 26, pg. 145]

Reference	Year	Country(ies) where study was performed	Summary of model	Patient population (average age, years)	QALYs (intervention, comparator)	Costs (currency) Intervention, comparator	ICER (per QALY gained)	Sensitivity analysis
El Ouagari et al[36] [abstract]	2012	Model: Canada Data: Europe	Markov model (ruxolitinib vs best available therapy (BAT)), Canadian societal perspective, 12 weeks per cycle, lifetime time horizon, simulated progression in 4 different health states	Data were derived from patients enrolled in the COMFORT-II study and included high-risk or intermediate-2-risk patients with MF	Ruxolitinib: 4.01 BAT: 2.82	<u>Total average lifetime costs</u> Ruxolitinib: CAD494,859 BAT:CAD421,755 <u>Drug costs</u> Ruxolitinib: CAD205,484 BAT: CAD59,289 <u>Other medical costs</u> Ruxolitinib: CAD217,527 (majority are resource costs) BAT: CAD266,008 <u>Indirect costs</u> Ruxolitinib: CAD71,848 BAT: CAD96,458	Overall (deterministic average): CAD61,444 Mean ICER from stimulations; CAD59,216 Ruxolitinib therapy cost-effective vs BAT	NR
Wade et al[37] [Full paper] Supplementary data from NICE technology appraisal guidance 289	2013	Model: UK Data: Europe, US, Australia and Canada	State-transition Markov model designed to simulate the natural course of MF, 12 weeks per cycle, 35-year time horizon, costs and benefits were both discounted at	The main clinical effectiveness data were derived from two RCTs: COMFORT-II and COMFORT-I and included patients who	<u>Base-case:</u> Ruxolitinib: 1.15	<u>Incremental cost</u> <u>Base-case</u> Ruxolitinib: £85,027	<u>Base-case</u> £73,980	A range of sensitivity analyses were carried out
					Company's revised economic analysis			
					<u>Revised base-case</u> Ruxolitinib vs BAT: 1.36	<u>Revised base-case</u> Ruxolitinib vs BAT: £77,437	<u>Revised base-case</u> Ruxolitinib vs BAT: £56,963	

			3.5%, the company's model consisted of 4 mutually exclusive health states	had intermediate-2 risk or high risk MF	**ERG's revised economic analysis**			
							<u>Revised base-case</u> Ruxolitinib vs BAT: Range £73,980 to £148,867	

BAT, best available therapy; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MF, myelofibrosis; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY, quality-adjusted life-year; RCT, randomised controlled trial; UK, United Kingdom; US, United States.

5.2 ERG's summary and critique of manufacturer's submitted economic evaluation

An overall summary of the company's approach and signposts to the relevant sections in the manufacturer's submission are reported in Table 11 below:

Table 11 Summary of the company's economic evaluation (and signposts to CS)

	Approach	**Source / Justification**	**Signpost (location in company submission)**
Model	The company created an individual patient discrete event simulation model. The decision model employs a lifetime patient horizon and uses a direct NHS and personal social services perspective.	The model is individual patient based and uses a time-to-event approach. This approach was chosen to model the progressive nature of MF (worsening in HRQoL in the supportive care health sate) and explore the impact of different structural assumption. Time horizon and healthcare perspective are as recommended as NICE methods guide.	Sections 5.2.2 and 5.2.3 pg. 147-153.
States and events	The model is composed of two sub-models to: estimate the duration spent in each phase of the treatment pathway/disease; and estimate the progression of HRQoL according to the phase of treatment/disease. The model contains essentially four mutually exclusive health states with alive states being defined by therapy phase. These four health states are as follows: • On ruxolitinib: receiving active therapy with ruxolitinib which provides improvements in symptoms, splenomegaly and HRQoL • On BAT: receiving BAT which may provide some symptom relief and control of haematological parameters but little impact on HRQoL • On supportive care: receiving only palliative treat, patients in this state can be considered to be treatment failures. HRQoL in this health state is assumed to decline representing continued disease progression, and • Death	COMFORT-II is the primary data which provided a direct comparison with the appropriate comparator.	Sections 5.2.2 pg. 147-153.
Comparators	Ruxolitinib is compared to BAT.	There is no currently established care pathway for MF, so a combination of currently used treatments comprises BAT.	Sections 5.2.4 pg.158-159

Subgroups	Analyses for specific subgroups are not conducted.		Sections 5.2.1 pg. 147
Treatment effectiveness	The company uses splenomegaly and symptoms reduction, overall survival, presence of adverse events, complications and Leukaemic transformation of MF to show clinical effectiveness.	COMFORT trials are the primary data sources.	Sections 5.3 pg.159-180
Adverse events	Grade 3 and 4 adverse event data was gathered from the COMFORT-II trial and input into the model.	COMFORT-II is the primary efficacy data for ruxolitinib. Costs per adverse events are derived using various sources, mainly using the NICE STA for Enzalutamide (XTANDITM) and NHS reference costs.	Sections 5.5.7 pg.209
Health related quality of life	The company uses disease specific preference based measure (using MF-8D v1) to estimate preference scores for the three health states (ruxolitinib, BAT and supportive care). Patients are assumed to experience constant benefits from both ruxolitinib and BAT and therefore constant HRQoL. The supportive care state in which HRQoL is assumed to steadily decline. Disutility decrements are applied for patients experience LT, but no decrements are assigned to AEs. The economic model structure implies progression is largely represented by movement between states. CS conducts scenario analysis using the MF-8D v2 (data from COMFORT-II) and EQ-5D (data from ROBUST study).	The utility values are derived from COMFORT-I and few assumptions are made based on published literatures.	Sections 5.4 pg.180-193
Resource utilisation and costs	The following cost categories are considered in the company analyses: drug acquisition costs, drug administration costs, drug monitoring costs, cost of managing MF patients including cost of blood transfusions, costs of Leukaemic transformation, cost of adverse events management, costs of palliative and end of life care.	The data sources use include COMFORT trials, ROBUST study, JUMP study, HMRN audit, published literatures and clinical expert opinion. The unit cost of drugs was based on BNF, NHS reference costs, PSSRU costs and published literatures.	Sections 5.5, pg. 193-212
Discount rates	A 3.5% discount rate is employed for both costs and health benefits. Scenario analysis is conducted using 1.5% discount rate on costs and/or health benefits.	In accordance with the NICE reference case approach.	Sections 5.2.3 pg.153
Sensitivity analysis	Scenario analyses and probabilistic sensitivity analysis (PSA) are undertaken.	Structural and deterministic sensitivity analyses and scenario analyses are presented. Cost effectiveness acceptability curves and cost-effectiveness acceptability plane are presented for the base-case.	Sections 5.8 pg.231-256

5.2.1 Model structure

The company created an individual patient discrete event simulation model (DES). The use of an individual patient simulation model can be considered novel, and in contrast to the majority of oncology models which utilise cohort Markov structures. The company justifies the use of this approach on the basis that this type of model allows for increased flexibility and allows the progressive nature of MF to be modelled in more transparent way than a Markov model, which would require the excessive use of tunnel states (short-term 'temporary' states). The use of this type of modelling approach appears justified given the progressive nature of the disease and appropriate to the decision question. Furthermore, the additional flexibility permitted by an individual patient model allows for a number of structural assumptions of the model to be evaluated which would not be possible if a Markov structure had been adopted. The use of DES model however, places considerable demands on the available data as it is necessary to model the transition of sometimes small numbers of patients through the different states of the model. This forces the company to make a number of assumptions the details of which are discussed in section 5.2.1, which while mostly plausible and justified by the available evidence are subject to degree of uncertainty. The CS includes a wide array of scenario analysis testing many of these assumptions on a univariate basis, however, it is not possible to fully evaluate this structural uncertainty resulting from these assumptions.

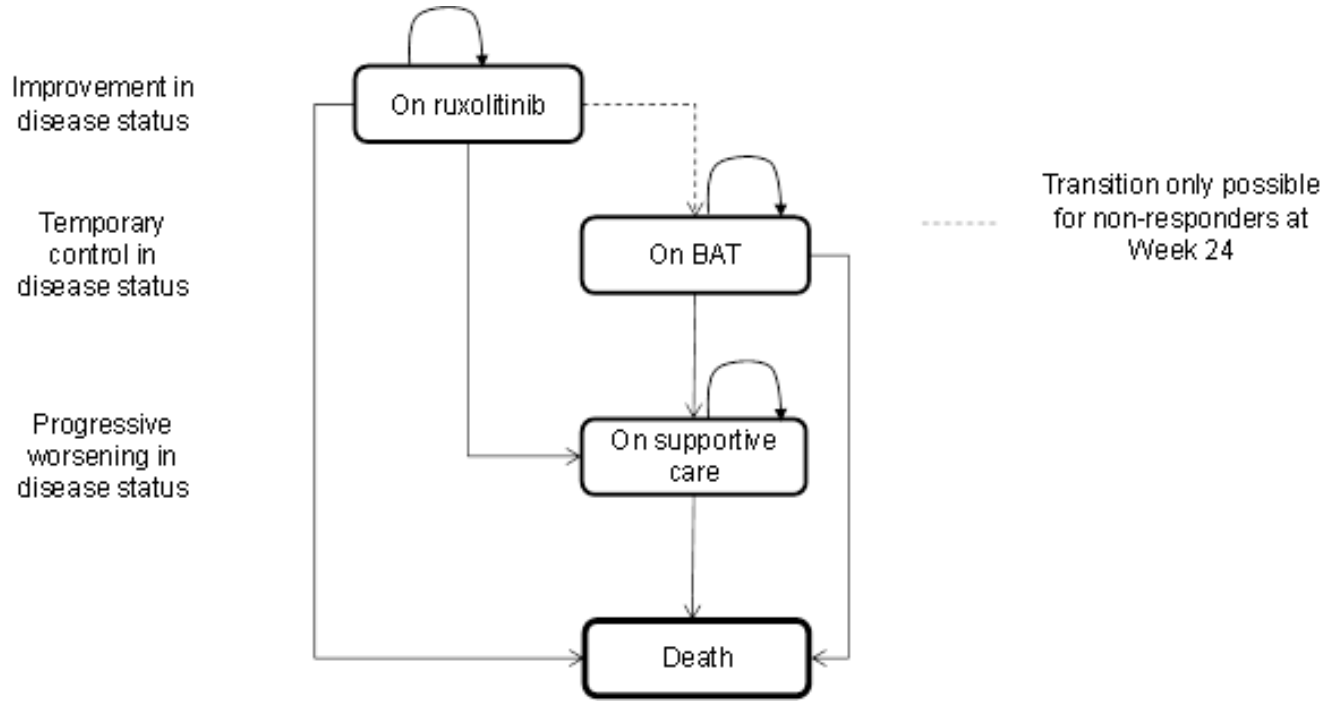
The model does not use time cycles though effectively a weekly cycle length is used in the model as this is the shortest unit of time used in the model. The time horizon used in the baseline analysis is 35 years which is designed to simulate a lifetime time horizon. Both costs and benefits are discounted at 3.5% in line with NICE recommendations and a NHS/PSS perspective is taken

A simplified schematic of the model structure is depicted in Figure 12 (CS Figure 42).

The model contains essentially four mutually exclusive health states with alive states being defined by therapy phase. These four health states are as follows:

- On ruxolitinib: receiving active therapy with ruxolitinib which provides improvements in symptoms, splenomegaly and HRQoL
- On BAT: receiving BAT which may provide some symptom relief and control of haematological parameters but little impact on HRQoL
- On supportive care: receiving only palliative treat, patients in this state can be considered to be treatment failures. HRQoL in this health state is assumed to decline representing continued disease progression.
- Death

Figure 12 Simplified schematic of the model structure [CS Figure 42, pg. 148]



BAT, best available therapy

The defining of health states by therapy state rather than indicative of severity of disease can also be considered somewhat novel as the model structure essentially implies that ruxolitinib is a beneficial treatment compared with BAT. This novelty does not, however, invalidate the model structure and the basic model structure can be considered representative of how ruxolitinib is likely to be used in the NHS and the disease progression of MF patients.

Transit through the model is determined by time to event approach and based on a series of time to event analyses presented in the CS. These are discussed further in Section 5.2.4. Patients in the BAT group are assumed to begin in the BAT health state. In this health state, patients receive a basket of treatments that constitute BAT which reflects the treatment received by patients in the control arm of the COMFORT-II study. Patients on BAT are assumed to achieve some control of symptoms but not splenomegaly. Patients may continue to receive BAT until death or they may stop receiving BAT (after exhaustion of possible options) and progress to the supportive care health state. In this health state patients experience a gradual worsening of the disease (symptoms and haematological parameters) and HRQoL until death. No formal stopping rule is applied to patients receiving BAT and discontinuation is modelled on discontinuation observed during the COMFORT-II trial.

Patients initiating ruxolitinib are categorised into four groups based on their outcomes at week 24 in the COMFORT-I/II trial and patients consider non-responders subject to a stopping rule. This stopping rule was based on criteria set out in the IWG-MRT/ELN guidelines.[1] Note this stopping rule was no applied in the COMFORT-I or COMFORT-II trials and the definition of response was not the definition of response reported in the clinical section which was based on spleen volume rather than spleen length. The four categories of response were as follows:

Responders: which consist of spleen responders who achieve a spleen response at week 24 (with or without a symptom response) and symptom responders who achieve a symptom response at week 24 but who do not achieve the required level of spleen response. Responders continue treatment with ruxolitinib until either death or failure of treatment response. Upon failure of treatment response patients move to the supportive care health state, which as stated above implies gradually declining HRQoL until death.

Non-responders: These patients are alive at the end of treatment, but fail to meet the criteria for spleen or symptom response at week 24. For these patients treatment with ruxolitinib is discontinued and they move in to the BAT health state. They progress through the model as described above for patients initiating on BAT.

Early discontinuation group: these are patients who are alive at week 24 but who discontinued therapy prior to week 24. These are considered treatment failures and are assumed to move to the supportive care health state.

Early death group: These are patients who die prior to the application of the week 24 stopping rule.

The transition path of the four groups was considered largely to be plausible and representative of the clinical pathway. As acknowledged in the CS the transition of treatment responders directly to supportive care may not be representative of clinical practice and at least a proportion of these patients are likely to go on to receive BAT therapy. This assumption is, however, a conservative one and likely to lead to an overestimation of the ICER. The ERG also considers the transition of those who discontinue early straight to supportive care, to be somewhat unrepresentative of clinical practice and it is not clear why they are not treated the same as non-responders such that they transition to BAT. It is, however, unlikely that this would have significant impact on the estimated ICER due to the small number of patients discontinuing early.

5.2.1 Population

The NICE scope defined the population of interest as adults with disease-related splenomegaly or symptoms of PMF, PPV-MF and PET-MF, which is within the licensed population.

Clinical effectiveness data used in the model was primarily derived from the COMFORT-II study, which enrolled intermediate-2 and high risk patients who were not refractory to other therapies. The COMFORT-II study compared ruxolitinib to BAT which include no therapy. Additionally data was, however, also independently used from the COMFORT -1 study which enrolled intermediate-2 and high risk patients who were refractory to all other therapies and compared ruxolitinib to placebo.

The population within the model therefore pragmatically reflects the patients in COMFORT-II. As indicated in section 3.1 the population included in this study is likely to represent a subset of the licenced population as low risk and intermediate-1 risk patients were excluded. Additionally, patient's inclusion was restricted to patients with a life expectancy of at least 6 months and platelet count of at least 100x109/L and peripheral blood blast count of less than 10%. While it is acknowledged that patients eligible for treatment with ruxolitinib will consist largely of Intermediate-2 and high risk patients, the licenced population within the UK will differ to the population included in the COMFORT–II study to include patients with a significantly different disease prognosis. The modelling presented therefore reflects cost-effectiveness of ruxolitinib in this more restricted population.

5.2.2 Interventions and comparators

The CS compared ruxolitinib with BAT therapy in the base-case analysis. Ruxolitinib dosing is subject to dose-intensity adjustment and varied according to platelet count, patient's tolerance of therapy and efficacy. To reflect this variable dosing individual patient data from the COMFORT-II trial were used to estimate dose given. Based on this data the dose of ruxolitinib used in the model varied between 5 mg to 25 mg twice daily or 5mg and 35mg once per day. For a small proportion of treatment days (1.38%) dose interruptions were also accounted for i.e. 0 mg dose. The most common doses used in the model were 5 mg twice daily (14.50% of treatment days), 10 mg twice a day (25.93% of treatment days), 15 mg twice daily (20.14% of treatment days) and 20 mg twice daily (30.66% of treatment days).

The comparator in the model, BAT, consisted of a number of different treatments for myelofibrosis including no treatment based on data from the COMFORT II trial. A summary of treatment included in BAT in the COMFORT II trial is presented in Section 5.2.7 (Table 16). Dose intensity, duration and treatment or order of treatment was not recorded in the COMFORT-II study. It is therefore not

clear from the data in what order the treatments are received, or how long patients remain on neither each treatment, nor how many treatment each patient might receive. For the purpose of calculating cost of BAT a number of assumption were made to account for this lack of data these are discussed further in Section 5.2.7. Based on the data from COMFORT between 6.67% and 29.41% of patients received no active treatment depending upon the time point under consideration.

The ERG has a number of concerns on the composition of BAT used in the model. The clinical advisor to the ERG team indicated that lenalidomide is not used in the UK, and the HMRN audit (HMRN audit) appears to confirm this assertion: no patients in the HMRN audit received lenalidomide. It is also clear from the published literature that there are other treatments used in the UK which are not included in the BAT bundle; as discussed in Section 2.2. Of note, the BCSH guidelines indicate that allo-HSCT is a potential therapy for myelofibrosis and is the only curative treatment for patients. This was also not included as part the BAT bundle. The ERG feels that allo-HSCT should have been considered either within the BAT bundle or as an alternative comparator. The ERG highlights that the omission of allo-HSCT is potentially particularly important as significant survival benefits have been observed using allo-HSCT[2]. The ERG, however, recognise that this treatment option would not be suitable for all patients and has a different treatment goal (curative as opposed to management of symptoms).

5.2.3 Perspective, time horizon and discounting

The economic perspective is the National Health Service (NHS) and the Personal Social Services (PSS) in accordance with the NICE reference case. The reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used is 35 years, which is effectively a lifetime horizon given life expectancy with MF. Costs and benefits in the model were discounted at an annual 3.5% rate as per the NICE reference case.

5.2.4 Model inputs

The following section describes and critiques the key inputs and assumptions that influence a patient's transit through the model and how costs and benefits accumulated.

5.2.4.1 Response rate and Stopping rule

As described above, patients who receive ruxolitinib are subject to a stopping rule at 24 weeks. The 24 week duration and decision was based on BCSH guidelines that state that treatment should be discontinued after 6 months if there has been no reduction in splenomegaly or improvement in

symptoms since initiation of therapy. The definition of response was based on the recent IWG-MRT/ELN guidelines,[1] and defined in terms of either a spleen response or a symptom response. Patients were therefore considered responders if they met the following criteria:

- **Spleen response:** non-palpable spleen in a patient with splenomegaly at baseline that is palpable at 5–10 cm below the left costal margin (LCM), or spleen decreases by ≥ 50% in a patient with splenomegaly at baseline that is palpable at > 10 cm below the LCM, or
- **Symptom response**: a ≥ 50% reduction from baseline in the MF-SAF TSS.

The CS notes that these criteria for response are quite stringent and that in clinical practice achieving a smaller reduction in spleen size or smaller decrease in symptoms may be considered clinically meaningful and patients will continue to receive treatment. As such, the CS also presents a number of scenario analyses using alternative definitions of response. The ERG agrees that in practice a less stringent definition of response is likely to be used in practice and the results of this scenario analysis are therefore considered further in section 5.2.9.2. The ERG also noted that response to treatment in ruxolitinib patients is often observed relatively quickly as supported by evidence presented in the CS pg. 190 and therefore in clinical practice a stopping rule may be in effect applied early than 24 weeks. The ERG requested at the points for clarification stage for an option for a 12 week stopping rule scenario to be added to the model. The company's response indicated that they did not consider this a plausible scenario and would be difficult to apply given the available data. The impact of employing a shorter initial treatment period would be to lower the estimated ICER.

Within the model the proportion of patients gaining a spleen response, discontinuing ruxolitinib treatment, and experiencing early death is based upon data from the COMFORT-II study. The COMFORT-II trial did not however, record symptom response and as such, it was not possible to estimate the proportion of symptom responders from the COMFORT-II study. The proportion of individuals gaining a symptom response, but no spleen response was therefore based on data from the COMFORT-I study. The use of this data may not be entirely appropriate and adds additional uncertainty regarding the effectiveness of ruxolitinib not acknowledged in the CS, as the patients enrolled in COMFORT-I differed significantly from those in the COMFORT-II study. Specifically, the COMFORT-I study limited enrolment to patients who were refractory to all other therapies while the COMFORT-II included patients were or were not refractory to other therapies.

This assumption also has a number of other implications for the model. Most importantly this means that no data are available to model overall survival and rates of discontinuation rates in a response group that includes both spleen and symptom responders. This forces the company to assume that OS

and discontinuation rates are the same for both spleen and symptom responders. Empirical justification is presented in the CS and these assumptions of equivalence can be considered reasonable. However, the equivalence of these rates is subject to uncertainty not accounted for in the probabilistic analysis. This may have some impact on the estimated ICER as OS in particular is key driver of the model. A further consequence of sourcing data from a source other than the COMFORT-II study is that the probabilistic sensitivity analysis fails to fully acknowledge that the distribution across the five groups (Spleen responders, symptom responders, non-responders, those discontinuing treatment and patients experiencing early death) are correlated, as the proportion of patients experiencing a symptom response is sampled independently. Correlation, between the remaining four groups is accounted for in the probabilistic sensitivity analysis. This, however, is not likely significantly impact on the results of the probabilistic sensitivity analysis.

5.2.4.2 Mortality

Mortality for both patients initiating on ruxolitinib and BAT in the model is based on that observed in COMFORT-II study. For those initiating on BAT death can occur either while on BAT or after discontinuation of BAT when patients have moved to the supportive care state.

The number of patients dying on BAT was based on data from the COMFORT-II study and time to death for this group was based on time to discontinuation of therapy. This is justified in the CS on the basis that 4/73 patients discontinued due to death. Modelling time to death in this way however, implies that time to discontinuation due to reasons other than death and time to death while on BAT follow the same function form. There is no reason that in fact this be the case. This assumption is not explicitly acknowledged or justified in the CS. Nor is any comparison of mean OS for patients discontinuing due to death and discontinuation for other reasons presented to enable assessment of whether these are likely to be similar. The impact of this implicit assumption in the ICER is however likely to be small as it impacts the survival time of only 5% of patients initiating BAT.

The application of OS post BAT discontinuation within the model is complicated by the fact that time to death and time to discontinuation of treatment are not independent and that sampling these independently would lead to inconsistencies whereby patients die prior to discontinuation. This requires the company to make a number of assumptions about the functional form of the post-BAT survival function. These were chosen based on visual fit of the OS data, but are essentially arbitrary assumptions. This is acknowledged in the CS and alternatives are considered in sensitivity analysis though these have little on the resulting ICER. Given the novel nature of this approach the CS also presents further scenario analysis in which time to discontinuation and post BAT survival are independently sampled. The resulting analysis produces very similar ICERs to the baseline model.

For patients initiating on ruxolitinib therapy all patients face the same mortality risk in the first 24 weeks and a proportion of patients are assumed to die within this initial 24 week treatment phase. Both the rate and mean survival time are derived from the COMFORT-II trial. After the initial treatment phase, treatment responders, non-responders and early discontinuers each face different mortality rates.

As with BAT, ruxolitinib treatment responders can die either while on treatment or post discontinuation. Data for both of these is derived from the COMFORT-II study. In the baseline model the mortality rate for ruxolitinib responders is assumed to be 0.0% i.e. no patients die while on ruxolitinib. This is justified in the CS on the basis that no deaths were observed in the COMFORT-II study during this period. This was considered somewhat implausible by the ERG. At the points for clarification stage the company was therefore asked to consider adding a strictly positive mortality rate for this phase or the model. The company's response reiterated the justification stated in the CS that as all deaths in the ruxolitinib arm occurred after discontinuation a zero rate of death was assumed. The company, however, added that this assumption may be somewhat optimistic for the following reasons:

- Patients achieving a spleen response experienced no discontinuation due to death in the trial, however it is uncertain whether any patients achieving a symptom response (but not a spleen response) died;
- Analyses are based on 3.5 years follow-up data and not all patients had discontinued ruxolitinib treatment. Longer follow-up may therefore reveal that some patients discontinue due to death.

As such the company provided additional scenario analysis assuming either the same probability of death upon discontinuation used for the BAT arm (5.48%) or assuming a probability equal to 10%. Both of these analysis resulted in only modest increases in the estimated ICER. The ERG acknowledges that including a positive rate would deviate from what was observed in the COMFROT-II study. However, as noted in the companies response there is some uncertainty regarding the mortality rate of responders and given the age of the cohort and the long mean period of time patients will receive treatment (246.30 weeks) one would expect to observe some deaths even based on national population level mortality rates. The ERG therefore carries out scenario analysis on this parameter, presented in Section 6.

For patients discontinuing ruxolitinib (both during the initial 24 week period and for responders after this initial period), duration alive following discontinuation was modelled based on observed survival in the COMFORT-II study. The same curve was used for both groups as the number of patients

discontinuing early was very small [redacted]). The ERG feels this assumption is justified given the presented data though note that the small number of patient means that there is significant uncertainty as to the validity of this assumption. Scenario analysis was presented by the manufacturer in which separate survival curves were used for each group. However, the survival data for early discontinuers was very skewed, with patients either surviving for a short period of time or a long period of time. As a result mean post discontinuation survival time was longer for ruxolitinib patients discontinuing early than those discontinuing following the initial 24 week period. It wasn't clear to the ERG how clinical plausible this is where separate survival curves are assume it implies that increasing the rate of early discontinuation lowers the generated ICER, which appears somewhat counter intuitive.

Non-responders to ruxolitinib are assumed to move to BAT therapy after 24 weeks and mortality is modelled in the same way as patients initiating on BAT accept that patients who are non-responders to ruxolitinib are assumed to receive a mortality benefit of an additional 24 weeks of life. This is justified in the CS on the basis of clinical opinion and no-empirical evidence was presented. The ERG requested further information to support this assumption at the points for clarification stage, but none was provided by the company. While the ERG feels it is plausible that some survival benefit be experienced by patients who fail to meet the stringent response criteria, the extension of life expectancy by 24 weeks is clearly arbitrary and as stated is not justified by any empirical evidence. The company presents a scenario analysis in which time on ruxolitinib is assumed to be part of the time patients would have been treated with BAT. Non-responders are therefore treated as far as is possible as if they had never received ruxolitinib. In the absence of evidence of survival benefit for this group of patients the ERG feels that this scenario, while conservative, is a more appropriate assumption.

5.2.4.3 Discontinuation rates

For patients initiating on ruxolitinib the model utilised two alternative discontinuation rates, one for the initial 24 week treatment phase of the model, and one which applies to spleen and symptom responders (who continue treatment) post 24 weeks. Both rates were derived from the COMFORT-II trial.

Patients discontinuing treatment early were assumed to receive treatment for a total of 14.083 weeks, based on the mean time on treatment for this group in the COMFORT-II trial. This parameter was not varied on the probabilistic sensitivity analysis. It was not stated in the CS why this was this case. Uncertainty around this parameter was therefore not explored.

In the post 24 week the rate of discontinuation was based on analysis of time to discontinuation for spleen responders. A range of parametric survival models (Weibull, exponential, Gompertz, log-normal) were considered to extrapolate beyond the observed data. Based on AIC and BIC criteria a Gompertz distribution was considered the most appropriate. Scenario analysis using the alternative distributions was also presented. A differential of discontinuation was not applied for spleen responders and symptom responders; this was justified on evidence from the COMFORT-I study which demonstrated no statistically significant rate in the discontinuation rate for these two groups. No scenario analysis exploring this assumption was, however, undertaken. The ERG was not able to undertake additional sensitivity analysis due lack of available data.

A single rate of discontinuation was applied for patients on BAT based on data from the COMFORT-II study as no stopping rule was applied to BAT. As with discontinuation from ruxolitinib a number of parametric survival models (Weibull, exponential, Gompertz, log-normal) were considered. The Gompertz distribution was found to be the most appropriate and scenario analyses carried out using alternative distributions presented. Reasons for discontinuing BAT included both:

- Discontinuation due to AEs, withdrawal of consent, disease progression or other reasons (38.4% of patients);
- Cross-over to ruxolitinib (61.6% of patients).

Cross-over to ruxolitinib was a major reason for discontinuation and it is therefore likely that if ruxolitinib had not been available patients fewer patients would have opted to discontinue BAT. The analysis presented in the CS is therefore likely to underestimate the time on BAT for the model. This issue is acknowledged in the CS, and scenario analyses are presented using a number of arbitrary adjustments factors. This issue is however, not addressed in the base-case analysis. The ERG considers this to be overoptimistic and is explored in the ERG's additional analysis; see Section 6.

5.2.4.4 Leukaemic transformation

Leukaemic transformation (LT) is a potential is risk for patients with MF and has significant impact on patients, life expectancy, and HRQoL, as well as having resource implications. The model presented by the manufacturer includes the possibility of LT by allowing this to occur as an "adverse event" with disutility and cost applied. That LT is not a separate health state within the model is justified in the CS on the grounds that the effectiveness data used within the model includes the impact on life expectancy, and to do so would double count the impact of LT. This simplifying assumption does not impact on the deterministic results as the OS impact of LT transformation will be accounted for, but it will impact on the probabilistic sensitivity analysis as not modelling LT as a

separate health state fails to acknowledge that uncertainty surrounding the rate of LT is correlated with OS and potentially also the rate of treatment discontinuations. This means that the impact of the uncertainty around the rate of LT transformation will not be fully accounted for in the probabilistic analysis.

The rate of LT from the COMFORT-II study is lower on ruxolitinib than BAT. However, the difference in the rates is small and is not statistically significant; there is therefore a case for using the same rates for both the ruxolitinib and BAT patients. Despite this, the ERG consider the approach reasonable as any uncertainty in the difference will be accounted for in the probabilistic analysis (subject to the caveat above) and the estimated difference is likely to be an underestimate due treatment crossovers which was not adjusted for. Furthermore, scenario analysis is presented where LT rates are assumed to be the same and this has minimal impact on the resulting ICER. See Section 5.2.9 for further details of this analysis.

5.2.5 The manufacturer's economic evaluation compared with the NICE reference case checklist

Table 12 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 12 Features of de novo analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	The ERG's clinical expert advised that lenalidomide is rarely used to treat MF in the NHS. The treatments comprise BAT are, however, otherwise consider broadly representative. The NICE scope indicated that a comparison with allogeneic hematopoietic stem cell transplantation would be desirable, this comparison was not carried out.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	A life time horizon assumed to be 35 years was used, this is considered to be sufficiently long to capture all difference in costs and benefits.
Synthesis of evidence on outcomes	Systematic review and mixed treatment comparison of relative effects.	Yes	

Measure of health effects	QALYs	Yes	
Source of data for measurement of HRQL	Reported directly by patients and/or caregivers	Yes	Utilities were derived using condition-specific preference-based measure for MF (MF-8D).
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes	
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was conducted as well as deterministic and structural sensitivity analyses. Mean increment results for the probabilistic sensitivity analysis were additionally presented using scatter plots, cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers.

5.2.6 Health related quality of life (HRQoL)

In the CS the main health benefit assessed is quality-adjusted life-years (QALYs). These are calculated using a disease specific preference based measure the development of which is described in the submission (CS, Section 5.4.1, pg. 180-184) rather than using utility estimated based on either EQ-5D or mapping from a disease specific measure of HRQoL. This is justified are the basis of psychometric analysis which examines the ability of EQ-5D and EORTC QLQ C30 to reflect changes in HRQoL and MF symptoms respectively. IN light of this analysis the he ERG considers the preference based tool developed by the company an appropriate source of utility values.

The preference based tool developed by the company is used to populate scores for the three health states (ruxolitinib, BAT and supportive care). Within the CS model patients are assumed to experience constant benefits from both ruxolitinib and BAT and therefore constant HRQoL in these health states. In contrast, in the supportive care state HRQoL is assumed to steadily decline. Disutility decrements are also applied for patients who experience LT, but no decrements are assigned to AEs. This is justified on the basis that HRQoLs are derived directly from the COMFORT-I and any decrements in HRQoL as a result of AEs would have been implicitly included within the economic analysis (CS pg. 185). The economic model structure implies progression is largely represented by

movement between states and justification for this based on empirical data presented in the CS, see CS pg.189 to 190). Table 13 shows the summary of utility values used in the economic model.

Table 13 Summary of utility values used in the cost-effectiveness analysis (CS, Table 37, pg. 189)

	Utility value: mean (standard error)	**Standard error**	**Source**	**Comment / justification**
Baseline HRQoL				
Unadjusted baseline	[redacted]	[redacted]	COMFORT-I	
Adjustment applied to baseline	0			The quality of life of patients in COMFORT-I is likely to be underestimated. No adjustment assumed in the base-case
Change in HRQoL				
On BAT				
• in patients treated with BAT	0		assumption	Disease assumed to be temporarily controlled whilst on BAT
On ruxolitinib				

• change in HRQoL at week 4 in patients achieving a spleen (Group 1) and or symptom response (Group 2)	[redacted]	[redacted]	COMFORT-I	The change in HRQoL at week 4 is maintained until ruxolitinib discontinuation. Long-term evidence suggests that the initial improvements in spleen length and MF-SAF-TSS happen as early as week 4 and are maintain over time.
• change in HRQoL at week 4 in patients achieving neither a spleen nor a symptom response (Group 3 - 5)	[redacted]	[redacted]	COMFORT-I	
On supportive care				
• every 24 weeks	[redacted]	[redacted]	COMFORT-I	
Events (decrement in QALYs)				
• AML	0.15		assumption	

BAT, best available therapy; HRQoL, health-related quality of life. MF-SAF, Myelofibrosis Symptom Assessment Form.

5.2.6.1 Baseline HRQoL

The baseline utility value used is assumed to be [redacted] based on the mean baseline MF-8D in COMFORT-I for the placebo and ruxolitinib group. It is likely this represents an underestimation of baseline utility value as this was based on patients in COMFORT-I which included only patients refractory to available therapy and therefore likely to have more severe symptoms and lower HRQoL than patients in COMFORT-III. A sensitivity analysis (CS, Figure 72, pg. 236) is conducted assuming the utility values in COMFORT-I to be under-estimated by a factor of 5%. This lowers the ICER estimate by several £1000s per QALY and may represent a more realistic estimate of ICER for ruxolitinib.

5.2.6.2 HRQoL on BAT

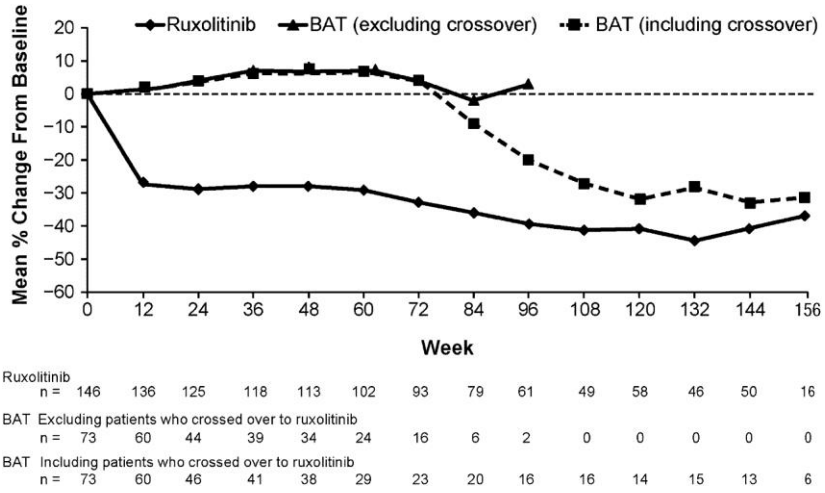
In the base-case the utility value for BAT patients is assumed to take baseline of [redacted]. This is justified on the basis that the placebo group in the COMFORT-I demonstrated small fall in HRQoL over 24 weeks and evidence presented in the CS suggests that placebo and BAT patients reporting similar outcomes according to EORTC QLQ-C30 scores. The company, however makes somewhat

conservative assumption that patients on BAT will maintain the same level HRQoL on average rather than experiencing a decline in HRQoL . This is supported by data from COMFORT-II which demonstrated there to be no statistically significant change in HRQoL using the FACT-Lym tool and the fact that current therapies for MF provide little improvement in spleen size, symptoms. . However, evidence presented in the clinical section suggests that BAT patients may experience a small improvement in HRQoL (See Section 4.2.1.1 pg. 39). The data shows the subgroup of BAT patients who received treatment (rather than just observation), achieved a clinically meaningful improvement (over 10 points from baseline) for Global Health Status/QoL, dyspnoea and appetite loss. The ERG concludes the base-case utility estimates might be underestimated in the economic model, however, there is minimal evidence that any benefit from BAT is maintained over any significant period of time and therefore ERG consider the assumption of no utility benefit from BAT reasonable.

5.2.6.3 HRQoL on ruxolitinib

The mean improvement in HRQoL at week 24 is calculated to be (after adjustment for age, treatment & outcome group, risk category, gender, spleen and MF-SAF): [redacted] in patients initiating ruxolitinib achieving neither a spleen response nor a symptom response [redacted] and [redacted] in patients [redacted] initiating ruxolitinib achieving a spleen or a symptom response. It is assumed in the base-case that the improvement in HRQoL is experienced as early as week 4. The assumption is supported by the evidence from Phase1/2 trials which suggested that receiving ruxolitinib experience benefits as early as 4 weeks (Figure 13) and maintain a similar (or greater) level of improvement at week 24. Scenario analyses are undertaken assuming the gain in HRQoL to occur at weeks 8, 12, 16, 20 respectively (CS, Table 73, pg. 253), this analysis showed little impact of the alternative assumptions on the estimated ICER.

Figure 13 Mean percentage change in spleen volume over time (CS, Figure 57, pg. 190)



BAT, best available therapy

The ERG has concern about combined analysis of spleen and symptom responders as they are likely to experience different HRQoL gains. The ERG requested information to clarify how this issue was dealt with in the probabilistic sensitivity analysis as uncertainty around composition of responders (i.e. how many are spleen responders and how many are symptom responders) should also be reflected in changes in the HRQoL value used for uncertainty in proportion of patients achieving each of the response categories to be accounted for properly. The company's response recognises this is an uncertainty and possibly a limitation of the model. The company's response agreed that an alternative approach could have been to estimate the utility value for spleen and symptom responders separately and apply the utility values according to the response group. However, the company stated that such an approach would reduce the sample size and therefore increase the uncertainty in the utility estimates. While the ERG acknowledges that combining spleen and symptom responders into a single group may be justified due to the limited data available, the ERG feels that further evidence could have been provided on the mean HRQoL in these two groups which would have potentially justified them being combined into a single group.

For the base-case analysis, the CS assumes that patients who achieve a response (spleen and/or symptoms) at week 24 remain on treatment, and on average maintain their initial gain in HRQoL until discontinuation from ruxolitinib therapy. The assumption is supported by the evidence from COMFORT trials and a phase two trial[39]. A scenario is conducted assuming that patients lose the initial gain in HRQoL over time until the point of discontinuation (CS, Table 75, pg. 254). In the base-case the non-responders withdraw from therapy at week 24, and the initial gain in HRQoL

experienced on treatment initiation, is lost and that the HRQoL returns to baseline levels a week after discontinuing treatment. The ERG considers this assumption supported by the presented evidence.

5.2.6.4 HRQoL on supportive care

In the economic model, the CS assumes that patients who entered into supportive care experienced disease progression, with worsening of their disease status and HRQoL until death. Patients in COMFORT-I had to be resistant or refractory to, intolerant of, or, in the investigator's opinion, not candidates for available therapy. The CS describes this population as corresponding to patients receiving supportive care. Therefore data from this group is used as a proxy for the change in HRQoL whilst on supportive care. The mean change in HRQoL at week 24 is calculated to be [redacted] in patients receiving placebo (after adjustment for age, treatment & outcome group, risk category, gender, spleen and MF-SAF). The adjusted change at week 24 is extrapolated over a lifetime horizon given patients on supportive care experience a progressive worsening of their disease status and HRQoL until death. Scenario analyses are conducted assuming the progression of HRQoL to be halved after 24, 48 or 72 weeks (CS, Table 72, pg. 252). The ERG concludes the assumption is reasonable and it has minimal impact on ICER.

5.2.6.5 Decrement in QALYs associated with transformation to AML

In the economic analysis, the CS assumes that patients with AML have a decrement in HRQoL of [redacted] (based on the difference between the baseline utility value used in the economic model and assuming the utility value with AML to be 0.257 as used in Tolley et al,[40] lasting 3.90 months on average (assuming the survival is exponentially distributed) leading to a decrement of 0.15 QALYs per AML event. The variation in this parameter is examined in sensitivity analysis (CS, Figure 72, pg. 236). The ERG considered this assumption plausible.

5.2.7 Resources and costs

The economic model presented by the company included the following costs:

- Drug acquisition costs (excluding administration costs);
- Monitoring costs;
- The cost of managing MF patients including cost of blood transfusions;
- The cost of treating/managing adverse events;
- Costs of Leukaemic transformation;
- The costs of palliative and end of life care.

Resource use data for MF patients is limited in the UK. The principal sources of resource data are the HMRN audit and the ROBUST study. The HMRN audit involved two adjacent UK Cancer Networks, with a total population 3.6 million and collected information about patients diagnosed with a haematological malignancy since 2004. The ROBUST study is a company sponsored single arm study involving 48 patients receiving ruxolitinib (see Section 4.2.2 for details). Data on resource use is also obtained from a number of additional sources including the COMFORT-II trial and the international JUMP study.

5.2.7.1 Treatment costs for patients treated with ruxolitinib

The weekly drug costs for patients treated with ruxolitinib are estimated based on the starting doses as defined in the SmPC and the actual dose usage in COMFORT-II. Over the trial period, Ruxolitinib doses increased, reduced or interrupted if deemed appropriate. The cost per drugs could range from £30 (cost/5mg tablet) to £60 (cost/10 or 15 or 20 mg table). Acquisition costs are provided below in Table 14. The daily cost of ruxolitinib has been reduced by [redacted] in a recent patient access scheme submission by the company (PAS 2015). Therefore, the cost per tablet ranged from [redacted] (cost/5mg tablet) to [redacted] (cost/10 or 15 or 20 mg table).

Table 14 List of price/pack and tablets/pack of ruxolitinib (CS, Table 38, pg.194)

Dose	Number of tablets per pack	Price per pack (NHS list price)
Ruxolitinib 5 mg	56	£1,680
Ruxolitinib 10 mg	56	£3,360
Ruxolitinib 15 mg	56	£3,360
Ruxolitinib 20 mg	56	£3,360

In the CS submission, a dose intensity adjustment is used to calculate the drug acquisition cost of ruxolitinib. A robust approach is used to account for the cost structure of ruxolitinib. First, Individual patient level data from the COMFORT-II trial are obtained to calculate the number of days patients received the different dosages (range 0 to 25 mg bid/qd) over the trial duration (Table 15). Second, an assumption is made that the minimum number of tablets would be prescribed, e.g. two 15 mg tablets would be given instead of six tablets of 5 mg for patients requiring 15 mg bid. Finally, the cost of ruxolitinib is calculated by multiplying the dosage received by the number of tablets received and respective costs. The more detailed information about the number of days treated with different dosage and assumption on costing used in the economic model are showed in Table 15.

Page superseded – see erratum

Table 15 Number of days treated with different dosage in COMFORT-II and assumption on costing used in the economic model (CS, Table 40, pg. 195)

Dosage received in COMFORT-II	Number of days patients are treated with different dosage	Proportion of days treated with the different dosage	Assumption[a]	Cost per day according to dosage
Missing	41			
0 mg	1,757	1.38%	None	£0
10 mg bid	32,917	25.93%	2 x 10 mg	£120
10 mg qd	167	0.13%	1 x 10 mg	£60
15 mg bid	25,565	20.14%	2 x 15 mg	£120
15 mg qd	199	0.16%	1 x 15 mg	£60
20 mg bid	38,911	30.66%	2 x 20 mg	£120
20 mg qd	218	0.17%	1 x 20 mg	£60
25 mg bid	8,553	6.74%	2 x 20 mg + 2 x 5 mg	£180
25 mg qd*	65	0.05%	1 x 20 mg + 1 x 5 mg	£90
35 mg qd	78	0.06%	1 x 20 mg + 1 x 15 mg	£120
5 mg bid	18,409	14.50%	2 x 5 mg	£60
5 mg qd	85	0.07%	1 x 5 mg	£30

[a]It should be noted that in the COMFORT studies, only the 5 mg tablets were available. Ruxolitinib is currently available as 5, 10, 15 or 20 mg tablets. bid, twice daily; qd, once daily

The cost per day (week) is estimated to be £113.33 (£793.30), taking into account dose interruptions/reductions. The CS expects treating physicians to minimise the cost (and number of tablets prescribed), it is possible to achieve a 25 mg dose by giving one 10 mg tablet and one 15 mg tablet, leading to a higher cost (compared to one 20 mg tablet and one 5 mg tablet). The CS also conducts sensitivity analysis [CS, Figure 72, pg. 236] assuming that 50% of patients on the 25 mg dosage receive a tablet of 10 mg and a tablet of 15 mg.

As currently constructed, the model assumes no drug wastage. This assumption may not accurately reflect drug usage in practice. The ERG has some concern about drug wastage considering that the shelf-life of the drug is only 30 days once a packet has been opened.[41] Given that most AEs are

managed by dose reduction or interruption it is possible that drugs would expire before all were used, leading to additional costs. There is no evidence to support what sort of impact drug expiry might have on overall costs. Additional scenario analysis is carried out by the ERG exploring alternative rates of drug wastage, see Section 6.

5.2.7.2 Administration and Monitoring Costs for patients treated with ruxolitinib

There is no administration cost of intervention as ruxolitinib is administered orally. However, the patients with MF are regularly monitored by their consultants throughout the course of the disease. The recommendations for the monitoring are specified in the SmPC and also by The Royal Surrey County Hospital NHS Foundation Trust[42] and London Cancer Alliance[43]. The following assumptions are made for the monitoring in the economic model in the CS: patients treated with ruxolitinib monitored in outpatients' visits and laboratory tests (including full blood count, liver function tests and urea and electrolytes) are done during each visit; and the frequency of the visit is on initiation, then every 3 weeks up to 12 weeks, then at week 24, then every 18 weeks thereafter. This is considered reasonable by the ERG clinical advisor.

5.2.7.3 Treatment costs for patients treated with BAT

The CS uses COMFORT-II trial data to estimate the drug acquisition cost. The decision is made based on clinical advice who felt that therapies used in the COMFORT-II trial are broadly representative of therapies used in the UK to treat patients with MF. During the trial period, the proportion of patients receiving each different therapy (or no treatment) is obtained for each 12-week interval (Table 15), but the duration for which patients received treatment within these 12 weeks periods is unclear. Therefore, the CS estimates the cost under two assumptions a conservative assumption and a more optimistic assumption. The conservative assumption where it is assumed the cost associated with only one pack (or injection) per 12 week period and the optimistic assumption where it is calculated the cost associated with the necessary number of pack (or injections) for the full 12 weeks duration. The dose intensity is taken from the BSCH guideline for the diagnosis and management of MF[3], the London Cancer Myelofibrosis guideline[44] and British National Formulary (BNF)[45] when appropriate. Unit costs are taken from the BNF.

ERG acknowledges the limited data availability on the BAT therapies. However, the ERG has some concern using COMFORT-II trial data the drugs used during trial period may be used more

commonly than indicated, but generally appropriate. The ERG's clinical advisor states that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed

low in the trial, compared with UK practice, and lenalidomide is not used in UK practice. Therefore ERG conducts additional analysis excluding lenalidomide cost, see Section 6.

No additional administration costs were included for the BAT arm, thus medications administered either intravenously or subcutaneously are assumed to incur no additional costs. Unit costs and assumptions about the number of tablets (injections) are summarised in Table 17 and are applied to the proportion of patients receiving BAT therapies at each 12 week period (Table 16) to estimate the 12-week drug acquisition costs of BAT. ERG has concerns about the lack of administration costs for intravenously or subcutaneously administered drugs. This assumption is, however, a conservative one.

Table 16 Number of patients receiving each treatment included in BAT in the COMFORT-II trial by time period (CS, Table 42, pg. 198)

	Weeks 0–12	**Weeks 12–24**	**Weeks 24–36**	**Weeks 36–48**
Patients	**n = 46/60**	**n = 42/45**	**n = 29/40**	**n = 24/34**
Aspirin	2	2	1	
Anagrelide	4	4	2	2
Cholchicine	1			
Cytarabine		2		
Danazol	3	3	3	2
Epoetin	5	5	4	4
Deferasirox	1			
Folic acid	1	1		
Hydroxycarbamide	33	29	21	17
Lenalidomide		2	2	1
Lysine acetylsalicylate			1	1
Melphalan	2	1	1	1
Mercaptopurine	2	2	2	1
Methylprednisolone	2	2	1	1

Peginterferon alfa-2a)	1	1		1
Prednisolone		1	1	
Prednisone	6	5	4	4
Interferon alfa-2a	1	1		
Thalidomide	3	2		
Tioguanine	1	1	1	1
No treatment	14	3	11	10

BAT, best available therapy.

Table 17 Assumptions on costing for medications included in the BAT bundle (CS, Table 43, pg. 199)

Drugs	**Dosage**	**Assumption about number of packs (injections)**		**Cost per pack/injection**	**Estimated cost per 12 week period**	
		Optimistic	**Conservative**		**Optimistic**	**Conservative**
Aspirin	75 mg/day	3 packs of 28 tablets (75 mg)	1 pack of 28 tablets (75 mg)	£0.94	£2.82	£0.94
Anagrelide	0.5 mg/ BID	2 pack of 100 capsules (0.5 mg)	1 pack of 100 capsules (0.5 mg)	£404.57	£809.14	£404.57
Cholchicine	0.5 mg TID for 7 days	1 pack of 100 tablets (0.5 mg)	1 pack of 100 tablets (0.5 mg)	£33.48	£33.48	£33.48
Cytarabine	100 mg/QD for 3 days	3 injections (100 mg)	1 injections (100 mg)	£3.90	£11.70	£3.90
Danazol	100 mg/BID	6 packs of 28 tablets (100mg)	1 packs of 28 tablets (100mg)	£7.64	£45.84	£7.64
Epoetin	Eprex: 80000 units weekly	12 injections of 8000 units	1 injection of 8000 units	£44.25	£531.00	£44.25
Deferasirox	500 mg / BID	6 packs of 28 tablets (500mg)	1 pack of 28 tablets (500mg)	£470.40	£2,822.40	£470.40
Folic acid	5 mg/QD	3 packs of 28 tablets (5mg)	1 pack of 28 tablets (5mg)	£1.09	£3.27	£1.09
Hydroxycarbamide	1000 mg/QD	2 packs of 100 tablets (500 mg)	1 packs of 100 tablets (500 mg)	£10.47	£20.94	£10.47

Lenalidomide	10 mg for 3 weeks (and one week rest)	3 packs of 21 tablets (10mg)	1 pack of 21 tablets (10mg)	£3,780.00	£11,340.00	£3,780.00
Lysine acetylsalicylate	Assume same as aspirin	same as aspirin	same as aspirin	same as aspirin	£2.82	£0.94
Melphalan	2 mg every other day	2 packs of 25 tablets (2mg)	1 pack of 25 tablets (2mg)	£42.88	£85.76	£42.88
Mercaptopurin	50 mg twice weekly	1 pack	1 pack	£50.47	£50.47	£50.47
Methylprednisolone	8 mg (every other day)	3 packs of 30 tablets (4mg)	1 pack of 30 tablets (4mg)	£6.19	£18.57	£6.19
Peginterferon alfa-2a	135 ug/QIW	12 injections (135µg)	1 injection (135µg)	£107.76	£1,293.12	£107.76
Prednisolone	10 mg/day[47]	6 packs of 28 tablets (5mg)	1 packs of 28 tablets (5mg)	£1.29	£7.74	£1.29
Prednisone	10 mg/day (assumed)	2 packs of 100 tablets (5mg)	1 pack of 100 tablets (5mg)	£89.00	£178.00	£89.00
Interferon alfa-2a	3000000 IU / 3 times a week	36 injections (3 million unit)	1 injection (3 million unit)	£14.20	£511.20	£14.20
Thalidomide	50 mg/QD	3 packs of 28 tablets (50 mg)	1 pack of 28 tablets (50 mg)	£298.48	£895.44	£298.48
Tioguanine	40 mg/TID	11 packs of 25 tablets (40mg)	1 packs of 25 tablets (40mg)	£103.54	£1,138.94	£103.54

BAT, best available therapy; bid, twice daily; qd, once daily;qiw, four times a week; tid, three times a day.

The CS estimates the 12 week cost for BAT (excluding monitoring) to range between £171.84 (conservative approach) to £556.97 (optimistic approach) respectively. In the base-case CS uses the average and assumed the cost of BAT (including no treatment) to be £364.40 per 12-week period (excluding monitoring), equating to a cost per day (week) of £4.34 (£30.37). It is unclear if this cost is an under- or over-estimation. Therefore a sensitivity analyses (CS, Figure 72, pg. 236) are conducted assuming the cost to range from £171.84 (conservative approach) to £556.97 (optimistic approach) per 12-week period.

5.2.7.4 Administration and Monitoring Costs for patients treated with BAT

It is assumed that patients on BAT have 0.24 outpatient visits per week based on the weighted number of outpatient visits (excluding visits associated for transfusion) per person per year reported in the HMRN audit in patients with intermediate-2 (10.48 ± 7.11; median, 8.01; range, 1.61 to 30.02) and high risk (12.45 ± 5.84; median, 11.80; range, 3.97 to 27.77) MF according to the IPSS classification. It is also assumed that patients on BAT have 0.32 full blood count tests per week based on the number of FBC tests per person per year reported in the HMRN audit in patients with high risk only (16.81 ± 14.16; median, 13.34; range, 3.73 to 70.69) according to the IPSS classification. Data on laboratory tests for high risk patients are used as one patient in the intermediate-2 risk group was an outlier and received 181.06 FBC tests. In the absence of data, liver function tests, urea and electrolytes are assumed to be monitored at the same time as performing full blood tests. The ERG clinical expert considers these assumptions reasonable.

5.2.7.5 Treatment, Administration and Monitoring Costs for patients on supportive care

It is assumed that patients on supportive care typically receive pain relief medication based on Clinical advice. In the base-case, CS assumes that patients on supportive care receive paracetamol 500 mg (net price 32-tab pack = 84p) and dihydrocodeine tartrate 30 mg (net price 28-tab pack = £1.15). The costs of full pack of two drugs are included to estimate the weekly cost of analgesics. It is assumed the number of outpatient visits and laboratory tests to be 50% lower compared with patients on BAT in the base-case to reflect for the fact that patients on supportive care are less monitored due to AEs from BAT treatments. Sensitivity analysis is conducted to reflect the uncertainty around the assumption (CS, Figure 72, pg. 236).

5.2.7.6 Estimating other resources used in MF (GP, A&E, Urgent care and RBC transfusions) in MF patients

Evidence from different sources is used, together with a number of assumptions, to approximate the potential healthcare burden of MF in the UK and healthcare costs from a NHS/PSS perspective. The main components of the management of the disease are included outpatient visits, RBC transfusions,

A & E visits, urgent care (walk in visits), inpatient stays, primary care visits and treatment (including medication and/or procedures/interventions). The outpatient attendances are included in the monitoring section. Hence, CS estimates other resources use in terms of GP visits, A&E visits, urgent care visits and RBC transfusions in this section. The key - data sources provide information on other resources use for the management of MF − the HMRN audit and the UK ROBUST study, the JUMP study and the COMFORT trials. For details of the resource use rates used see pg. 202-205 of CS.

ERG has concern about assumptions made using the data from the ROBUST UK study. Patients treated with BAT/supportive care are expected to experience more complications compared with patients on ruxolitinib and therefore are likely to utilise more healthcare resources. In the ROBUST UK study, the patients were on ruxolitinib treatment and the resource used might not reflect the resource used by patients on BAT therapy. The rate of resource use used in the model for the BAT arm may therefore be underestimated, overestimating the ICER. The ERG is, however, not able to conduct further analysis due to lack of alternative data.

The CS notes that patients on ruxolitinib are expected to experience fewer complications compared with patients treated with BAT/supportive care and therefore are likely to utilise less healthcare resource. The impact of ruxolitinib on resource use is sourced from the JUMP study a large international study with patients mostly recruited from continental Europe (there were no UK centres in the study). The choice of this instead of the UK based ROBUST study is justified in the CS on the grounds that the ROBUST study is too small to detect changes in resource use and that data was collected over too short a time interval. The ERG in principal accepts this argument, but noted that some of the reductions in resource are on very large reaching 100% in a number of cases. A comparison with the resource reductions observed in the UK based ROBUST study as a validity check would therefore have been useful. The ERG is not able to validate these reductions independently as the appropriate figures are not reported in either the JUMP or ROBUST study reported.

5.2.7.7 Resource use whilst on supportive care

For patients on supportive care the rate of hospitalisations, GP appointments, A&E visits and urgent care visits are assumed to be the same as for patients on BAT. A different rate of RBC transfusion is, however used for patients on supportive care. The number of units per person per month is based on the number of units used by patients in placebo group of the COMFORT-I study and is estimated to be 0.19 per week or 9.3 units transfused per year (excluding transfusions at the end of life). The rate of RBC transfusions is assumed to be constant in the supportive care phase. Scenario analysis is, however, carried out assuming an increase by 5% every 24 weeks in the number of RBC transfusions

for patients on supportive care (up to week 72). This scenarios analysis does not result in a significant change in the ICER estimate (CS, Table 76, pg. 255).

5.2.7.8 Management costs associated with AML

The cost associated with the management of AML in the UK is taken from results of a probabilistic decision model. In the base-case, CS assumes a one-off cost of £44,903 (middle range of the cost reported by Wang et al 2014[46]). Sensitivity analysis (CS, Figure 72, page 236) is conducted using the lower (£8,170) and upper range (£81,636) from the same study as mentioned above.

5.2.7.9 End of life (one-off costs)

The CS model includes a one-off cost in the period proceeding to death. Based on clinical advice these addition costs are assumed to consist of the following. Patients receive two units of RBC transfusion every week and one visit to haematologist during this period for the final 18 weeks of life.

In addition to this cost, a one-off cost of £ 6,016[47] is included at the time of death to reflect the cost associated with palliative care/end of life based on the community and inpatient hospital care cost for patients with cancer in the last 8 weeks of life. This cost is comparable to other cancer end of life costs.

5.2.7.10 Adverse events resource use and unit costs

CS includes the non-haematological events management cost using the data from the COMFORT-II trial, but no additional costs are included for the management of thrombocytopenia and anaemia as a cost is already included in the model for monitoring and RBC transfusions. The COMFORT-II study reported data for four groups of patients: patients randomised to ruxolitinib (core study), patients randomised to ruxolitinib and who received ruxolitinib in the extension phase, patients randomised to BAT (core study) and patients randomised to BAT who crossed over to ruxolitinib. Data from patients randomised to ruxolitinib and who continued to receive ruxolitinib in the extension phase are used to characterise the safety profile of ruxolitinib as this provides a longer follow-up (304.87 weeks) compared with data for the core phase of the study alone (170.12 weeks). The costs for management of these AEs are taken from a range of sources; however most of the cost are used from NICE STA for Enzalutamide (XTANDITM)[48]. The summary of the costs are presented in Table 19. The CS estimates the annual costs associated with the management of grade 3 or 4 non-haematological AEs are to be £61.11 for patients treated with ruxolitinib and £46.75 for patients treated with BAT. It is also assumed that patients experienced no AEs while receiving supportive care. The ERG considers that rates and resource costs to be appropriate.

Table 18 Adjusted incidence (%) of grade 3 or 4 AEs in COMFORT-II and associated medical management/health care cost [CS, Table 46, pg. 210]

Adjusted rate per 100-patient year exposure	**Ruxolitinib (core phase and extension) n = 146**	**BAT (core phase) n = 73**	**Management cost per adverse event**
Patient-year exposure	304.87	66.98	
	Grade 3/4	Grade 3/4	
Oedema peripheral	0	1.5	£914[48]
Diarrhoea	0.7	0	£47.03*
Asthenia	1.6	1.5	£12[48]
Dyspnoea	1.3	4.5	£0[48]
Pyrexia	1.3	0	£3076.99[49]
Fatigue	0.7	0	£12[48]
Bronchitis	1.3	1.5	£49.92**
Cough	0	1.5	£49.92**
Arthralgia	0.7	0	£101[48]
Weight increased	1.3	0	£92***
Nausea	0.3	0	£47.03*
Pain in extremity	0.3	0	£101[48]
Headache	0.7	0	£117[50]
Back pain	1.3	0	£460[48]
Abdominal pain	1.6	4.5	£697[48]
Epistaxis	0.7	0	£0[51]

AE, adverse event; BAT, best available therapy.

* assumed 1 GP consultation (£46) [PSSRU] and loperamide hydrochloride (£1.03) [BNF]

** assumed 1 GP consultation (£46) [PSSRU] and clarithromycin (£3.92) [BNF]

*** assumed 2 GP consultations (dietary advice)

Cervantes et al. 2013[52]

5.2.7.11 Economic impact of carers and patients

The CS discusses the potential impact of ruxolitinib on carer costs and impact on productivity. However, carer costs and costs of productivity loss are not included in the economic evolution due to limited data available for UK.

5.2.8 Cost effectiveness results

The base-case cost-effectiveness analysis presented in the CS compared ruxolitinib with BAT for a population of intermediate-2 and high-risk MF patients. The manufacturer reports both deterministic and probabilistic results. These are respectively presented in Table 19 and Table 20. Here we present the results from both for the company's original model and the new ICER following the introduction of the PAS which was forwarded to the ERG during the evaluation process. The increased QALYS were due to a combination of improved HRQoL and improved survival with the majority of the QALY gain as a result of an increase in life expectancy. The total incremental costs with ruxolitinib compared to BAT were driven by differences in the higher cost of ruxolitinib compared with BAT and the extended life expectancy increasing both duration of treatment and resource use.

Table 19 Deterministic CS base-case results

Analysis	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£) (QALYs)
Without PAS	[redacted]	[redacted]	[redacted]	[redacted]
With PAS	£112,843	3.81	2.51	£44,905

The ICER generated in the probabilistic sensitivity analysis was essentially similar to that observed in the deterministic analysis. The probability of ruxolitinib being cost effective using a threshold of £30,000, £40,000, £50,000 and £60,000 per QALY was respectively [redacted] without the PAS and 0.33%, 4.32%, 95.02% and 100% with the PAS.

Table 20 Probabilistic CS base-case results

Analysis	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£) (QALYs)
Without PAS	[redacted]	[redacted]	[redacted]	[redacted]
With PAS	£114,445	3.96	2.56	£44,625

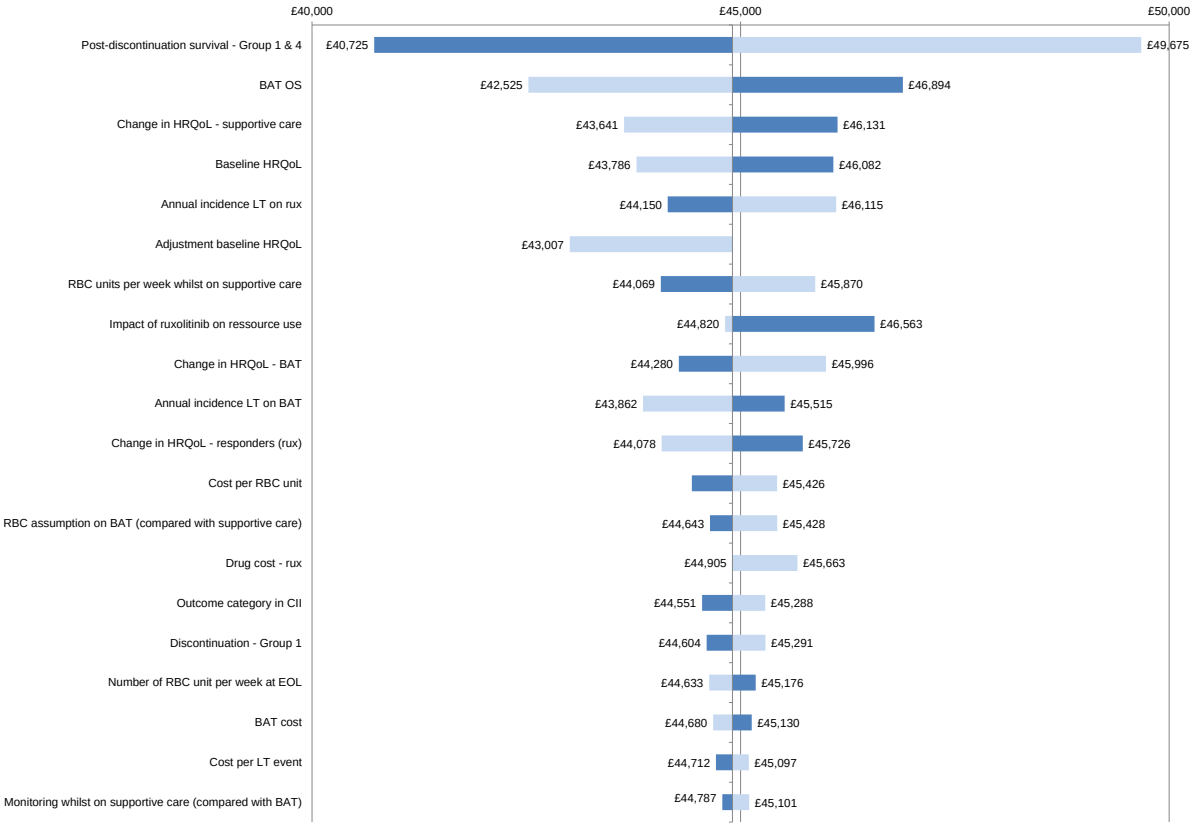
5.2.9 Sensitivity analysis

To evaluate uncertainty in submitted cost-effectiveness model an extensive number of one-way sensitivity analyses, deterministic scenario analysis and probabilistic sensitivity analysis were presented in the CS. These one way analyses allowed the testing of extreme values and diagnosing the drivers of the model results; while the scenario analysis allows examination of the impact of varying the structural assumptions in the model. The probabilistic analysis allows the uncertainty in all parameters to be jointly accounted for by drawing values from a distribution rather than using point estimates. Note all results presented in this sub section include the PAS discount.

5.2.9.1 One-way sensitivity analysis

One-way sensitivity analysis was carried out on nearly all parameters input parameters in the model. The results of the 20 inputs with the largest impact were presented as a tornado diagram which is presented here, see Figure 14 (Figure 72 in CS). The CS did not report the results of all other univariate sensitivity analysis stating that in all cases these input parameters had limited impact, with no greater than a £2000 change in the ICER. This was verified by the ERG.

Figure 14 Univariate sensitivity analysis [PS, Figure 1, pg. 12]



The one-way sensitivity analysis is described as varying parameters within the 95% CI or a reasonable range. It was not defined what was considered reasonable and the magnitude with which parameters were changed does not follow any obvious consistent approach e.g. +/- 30% of the mean. Nonetheless, the ranges used can be considered to be sufficiently large to evaluate the impact of the uncertainty surrounding these parameters.

The majority of inputs had minimal impact on the ICER estimate with post-ruxolitinib discontinuation survival and OS on BAT having the largest impact. In no case did the estimated ICER exceed a £50,000 threshold.

5.2.9.2 Scenario analysis

The CS presents an extensive number of scenario analyses testing a number of structural assumptions in the model. The vast majority of these have relatively modest impact on the estimated ICER. An exhaustive analysis of the all scenarios considered is not present here (see CS pg. 237 to 255), but instead a number of scenarios testing where either the justification behind assumptions was weaker or/and are inconsistent with standard methods. The following scenarios are therefore considered in more detail:

- Alternative response criteria;
- Alternative measure of HRQOL;
- Survival following ruxolitinib discontinuation;
- Estimation of time to BAT discontinuation;
- Survival following BAT discontinuation.

Alternative response criteria: Within the CS patients are considered to respond to treatment if they experience a (≥50% reduction in spleen length and or ≥50% reduction in MF-SAF score. The CS notes that BCSH guidelines state that treatment should be discontinued if after 6 months there is has been no clinically meaningful reduction in splenomegaly or improvement in symptoms. They also note that there is no consensus regarding the definition of response and therefore CS bases this definition on response criteria set out by in the recent IWG-MRT/ELN guidelines[1]. The ERG feels that this may be too conservative an assumption and that within clinical practice patients experiencing smaller clinical benefits may continue to receive ruxolitinib. Table 21 (PS Table 11) presents the result of scenario analysis presented in the PS using a number of alternative definitions of response. As Table 21 illustrates, alternative definitions have very little impact on the estimated ICER as, while relaxing the response criteria increases the total QALYs gained, it also has a commensurate impact on total costs.

Table 21 Scenario analysis 8: response criteria [PS, Table 11, pg. 18]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base-case	5.960	3.989	£149,114	2.154	1.476	£36,271	£44,905
Response definition (≥50% spleen reduction & ≥25% MF-SAF reduction)	6.351	4.220	£160,215	2.154	1.476	£36,271	£45,169
Response definition (≥25% spleen reduction & ≥50% MF-SAF reduction)	6.358	4.141	£156,204	2.154	1.475	£36,271	£44,992
Response definition (≥25% spleen reduction & ≥25% MF-SAF reduction)	6.613	4.292	£162,896	2.154	1.476	£36,271	£44,966
Response definition (≥50% spleen reduction & ≥ upper MID FACT-Lym)	5.923	3.965	£148,159	2.154	1.476	£36,271	£44,952
Response definition (≥50% spleen reduction & ≥ lower MID	6.421	4.267	£162,161	2.154	1.476	£36,271	£45,112

FACT-Lym)							
Response definition (≥25% spleen reduction & ≥ upper MID FACT-Lym)	6.412	4.173	£157,552	2.154	1.475	£36,271	£44,952
Response definition (≥25% spleen reduction & ≥ lower MID FACT-Lym)	6.752	4.382	£166,957	2.154	1.476	£36,271	£44,981

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Alternative measures of HRQoL: The base-line cost effectiveness model presented in the CS is not estimated using the EQ-5D as this was not considered appropriate. CS notes that evidence from the psychometric analyses indicate that the performance of the EQ-5D in MF is of concern.[53, 54] The CS presents one study which explored the appropriateness of the EQ-5D in the MF population using ROBUST study data. The appropriateness of the EQ-5D in the MF population was examined in terms of the psychometric criteria of convergent validity and responsiveness of the EQ-5D relative to the MF-SAF. The psychometric analysis suggested that the EQ-5D preference based and health dimensions had poor association with key symptoms in MF. Although the EQ-5D captured some changes, these changes were much smaller than when assessed using the MF-SAF. This exploratory analysis suggested that the EQ-5D measures' ability to capture the effect of key symptoms in MF is limited to pain rather than the specific MF symptoms such as night sweat, itchiness. However, results of this analysis need to be interpreted with caution due to the small number of patients (n = 48) and the potentially non-representative nature of the sample as 29% of the patient population had intermediate -1 risk disease which was not included in the COMFORT-I and COMFORT-II studies. Table 22 (PS Table 19) presents the results of scenario analysis carried presented in the PS where HRQoL measured using the EQ5D.

Table 22 HRQoL measure [PS, Table 19, pg. 21]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base-case	5.960	3.989	£149,114	2.154	1.476	£36,271	£44,905
HrQoL measured using the MF-8Dv2	5.960	3.725	£149,114	2.154	1.349	£36,271	£47,499
HrQoL measured using the EQ-5D	5.960	3.853	£149,114	2.154	1.468	£36,271	£47,313

BAT, best available therapy; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Survival following ruxolitinib discontinuation: Within the CS the baseline model present assumes that non-responders to ruxolitinib are assumed to benefit from an increase in life expectancy of 24 weeks. While the ERG felt it is clinically plausible that non-responders experience some life expectancy gain, the magnitude of the benefit was not justified by the company. This assumption was therefore considered to be unjustified. Table 23 (PS Table 17) presents the results of scenario analysis carried presented in the PS where this assumption is relaxed such that the time spent on ruxolitinib is part of the period of time on treatment on BAT.

Table 23 Survival following ruxolitinib discontinuation in patients not achieving response [PS, Table 17, pg. 21]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base-case	5.960	3.989	£149,114	2.154	1.476	£36,271	£44,905
Reduced survival for patients on ruxolitinib (Group 3)	5.892	3.943	£148,582	2.154	1.476	£36,271	£45,526

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Estimation of time to BAT discontinuation: Estimation for time to BAT discontinuation was based on survival analysis of time to discontinuation observed in the COMFORT-II study. AS note in the CS, however, a large proportion (61.6%) of the discontinuations from BAT therapy were due to patients crossing over to BAT therapy. The estimated time on BAT is therefore likely to be underestimated. To reflect this uncertainty the CS presents a number of scenario analyses assuming that duration on BAT was underestimated by factor of 10% to 40%. THE results of this analysis are presented in below in Table 24 (PS Table 6). As can be seen from Table 25 alternative assumptions about time on BAT have very little impact on the resulting ICER.

Table 24 Scenario analysis 3: Duration on BAT [PS, Table 6, pg. 15]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base-case	5.960	3.989	£149,114	2.154	1.476	£36,271	£44,905
BAT discontinuation reduced by 10%	5.960	3.990	£149,123	2.154	1.479	£36,356	£44,920
BAT discontinuation reduced by 20%	5.960	3.991	£149,158	2.154	1.483	£36,444	£44,947
BAT discontinuation reduced by 30%	5.960	3.991	£149,212	2.154	1.487	£36,520	£44,994
BAT discontinuation reduced by 40%	5.959	3.992	£149,237	2.154	1.491	£36,676	£44,996

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Survival following BAT discontinuation: The CS notes that the estimation of post BAT survival poses a problem due to the correlation that exists between time to discontinuation of BAT and time to death and the CS presents an approach which makes a number of essentially arbitrary assumptions regarding the shape of the post BAT survival curve. The CS acknowledges the arbitrary nature of

these assumptions and a series of scenario analysis are carried out in which alternative values of the shape parameter are used. These are presented here in Table 25 (PS Table 9). Additionally, the CS also presents scenario analysis in which OS and time to BAT discontinuation are sampled independently and therefore assumed to be uncorrelated. Under the first of these scenarios time to discontinuation is adjusted down and time to death left unchanged, and in the second one, time to death is adjusted up and time to discontinuation is left unchanged. The results of this scenario analysis are presented here in Table 26 (PS Table 10).

Table 25 Shape of the post-BAT survival curve [PS, Table 9, pg. 16]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base-case	5.960	3.989	£149,114	2.154	1.476	£36,271	£44,905
BAT post-discontinuation survival (shape of Weibull = -1)	5.917	3.907	£148,627	2.075	1.191	£34,841	£41,885
BAT post-discontinuation survival (shape of Weibull = -0.8)	5.934	3.928	£148,820	2.124	1.269	£35,366	£42,659
BAT post-discontinuation survival (shape of Weibull = -0.6)	5.941	3.946	£148,922	2.143	1.332	£35,775	£43,294
BAT post-discontinuation survival (shape of Weibull = -0.4)	5.947	3.959	£149,005	2.150	1.381	£35,963	£43,844
BAT post-discontinuation survival (shape of Weibull = -0.2)	5.951	3.969	£149,060	2.151	1.415	£36,107	£44,229
BAT post-discontinuation	5.954	3.977	£149,069	2.152	1.439	£36,219	£44,473

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
survival (shape of Weibull = 0)							
BAT post-discontinuation survival (shape of Weibull = 0.2)	5.956	3.982	£149,093	2.152	1.456	£36,184	£44,697
BAT post-discontinuation survival (shape of Weibull = 0.4)	5.958	3.986	£149,115	2.153	1.467	£36,226	£44,823
BAT post-discontinuation survival (shape of Weibull = 0.6)	5.959	3.988	£149,113	2.154	1.475	£36,258	£44,899
BAT post-discontinuation survival (shape of Weibull = 0.8)	5.961	3.990	£149,122	2.154	1.480	£36,300	£44,947
BAT post-discontinuation survival (shape of Weibull = 1)	5.962	3.992	£149,156	2.155	1.485	£36,303	£45,006

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 26 Examining structural assumption regarding the estimate for post-BAT survival [PS, Table 10, pg. 17]

Description	Ruxolitinib			BAT			ICER
	Life years	QALYs	costs	Life years	QALYs	costs	
Base-case	5.960	3.989	£149,114	2.154	1.476	£36,271	£44,905
Approach 1: BAT OS and discontinuation sampled	5.965	3.991	£149,105	2.162	1.477	£36,252	£44,899

(discontinuation adjusted)							
Approach 2: BAT OS and discontinuation sampled (OS adjusted)	5.981	4.002	£149,226	2.215	1.515	£36,681	£45,255
Approach 3: BAT post-discontinuation survival calibrated	5.959	3.990	£149,131	2.146	1.478	£36,257	£44,925

BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

5.2.9.3 Probabilistic sensitivity analysis

As reported above a probabilistic sensitivity analysis was carried out, the results which were presented in a cost effectiveness plane presented here, see Figure 15. (PS Figure 3) The results show only a modest variation in simulated points with [redacted] of estimated points lying between a threshold of £40,000 and £60,000 per QALY.

[redacted] 15 [redacted] CONFIDENTIAL

QALY, quality-adjusted life year. WTP, willingness to pay threshold

5.2.10 Model validation and face validity check

The submitted economic model has been checked by the ERG for functionality, clarity, accuracy, consistency, validity.

5.2.10.1 Internal consistency

The CS states that Excel formulas, model logic and input data were checked as part of quality assurance process by an experienced modeller involved in the model development. Furthermore, the CS describes a quality assurance process in which parameters were varied within extreme values beyond what would be considered "reasonable" to ascertain whether the change in the simulated costs and utilities was consistent with a priori expectation. However, no further details of the review process are provided.

The ERG undertook a review of the manufacturer's base-case and sensitivity analysis. Parameter inputs have been checked for corrective predictive validity (i.e. independent sensitivity analyses have been undertaken and results were mostly consistent with those expected, e.g. increasing the response rate to ruxolitinib increases its effectiveness). Further the VBA code used in the model was checked for potential errors, it was however not possible to complete a line by check of every single element of VBA code. This review identified a number of errors/potential inconsistencies:

- The formula used to calculator in the subroutine "GenHealthState" the probability of LT for both BAT and ruxolitinib patients were calculated incorrectly. For BAT patients the calculation used was

  probLTbat = (bDth/52) * LTonBAT_

  , and should be:

  probLTbat =1-((1-LTonBAT_)^(bDth/52))

  For ruxolitinib patients the calculation used is:

  If respCat = 3 Then

  probLTrux = ((rStop/52) * LTonRux_)+((rDth - rStop)/ 2) * LTonBAT_

  Else

  probLTrux = (rDth/52) * LTonRux

End If

, and should be:

If respCat = 3 Then

probLTrux = 1-(((1-LTonRux_)^(rStop/52))*((1-LTonBAT_)^((rDth – rStop)/ 52)))

Else

probLTrux=1-((1-LTonRux_)^(rDth/52))

End If

- On the sheet "Probabilistic_Analysis" Cells J8:O8 should average over the range J11:O5013 not J10::5013
- On the sheet "Probabilistic_Analysis" The formula present in cells J11:O310 should apply to J11 through to 5013 instead.

These errors only have a very small impact on the generated ICER with the latter two impacting only on the results of the probabilistic analysis. Results presented in section 6 have been corrected for these errors.

5.2.10.2 External consistency

The company externally validated the result of the model against those of the COMFORT-II study. In this the company compared the predicted OS, discontinuation rates and response rate to that observed in the COMFORT-II study. The results of this analysis show the models predictions to be largely consistent with the COMFORT-II data, see CS Section 5.7.2 pg. 225 for further details.

5.3 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case and is broadly in-line with the decision problem specified in the scope. The licenced population for ruxolitinib is however, somewhat broader than included in the model and excludes patients with less severe MF. The impact of the omission of these patients on the resulting ICER is uncertain. The intervention modelled in the economic analysis can be consider appropriate though the ERG note that the failure to account for possible drug wastage leads to underestimation of the ICER. The comparator was considered to be largely reflective of UK practice by the ERG clinical expert. However, the ERG

note the absence of allo-HSCT which is a potentially valid comparator to ruxolitinib and should have been included as either a separate comparator or included within BAT. While the ERG acknowledges that allo-HSCT is not an appropriate treatment for all MF patients, the ERG note recent evidence supporting a considerable survival benefit from the use of allo-HSCT in some MF patients.[2] The omission of allo-HSCT is therefore likely to have led to underestimation of the ICER. The outcomes included in the economic model were considered appropriate and likely to reflect any benefits of ruxolitinib.

The model structure is a reasonable representation of MF and patients clinical pathway. The model structure, however, places significant demands upon the available data and at this means that a number of assumptions are made about patients' transition through the model. These assumptions include:

- Post-discontinuation survival for patients initiating on ruxolitinib is the same for both early discontinuers and responders to treatment
- Spleen responders and symptom responders are assumed to have the same time on ruxolitinib, BAT and survival time.
- Time to death for patients on BAT is assumed to follow the same survival curve as used for discontinuation for other reasons.
- A 24 week survival benefit for non-responders is assumed for patients initiating on ruxolitinib.

CS presents empirical justification and/or extensive scenario analysis for all of these assumptions and there is general very limited impact on the ICER generated. However, this scenario analysis does not allow the joint uncertainty in the assumptions to be analysed and as such a degree of uncertainty over the overall impact of these structural assumptions remains unexplored.

The cost-effectiveness results showed that ruxolitinib results in significant QALY benefits most due increased life expectancy and a resulting ICER of £44,905 per QALY. The results were generally robust in both the sensitivity analyses (both deterministic and probabilistic) and scenario analysis conducted. In none of the deterministic sensitivity analyses and very few of the scenario analyses did the ICER exceed a £50,000 threshold.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

The ERG has undertaken additional analyses focusing on the issues and uncertainties highlighted in Section 5 and correcting for a small number of minor calculation errors. This additional analysis addresses the following issues:

- Assumption of no drug wastage for ruxolitinib patients;
- Inclusion of lenalidomide in BAT basket of therapies;
- Mortality of responders while receiving ruxolitinib;

Additionally, as noted in Section 5 while a number of structural assumptions are explored in the extensive scenario analysis presented in the CS, the cumulative impact of these assumptions is not assessed. The ERG has therefore undertaken a number of additional analyses based on a combination of a number of scenario analyses present by the company. All univariate analyses are undertaken using the corrected version of model using deterministic analyses. Deterministic analyses were used to show the effect of independent variable changes without the variation caused by the probabilistic analysis and because running the probabilistic analysis was more time consuming. Each scenario is also run using the PAS price for ruxolitinib. In the final section the ERG selects its preferred univariate analysis in each previous section and combines them to present the ERG's preferred analysis. Both deterministic and probabilistic results are presented for the ERG's preferred analysis.

6.2 Drug wastage

As reported in Section 5 the model does not allow for any drug wastage. The ERG considered this unlikely given the short shelf life of ruxolitinib once open (30 days) and that management of adverse events often involves dosage interruptions or reductions. The ERG therefore undertook an analysis assuming a number of alternative rates of drug wastage. The results of this analysis are presented in Table 27 and Table 28.

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Table 27 Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib without PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% ruxolitinib wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% wastage of Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15% wastage of Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28 Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib without PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	5.96	3.989	£148,920	2.15	1.476	£36,238	£44,831
5% ruxolitinib wastage in every cycle	5.96	3.989	£154,243	2.15	1.476	£36,238	£46,949
10% wastage of Ruxolitinib	5.96	3.989	£159,566	2.15	1.476	£36,238	£49,066
15% wastage of Ruxolitinib	5.96	3.989	£164,889	2.15	1.476	£36,238	£51,184

This analysis shows that drug wastage has moderate impact on the resulting ICER. Consultation with the ERG clinical expert suggests that a rate of 5% would be most appropriate though this is subject to a degree of uncertainty.

6.3 Alternative BAT

The ERG identified that basket of therapies that made up BAT currently includes lenalidomide, a drug not used in the UK. The ERG therefore requested at the points for clarification stage, that an option be added to the model in which lenalidomide is replaced with hydroxycarbamide; a conservative assumption designed to replace lenalidomide with the most commonly prescribed drug in MF treatment. If the cost of lenalidomide is substituted for hydroxycarbamide, the overall cost of BAT

treatment falls from £364.40 to £153.67 per 12 week period. The resulting ICERs with this substitution are presented in Table 29 and Table 30 below.

Table 29 Incremental cost-effectiveness ratios with hydroxycarbamide substituted for lenalidomide without PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion of lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30 Incremental cost-effectiveness ratios with hydroxycarbamide substituted for lenalidomide with PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	5.96	3.989	£148,920	2.15	1.476	£36,238	£44,831
Exclusion of lenalidomide	5.96	3.989	£148,698	2.15	1.476	£35,397	£45,077

6.4 Mortality of ruxolitinib non-responders

In the base-case model presented in the CS the mortality rate for ruxolitinib responders while on treatment was assumed to be 0.0%. This was justified on the basis that in the COMFORT-II study no ruxolitinib responders died while on treatment. The ERG considered this to be somewhat optimistic and requested at the points for clarification stage the company add a positive mortality rate. The company response suggested that this was not appropriate as no deaths were observed in the COMFORT-II, but did provide a number of additional scenario analyses assuming alternative mortality rates. While the ERG felt these scenarios were a useful exploration of alternative mortality rates these rates were based on assumptions rather than any data source. The ERG therefore presents alternative analysis using data on the mean time responders spent on ruxolitinib and mortality rates from life tables to estimate a conservative estimate of expected mortality during this period. This was done by assuming that the cohort of patients was 66 years of age at the beginning of the trial based on the median age of COMFORT-II patients and those patients spent on average 222.3 weeks on ruxolitinib post the initial treatment period as described in the CS. The ERG acknowledges that this is a somewhat crude estimate as this assumes all patients are the same age which is not true, but a more

complicated analysis accounting for the age distribution in COMFORT-II was not possible in the in the time available. On the basis of this analysis the expected mortality rate would be 7.06% during this [redacted] week period. This rate was therefore added to the model and the results of this analysis are presented in Table 31 and Table 32 below.

Table 31 Incremental cost-effectiveness ratios with alternative mortality rate for ruxolitinib responders without PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative mortality rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 32 Incremental cost-effectiveness ratios with alternative mortality rate for ruxolitinib responders with PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	5.96	3.989	£148,920	2.15	1.476	£36,238	£44,831
Alternative mortality rate	5.84	3.931	£148,396	2.15	1.476	£35,397	£45,683

6.5 ERG preferred analysis

The CS presents extensive scenario analysis to test the impact of a number of structural assumptions in the model. As a final sensitivity analysis the ERG undertook an analysis of another scenario using alternative plausible data and assumptions to combine several of the uncertainties used in the model. These changes to the CS base-case involved:

- Adding in drug wastage in ruxolitinib at a rate of 5%;
- Removing lenalidomide from the basket of therapies that make up BAT;
- Assuming that time on ruxolitinib is part of the period of time on treatment on BAT for non-responders;
- Assuming that the BAT discontinuation rate is underestimated by 20%;

This alternative base-case is presented assuming both 0.00% mortality rates for ruxolitinib responders and the alternative ERG rate of 7.06%. It is the opinion of the ERG that these data/assumptions are as plausible as those presented in the CS base-case and with regard to the first two are likely to be more representative of practice in the UK. The deterministic results of this analysis are presented in Table 33 and probabilistic results in Table 34; note results are with the PAS applied.

Table 33 Incremental cost-effectiveness ratios ERG alternative base-case (Deterministic analysis) (+PAS)

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	5.96	3.989	£148,920	2.15	1.476	£36,238	£44,831
Alternative ERG base-case with CS mortality rate	5.90	3.948	£153,621	2.15	1.483	£35,435	£47,950
Alternative ERG base-case with ERG mortality rate	5.78	3.890	£153,097	2.15	1.483	£35,435	£48,894

Table 34 Incremental cost-effectiveness ratios ERG alternative base-case (Probabilistic analysis)(+PAS)

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	6.10	4.03	£150,585	2.17	1.49	£36,629	£44,765
Alternative ERG base-case with CS mortality rate	6.02	3.98	£154,960	2.16	1.49	£35,862	£47,800
Alternative ERG base-case with ERG mortality rate	5.90	3.93	£154,988	2.16	1.48	£36,168	£48,553

These modifications to the model lead to a moderate increase in the ICER. The probability of ruxolitinib representing a cost-effective treatment strategy is 0.0%, 0.3%, 66.2% and 100% at a respective threshold of £30,000, £40,000, £50,000 and £60,000 (including the PAS discount).

6.6 Conclusions from ERG analyses

In this Section the ERG has presented a number of additional analyses to explore a number of issues raised in Section 5. An alternative base-case was also presented combining a number scenarios presented by the company and the alternative assumptions explored in this section. The results of this analysis show that the estimated ICER is relatively robust to the alternative assumptions explored by the ERG as these led to only modest increases in the estimated ICER. The alternative base-case conducted by the ERG showed a somewhat larger increase in the estimated ICER, but remained under a threshold of £50,000 per QALY. Probabilistic analysis using the ERG's alterative base-case showed there to be a high probability of the ICER being under a £50,000 per QALY threshold. The probability of the ICER being below £30,000 per QALY threshold was, however, negligible.

The ERG's additional analysis can be considered to be consistent with the extensive univariate sensitivity and scenario analysis presented in the CS, which similarly demonstrated that the estimated ICER is robust to a wide range of alternative input values and assumptions.

7 End of life

The life expectancy of patients with MF does not meet the end of life criterion set by NICE, of normally less than 24 months. The CS reported that median survival using the various prognostic scoring systems varies from 1.3 to 15.4 years, depending on the system and the risk classification. Data from a recent Haematological Malignancy Research Network (HMRN) audit of 98 patients indicated that the median survival for the total cohort, regardless of risk classification, was 3.36 years (range 2.8 to 4.4).[10] The ERG reports the figures from the IPSS and DIPSS development studies.[4, 9] Using IPSS median overall survival is: low >10 years; intermediate-2 approximately 8 years; intermediate-2 approximately 4 years; and high risk approximately 2 years (27 months (95% CI: 23-31). Using DIPSS median survival was not reached in low-risk patients; it was 14.2 years in intermediate-1, 4 years in intermediate-2, and 1.5 years in high risk patients. In the COMFORT-II trial, which included patients with intermediate-2 and high risk MF, patients in the BAT group survived for 26 months (median 28 months).[14] The company states that the COMFORT-II trial population is more representative of current treatment and the patients who would be eligible for ruxolitinib treatment than historical controls.

Because median overall survival was not reached in the ruxolitinib arm of the COMFORT-II trial it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT directly from the data. An indirect comparison using a subset of the ruxolitinib arm of COMFORT-II and the DIPSS cohort (Primary MF patients only) generated a median survival of 5 years (95% CI: 2.9-7.8) on ruxolitinib compared with 3.5 years (95% CI: 3.0- 3.9) for the DIPSS cohort.[31] Therefore it would appear that the improvement in survival with ruxolitinib exceeds the end of life threshold of 3 months.

As the information is derived from cohorts of patients with PMF and given a lack of information relating to survival of patients with other forms of MF, it is unclear how well the end of life criteria apply to patients with post-polycythaemia vera MF (PPV-MF) and post-essential thrombocythaemia MF (PET-MF).

The number of patients indicated for ruxolitinib treatment in the UK is small. The prevalence of MF has been estimated to be 2.2 per 100,000 population based on audit data for a region of England, thus 1185 patients in England and 70 patients in Wales are estimated to be living with the disease.

8 Overall conclusions

Evidence from two good quality RCTs demonstrates that ruxolitinib is effective at reducing splenomegaly and its associated symptoms and can increase overall survival in intermediate-2 and high risk MF patients who can tolerate ruxolitinib and remain on therapy. However withdrawal rates are high and around half of patients will have discontinued therapy after three years. Evidence relating to patients with lower risk disease or low platelet counts (50 to 100 x 10^9/L) is less robust.

The *de novo* model was well presented and had an appropriate model structure, which shows good validation with the trial data from the COMFORT-II study. The extensive sensitivity and scenario analysis presented in the company show the estimated ICER to be largely robust to a range of input values and assumptions made in the model. The alternative scenarios presented by the ERG show a modest increase in the estimated ICER primarily as a result of including an element of drug wastage within the model. This takes the estimated ICER close to a £50,000 threshold and as a consequence a wide set of alternative assumptions input values cause the estimated ICER to exceed £50,000 per QALY. Probabilistic analysis suggests there is a 66.2% chance that the ICER is below £50,000 per QALY. The probability that the ICER was below a threshold of £30,000 was 0.0%.

8.1 Implications for research

Long-term follow-up data are being collected for the COMFORT trials and the JUMP study which will provide further data on the effectiveness of ruxolitinib and particularly the impact of ruxolitinib on OS. In addition to these trials, there are a number of ongoing trials of ruxolitinib for patients with myeloproliferative neoplasms, as described in Section 4.1.7. Study NCT01317875 will assess ruxolitinib in patients with low platelet counts (< 100 x 10^9/L), which will fill an important gap in the evidence base. Study NCT00509899 (INCB018424) will evaluate the safety, tolerability and effectiveness of ruxolitinib, and will report adverse events. Study NCT01392443 (INC424) will assess the efficacy of INC424 by reduction in spleen volume. In addition, study NCT01969838 will assess efficacy of momelotinib versus ruxolitinib (a phase 3, randomised, double-blind active-controlled study).

Currently there is minimal evidence examining the relative effectiveness of ruxolitinib and allo-HSCT or the use of ruxolitinib as bridging therapy to allo-HSCT. Given the curative potential of allo-HSCT additional randomised trials comparing these alternative therapy options maybe warranted.

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ERG responses to Novartis Factual Error report

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) [ID831]

Issue 1 Median overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, para 3, page 12: "Because median overall survival was not reached in the ruxolitinib arm of the COMFORT-II trial it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT directly from the data. An indirect comparison using a subset of the ruxolitinib arm of COMFORT-II and the DIPSS cohort (Primary MF patients only) generated a median survival of 5 years on ruxolitinib compared with 3.5 for the DIPSS cohort"	"**While** median survival was not reached in the ruxolitinib arm of the COMFORT-II trial, **the analysis adjusted for cross-over presented by the company showed that BAT patients survived for only 26 months (median 28 months). The mean survival gain in the COMFORT-II trial was at least 21 months (ruxolitinib arm has not yet reached the median).** An indirect comparison using a subset of the ruxolitinib arm of COMFORT-II and the DIPSS cohort (Primary MF patients only) generated a median survival of 5 years on ruxolitinib compared with 3.5 for the DIPSS cohort"	Data presented in the Novartis submission have been omitted. While the median survival has not been reached for ruxolitinib, we reported on page 140 of the CS a median survival advantage of at least 21 months for ruxolitinib compared to BAT based on COMFORT-II data (after adjustment for cross-over). Novartis feel that direct data from COMFORT-II are more robust and relevant than the DIPSS analysis which is from diagnosis, only included PMF patients and only included a subset of patients in the COMFORT-II trial.	Not a factual inaccuracy. The survival benefit estimated in the COMFORT II trial is acknowledged and the risk group specific survival estimates from the COMFORT – II trial are discussed elsewhere in the report.

Issue 2 Rate of bronchitis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, para 4, page 12: "The incidence of bronchitis increased over time."	"The incidence of bronchitis **fluctuated** over time."	The incidence rates of bronchitis did not increase over time in absolute terms but rather fluctuated, first increasing then decreasing to increase and decrease again. Table 14.3.1-4.4 of the COMFORT-II CSR provides the incidence of adverse events of special interest by 24-weekly intervals by treatment (safety set).[1] The rates of bronchitis were: • 0-24 weeks: 5 (3.4%) • 24-48 weeks: 9 (6.7%) • 48-72 weeks: 10 (8.6%) • 72-96 weeks: 3 (3.0%) • 96-120 weeks: 10 (10.8%) • 120-144 weeks: 4 (4.9%) • 144- 168 weeks: 3 (4.2%)	**Changed from:** "The incidence of bronchitis increased over time" to "The incidence of bronchitis fluctuated over time, peaking at 48 to 72 weeks and 96 to 120 weeks."

Issue 3 Trials nor powered for overall survival differences

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, para 3, page 13: "Firstly, neither of the COMFORT trials was designed to be sufficiently powered to detect a significant difference in survival outcomes."	"Firstly, neither of the COMFORT trials was designed to be sufficiently powered to detect a significant difference in survival outcomes **although OS was a predefined secondary endpoint in both studies**."	The COMFORT studies were not designed to detect statistical differences in OS between the treatment arms and therefore were not powered for this analysis. However, OS was a predefined secondary endpoint in both of the	Not a factual inaccuracy. This section is discussing limitations of the OS data. The fact that OS was predefined therefore not relevant to this section.

Section 4.2,1, last para, page 33 "Neither of the COMFORT trials were designed to be sufficiently powered to detect a significant difference in survival outcomes. The COMFORT-II trial assessed overall survival, progression-free survival and leukaemia-free survival. The COMFORT-I trial assessed overall survival."	"**While** neither of the COMFORT trials were designed to be sufficiently powered to detect a significant difference in survival outcomes, **OS was included as a secondary endpoint in both trials**. The COMFORT-II trial assessed overall survival, progression-free survival and leukaemia-free survival. The COMFORT-I trial assessed overall survival."	COMFORT studies.	

Issue 4 Evidence to support OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, bullet point 1, page 15: "No clinical evidence was provided to support this assumption, and while the ERG accepts that some OS benefit may be experienced by these patients, the evidence does not support the OS benefit assumed in the model."	"No clinical evidence **is available to judge the validity of** this assumption….."	This sentence as it stands is misleading. No data are available to justify (or not) this assumption.	Amended to reflect lack of evidence.

Issue 5 Lenalidomide included in the best available therapies (BAT) basket of treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, last bullet point, page 15: "The comparator used in the model was BAT which comprised of a basket of treatments used in the COMFORT-II trial. There were concerns regarding the composition of this basket of therapies and how well it represented UK practice. In particular the inclusion of lenalidomide was considered inappropriate as this drug is not used in the UK." Section 2.2, first para, page 20: "Lenalidomide is not included in the CS description of commonly used treatments; the ERG's clinical advisor agrees that lenalidomide is not used in UK practice." Section 4.2.1, last para, page 32: "The COMFORT-II trial compared ruxolitinib with best available therapy (BAT), including observation alone (33% patients), hydroxycarbamide (47% patients), glucocorticoids (16% patients), epoetin-alpha (7% patients), immunomodulators (thalidomide	The statements should be changed to "…lenalidomide is **rarely** used in the UK."	Current usage of lenalidomide in the UK for the treatment of myelofibrosis is very low but not non-existent. It is not surprising that the HMRN audit did not record any lenalidomide usage since the study covers patients diagnosed with MF during the period 1 Sept 2004 to 31 August 2010 with follow up to March 2012.[2] It was not until June 2012 that the BCSH guidelines were published, which included a recommendation for medical management of splenomegaly using lenalidomide under defined conditions.[3] In subsequent years, usage of lenalidomide, while still very small, has shown a small increase, with market research indicating that, in 2014, approximately 3% of MF patients in the UK were treated with lenalidomide.[4]	Amended as suggested.

and lenalidomide, 7% patients), purine analogs (6% patients), androgens (4% patients), interferons (4% patients), nitrogen mustard analogues (3% patients) and pyrimidine analogues (3% patients). These comparators were generally appropriate, although the ERG's clinical advisor stated that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is not used in UK practice." Section 5.2.2, para 2, page 79: "The ERG has a number of concerns on the composition of BAT used in the model. The clinical advisor to the ERG team indicated that lenalidomide is not used in the UK, and the HMRN audit (HMRN audit) appears to confirm this assertion: no patients in the HMRN audit received lenalidomide.." Section 5.2.7.3 para 2, page 94: The ERG's clinical advisor states that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is not			

used in UK practice.			

Issue 6 Allo-HSCT excluded from the BAT basket of treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, last bullet point, page 15: "Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments."	"Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments **excluding ruxolitinib**."	The referenced retrospective study[5] specifically excluded patients receiving ruxolitinib from the two study cohorts and concludes that "…this study indicates that **non-ruxolitinib-treated** PMF patients 65 years of age or younger at diagnosis with int-2 or high-risk disease are likely to benefit from allogenic SCT…"	Amended as suggested.
Section 1.1, para 2, page 11: "However, the company excluded allogeneic haematopoietic stem cell transplantation (allo-HSCT) from the economic analysis because of the small number of patients that are eligible for allo-HSCT and lack of relevant data. As allo-HSCT is a potentially curative treatment for MF the ERG suggests that allo-HSCT, and possibly also ruxolitinib as a **bridge** to allo-HSCT, should have been included as a comparator. "	**Use of ruxolitinib as a bridge to all-HSCT**: please acknowledge that we consider it premature to evaluate ruxolitinib prior to allo-HSCT vs allo-HSCT	We fully support the clinical opinion that ruxolitinib has the potential to be used as a bridge to allo-HSCT. Indeed, this approach is currently being evaluated in an ongoing phase 2 clinical trial (NCT01790295). However, we do not yet have data to support the use of ruxolitinib in this setting and consequently it is outside the ruxolitinib marketing authorisation. We therefore considered it inappropriate to compare the use of ruxolitinib prior to allo-HSCT vs allo-HSCT in our economic analysis.	Not a factual inaccuracy.

Section 1.5, last bullet point, page 15: "Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments." Section 5.3, para 1, page 114: "However, the ERG note the absence of allo-HSCT which is a potentially valid comparator to ruxolitinib and should have been included as either a separate comparator or included within BAT. While the ERG acknowledges that allo-HSCT is not an appropriate treatment for all MF patients, the ERG note recent evidence supporting a considerable survival benefit from the use of allo-HSCT in some MF patients. The omission of allo-HSCT is therefore likely to have led to underestimation of the ICER. The outcomes included in the economic model were	**Use of allo-HSCT as a comparator**: please acknowledge that the "recent evidence supporting a considerable survival benefit from the use of allo-HSCT in some MF patients" was published too late for evaluation in our submission	We fully agree that allo-HSCT is the only curative therapy available for MF and could potentially have been used as a comparator in the economic analysis. However, we would like to point out the following: • As acknowledged in the guideline for diagnosis and management of MF,[3] there are no RCTs comparing allo-HSCT to any alternative/supportive therapy. Therefore it is necessary to rely on non-comparative studies with substantial heterogeneity of the patient populations when evaluating the benefit of all-HSCT in the treatment of MF. • The new evidence mentioned in the ERG report[5] was published three weeks before the ruxolitinib submission deadline and therefore could not be fully evaluated for inclusion in the cost-effectiveness analysis. It should be noted though, that this evidence is also from a retrospective cohort analysis and therefore RCT evidence continues to be lacking.	Not a factual inaccuracy.

considered appropriate and likely to reflect any benefits of ruxolitinib."			

Issue 7 Drug wastage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, first bullet point, page 16: "The model presented in the CS does not allow for any drug wastage. This was considered inappropriate due to the relatively short shelf life of ruxolitinib of 30 days once opened, and the fact that adverse events are often treated with either dose reductions or interruptions." Section 5.2.7.1, last para, page 93: "As currently constructed, the model assumes no drug wastage. This assumption may not accurately reflect drug usage in practice. The ERG has some concern about drug wastage considering that the shelf-life of the drug is only 30 days once a packet has been opened. Given that most AEs are managed by dose reduction or interruption it is possible that drugs would expire	Mention of wastage due to the fact that the shelf-life of the drug is only 30 days once a packet has been opened should be removed.	While it is true that the shelf life of tablets is 30 days after bottles have been opened, all ruxolitinib tablets supplied in the UK are blister packed. The 30 day shelf life does not apply to this packaging.[6]	Reference to drug shelf life removed as suggested.

before all were used, leading to additional costs."			

Issue 8 DES approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.6.2, para 2, page 16: "The DES structure used in the model makes significant demands on the clinical data, which forces the adoption of a number of assumptions with regards to how patients move through the model." Section 5.2.1, para 1, page 75: "The use of DES model however, places considerable demands on the available data as it is necessary to model the transition of sometimes small numbers of patients through the different states of the model. This forces the company to make a number of assumptions the details of which are discussed in section 5.2.1, which while mostly plausible and justified by the available evidence are subject to degree of uncertainty."	These statements should be removed	These statements are misleading as the use of a DES approach does not require additional assumptions compared with a cohort approach. The same assumptions/data would be required using a cohort approach.	Amended to clarify ERGs point. The DES model presented in the CS is fairly complex. A Markov model such as the one presented in the previous submission would likely have been simpler and as such would not have placed such significant demands on the data. A Markov would, however also been less realistic model and potentially less accurate. The advantages of the DES structure used are noted in Section 5.2.1, however the, ERG has added additional text to acknowledge the tradeoff between simplicity and realism.

Issue 9 Uncertain impact of treatment with ruxolitinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.6.2, para 2, page 17 "Uncertainty regarding the impact of treating patients with ruxolitinib therefore remains."	"Uncertainty regarding the impact of ruxolitinib **on the management of MF** therefore remains."	The statement is misleading if taken out of context.	Not a factual inaccuracy.

Issue 10 Prognostic scoring systems

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1, last para, page 19: "The CS did not describe the relevant prognostic systems, summarised here by the ERG as follows."	"The CS **described the relevant prognostic systems in Appendix Section 8.15, page 113**, **and the systems are summarised here** by the ERG as follows."	While we acknowledge that the description of the relevant prognostic systems was not included in the main body of the submission, the information was included in the appendix.	Amended as suggested.

Issue 11 Survival using different risk classifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.1, para 2, page 20: On page 20, the ERG reports the survival using different risk classifications. However, data presented by Novartis have been omitted	The following information should be included: "On Page 52 of the CS is the statement that the COMFORT-II trial population is more representative of current treatment and the patients who would be eligible for ruxolitinib treatment than historical controls. The company reports that BAT patients survived for only 26 months (median 28 months) after adjustment for cross-over."	Data presented in the company submission have been omitted	Not a factual inaccuracy. Data have not been omitted and are described in the first sentence.

Issue 12 Impact on progression-free survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1, para 1, page 25: "There was no evidence of any improvement in progression-free survival with ruxolitinib…." Section 4.2.1.2, last para, page 51:	**"There was evidence of reduced risk of disease progression for patients treated with ruxolitinib versus those in the BAT arm…."**	As recorded on page 51 of the ERG report, patients who received ruxolitinib had a reduced risk of disease progression (HR = 0.80; 95% CI, 0.54-1.19) compared with that of patients who received BAT. The Kaplan-Meier estimate of PFS at 3.5 years was 0.27 for the ruxolitinib arm (95% CI, 0.18-0.35) and 0.23 for the BAT arm (95% CI, 0.1-0.37).	The text referred to relates to the previous appraisal not the current one. The ERG accepts that there is potential for confusion here and therefore the three sentences referring to the results of the previous appraisal have been deleted. Not a factual inaccuracy.

"The CS reports that at 3.5 years follow-up patients who received ruxolitinib had a reduced risk of disease progression (HR, 0.80; 95% CI 0.54 to 1.19) compared with that of patients who received BAT. The Kaplan–Meier estimate PFS at 3.5 years was 0.27 for the ruxolitinib arm (95% CI 0.18 to 0.35) and 0.23 for the BAT arm (95% CI 0.1 to 0.37). The ERG could not find the source of the table presented."		The information presented in the table is from the poster for the COMFORT-II 3.5 year data presented at the European Haematology Association annual meeting in 2014 (abstract originally referenced, poster now provided)[7,8]	

Issue 13 Systematic review flow chart

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.6, para 1, page 28: "The flow chart of the study selection process presented in the CS was inaccurate, as it stated that 61 references were included, whereas only 30 references were included in the submission."	"The flow chart of the study selection process presented in the CS stated that 61 references were **identified and** 30 **of these** references were included in the submission. **Data and the reasons for not including the other 31 were provided."**	The flow chart presented an accurate representation of the systematic review. Only 30 of the 61 references were included in the CS and the reasons for not including the other 31 references were provided.	Not a factual inaccuracy. The flow chart in the CS (figure 8) states, "References included: 61"

Issue 14 Thalidomide usage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.1, para 3, page 32: The ERG's clinical advisor states that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is not used in UK practice.	"The proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) **was** low in the trial **and seemed to correlate with UK clinical practice**….. "	In the COMFORT-II trial, proportions of patients receiving the mentioned treatments were as follows: Epoetin-alpha 6.8% Thalidomide 4.1% Danazol 4.1% Market research indicates that the usage of thalidomide is declining, with < 3% of MF patients in the UK treated with thalidomide in 2014.[4] The other treatments were also used in <3% of MF patients in 2014.	Not a factual inaccuracy: the statement refers to the EG's clinical advisors expert opinion.

Issue 15 Structural uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.1, para 1, page 75: "…however, it is not possible to fully evaluate this structural uncertainty resulting from these assumptions."	Could the ERG check the meaning of this sentence and amend appropriately	The sentence in the ERG report is unclear	Amended to increase clarity.

Issue 16 HRQoL base line estimation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.1, para 1, page 88: "A sensitivity analysis (CS, Figure 72, pg. 236) is conducted assuming the utility values in COMFORT-I to be under-estimated by a factor of 5%. This lowers the ICER estimate by several £1000s per QALY and my represent a more realistic estimate of ICER for ruxolitinib."	The ERG expressed the opinion that the scenario analysis assuming the baseline HRQoL to be under-estimated by 5% to be a more realistic estimate of the ICER. As such, Novartis feels that this assumption should be included in the ERG preferred base-case.	The ERG states that this assumption is more realistic and therefore should be included in the ERG preferred base-case.	Not a factual inaccuracy. The ERG do not state that the alternative is a more realistic, simply that that it **may be** and are drawing the committee's attention to this uncertainty.

Issue 17 Table 28 label

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.2, Table 28, page 117 Label for Table 28: "Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib without PAS"	Label for Table 28 should read: "Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib **with** PAS"	The label for Table 28 is incorrect	Correction made as suggested

Issue 18 End of Life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 7, para 1, page 122: "The life expectancy of patients with MF does not meet the end of life criterion set by NICE, of normally less than 24 months."	"The life expectancy of **the total cohort of** patients with MF does not meet the end of life criterion set by NICE, of normally less than 24 months, **although patients with higher risk MF have a life expectancy of less than 24 months**."	The first sentence of the section gives the incorrect impression that the life expectancy for all MF patients is greater than 24 months and that, as a result, fulfilling the end of life criteria is not possible in this patient population. The following should be noted: • Using the DIPSS prognostic scoring system, median survival for high risk patients is 1.5 years;[9] • As indicated in the ERG report, in the COMFORT-II trial, which included patients with intermediate-2 and high risk patients, patients in the BAT group survived for 26 months (median 28 months). This only marginally exceeds the criterion of a life expectancy of less than 24 months.	Not a factual inaccuracy. The variation in mean survival by risk group is acknowledged in the remainder of the paragraph. With regards to marginally exceeding the 24 months, this is acknowledged, but the statement is correct as this does not meet the normal threshold of 24 months.

References

1 Table14.3.1-4.4. Incidence of adverse events of special interest by 24-weekly intervals by treatment (safety set). COMFORT-II CSR. 2013.

2 HMRN. Haematological Malignancy Research Network: Myelofibrosis Audit. 2012.

3 Reilly JT, McMullin MF, Beer PA *et al.* Guideline for the diagnosis and management of myelofibrosis. *British journal of haematology* 2012; **158**: 453-71.

4 JAK-004-15. Lenalidomide market share Q4 2014 MAT; IPSOS Oncology Monitor. In. 2015.

5 Kroger N GT, Scott BL et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. *Blood* 2015; **125**: 3347-50.

6 http://www.medicines.org.uk/emc/medicine/26991. Jakavi Summary of Product Characteristics. In. 2015.

7 Harrison C, Niederwieser D, Vannucchi AM *et al.* Results from a 3.5-year update of COMFORT-II, a phase 3 study comparison ruxolotinib (RUX) with best available therapy (BAT) for the treatment of myelofibrosis. *Haematologica* 2014; **99(Suppl 1)**: 126.

8 Harrison C ND, Vannucchi A et al. Results from a 3.5-year update of COMFORT-II, a phase 3 study comparing ruxolitinibwith best available therapy for the treatment of myelofibrosis. *Presented at the 19th Congress of EHA, June 12-15 2014, Milan, Italy* 2014.

9 Passamonti F, Rumi E, Caramella M *et al.* A dynamic prognostic model to predicct survival post-polycythemia vera myelofibrosis. *Blood* 2008; **111**: 3383-87.

Evidence Review Group Report

Ruxolitinib for disease-related splenomegaly or symptoms in adults with myelofibrosis (review of TA289) [ID831]

Erratum

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted],

Amended paragraphs

Section 1.2, para 4, page 12

"The incidence of bronchitis increased over time."

Amended to

"The incidence of bronchitis fluctuated over time peaking at 48 to 72 weeks and 96 to 120 weeks."

Section 1.5, bullet point 1, page 15

"No clinical evidence was provided to support this assumption, and while the ERG accepts that some OS benefit may be experienced by these patients, the evidence does not support the OS benefit assumed in the model."

Amended to

"No clinical evidence was provided to support this assumption, and while the ERG accepts that some OS benefit may be experienced by these patients, there is no clinical evidence available to judge the validity of this assumption."

Section 1.5, last bullet point, page 15

"In particular the inclusion of lenalidomide was considered inappropriate as this drug is not used in the UK."

Amended to

"In particular the inclusion of lenalidomide was considered inappropriate as this drug is rarely used in the UK."

Section 1.5, last bullet point, page 15:

Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments.

Amended to

Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments excluding ruxolitinib.

Section 1.5, first bullet point, page 16

"This was considered inappropriate due to the relatively short shelf life of ruxolitinib of 30 days once opened, and the fact that adverse events are often treated with either dose reductions or interruptions."

Amended to

"This was considered inappropriate due the fact that adverse events are often treated with either dose reductions or interruptions."

Section 1.6.2, para 2, page 16

The DES structure used in the model makes significant demands on the clinical data, which forces the adoption of a number of assumptions with regards to how patients move through the model.

Amended to

"The DES structure used in the model, while allowing of for a more complex and potentially more accurate representation of the patient pathway, makes significant demands on the clinical data, which forces the adoption of a number of assumptions with regards to how patients move through the model."

Section 2.1, last para, page 19

"The CS did not describe the relevant prognostic systems, summarised here by the ERG as follows."

Amended to

"The CS described the relevant prognostic systems in Appendix Section 8.16, page 114, and the systems are summarised here by the ERG as follows."

Section 2.2, first para, page 20

"Lenalidomide is not included in the CS description of commonly used treatments; the ERG's clinical advisor agrees that lenalidomide is not used in UK practice."

Amended to

"Lenalidomide is not included in the CS description of commonly used treatments; the ERG's clinical advisor agrees that lenalidomide is rarely used in UK practice."

Section 4.1, para 1, page 25

"The CS described an update of a systematic review evaluating the clinical effectiveness and tolerability of ruxolitinib for patients with MF. The original review, referred to as the 2011/2012 review in the CS, was critically appraised in a previous NICE STA of ruxolitinib for the treatment of myelofibrosis (TA289).[29] The previous appraisal concluded that evidence from two good quality RCTs (the COMFORT-I and COMFORT-II trials) demonstrated that ruxolitinib was effective at reducing splenomegaly and its associated symptoms. However, haematological symptoms of MF (in particular anaemia and thrombocytopenia) were worsened by ruxolitinib in some patients, at least in the short term. There was no evidence of any improvement in progression-free survival with ruxolitinib, although there was some evidence that overall survival may be increased with ruxolitinib, although data were uncertain (follow-up data were available up to 112 weeks)."

Amended to

"The CS described an update of a systematic review evaluating the clinical effectiveness and tolerability of ruxolitinib for patients with MF. The original review, referred to as the 2011/2012 review in the CS, was critically appraised in a previous NICE STA of ruxolitinib for the treatment of myelofibrosis (TA289).[29] "

Section 4.2.1, last para, page 32

"These comparators were generally appropriate, although the ERG's clinical advisor stated that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is not used in UK practice."

Amended to

"These comparators were generally appropriate, although the ERG's clinical advisor stated that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is rarely used in UK practice."

Section 5.2.1, para 1, page 75:

"The use of DES model however, places considerable demands on the available data as it is necessary to model the transition of sometimes small numbers of patients through the different states of the model. This forces the company to make a number of assumptions the details of which are discussed in section 5.2.1, which while mostly plausible and justified by the available evidence are subject to degree of uncertainty."

Amended to

"The use of DES model however, means that the model, while potential more accurate, is also more complex and places additional demands on the available data. As such, it is necessary to model the transition of sometimes small numbers of patients through the different states of the model. This forces the company to make a number of assumptions the details of which are discussed in section 5.2.1, which while mostly plausible and justified by the available evidence are subject to degree of uncertainty."

Section 5.2.1, para 1, page 75

"The CS includes a wide array of scenario analysis testing many of these assumptions on a univariate basis, however, it is not possible to fully evaluate this structural uncertainty resulting from these assumptions."

Amended to

"The CS includes a wide array of scenario analysis testing many of these assumptions on a univariate basis, however, it is not possible to fully evaluate the joint uncertainty resulting from these assumptions."

Section 5.2.2, para 2, page 79

"The ERG has a number of concerns on the composition of BAT used in the model. The clinical advisor to the ERG team indicated that lenalidomide is not used in the UK, and the HMRN audit (HMRN audit) appears to confirm this assertion: no patients in the HMRN audit received lenalidomide."

Amended to

"The ERG has a number of concerns on the composition of BAT used in the model. The clinical advisor to the ERG team indicated that lenalidomide is rarely used in the UK, and the HMRN audit (HMRN audit) appears to confirm this assertion: no patients in the HMRN audit received lenalidomide."

Section 5.2.7.1, last para, page 93

"The ERG has some concern about drug wastage considering that the shelf-life of the drug is only 30 days once a packet has been opened. Given that most AEs are managed by dose reduction or interruption it is possible that drugs would expire before all were used, leading to additional costs. There is no evidence to support what sort of impact drug expiry might have on overall costs."

Amended to

"The ERG has some concern about drug wastage given that most AEs are managed by dose reduction or interruption, leading to additional costs."

Section 5.2.7.3 para 2, page 94

"The ERG's clinical advisor states that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is not used in UK practice. Therefore ERG conducts additional analysis excluding lenalidomide cost, see Section 6."

Amended to

"The ERG's clinical advisor states that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is rarely used in UK practice. Therefore ERG conducts additional analysis excluding lenalidomide cost, see Section 6."

Section 6.2, Table 28, page 117

"Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib without PAS"

Amended to

"Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib with PAS"

patients and placebo patients at week 24. The primary endpoint was the same in both COMFORT trials; proportion of patients achieving a 35% or greater reduction of spleen volume. This endpoint was met in significantly more patients in the ruxolitinib group than the control group in both trials (28% of ruxolitinib patients versus 0% of BAT patients at 48 weeks in the COMFORT-II trial), with most patients achieving this level of response by week 12 and maintaining their response for a year or more. However, most patients (63%) had discontinued treatment at 3.5 year follow-up in the COMFORT-II trial and half of the patients in the COMFORT-I trial had discontinued treatment at 3 year follow-up, primarily because of disease progression or adverse events.

Ruxolitinib was associated with clinically meaningful improvements in MF-associated symptoms at week 24, whereas placebo-treated patients had worsening of symptoms. Both COMFORT trials also assessed HRQoL as an exploratory endpoint, ruxolitinib patients in both trials had an improvement from baseline in Global Health Status/QoL assessed using the EORTC QLQ-C30 scale.

Long term data from the COMFORT-II trial (3.5 years) demonstrated a statistically significant difference in overall survival favouring ruxolitinib over BAT, using both ITT and RPSFT analyses. However, the overall survival benefit at 3 years in the COMFORT-I trial did not reach statistically significance, even after adjustment for crossover. Because median overall survival was not reached in the ruxolitinib arm of the COMFORT-II trial it was not possible to calculate the median (or mean) survival benefit associated with ruxolitinib compared with BAT directly from the data. An indirect comparison using a subset of the ruxolitinib arm of COMFORT-II and the DIPSS cohort (Primary MF patients only) generated a median survival of 5 years on ruxolitinib compared with 3.5 for the DIPSS cohort

The incidence of serious adverse events was similar between treatment groups in both COMFORT trials. However, the incidence of grade 3 or 4 adverse events was higher in the ruxolitinib group than the BAT group in the COMFORT-II trial (42% versus 25%). In the COMFORT-II trial the incidence of adverse events of special interest generally decreased over time, although the incidence of infections remained quite high at between 25 to 43% over the 3 year follow-up (dropping from 50% during the first 24 weeks). The incidence of bronchitis fluctuated over time. It should be noted that the data presented were for those patients who remained on treatment, excluding those who dropped out because of adverse events. Haematological adverse events were very common with ruxolitinib.

severity in MF patients. A 35 year time-horizon is used in the model. Both costs and benefits are discounted at 3.5%.

The CS presents both deterministic and probabilistic sensitivity analyses to demonstrate the robustness of the estimated ICER along with extensive scenario analysis examining the impact of a number structural assumptions made in the base-case model. The base-case incremental cost-effectiveness ratio (ICER) presented in the CS (including PAS) is estimated to be £44, 905 per QALY in the deterministic analysis, and £44,625 per QALY in the probabilistic sensitivity analysis. The cost the probability of ruxolitinib being is a cost-effective strategy at thresholds of £30,000, £40,000, £50,000 and £60,000 per QALY was 0.33%, 4.32%, 95.02% and 100%, respectively. The sensitivity and scenario analyses presented by the company showed that the ICER rarely exceeded £50,000. Exceptions to this included:

- Reducing the time horizon to 5 years;
- Using an alternative parametric function to estimate OS in BAT patients;
- Using ITT (rather than cross-over adjusted) analysis to estimate OS on BAT.

None of these scenarios can be considered particularly plausible.

1.1 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model described in the CS is considered by the ERG to address the decision problem specified by NICE and meets the NICE reference case. The following issue were however identified in by the ERG:

- For patients who are considered non-responders to ruxolitinib after an initial 24 week treatment period it is assumed that overall survival will be increased by 24 weeks over patients initiating on BAT. No clinical evidence was provided to support this assumption, and while the ERG accepts that some OS benefit may be experienced by these patients, there is no clinical evidence available to judge the validity of this assumption.
- The comparator used in the model was BAT which comprised of a basket of treatments used in the COMFORT-II trial. There were concerns regarding the composition of this basket of therapies and how well it represented UK practice. In particular the inclusion of lenalidomide was considered inappropriate as this drug is rarely used in the UK. Furthermore, it was felt that this basket of therapies should have included allo-HSCT as, while not suitable for all MF patients, allo-HSCT is the only curative therapy available for MF and has been observed to result in significant survival benefit over other MF treatments excluding ruxolitinib.[2]

- The model presented in the CS does not allow for any drug wastage. This was considered inappropriate due the fact that adverse events are often treated with either dose reductions or interruptions.

1.2 ERG commentary on the robustness of evidence submitted by the company

1.2.1 Strengths

The evidence presented for the effectiveness of ruxolitinib was identified through a systematic review and primarily based on two good quality RCTs. The effectiveness of ruxolitinib was compared with generally relevant comparators and the outcomes assessed were appropriate.

The company presented a well conducted review of cost-effectiveness studies. The *de novo* model was well presented and an appropriate model structure used, which shows good validation with the trial data from the COMFORT-II study. The CS presents extensive scenario and sensitivity analysis and the cost-effectiveness results appear to be robust: the majority of the sensitivity analyses did not alter the ICER substantially.

1.2.2 Weaknesses and areas of uncertainty

The RCTs of ruxolitinib included patients with intermediate-2 or high risk MF and a platelet count of at least $100x10^9$/L, which is only a subset of the licensed population. The evidence for the use of ruxolitinib in patients with lower risk disease or low platelet counts was less robust, being based on four studies that did not include a non-ruxolitinib control group and three of the studies were very small.

The DES structure used in the model, while allowing of for a more complex and potentially more accurate representation of the patient pathway, makes significant demands on the clinical data, which forces the adoption of a number of assumptions with regards to how patients move through the model. These assumptions are generally well justified by empirical evidence presented in the CS and the uncertainty explored in the scenario analysis included in the CS. However, this analysis only allows the uncertainty resulting from the assumptions to be explored on a univariate basis and the joint uncertainty resulting from these assumptions remains unexplored.

The presented *de novo* model very closely models the presented clinical evidence and in particular the COMFORT-II trial. Using alternative clinical evidence may therefore have a significant impact on the estimated ICER. The *de novo* model can therefore is only as generalizable to the UK setting in so a far as the COMFORT-II trial can be considered to be representative of UK clinical practice. Particular areas of concern regards the generalizability of the COMFORT-II trial include the treatments included within BAT, and the patient population which as noted above excludes low and intermediate-I risk

2 Background

2.1 Critique of company's description of underlying health problem

The description of the underlying health problem in the company's submission (CS) is appropriate and relevant to the decision problem under consideration.

Myelofibrosis (MF) is a myeloproliferative neoplasm which can develop *de novo* as primary MF (PMF) or secondary to polycythaemia vera or essential thrombocythaemia, known as post-polycythaemia vera MF (PPV-MF) and post-essential thrombocythaemia MF (PET-MF). MF is a rare and debilitating disease associated with substantial morbidity and early mortality. The clinical features of MF are described in the British Committee for Standards in Haematology (BCSH) guideline as "variable and include progressive anaemia, leucopenia or leucocytosis, most commonly causing hepatomegaly and symptomatic splenomegaly. Patients with advanced disease experience severe constitutional symptoms, the consequences of massive splenomegaly (pain, early satiety, splenic infarction, portal hypertension and dyspnoea), progressive marrow failure, pulmonary hypertension, transformation to leukaemia and early death."[3]

The over-activation of the JAK/STAT signalling pathway, resulting in over-proliferation of blood cell precursors, is described in the CS. The clinical course of the disease and symptoms are appropriately described. Survival varies considerably and the life expectancy figures reported in the CS seem reasonable, according to the evidence review group's (ERG) clinical advisor. The CS states that median survival following diagnosis for patients with PMF is 4.0 to 5.7 years overall, according to historical data,[4, 5] while for patients with secondary MF, median survival following diagnosis is 5.7 to 7.5 years.[6, 7] However, these figures are low compared to other estimates and furthermore, within each of these groups survival varies considerably. More recently prognostic systems have been devised with the aim of assisting therapeutic decision making.[4, 8, 9]

The CS described the relevant prognostic systems in Appendix Section 8.16, page 114, and the systems are summarised here by the ERG as follows. A highly discriminative prognostic system was developed by the International Working Group for Myelofibrosis research and Treatment (IWG-MRT) – the International Prognostic Scoring System (IPSS).[4] A study was conducted using a database of 1054 MF patients. Five prognostic factors present at diagnosis were identified: age greater than 65 years, presence of constitutional symptoms, haemoglobin level less than 10 g/dL, leukocyte count greater than 25 _ 109/L, and circulating blast cells 1% or greater. Four risk categories were defined based on the presence of these prognostic factors: 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2) and 3 or more (high risk). To allow risk categorisation to be applied as MF progressed over time, a later study by the IWG-MRT

developed a second risk score: the Dynamic International Prognostic Scoring System (DIPSS).[9] This study based on data from 525 patients found that the 5 previously identified variables were still prognostic but different weights were to be applied. In particular a higher weight is given to anaemia (though not treatment induced anaemia): the presence of anaemia counts as two. An age adjusted version of DIPSS was also developed so that risk stratification could be applied to patients aged less than 65 years.

The CS reported that median survival using the various prognostic scoring systems varies from 1.3 to 15.4 years, depending on the system and the risk classification. Data from a recent Haematological Malignancy Research Network (HMRN) audit of 98 patients indicated that the median survival for the total cohort, regardless of risk classification, was 3.36 years (range 2.8 to 4.4).[10] The ERG reports the figures from the IPSS and DIPSS development studies.[4, 9] Using IPSS median overall survival is: low >10 years; intermediate-2 approximately 8 years; intermediate-2 approximately 4 years; and high risk approximately 2 years (27 months (95% CI: 23-31). Using DIPSS median survival was not reached in low-risk patients; it was 14.2 years in intermediate-1, 4 years in intermediate-2, and 1.5 years in high risk patients.

The CS reported that the prevalence of MF is estimated to be 2.2 per 100,000 population based on audit data for a region of England, thus 1185 patients in England and 70 patients in Wales are estimated to be living with the disease. These figures appear reasonable. Ruxolitinib is also licenced for the treatment of patients with polycythaemia vera who are resistant or intolerant to hydroxycarbamide (HC), however, this appraisal only relates to ruxolitinib for the treatment of disease-related splenomegaly or symptoms in adults with MF.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is generally appropriate and relevant to the decision problem under consideration. It correctly states that there is no clear standard therapy; treatments such as hydroxycarbamide, steroids and thalidomide are commonly used in the UK and are recommended for use by the BCSH guidelines. A survey of UK physicians treating patients with MF reported that erythropoiesis stimulating agent (ESA) and thalidomide were principally used to treat anaemia, hydroxycarbamide for leucocytosis, thrombocytopenia, splenomegaly, night sweats and fever, and steroids for weight loss.[11] Lenalidomide is not included in the CS description of commonly used treatments; the ERG's clinical advisor agrees that lenalidomide is rarely used in UK practice.

Ruxolitinib is licenced for the treatment of disease-related splenomegaly or symptoms in adults with PMF, PPV-MF or PET-MF. The BCSH guideline for the diagnosis and management of MF was

4 Clinical Effectiveness

This section contains a critique of the methods of the systematic review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies. The ERG's conclusions on the clinical effectiveness of ruxolitinib for disease-related splenomegaly or symptoms in adults with MF are presented at the end of this section.

4.1 Critique of the methods of review(s)

The CS described an update of a systematic review evaluating the clinical effectiveness and tolerability of ruxolitinib for patients with MF. The original review, referred to as the 2011/2012 review in the CS, was critically appraised in a previous NICE STA of ruxolitinib for the treatment of myelofibrosis (TA289).[29]

The update was referred to as the 2013/2014 review in the CS.

4.1.1 Search strategy

The CS described the search strategies used to identify relevant clinical effectiveness studies for ruxolitinib and other agents for the treatment of disease-related splenomegaly or symptoms in adult patients with primary MF, PPV-MF or PET-MF. The searches were designed to capture any new studies since the last searches for the 2011/2012 review. Brief details of the searches were provided in the main submission with full details, including the information sources searched, reported in Appendix 2, Section 8.2. Search strategies for both the previous 2011/2012 review and the 2013/2014 update review were reported in Appendix 2, Section 8.2.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE, the Cochrane Library (including Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), NHS Economic Evaluations database (NHS EED)) and the Cost Effectiveness analysis (CEA) registry were searched in December 2013 and again in December 2014 to identify clinical studies of myelofibrosis. In addition, the company searched the abstracts of

Haemoglobin Median (range), g/dL < 10 g/dL, %	 10.5 (6.6−17.0) −	 10.5 (3.5−17.3) −	 − 45	 − 52
JAK2V617F mutation positive,%	72.9	79.9	75	67

[a] One patient had a baseline spleen length recorded as non-palpable in error but had a prior measurement of 16 cm and a baseline spleen volume of 2450 cm^3; BAT, best available therapy; COMFORT, controlled myelofibrosis study with oral JAK inhibitor treatment; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; HRQoL, health-related quality of life; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; PET-MF, post-essential thrombocythaemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythaemia vera myelofibrosis; PROMIS, Patient-Reported Outcomes Measurement Information System; RCT, randomised controlled trial; ULN, upper limit of normal, WHO, World Health Organisation.

As shown in Table 3, the COMFORT trials were conducted only in patients with splenomegaly and intermediate-2 or high-risk MF, who had a platelet count ≥ 100 x 10^9/L and an absolute neutrophil count >1 x 10^9/L,[14, 15] therefore the results may not be generalisable to patients without splenomegaly or with lower risk disease or lower platelet or absolute neutrophil count. In addition, patients suitable for allo-HSCT at the time of study enrolment were excluded from the trials. Within this narrower population, the trial inclusion criteria appear to have been appropriate, and were similar between the two trials, with the exception that patients in the COMFORT-I trial had disease that was refractory to available therapies, had side effects requiring their discontinuation, or were not candidates for available therapies, therefore, in this trial ruxolitinib was used in the second-line setting.[15]

The company stated that patients in the COMFORT-II trial may be healthier than the general MF population because of clinical trial exclusion criteria, such as uncontrolled hypertension, unstable angina and a life expectancy of less than 6 months. The ERG understands this to mean healthier than the general intermediate-2 or high risk MF population as lower risk MF patients were not included in the trial.

The COMFORT-II trial compared ruxolitinib with best available therapy (BAT), including observation alone (33% patients), hydroxycarbamide (47% patients), glucocorticoids (16% patients), epoetin-alpha (7% patients), immunomodulators (thalidomide and lenalidomide, 7% patients), purine analogs (6% patients), androgens (4% patients), interferons (4% patients), nitrogen mustard analogues (3% patients) and pyrimidine analogues (3% patients). These comparators were generally appropriate, although the ERG's clinical advisor stated that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is rarely used in UK practice. The COMFORT-I trial compared ruxolitinib with placebo. However, as patients in this trial were refractory to, or were not candidates

5.2.1 Model structure

The company created an individual patient discrete event simulation model (DES). The use of an individual patient simulation model can be considered novel, and in contrast to the majority of oncology models which utilise cohort Markov structures. The company justifies the use of this approach on the basis that this type of model allows for increased flexibility and allows the progressive nature of MF to be modelled in more transparent way than a Markov model, which would require the excessive use of tunnel states (short-term 'temporary' states). The use of this type of modelling approach appears justified given the progressive nature of the disease and appropriate to the decision question. Furthermore, the additional flexibility permitted by an individual patient model allows for a number of structural assumptions of the model to be evaluated which would not be possible if a Markov structure had been adopted. The use of DES model however, means that the model, while potential more accurate, is also more complex and places additional demands on the available data. As such, it is necessary to model the transition of sometimes small numbers of patients through the different states of the model. This forces the company to make a number of assumptions the details of which are discussed in section 5.2.1, which while mostly plausible and justified by the available evidence are subject to degree of uncertainty. The CS includes a wide array of scenario analysis testing many of these assumptions on a univariate basis, however, it is not possible to fully evaluate the joint uncertainty resulting from these assumptions.

The model does not use time cycles though effectively a weekly cycle length is used in the model as this is the shortest unit of time used in the model. The time horizon used in the baseline analysis is 35 years which is designed to simulate a lifetime time horizon. Both costs and benefits are discounted at 3.5% in line with NICE recommendations and a NHS/PSS perspective is taken

A simplified schematic of the model structure is depicted in Figure 12 (CS Figure 42).

The model contains essentially four mutually exclusive health states with alive states being defined by therapy phase. These four health states are as follows:

- On ruxolitinib: receiving active therapy with ruxolitinib which provides improvements in symptoms, splenomegaly and HRQoL
- On BAT: receiving BAT which may provide some symptom relief and control of haematological parameters but little impact on HRQoL
- On supportive care: receiving only palliative treat, patients in this state can be considered to be treatment failures. HRQoL in this health state is assumed to decline representing continued disease progression.
- Death

clear from the data in what order the treatments are received, or how long patients remain on neither each treatment, nor how many treatment each patient might receive. For the purpose of calculating cost of BAT a number of assumption were made to account for this lack of data these are discussed further in Section 5.2.7. Based on the data from COMFORT between 6.67% and 29.41% of patients received no active treatment depending upon the time point under consideration.

The ERG has a number of concerns on the composition of BAT used in the model. The clinical advisor to the ERG team indicated that lenalidomide is rarely used in the UK, and the HMRN audit (HMRN audit) appears to confirm this assertion: no patients in the HMRN audit received lenalidomide. It is also clear from the published literature that there are other treatments used in the UK which are not included in the BAT bundle; as discussed in Section 2.2. Of note, the BCSH guidelines indicate that allo-HSCT is a potential therapy for myelofibrosis and is the only curative treatment for patients. This was also not included as part the BAT bundle. The ERG feels that allo-HSCT should have been considered either within the BAT bundle or as an alternative comparator. The ERG highlights that the omission of allo-HSCT is potentially particularly important as significant survival benefits have been observed using allo-HSCT[2]. The ERG, however, recognise that this treatment option would not be suitable for all patients and has a different treatment goal (curative as opposed to management of symptoms).

5.2.3 Perspective, time horizon and discounting

The economic perspective is the National Health Service (NHS) and the Personal Social Services (PSS) in accordance with the NICE reference case. The reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The time horizon used is 35 years, which is effectively a lifetime horizon given life expectancy with MF. Costs and benefits in the model were discounted at an annual 3.5% rate as per the NICE reference case.

5.2.4 Model inputs

The following section describes and critiques the key inputs and assumptions that influence a patient's transit through the model and how costs and benefits accumulated.

5.2.4.1 Response rate and Stopping rule

As described above, patients who receive ruxolitinib are subject to a stopping rule at 24 weeks. The 24 week duration and decision was based on BCSH guidelines that state that treatment should be discontinued after 6 months if there has been no reduction in splenomegaly or improvement in symptoms since initiation of therapy. The definition of response was based on the recent IWG-

Table 1 Number of days treated with different dosage in COMFORT-II and assumption on costing used in the economic model (CS, Table 40, pg. 195)

Dosage received in COMFORT-II	Number of days patients are treated with different dosage	Proportion of days treated with the different dosage	Assumption[a]	Cost per day according to dosage
Missing	41			
0 mg	1,757	1.38%	None	£0
10 mg bid	32,917	25.93%	2 x 10 mg	£120
10 mg qd	167	0.13%	1 x 10 mg	£60
15 mg bid	25,565	20.14%	2 x 15 mg	£120
15 mg qd	199	0.16%	1 x 15 mg	£60
20 mg bid	38,911	30.66%	2 x 20 mg	£120
20 mg qd	218	0.17%	1 x 20 mg	£60
25 mg bid	8,553	6.74%	2 x 20 mg + 2 x 5 mg	£180
25 mg qd*	65	0.05%	1 x 20 mg + 1 x 5 mg	£90
35 mg qd	78	0.06%	1 x 20 mg + 1 x 15 mg	£120
5 mg bid	18,409	14.50%	2 x 5 mg	£60
5 mg qd	85	0.07%	1 x 5 mg	£30

[a]It should be noted that in the COMFORT studies, only the 5 mg tablets were available. Ruxolitinib is currently available as 5, 10, 15 or 20 mg tablets. bid, twice daily; qd, once daily

The cost per day (week) is estimated to be £113.33 (£793.30), taking into account dose interruptions/reductions. The CS expects treating physicians to minimise the cost (and number of tablets prescribed), it is possible to achieve a 25 mg dose by giving one 10 mg tablet and one 15 mg tablet, leading to a higher cost (compared to one 20 mg tablet and one 5 mg tablet). The CS also conducts sensitivity analysis [CS, Figure 72, pg. 236] assuming that 50% of patients on the 25 mg dosage receive a tablet of 10 mg and a tablet of 15 mg.

As currently constructed, the model assumes no drug wastage. This assumption may not accurately reflect drug usage in practice. The ERG has some concern about drug wastage given that most AEs

are managed by dose reduction or interruption, leading to additional costs. Additional scenario analysis is carried out by the ERG exploring alternative rates of drug wastage, see Section 6.

5.2.7.2 Administration and Monitoring Costs for patients treated with ruxolitinib

There is no administration cost of intervention as ruxolitinib is administered orally. However, the patients with MF are regularly monitored by their consultants throughout the course of the disease. The recommendations for the monitoring are specified in the SmPC and also by The Royal Surrey County Hospital NHS Foundation Trust[42] and London Cancer Alliance[43]. The following assumptions are made for the monitoring in the economic model in the CS: patients treated with ruxolitinib monitored in outpatients' visits and laboratory tests (including full blood count, liver function tests and urea and electrolytes) are done during each visit; and the frequency of the visit is on initiation, then every 3 weeks up to 12 weeks, then at week 24, then every 18 weeks thereafter. This is considered reasonable by the ERG clinical advisor.

5.2.7.3 Treatment costs for patients treated with BAT

The CS uses COMFORT-II trial data to estimate the drug acquisition cost. The decision is made based on clinical advice who felt that therapies used in the COMFORT-II trial are broadly representative of therapies used in the UK to treat patients with MF. During the trial period, the proportion of patients receiving each different therapy (or no treatment) is obtained for each 12-week interval (Table 15), but the duration for which patients received treatment within these 12 weeks periods is unclear. Therefore, the CS estimates the cost under two assumptions a conservative assumption and a more optimistic assumption. The conservative assumption where it is assumed the cost associated with only one pack (or injection) per 12 week period and the optimistic assumption where it is calculated the cost associated with the necessary number of pack (or injections) for the full 12 weeks duration. The dose intensity is taken from the BSCH guideline for the diagnosis and management of MF[3], the London Cancer Myelofibrosis guideline[44] and British National Formulary (BNF)[45] when appropriate. Unit costs are taken from the BNF.

ERG acknowledges the limited data availability on the BAT therapies. However, the ERG has some concern using COMFORT-II trial data the drugs used during trial period may be used more commonly than indicated, but generally appropriate. The ERG's clinical advisor states that the proportion of patients receiving epoetin-alpha, thalidomide and androgens (anabolic steroids) seemed low in the trial, compared with UK practice, and lenalidomide is rarely used in UK practice. Therefore ERG conducts additional analysis excluding lenalidomide cost, see Section 6.

Table 2 Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib without PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% ruxolitinib wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% wastage of Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15% wastage of Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Incremental cost-effectiveness ratios with alternative drug wastage scenarios for ruxolitinib with PAS

	RUXOLITINIB			BAT			
	Life years	QALYs	Costs	Life years	QALYs	Costs	ICER
CS's Base-case (Corrected model)	5.96	3.989	[redacted]	2.15	1.476	£36,238	£44,831
5% ruxolitinib wastage in every cycle	5.96	3.989	[redacted]	2.15	1.476	£36,238	£46,949
10% wastage of Ruxolitinib	5.96	3.989	[redacted]	2.15	1.476	£36,238	£49,066
15% wastage of Ruxolitinib	5.96	3.989	[redacted]	2.15	1.476	£36,238	£51,184

This analysis shows that drug wastage has moderate impact on the resulting ICER. Consultation with the ERG clinical expert suggests that a rate of 5% would be most appropriate though this is subject to a degree of uncertainty.

6.3 Alternative BAT

The ERG identified that basket of therapies that made up BAT currently includes lenalidomide, a drug not used in the UK. The ERG therefore requested at the points for clarification stage, that an option be added to the model in which lenalidomide is replaced with hydroxycarbamide; a conservative assumption designed to replace lenalidomide with the most commonly prescribed drug in MF